HEART FAILURE
IN THE ELDERLY

B. Cost

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Aan mijn familie,
Guyonne en Thijs

Contents

Chapter 1

Introduction

Introduction

Heart failure is a clinical syndrome with various causes for which no universally accepted definition exists.[1] Packer's definition of heart failure "representing a complex clinical syndrome characterised by abnormalities of left ventricular function and neurohumoral regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity" reveals the complexity of the syndrome.[2]

Heart failure is one of the commonest cardiovascular disorders in Western Society and a growing major public health problem. It has been estimated that in the Netherlands the number of hospital discharges for heart failure rose from 14441 in 1980 to 25966 in 1993.[3] The prevalence of heart failure rises rapidly with age from 0.7% in those aged 55-64 to 13.0% in those aged 74-84.[4] This indicates a rapidly expanding problem mainly due to an increase in the number of elderly.

Despite the fact that heart failure and its precursor left ventricular systolic dysfunction are increasingly being recognised as important causes for morbidity and mortality, epidemiologic data are scarce.[1] For example, reliable information on the incidence of the syndrome is very limited. One of the reasons of the lack of epidemiologic data on heart failure is the difficulty of diagnosing early stages of heart failure and the virtual absence of target cohort studies. In the Netherlands and in the UK most heart failure patients are detected and treated in general practice. Heart failure is difficult to diagnose by the general practitioner due to the unavailability of more sophisticated or invasive diagnostic tools and is primarily based on clinical judgement. In recent years neurohumoral and Doppler echocardiographic measurements have emerged as non-invasive tools that could aid in the diagnosis of heart failure, also in a non-hospital setting.[5-8]

Heart failure carries a poor prognosis, but, again, data from population-based studies, notably those addressing the prognostic implications of asymptomatic ventricular dysfunction, is limited.

In recent decades the therapeutic management of heart failure has changed dramatically. Currently available treatment options (e.g. ACE-inhibitors, ß-blockers, diuretics and spironolactone) can reduce morbidity and mortality.[9-13] Moreover, it is suggested that in asymptomatic patients with left ventricular dysfunction prognosis can be improved by means of ACE-inhibition.[9,14] It is therefore important to identify determinants of the presence or development of heart failure and left ventricular dysfunction, to enable targeting of effective preventive or therapeutic strategies. The Rotterdam Study provided an excellent opportunity to study some of the issues mentioned above.

In the following chapters of this thesis, various epidemiologic aspects of heart failure and its precursor left ventricular systolic function will be addressed. In chapter 2 of this thesis, an overview of the epidemiology of asymptomatic left ventricular systolic function in the general population is presented. Reproducibility of the use of a heart failure score by general practitioners is described in chapter 3. Chapter 4 reports on the incidence and management of heart failure in general practice using data from the Dutch National Survey of Morbidity and Interventions in General Practice (NIVEL). In chapter 5 a study on the incidence and risk factors of heart failure is presented. The diagnostic value of the measurement of neurohormones to assess the presence of heart failure in patients suspected of heart failure is presented in chapter 6. Prognostic implications of left ventricular dysfunction and heart failure in the population at large are provided in chapter 7 and 8. Finally, in chapter 9 the results presented in the foregoing chapters are discussed and suggestions for further research are given.

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2. Packer M. Pathophysiology of chronic heart failure. [Review]. *Lancet* 1992;340:88-92.
3. Reitsma JB, Mosterd A, de Craen AJ, Koster RW, van Capelle FJ, Grobbee DE, Tijssen JG. Increase in hospital admission rates for heart failure in The Netherlands, 1980-1993. *Heart* 1996;76:388-92.
4. Mosterd A, Hoes AW, de Bruijne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population. The Rotterdam Study. *Eur Heart J* 1999;20:447-55.
5. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
6. McDonagh TA, Rodd SD, Murdoch DR, Morton J, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1997;351:9-13.
7. Francis CM, Caruana L, Kearney P, Love M, Sutherland GR, Starkey IR, Shaw TR, McMurray JJ. Open access echocardiography in management of heart failure in the community. *BMJ* 1995;310:634-6.
8. Murphy JJ, Frain JP, Ramesh P, Siddiqui RN, Bossingham CM. Open-access echocardiography to general practitioners for suspected heart failure. *Br J Gen Pract* 1996;46:475-6.
9. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
10. Carson P, Johnson G, Fletcher R, Cohn J. Mild systolic dysfunction in heart failure (left ventricular ejection fraction >35%): baseline characteristics, prognosis and response to therapy in the Vasodilator in Heart Failure Trials (V-HeFT). *J Am Coll Cardiol* 1996;27:642-9.
11. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
12. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184-91.
13. Anonymous. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol* 1996;78:902-7.
14. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.

Chapter 2

Asymptomatic left ventricular systolic dysfunction in the general population

Manuscript based on chapter 2:

B. Cost, D.E. Grobbee, A. Mosterd, A.W. Hoes. Asymptomatic left ventricular systolic dysfunction in the general population (submitted).

Introduction

Heart failure is very common, especially in the elderly, and has become one of the most important health care problems in cardiovascular medicine. The public health and economic burden of heart failure is expected to increase further due to ageing of the population and the success in treatment of cardiac diseases, notably ischaemic heart disease.[1,2] The prognosis of patients with heart failure is poor; within 5 years of a diagnosis of heart failure in the Framingham Heart Study, 75% of the men and 62% of the women had died.[3] Heart failure is a clinical syndrome that largely defies definition. The working group on heart failure of the European Society of Cardiology emphasized that the definition of heart failure encompasses objective evidence of cardiac dysfunction and clinical symptoms.[4] Thus, heart failure could be defined as symptomatic left ventricular dysfunction. When no symptoms are present, the term asymptomatic left ventricular dysfunction should be used. Left ventricular dysfunction can be attributable to systolic dysfunction, diastolic dysfunction or both. Hospital-based studies have shown that impaired systolic function is associated with a poorer prognosis in patients with myocardial infarction or congestive heart failure. Several studies have demonstrated the prognostic benefits of treatment of symptomatic left ventricular dysfunction (i.e. heart failure).[5-10] Asymptomatic systolic left ventricular dysfunction is increasingly being recognized as an important precursor of heart failure; 30% of the participants in the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial with asymptomatic impaired systolic function developed symptoms within three years.[7] Theoretically, prevention and early detection and treatment of asymptomatic systolic dysfunction might lead to a significant reduction of morbidity and mortality in the elderly. Epidemiologic data on left ventricular systolic dysfunction (LVSD) in the population at large are, however, scarce.[11] Even less is known about left ventricular diastolic dysfunction.[12,13] Most patients with heart failure and left ventricular diastolic dysfunction also have LVSD. In the study reported by Cowie et al. less than 15% of the incident cases of heart failure predominantly had left ventricular diastolic dysfunction.[14] Currently, no standardized method exists to establish diastolic dysfunction and specific treatment options for left ventricular diastolic dysfunction are lacking. For those reasons, left ventricular diastolic dysfunction will not be addressed in the following.
Echocardiography is recommended as the most appropriate diagnostic tool to assess the presence of cardiac dysfunction. Echocardiography has only recently been used in population-based studies and in studies in general practice to determine the occurrence of left ventricular dysfunction.

In this article, we will give an overview of recent data on the epidemiology of left ventricular systolic (dys)function in the general population, with emphasis on asymptomatic left ventricular systolic dysfunction.

Methods

The Medline Literature Database from January 1966 till April 1999 was searched using the medical subject headings "heart failure (congestive)", "cardiomyopathy (congestive)", "left ventricular function" and "epidemiology". In addition, we searched for the text words "symptomless", "asymptomatic", "symptomatic", "systolic function", "general practice", "primary care" and "general population". The search was extended using lateral references and personal communications with investigators.

Diagnosis

Left ventricular systolic dysfunction is a diminished ability of the heart to contract against a load; the ventricle has a reduced capacity to eject blood into a high-pressure aorta and the ejection fraction is reduced.[15] There are several methods by which left ventricular systolic function can be measured. Clinical findings, for example previous myocardial infarction, dyspnoe, oedema, rales and electrocardiographic abnormalities such as atrial fibrillation are not useful in detecting left ventricular dysfunction.[16] Traditionally, left ventricular function (pump performance) is measured during cardiac catheterization and contrast left ventricular angiography. The invasive nature of this procedure largely precludes its use in population-based studies. There are four non-invasive methods to assess left ventricular function: radionuclide angiography, electron-beam computed tomography (EBCT) scanning, ultrafast magnetic resonance imaging (MRI) and echocardiography. Nuclear angiography exposes patients to radiation and is relatively expensive. Although EBCT and MRI are highly reproducible and accurate in determining left ventricular function, they are not widely available, expensive and the cost-effectiveness of EBCT and MRI scans compared to echocardiography has not been adequately evaluated.[17-20] Up till now, MRI has only been used in highly selected patient groups. Furthermore, an MRI scan is judged to be unpleasant by many patients because they have to lie still for quite some time in a very noisy surrounding. Furthermore, MRI assessment of left ventricular function is time-consuming, both on- and off-line, making it unsuitable for rapid assessment. For the assessment of

ventricular function with EBCT, contrast has to be administrated intravenously and the patient is exposed to high radiation. Therefore, echocardiography is most widely used in clinical practice and seems a suitable tool for assessment of left ventricular systolic function in the population at large. From 2D echocardiographic images, left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) can be determined and the ejection fraction (EF), an index of left ventricular function can be calculated. Ejection fraction is the ratio of the difference between EDV and ESV to EDV and is expressed as a percentage (EF(%)=(EDV-ESV)/EDV×100). There are different methods (e.g. Simpson's rule, single and biplane ellipse methods) to determine left ventricular volumes, which are all tedious and time-consuming measurements. Left ventricular systolic function can also be estimated more simply by calculating the fractional shortening (FS) as the difference between left ventricular internal dimension at end diastole (LVIDed) and left ventricular internal dimension at end systole (LVIDes) divided by LVIDed (FS(%)=(LVIDed-LVIDes)/LVIDed×100). In the absence of major wall motion abnormalities fractional shortening can be assumed to reliably reflect left ventricular systolic function.[21] Furthermore, a semi-quantitative visual assessment of left ventricular function is sometimes used, since calculation of the ejection fraction is not always possible in routine medical practice. These visual estimates by experienced observers correlate reasonably well with the ejection fraction measured by radionuclide scan.[16,22]

Usually, the ventricle ejects more than 50% of its end-diastolic volume, but it is generally accepted that a ejection fraction of less than 40% can be considered abnormal. However, different cut-off values are used. Precise measurements of left ventricular function with echocardiography are not always possible, because a suitable echocardiographic window can not always be obtained. This is particularly prevalent in subjects with obesity and/or pulmonary disease and in the very old. Furthermore, atrial fibrillation reduces the reliability of the left ventricular systolic function measurements.

Routine application of echocardiography requires considerable expertise, is time-consuming and resource availability is limited.[23] Prescreening using prediction rules based, on signs and symptoms or on electrocardiography and neurohormone assessment may help to target echocardiography at those subjects most likely to have left ventricular dysfunction, but up to the present, the effectiveness of such prescreening strategies has not been addressed.

Prevalence

Estimates of the prevalence of left ventricular systolic dysfunction in the general population are available from five recent studies.[11,24-27] The estimates vary considerably. This is mainly attributable to differences in methodology (table 1). Estimates of asymptomatic LVSD are given in three studies only.

In the Rotterdam Study, a community-based prospective cohort study in Rotterdam, The Netherlands, the presence of heart failure was determined in 5540 participants aged 55 years or over (mean age 69 years, 41% male).[11] In 2267 subjects M-mode echocardiography was performed. Left ventricular dysfunction was defined as a fractional shortening of 25% or lower (comparable to an ejection fraction of ≤ 42.5%). In about 20%, M-mode registrations were deemed inadequate to measure fractional shortening. The overall prevalence of impaired systolic function was 5.5% (95% CI 4.1-7.0) in men and 2.2% (95% CI 1.4-3.2) in women. Sixty percent of persons with left ventricular systolic dysfunction was asymptomatic, i.e. did not report symptoms or had signs of heart failure, such as shortness of breath, ankle edema or pulmonary crepitations.

In the Glasgow MONICA risk factor survey among 2000 participants, the prevalence of left ventricular dysfunction was determined in 1640 participants aged 25-74 years (mean age 50 years; 48% male).[25] All participants underwent echocardiography and ejection fraction was assessed by the biplane Simpson's rate method. Left ventricular systolic dysfunction was defined as an ejection fraction of 30% or lower. Ejection fraction was measurable in approximately 90% of the participants. The prevalence of impaired systolic function was 2.9% (95% CI not given), was higher in men than in women (respectively 4.0% and 2.0%) and clearly increased with age. Impaired systolic function was asymptomatic in about half of the cases. With systolic dysfunction defined as an ejection fraction of less than 35% the overall prevalence was 7.7%, with 77% being asymptomatic.

In the study by Morgan et al, the prevalence of impaired ventricular function was assessed in a random sample of 1200 subjects aged 70-84 years (mean age 76 years; 46% male) enlisted with a four centre group general practice in Poole, Dorset.[24] Impaired systolic function was determined qualitatively in 1056 subjects eligible for echocardiography and quantitatively by measuring the biplane Simpson's rate method in 817 patients (77.4%). This yielded overall prevalence estimates of impaired systolic function of 7.5% (95% CI 5.8-9.5); 12.8% in men and 2.9% in women. Approximately 50% of those with systolic dysfunction had been diagnosed with heart failure before.

Table 1: Prevalence of left ventricular systolic dysfunction in the general population

Age (years)	Rotterdam Study[11] (FS ≤25%; mean age 69) (n=2267)			MONICA[25] (EF ≤30%; mean age 50) (n=1467)			Morgan[24] (EF qual; mean age 76) (n=817)			CHS[26] (EF qual; mean age 73) (n=5069)			Framingham[27] (FS ≤ 30%; mean age 46) (n=1493)		
	Men	Women	All	Men	Women	All	Men	Women	All	Men	women	All	Men	Women	All
25-34	-	-	-	0	0	-	-	-	-	-	-	-	-	-	-
35-44	-	-	-	0.7	0	-	-	-	-	-	-	-	-	-	-
45-54	-	-	-	5.8	2.4	-	-	-	-	-	-	-	-	-	-
55-64	3.7	1.2	2.3	5.7	2	-	-	-	-	-	-	-	-	-	-
65-69	7.6	3.1	5.3	6.4	4.9	-	-	-	-	-	-	2.3	-	-	-
70-74	6.9	3.3	4.8	-	-	-	9.4	2.2	5.8	-	-	3.6	-	-	-
75-79				-	-	-	13.1	2.4	6.9	-	-	5.2	-	-	-
80-84	10.0	10.5	10.3	-	-	-	20.5	5.4	12.1	-	-	5.5	-	-	-
85-94				-	-	-	-	-	-	-	-	-	-	-	-
Total	5.5	2.2	3.7	4.0	2.0	2.9	12.8	2.9	7.5	6.3	1.8	-	5.1	-	-

FS = fractional shortening, EF = ejection fraction, qual = assessed qualitatively, - = not reported

The Cardiovascular Health Study from the USA estimated the prevalence of left ventricular dysfunction in 5069 participants aged 65 years and older (mean age 73 years; 43% male).[26] Left ventricular function was assessed qualitatively in 99% of the participants. Again, the prevalence of impaired systolic function was higher in men (6.3%) than in women (1.8%). No estimates of the prevalence of asymptomatic LVSD were given.

In a subgroup of 1493 men (mean age 46 years; 100% male) free from overt cardiovascular disease of the Framingham Heart Study the overall prevalence of asymptomatic left ventricular dysfunction was 5.1% (95%CI not given).[27] Impaired systolic function was defined as a fractional shortening ≤ 30%.

Despite large differences in the applied definitions of left ventricular dysfunction, geographic regions and populations, resulting in different prevalence estimates, these studies clearly indicate that left ventricular systolic dysfunction is common, and that its prevalence strongly increases with age and is considerably higher in men than in women. In addition, LVSD is not accompanied by symptoms of heart failure in about 50% of the cases.

Incidence

As far as we know no data on the incidence of asymptomatic left ventricular systolic dysfunction are available. For symptomatic LVSD (i.e. heart failure) the only available population based data come from a study by Cowie et al.[14] In this study incident cases of heart failure were identified through a rapid access outpatient heart failure clinic to which GPs referred all cases of suspected heart failure and through examining all hospital admissions for heart failure. A panel of three cardiologists decided on the presence of heart failure using the guidelines of the Task Force on Heart Failure of the European Society of Cardiology.[4] The overall incidence was 1.3 per 1000 person-years; 1.4 in men and 1.2 in women. LVSD was found to be present in more than 85% of the incident cases of heart failure. Ideally, the incidence of asymptomatic LVSD should be studied in a population-based prospective cohort study using echocardiography to assess ventricular function. The baseline prevalent cases with LVSD should be excluded and during regular repeated echocardiographic assessments the presence of LVSD should be studied in all other subjects. Such a study, however, is logistically difficult, time consuming and expensive.

Etiology

Although much remains to be learned about the etiology of heart failure, coronary artery disease, diabetes and hypertension have been identified as the main risk factors in Western societies. As far as we know only McDonagh and Morgan et al. reported risk factors for left ventricular systolic dysfunction in the general population.[24,25] In the Glasgow Monica risk factor survey, ischaemic heart disease (i.e. history of angina, history of myocardial infarction and ischaemia or infarction on ECG) was found to be the main risk factor for LVSD. Furthermore, hypertension was an important risk factor, but only in the presence of ischaemic heart disease. Morgan et al. reported that self reported history of angina, myocardial infarction, heart failure and stroke were related to the presence of LVSD. However, the studies of Morgan et al and McDonagh et al were cross-sectional surveys. Although, cross-sectional surveys can be used in etiologic studies, one should keep in mind that in cross-sectional studies the determinants and outcome are measured at a single point in time. Cross-sectional studies designs are susceptible to bias (e.g. selection bias and cause-effect bias) and therefore may pose problems in the interpretation regarding causality. Additional prospective studies may provide further knowledge on the etiology of LVSD.

Prognosis

Little is known about the prognostic implications in terms of future cardiovasculair events and mortality of symptomatic and asymptomatic LVSD in the population at large. Currently available data originates from trials (e.g. SAVE and SOLVD) including selected placebo treated patients with LVSD. Population based prognostic studies in subjects with (asymptomatic) LVSD are urgently needed.

Management

Interventions could be aimed at reducing the risk of developing LVSD, decreasing the progression of asymptomatic LVSD to heart failure and reducing signs and symptoms accompanying symptomatic LVSD.

Prevention of LVSD, the first step in the management of LVSD, should focus on the modification of risk factors for LVSD, and in particular those related to the progression of coronary artery disease. Therefore, interventions should be directed at

preventing, detecting and treating hypertension, diabetes, hypercholesterolemia and smoking.

In subjects with asymptomatic LVSD, screening for LVSD might be useful and interventions should aim at postponing or preventing the development of symptomatic LVSD (i.e. heart failure). There are only two studies suggesting that in selected patients with ischaemic heart disease and asymptomatic LVSD (mean age of sixty years), morbidity and mortality can be reduced by treatment with ACE-inhibitors.[7,10] This benefit needs to be confirmed in a trial with larger groups of asymptomatic LVSD patients, demonstrating the added value of treating those with asymptomatic LVSD compared to those treated when symptoms developed. Only then screening for and treatment of asymptomatic LVSD could be considered in a larger population.

The treatment of heart failure has been discussed extensively in several guidelines.[28,29] In short, ACE inhibitors form the cornerstone of heart failure treatment. Additionally, diuretics, digoxin, spironolactone and ß-blockers may be prescribed depending on signs and symptoms. Studies addressing the efficacy of some of these drugs in asymptomatic LVSD are underway.

Summary and conclusion

Left ventricular systolic dysfunction is common, its prevalence and incidence increases sharply with age, LVSD is more common in men and LVSD very often is asymptomatic. Left ventricular systolic dysfunction and its subsequent progression to heart failure places a major public health and economic burden on society. Prevention and early interventions may be the key to reduce this burden. Before early detection of or screening for and subsequent treatment of patients with asymptomatic left ventricular systolic dysfunction can be recommended with confidence more information on its incidence, etiology, prognosis and therapeutic possibilities is required.

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2. Bonneux L, Barendregt JJ, Meeter K, Bonsel GJ, van der Maas PJ. Estimating clinical morbidity due to ischemic heart disease and congestive heart failure: the future rise of heart failure. *Am J Public Health* 1994;84:20-8.
3. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.
4. The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741-51.
5. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
6. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
7. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
8. Anonymous. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol* 1996;78:902-7.
9. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184-91.
10. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
11. Mosterd A, Hoes AW, de Bruijne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population. The Rotterdam Study. *Eur Heart J* 1999;20:447-55.
12. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565-74.
13. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. *Arch Intern Med* 1996;156:146-57.
14. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure: a population-based study. *Eur Heart J* 1999;20:421-8.
15. Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. *JAMA* 1994;271:1276-80.
16. Choy AM, Darbar D, Lang CC, Pringle TH, McNeill GP, Kennedy NS, Struthers AD. Detection of left ventricular dysfunction after acute myocardial infarction: comparison of clinical, echocardiographic, and neurohormonal methods. *Br Heart J* 1994;72:16-22.

17. Schmermund A, Rensing BJ, Sheedy PF, Rumberger JA. Reproducibility of right and left ventricular volume measurements by electron-beam CT in patients with congestive heart failure. *Int J Card Imaging* 1998;14:201-9.
18. Becker A, Becker C, Knez A, Haberl R, Bruning R, Reiser M, Steinbeck G. Funktionsuntersuchungen des Herzens mit der Elektronenstrahltomographie [Functional imaging of the heart with electron-beam computed tomography]. *Radiologe* 1998;38:1021-8.
19. Butler SP, McKay E, Paszkowski AL, Quinn RJ, Shnier RC, Donovan JT. Reproducibility study of left ventricular measurements with breath-hold cine MRI using a semiautomated volumetric image analysis program. *J Magn Reson Imaging* 1998;8:467-72.
20. Sinha S, Mather R, Sinha U, Goldin J, Fonarow G, Yoon HC. Estimation of the left ventricular ejection fraction using a novel multiphase, dark-blood, breath-hold MR imaging technique. *Am J Roentgenol* 1997;169:101-12.
21. Quinones MA, Pickering E, Alexander JK. Percentage of shortening of the echocardiographic left ventricular dimension. Its use in determining ejection fraction and stroke volume. *Chest* 1978;74:59-65.
22. Willenheimer RB, Israelsson BA, Cline CM, Erhardt LR. Simplified echocardiography in the diagnosis of heart failure. *Scand Cardiovasc J* 1997;31:9-16.
23. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-83.
24. Morgan S, Smith H, Simpson I, Liddiard GS, Raphael H, Pickering RM, Mant D. Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. *BMJ* 1999;318:368-372.
25. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997;350:829-33.
26. Gardin JM, Siscovick D, Anton-Culver H, Lynch JC, Smith VE, Klopfenstein HS, Bommer WJ, Fried L, O'Leary D, Manolio TA. Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly. The Cardiovascular Health Study. *Circulation* 1995;91:1739-48.
27. Lauer MS, Evans JC, Levy D. Prognostic implications of subclinical left ventricular dilatation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). *Am J Cardiol* 1992;70:1180-4.
28. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. *Eur Heart J* 1997;18:736-53.
29. Cohn JN. The management of chronic heart failure. *N Engl J Med* 1996;335:490-8.

Chapter 3

Use of a score based on history and physical examination to diagnose heart failure in general practice: interobserver variability

Manuscript based on chapter 3:

B. Cost, D.E. Grobbee, J. van der Schoot-van Venrooy, R. Bernsen, A.H.M.M. Balk, A.W. Hoes. Use of a score based on history and physical examination to diagnose heart failure in general practice: interobserver variability (submitted).

Introduction

The diagnosis of (early stages of) heart failure is a difficult and challenging task. This particularly applies to primary care, where the diagnosis of heart failure is mainly based on clinical judgement of the general practitioner (GP). Prior studies showed that the validity of the clinical diagnosis of heart failure is limited, particularly in women, the obese and the elderly.[1-3] Incorrect diagnosis has major consequences for both patients and health services. Therefore, methods to improve the early recognition of heart failure are required. The presence of heart failure can be assessed with the use of scoring systems.[4] All scores have a high sensitivity for diagnosing definite heart failure and a much lower sensitivity for the detection of possible heart failure. The presentation of early stages of heart failure is atypical and the applicability of heart failure scores as a screening test to detect heart failure requires further study. In our study on the incidence and risk factors of heart failure we trained general practitioners in the use of a score in order to refer all possible cases of heart failure. The purpose of this study was to assess the interobserver variation among participating GPs in the use of a scoring system to detect possible heart failure.

Methods

This study forms part of a 2.5 year follow-up study on the incidence and risk factors of heart failure among participants of the Rotterdam Study. The Rotterdam Study is a population-based study among 7983 inhabitants of 55 years and older of a suburb of Rotterdam. Rationale and design of the Rotterdam Study were described in detail elsewhere.[5] For logistic reasons, we included only participants who were enlisted with 18 general practitioners working in the Ommoord area in the incidence study. As part of this study, the 18 participating general practitioners were trained in the application of a heart failure score to standardize referral for diagnostic work-up at the research centre. The Rotterdam Heart Failure Score (table 1) included signs, symptoms and history of a patient, based on the "Boston criteria for heart failure" scoring system.[6] Furthermore, we added several criteria, based on a review of the literature, to increase sensitivity for case finding of heart failure patients as much as possible. During the study period, the GPs were asked to determine the Heart Failure Score in all Rotterdam Study participants presenting with dyspnoea, progressive fatigue/anorexia of possible cardiac origin, paroxysmal nocturnal cough, leg oedema and nocturia and in any other Rotterdam Study participant suspected by the GP of having heart failure. Participants

who scored three or more points had to be referred for a diagnostic work-up. For the present study we added two questions on estimated diagnostic presence of heart failure to the score to assess the agreement on the presence of heart failure by the GPs. Out of the 18 participating GPs, five were selected randomly to take part in the present study. The selected GPs were asked to examine 15 patients and fill in the heart failure score.

Table 1: Rotterdam Study heart failure score

History	Points	Physical examination	Points
• Rest dyspnoea	4	• Heart rate 90-110 beats/min	1
• Orthopnoea	4	> 110 beats/min	2
• Paroxysmal nocturnal dyspnoea	3		
• Dyspnoea on walking on level	2	• Raised jugular venous pressure	2
• Dyspnoea on climbing	1	• Raised jugular venous pressure & hepatomegaly or edema	3
• Paroxysmal nocturnal cough	1		
		• Third heart sound / gallop rhythm	3
Past history			
• Myocardial infarction	2	• Crepitations basilar	1
• Hypertension	1	> basilar	2
• Angina pectoris	1	• Rhonchi	3
• CABG or PTCA	1		
• Atrial fibrillation	1	**Diagnosis**	
• Heart valve disease	1	• Heart failure present	no/probably/ yes
• Peripheral arterial disease	1	• Estimated as percentage	..... %

The same patients were also examined by one cardiologist (AHMMB). The patients were selected from participants in the Rotterdam Study registered at the practice of one GP (JSV). We chose to select 5 heart failure patients, 1 patients with chronic obstructive pulmonary disease (COPD) and a myocardial infarction, 1 patient with COPD and hypertension, 1 patient with diabetes mellitus and myocardial infarction, 1 obese patient and 6 'healthy' controls. All 15 patients were invited to visit the research centre on the same evening. In three rounds, the five GPs and the cardiologist examined all patients. During each round 6 rooms were used, in five of these a participant of the Rotterdam Study was placed. The five GPs and the cardiologist were randomly assigned to one of the rooms. Within 10 minutes, the doctors had to go to the assigned room, examine the patient if present (one room was empty) and fill in the form. Every 10 minutes thereafter, the doctors rotated in a clockwise direction to the next room until each doctor had seen all 5 patients of the first round. The same procedure was used during rounds two and three. The physicians were not permitted to discuss their findings during the study session.

Table 2: Interobserver agreement.

	Intraclass correlations (95% CI)			
	5 GPs		6 physicians*	
History				
Rest dyspnoea	0.16	(-0.04,0.42)	0.24	(0.04,0.49)
Orthopnoea	0.44	(0.18,0.68)	0.50	(0.25,0.72)
Paroxysmal nocturnal dyspnoea	0.00**		0.00**	
Dyspnoea on walking up-hill	0.28	(0.05,0.55)	0.30	(0.08,0.55)
Dyspnoea on climbing	0.24	(0.02,0.50)	0.22	(0.03,0.47)
Paroxysmal nocturnal cough	0.00**		0.00**	
Myocardial infarction	0.82	(0.64,0.92)	0.78	(0.59,0.89)
Hypertension	0.60	(0.34,0.79)	0.63	(0.39,0.81)
Angina pectoris	0.46	(0.20,0.70)	0.48	(0.23,0.70)
PTCA or CABG	0.78	(0.58,0.90)	0.82	(0.65,0.92)
Atrial fibrillation	0.89	(0.77,0.95)	0.91	(0.81,0.96)
Heart valve disease	0.76	(0.55,0.89)	0.80	(0.62,0.91)
Peripheral arterial disease	0.47	(0.20,0.70)	0.53	(0.28,0.74)
Physical examination				
Heart rate	0.43	(0.17,0.67)	0.42	(0.18,0.65)
Raised jugular venous pressure	0.32	(0.08,0.58)	0.32	(0.10,0.57)
Third heart sound / gallop	0.02	(-0.12,0.25)	0.05	(-0.08,0.25)
Crepitations	0.30	(0.06,0.56)	0.21	(0.02,0.45)
Rhonchi	0.14	(-0.05,0.39)	0.18	(0.00,0.42)
Diagnosis				
Presence of heart failure 0/1	0.40	(0.14,0.65)	0.44	(0.20,0.67)
Presence of heart failure (estimated as %)	0.51	(0.25,0.73)	0.52	(0.27,0.73)
Total score				
Score ≥ 3	0.67	(0.43,0.84)	0.63	(0.39,0.81)
Score in total	0.83	(0.61,0.91)	0.81	(0.64,0.91)

* 5 GPs and one cardiologist. ** Could not be determined, since there was no variation between patients.

Intraclass correlation coefficients were calculated along with 95% confidence intervals (CI) to determine reproducibility of the heart failure score by the physicians according to Fisher.[7] The interobserver variability is defined as the variation in the heart failure score among the GPs. Intraclass correlation is the proportion of the total variability accounted for by the variability among subjects. If it is high not much of the variability is due to variability in measurements of different observers. The values of the intraclass correlation range from 0 to 1 and the strength of agreement can be interpreted as: poor

(<0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80) and very good (0.81-1.00).[8]

In case an item had more than two categories (e.g. heart rate, crepitations), the item was dichotomized (i.e. presence or absence) in the analyses.

To determine how interobserver variability may influence the possibility of referral of patients for diagnostic work-up at the research centre we calculated the total score to determine if a patient would have been referred and we calculated the intraclass correlation coefficients for referral. For calculation of the total score, only the highest score of the dyspnoe questions was used. The same was done for heart rate, raised jugular venous pressure and crepitations. As mentioned above, our criterion for referral was a heart failure score of three or more points. All data analyses were performed using the SPSS statistical package 7.5.2.

Table 3: Mean values (95% CI) and ranges of the total score of the different selected cases.

	Total score		
Case	**Mean (95% CI)**		**Range**
'Healthy subjects'			
#1	1.4	(0,4.0)	0 – 5
#2	0.2	(0,0.8)	0 – 1
#3	0.2	(0,0.8)	0 – 1
#4	1.2	(0,3.9)	0 – 5
#5	0.4	(0,1.1)	0 – 1
#6	0.2	(0,0.8)	0 – 1
Heart failure patients			
#7	11.6	(9.3,13.9)	9 – 14
#8	8.4	(5.3,11.5)	6 – 12
#9	12.0	(6.4,17.6)	7 – 18
#10	10.8	(7.4,14.2)	8 – 15
#11	7.0	(3.8,10.2)	3 – 9
Other patients			
#12 (Obese)	4.9	(3.8,6.0)	2 – 8
#13 (COPD & MI)	9.4	(6.8,12.0)	8 – 13
#14 (COPD & HT)	3.6	(0.7,6.5)	1 – 6
#15 (DM & MI)	2.8	(1.8,3.8)	2 – 4

COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, HT = hypertension, DM = diabetes mellitus

Results

Table 2 shows the intraclass correlations on each of the items of the heart failure score. Except for the variables included in the medical history as well as orthopnoea and heart rate, interobserver agreement was poor to fair. The agreement on the presence of heart failure was moderate. The agreement on referral (i.e. score $\geq$ 3) was good and agreement on the total score was very good. All pre-selected heart failure patients had a mean total score of more than three points and were referred. All 'healthy' subjects had a mean total score lower than 3 points. The vast majority (94%) of these subjects would not be referred (table 3).

Discussion

Our study shows that the interobserver agreement on the presence of heart failure and on the signs and symptoms suggestive of heart failure was estimated to be equal or less than moderate. The agreement on referral by the use of the score, however, was good. Furthermore, all preselected heart failure cases were referred by the GPs using the score.

A limitation of our study is the number of participating subjects and participating GPs, resulting in large confidence intervals. Although inclusion of the cardiologist enhanced the interobserver variation we do not think that the correlation would be higher when more GPs would have been included. Only the confidence intervals would have been smaller.

The rather low intraclass correlations on the presence of heart failure may be partly attributable to the fact that we selected patients with disorders (such as COPD and obesity) known to pose difficulties in diagnosing heart failure, based on clinical findings only. This is illustrated in figure 1. When heart failure is evident all observers rate the probability of heart failure as high. When heart failure is absent all observers give a low rating. However, in one patient with COPD and MI the estimated probability on the presence of heart failure ranged from 10 to 90%, thereby reducing interobserver agreement.

Although the interobserver agreement on most items of the score and on the presence of heart failure was low, the agreement on referral was good and referral was correct in all patients with documented heart failure patients.

We conclude that for assessment of signs, symptoms and history of heart failure the interobserver agreement among GPs is low. When the aim is referral of those with possible heart failure a heart failure score appears to be a useful tool.

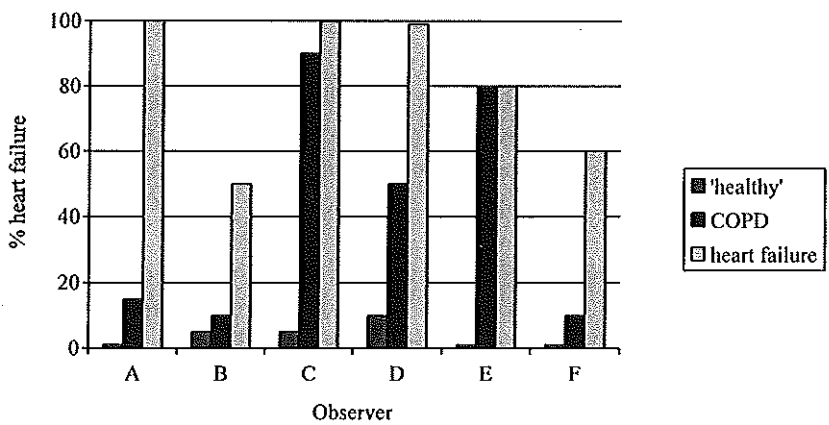

Figure 1: Example of estimated percentages of presence of heart failure by all the observers for 3 different patients (1 healthy, 1 with documented COPD and myocardial infarction and 1 with documented heart failure).

References

1. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
2. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.
3. Cowie M, Struthers A, Wood D, Coats A, Thompson S, Poole-Wilson P, Sutton G. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
4. Mosterd A, Deckers JW, Hoes AW, Nederpel A, Smeets A, Linker DT, Grobbee DE. Classification of heart failure in population based research: an assessment of six heart failure scores. *Eur J Epidemiol* 1997;13:491-502.
5. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
6. Carlson KJ, Lee DC, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis* 1985;38:733-9.
7. Fisher RA. Statistical methods, experimental design, and scientific inference. Oxford: Oxford University Press, 1990.
8. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-74.

Chapter 4

Heart failure in general practice in the Netherlands: incidence and management

Manuscript based on chapter 4:

B. Cost, M.A. Bruijnzeels, H.J.C.M. Pleumeekers, J. van der Schoot-van Venrooy, D.E. Grobbee, Arno W. Hoes. Heart failure in general practice in the Netherlands: incidence and management (submitted).

Introduction

Heart failure is a growing health problem in western societies. The increase in the occurrence of heart failure is mainly attributable to the ageing of the population and improvement in therapy of cardiovascular disorders, including ischemic heart disease and hypertension.[1] The prognosis of a patient with heart failure is poor; within 5 years of the diagnosis heart failure in the Framingham Study, 75% of the men and 62% of the women died.[2] Early recognition and treatment of a patient with heart failure can reduce the number of hospital admissions for heart failure and increase life expectancy.[3,4] In the Netherlands and in the UK most heart failure patients are detected and treated in general practice. Data on the incidence of heart failure in primary care are, however, relatively scarce.[5,6] Studies from the UK indicate that heart failure patients treated in general practice in the UK do not receive optimal treatment.[7-9] There is little information on the management of heart failure in the Netherlands. Such information is, however, crucial to facilitate the development of strategies to improve the care for heart failure patients. We studied the incidence of heart failure as presented to primary care in the Netherlands and the subsequent management of heart failure patients by their general practitioner. In addition, the availability of more recent data enabled us to study the time trends in the GP's patient management of this condition.

Methods

We used data from the Dutch National Survey of Morbidity and Interventions in General Practice, carried out in 1987 and 1988 by the Netherlands Institute of Primary Health Care (NIVEL), in which 161 general practitioners (GPs), with in total 74,153 patients aged 55 years or over, participated.[10] The GPs were divided in four groups. The four groups registered every contact between patients and the practice during consecutive periods of three months. The total registration period lasted from April 1st 1987 to April 1st 1988. A special form was designed to register all contacts including diagnosis, referrals and prescriptions. The GPs recorded the reason for encounter in diagnostic terms on the registration form. Diagnosis were coded according to the International Classification of Primary Care (ICPC) by specially trained coders. Medication was coded using the Anatomical-Therapeutical-Chemical (ATC)-code. The registration of morbidity in the National Survey is episode-oriented. To study the incidence of heart failure all new episodes registered with the ICPC-code K77 (heart failure) were studied. Age- and sex-specific incidence of heart failure per 1000 person

years with 95% confidence intervals were calculated. In addition, information on subsequent management of these patients was studied.

In addition, we used data of the Rotterdam General Practitioners Project (ROHAPRO), a computerized network of general practices in Rotterdam. Methods of the ROHAPRO-database are described in detail elsewhere.[11] Briefly, the ROHAPRO-database is a database containing demographic and medical data of in total 44,340 patients enlisted in seven computerized general practices. Data was available from 1991 till 1997. Information was entered in the computer by the GPs during consultation or afterwards in case of home-visits, and included symptoms, ICPC classified diagnoses, referrals, and medication. Medication is coded using the ATC-code. In addition the indication for medication prescription is coded routinely in ICPC-codes. Heart failure patients were defined as patients with the ICPC-code K77 in their patient record. Information on prescribed medications and referral of these patients were studied.

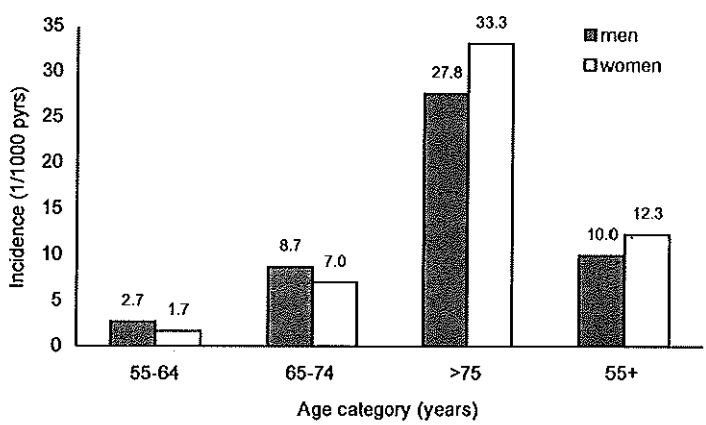

Figure 1: The incidence rate of heart failure in primary care in the Netherlands (per 1000 person years)

Results

During the 1987-1988 (NIVEL) study period, comprising 18,538 person years, 210 incident cases of heart failure were diagnosed by the general practitioners; 81 men and 129 women. The overall incidence rate of heart failure was 11.3 per 1000 person years (95% CI 9.8-12.9); 10.0 (95 % CI 7.8-12.2) in men and 12.3 (95 % CI 10.2-14.5) in women. The incidence rate of heart failure increased sharply with age. In men, the

incidence rate increased from 2.7/1000 person years (95% CI 1.4-5.0) in those aged 55-64 years, to 27.8/1000 person years (95% CI 19.9-35.6) in those aged >75 years, and in women in the same age categories from 1.7/1000 person years (95% CI 0.8-3.6) to 33.3/1000 person years (95% CI 26.7-39.9) (Figure 1).

The GPs prescribed medication in the vast majority (77%) of the 210 cases. Most patients (90) received a loop diuretic, 48 another diuretic (predominantly thiazides), while only seven patients received an ACE-inhibitor (Table 1). Of the 210 incident cases of heart failure diagnosed in 1987-1988, 45 (21%) were referred to a specialist, notably to an internist (n=21) or cardiologist (n=21) (Table 1).

358 patients (8.1%) were diagnosed with heart failure from 1991 to 1997 in the ROPHAPRO-database. Data on prescribed medication by the GP was available in 309 of these patients. Most patients (286) received a diuretic (93%) of which 204 received a loop-diuretic, 159 (51%) received an ACE-inhibitor, 6 (2%) received a combination-drug of ACE-inhibitor and diuretic and 125 (40%) received digoxin. 169 (47%) of these heart failure patients were referred to a cardiologist.

Table 1: Referral rate and drug prescription in patients with heart failure in general practice.

	1987 - 1988 (n=210)		1991 - 1997 (n=358)	
Management	**Number (%)**		**Number (%)**	
Referral;	45	(21%)		
Cardiologist	21	(10%)	169	(47%)
Internist	21	(10%)	152	(43%)
Drug prescription;	162	(77%)	309	
Loop diuretic	90	(43%)	204	(66%)
Thiazide	48	(23%)	82	(27%)
ACE-inhibitor	7	(3%)	59	(51%)
Digoxin	54	(16%)	25	(40%)

Discussion

This study shows that the incidence of heart failure as diagnosed in general practice is high and increases sharply with age in both men and women. In 1987-88 almost all incident cases were prescribed medication (notably loop diuretics, seldom ACE-

inhibition) and only 21% was referred to a specialist. In 1991-1997 about 50% of the heart failure patients received ACE-inhibition, and 47% was referred to a cardiologist. Our specific incidence estimates are comparable to the findings of the fourth national study from the UK, but somewhat lower than those reported from two other Dutch studies.[5,6,12] The differences might be due to different definitions of heart failure and different study populations. An increase in the incidence with advancing age in both men and women, is a consistent finding in all studies.

It should be emphasised that the diagnosis of heart failure in this study was based on the clinical judgement of the GP. The clinical diagnosis of patients with heart failure is difficult, especially in a primary care setting.[13-15] Although our method closely reflects day-to-day clinical practice, a diagnosis based on history taking and physical examination could lead to both underestimation (notably non-recognition of early stages of the syndrome) and overestimation (for example, diagnosing COPD as heart failure). To more reliably assess the incidence of the syndrome, ideally, each person with signs and symptoms suggestive of heart failure should undergo a complete comprehensive cardiovascular work-up. This approach is used in the Hillingdon Heart Failure Study and in a similar study by our own group (chapter 5).[15,16] Comparison with findings from the Hillingdon study shows that the incidence of heart failure as diagnosed by GPs is an overestimation of the 'true incidence'. This emphasises the need to optimize early recognition of heart failure in general practice. Both the number of false-positive diagnoses and non-recognized heart failure patients may be reduced by increasing the diagnostic possibilities of GPs through open access echocardiography or determination of neurohumoral parameters, notably brain natriuretic peptide.[15,17,18]

Only a small proportion of the patients diagnosed with heart failure in the 1987-88 population received an ACE-inhibitor. This is understandable since ACE-inhibitors were introduced not long before 1988 and major trials showing the effect of ACE inhibitors in heart failure patients were published in the 90s.[4,19,20] Our finding that currently about 50% of the Dutch heart failure patients receives an ACE-inhibitor may indicate that the management of heart failure is improving.[21]

In 1988, the year of the NIVEL study, only a minority of the heart failure patients was referred to a specialist. The ROHAPRO-database showed that currently about 50% of the heart failure patients were referred to a cardiologist. Several recent clinical guidelines advice to refer all heart failure patients for diagnostic evaluation (notably echocardiography) to establish the diagnosis and determine the possible etiology.[22-24] It is noteworthy that the current two Dutch guidelines are not consistent in their advice which patient to refer to a specialist for a diagnostic work-up.[25,26] Consensus on this point is required to guide current practice.

In conclusion, the incidence rate of heart failure in general practice is high and clearly increases with age in both men and women. In contrast to most current clinical guidelines only a minority of the heart failure patients is referred to a specialist and only half of the patients with heart failure receives ACE-inhibition. These findings call for increased interest in diagnosis and management of heart failure in general practice.

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.
3. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
4. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
5. Lisdonk van de EH, Bosch van den WJHM, Huygen FJA, Lagro-Jansen ALM. Diseases in general practice [In Dutch]. Utrecht: Bunge, 1990.
6. Lamberts H, Brouwer H, Mohrs J. Reason for encounter- & episode & process oriented standard output from the Transition Project. Part 1 & 2. Amsterdam: Department of General Practice/Family Medicine, University of Amsterdam, 1993.
7. Parameshwar J, Shackell MM, Richardson A, Poole-Wilson PA, Sutton GC. Prevalence of heart failure in three general practices in north west London. *Br J Gen Pract* 1992;42:287-9.
8. Clarke KW, Gray D, Hampton JR. Evidence of inadequate investigation and treatment of patients with heart failure. *Br Heart J* 1994;71:584-7.
9. Mair FS, Crowley TS, Bundred PE. Prevalence, aetiology and management of heart failure in general practice. *Br J Gen Pract* 1996;46:77-9.
10. Foets M, Velden van der J, Bakker de D. Dutch national survey of general practice. A summary of the survey design. Utrecht: Netherlands Institute of Primary Health Care, 1992.
11. Middelkoop BJ, Bohnen AM, Duisterhout JS, Hoes AW, Pleumeekers HJ, Prins A. Rotterdam general practitioners report (ROHAPRO): a computerised network of general practices in Rotterdam, The Netherlands. Rotterdam's HuisArtsen Project. *J Epidemiol Community Health* 1995;49:231-3.
12. McCormick A, Fleming D, Carlton J. Morbidity statistics from general practice : fourth national study 1991-1992/ A study carried out by the Royal College of General Practitioners, the Office of Population Censuses and Surveys, and the Department of Health. London: HMSO, 1995.
13. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
14. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.
15. Cowie M, Struthers A, Wood D, Coats A, Thompson S, Poole-Wilson P, Sutton G. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
16. Hoes AW, Mosterd A, Grobee DE. An epidemic of heart failure? Recent evidence from Europe. *Eur Heart J* 1998;19:L2-L8.
17. McDonagh TA, Rodd SD, Murdoch DR, Morton J, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1997;351:9-13.

18. Francis CM, Caruana L, Kearney P, Love M, Sutherland GR, Starkey IR, Shaw TR, McMurray JJ. Open access echocardiography in management of heart failure in the community. *BMJ* 1995;310:634-6.
19. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
20. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr., Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
21. Bourassa MG, Gurne O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, Johnstone DE, Yusuf S. Natural history and patterns of current practice in heart failure. The Studies of Left Ventricular Dysfunction (SOLVD) Investigators. *J Am Coll Cardiol* 1993;22:14A-19A.
22. The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741-51.
23. Anonymous. Guidelines for the evaluation and management of heart failure. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 1995;26:1376-98.
24. Dargie HJ, McMurray JJ. Diagnosis and management of heart failure. *BMJ* 1994;308:321-8.
25. Anonymous. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (CBO). Consensus hartfalen [In Dutch]. Utrecht: CBO, 1994.
26. Walma EP, Bakx HCA, Besselink RAM, Hamstra PWJ, Hendrick JMA, Kootte JHA, Veelen van AWC, Vink R, Geijer RMM. NHG standaard hartfalen [In Dutch]. *Huisarts en Wetenschap* 1995;38:471-87.

Chapter 5

Incidence and risk factors of heart failure

Manuscript based on chapter 5:

B. Cost, D.E. Grobbee, J. van der Schoot-van Venrooy, A.H.M.M. Balk, A.J. Man in 't Veld, A. Prins, A.W. Hoes. Incidence and risk factors of heart failure (submitted).

Introduction

The importance of heart failure as a cause for morbidity and mortality is increasingly recognised, but data on its epidemiology, and notably the incidence of the syndrome are scarce.[1] One of the reasons of the lack of epidemiologic data on heart failure is the difficulty of diagnosing early stages of heart failure and the virtual absence of target cohort studies. In the Netherlands and in the UK most heart failure patients are detected and treated in general practice. Heart failure is difficult to diagnose by the general practitioner due to the unavailability of more sophisticated or invasive diagnostic tools and is primarily based on clinical judgement. Heart failure carries a rather poor prognosis, notwithstanding the current available treatment options, therefore it is important to identify determinants of the development of heart failure, to enable targeting of effective preventive strategies. Based on data collected in the mid eighties in Western societies, hypertension, coronary heart disease and diabetes mellitus appear to be among the major risk factors for heart failure, but, more research is needed to identify additional etiologic factors.

We studied the incidence of heart failure in the Netherlands between February 1996 and December 1997. In addition, we determined the risk factors for incident heart failure in the elderly.

Methods

Study population

This study forms part of the Rotterdam Study, a population-based prospective cohort study on prevalence, incidence and determinants of chronic disabling diseases in the elderly. Rationale and design of the Rotterdam Study were described in detail elsewhere.[2] In short, all 10,275 inhabitants of Ommoord, a suburb of Rotterdam, who were 55 years or older were invited to participate. In total, 7,983 (78%) agreed to participate and signed informed consent. Between 1990 and 1993 all subjects were interviewed at home and invited to visit the research centre twice for clinical measurements. The data collected at baseline included history, use of medication, height, weight, blood pressure levels, electrocardiography (ECG) and serum cholesterol sampling.

Subjects were categorized in groups of current smokers, former smokers and those who never smoked. The number of pack-year exposure was calculated by the average daily number of cigarettes divided by 20 and multiplied with the number of

years smoked. Alcohol consumption was calculated from beverage specific information obtained by a semiquantitative food frequency questionnaire. One drink was considered approximately equivalent to 10 grams of alcohol. Body mass index was calculated as weight/length^2 in kg/m^2. Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer. Hypertension was defined as systolic blood pressure above 160 mmHg or diastolic blood pressure above 95 mmHg or use of antihypertensive medication for the indication hypertension. Diabetes mellitus was defined as a non-fasting blood glucose above 11.0 mmol/l or the current use of an antidiabetic drug.[3] All electrocardiograms were digitally stored and analysed using the MEANS program. History of myocardial infarction (MI) was defined as self-reported MI confirmed by a physician, or MI on the ECG.[4] Electrocardiographic T axes were computed, applying methods that have been described in detail elsewhere.[5] The ECG was also used to determine the presence of atrial fibrillation and left ventricular hypertrophy. Presence of angina pectoris was diagnosed using the Rose questionnaire.[6] Ankle-arm index (AAI), used as a measure of peripheral atherosclerosis, was calculated as the ratio of the systolic blood pressure level at the ankle and the arm. Peripheral arterial disease (PAD) was considered present when the AAI was lower than 0.90 at at least one leg. Serum total cholesterol and high density lipoprotein (HDL) cholesterol were determined with an automated enzymatic procedure.[7]

Table 1: Rotterdam Heart Failure score

History	Points	Physical examination	Points
• Rest dyspnoea	4	• Heart rate 90-110 beats/min	1
• Orthopnoea	4	> 110 beats/min	2
• Paroxysmal nocturnal dyspnoea	3		
• Dyspnoea on walking on level	2	• Raised jugular venous pressure (JVP)	2
• Dyspnoea on climbing	1	• Raised JVP & hepatomegaly or edema	3
• Paroxysmal nocturnal cough	1	• Third heart sound / gallop rhythm	3
Past history		• Crepitations basilar	1
• Myocardial infarction	2	> basilar	2
• Hypertension	1	• Rhonchi	3
• Angina pectoris	1		
• CABG or PTCA	1	If score ≥ 3, the patient was referred for diagnostic work-up.	
• Atrial fibrillation	1		
• Heart valve disease	1		
• Peripheral arterial disease	1		

Of the 7,983 participants of the Rotterdam Study we excluded 597 participants because they were diagnosed as prevalent cases of heart failure. Prevalent cases were

defined as participants who were diagnosed with heart failure based on a classification of heart failure at the baseline examinations in 1990-1993, or participants who developed heart failure during the follow-up period thereafter till 1-2-1996 (the data of the initiation of our incidence study). The follow-up procedures of the Rotterdam Study and the procedures for the classification of heart failure at baseline were described in detail elsewhere.[8,9] Furthermore, 979 participants of the remaining cohort at risk for heart failure died before the start of the incidence study. For logistic reasons we included only participants who were enlisted with 18 general practitioners working in Ommoord. This resulted in a cohort of 5281 participants free from heart failure in February 1996.

Table 2: Baseline characteristics of the 5253 subjects at risk for heart failure and in those with and without incident heart failure during the follow-up period.*

Characteristics	Total population (n=5253)	Heart failure during follow-up Yes (n=127)	No (n=5126)	p-value†
Age (years)	68.4	74.6	68.2	<0.0001
Sex (% female)	62	56	62	<0.005
Diabetes mellitus (%)	7	13	06	<0.05
Hypertension (%)	26	41	26	<0.005
Peripheral arterial disease (%)	15	34	14	<0.005
History of MI (%)	10	22	10	<0.005
Angina pectoris (%)	8	13	8	0.41
Heart rate (/min)	69.8	70.1	69.8	0.87
Atrial fibrillation (%)	2	4	2	0.99
ECG LVH (%)	2	3	2	0.95
T-axis (%)				
Borderline	17	26	16	0.10
Abnormal	7	20	7	<0.05
Body mass index (kg/m^2)	26.4	27.6	26.3	<0.005
Smokers (%)				
Current	23	24	23	0.13
Former	40	41	40	0.90
Alcohol intake (g/day)	10.0	9.4	10.0	0.76
Cholesterol (mmol/l)	6.67	6.42	6.68	0.38
HDL cholesterol (mmol/l)	1.36	1.27	1.36	0.08
Total cholesterol /HDL ratio	5.24	5.43	5.23	0.13
Fibrinogen (g/l)	2.74	3.02	2.73	<0.05
Use of COPD medication (%)	5	7	5	0.16

MI=myocardial infarction; LVH=left ventricular hypertrophy; COPD=chronic obstructive pulmonary disease. * values are proportions or means. † comparison of between those with and without heart failure during follow-up, adjusted for age and sex when appropriate.

Case-finding

Three methods (rapid-access diagnostic work-up, identification by computerised registries of the GPs and pharmacy data) were used to identify possible new cases of heart failure. The aim was to include all possible cases of heart failure emerging from the cohort during the follow-up period.

Table 3: Age- and sex-specific incidence rates (per 1000 person-years, with 95% confidence intervals) in a general Dutch population, aged 55 years or over (the Rotterdam Study, 1996-1997)

Age-group (years)	Women (n=3258)				Men (n=1995)				Total (n=5253)			
	Pyrs	N	Rate	95% CI	Pyrs	N	Rate	95% CI	Pyrs	N	Rate	95% CI
57-64	1092	2	1.8	0.2-6.6	786	2	2.5	0.3-9.2	1878	4	2.1	0.6-5.5
65-74	2351	14	6.0	3.3-10.0	1691	25	14.8	9.6-21.8	4042	39	9.6	6.9-13.2
75-84	1843	24	13.0	8.3-19.4	969	21	21.7	13.4-33.1	2812	45	16.0	11.7-21.4
85+	711	31	43.8	29.6-61.9	187	8	42.8	18.5-84.3	898	39	43.4	30.9-59.4
Total	5997	71	11.8	9.2-14.9	3633	56	15.4	11.6-20.0	9630	127	13.2	11.0-15.7

Rapid-access diagnostic work-up

As part of the study, the 18 participating general practitioners (GPs) were trained in the application of a heart failure score. The Rotterdam Heart Failure Score (table 1) included signs, symptoms and medical history of a patient based on the "Boston criteria for heart failure" scoring system.[10] We added several criteria, based on review of the literature, to increase sensitivity for case finding as much as possible. During the study period, the GPs were asked to determine the Heart Failure score in all Rotterdam Study participants presenting with dyspnoea, progressive fatigue/anorexia of possible cardiac origin, paroxysmal nocturnal cough, leg oedema and nocturia and any other patient suspected by the GP of having heart failure. Patients who scored 3 or more points and any other patient suspected by the GP of heart failure were referred for a diagnostic work-up at the research centre, preferably before therapeutic interventions were initiated. A low threshold for referral was chosen to minimize non-referral of potential cases and to assure a high sensitivity for case finding. A high specificity was judged to be irrelevant in view of the aim of the study.

Table 4a: Risk factors for heart failure.

Risk factor	Adjusted for	Total population HR (95% CI)	Age <70 HR (95% CI)	Age >=70 HR (95% CI)	Men HR (95% CI)	Women HR (95% CI)
Age (years)	1	1.09 (1.07-1.12)	1.15 (1.06-1.24)	1.10 (1.06-1.14)	1.06 (1.03-1.10)	1.11 (1.08-1.14)
Sex (female)	1	0.57 (0.40-0.82)	0.34 (0.18-0.64)	0.76 (0.48-1.21)	—	—
History						
Diabetes mellitus	1	1.81 (1.08-3.20)	1.51 (0.54-4.25)	1.88 (1.04-3.39)	2.06 (0.98-4.37)	1.60 (0.80-3.22)
	1-4	1.61 (0.96-2.70)	1.14 (0.39-3.32)	1.70 (0.93-3.08)	2.03 (0.95-4.34)	1.36 (0.67-2.76)
Hypertension	1	1.76 (1.22-2.55)	1.28 (0.63-2.57)	2.00 (1.28-3.11)	0.97 (0.51-1.85)	2.60 (1.60-4.22)
	1,3,5	1.62 (1.11-2.36)	1.12 (0.55-2.31)	1.87 (1.19-2.96)	0.85 (0.44-1.64)	2.43 (1.47-4.04)
Peripheral arterial disease	1	2.09 (1.37-3.20)	3.14 (1.50-6.57)	1.68 (1.00-2.80)	2.30 (1.19-4.45)	1.88 (1.07-3.29)
	1,2,5-8	1.94 (1.25-2.99)	2.92 (1.37-6.25)	1.55 (0.92-2.63)	2.15 (1.09-4.27)	1.65 (0.94-2.90)
History of MI	1	1.83 (1.15-2.93)	2.45 (1.17-5.12)	1.51 (0.82-2.78)	1.91 (1.01-3.66)	1.80 (0.91-3.54)
	1,2,4,5	1.74 (1.09-2.78)	2.20 (1.04-4.68)	1.47 (0.80-2.71)	1.81 (0.94-3.47)	1.62 (0.82-3.21)
Angina pectoris	1	1.25 (0.74-2.13)	1.34 (0.48-3.78)	1.24 (0.67-2.30)	1.25 (0.56-2.79)	1.31 (0.65-2.64)
ECG measures						
Heart rate (/min)	1	1.00 (0.99-1.01)	0.99 (0.97-1.02)	1.00 (0.99-1.02)	1.00 (0.98-1.02)	1.00 (0.98-1.02)
Atrial fibrillation	1	1.02 (0.37-2.81)	5.87 (1.39-24.74)	0.59 (0.14-2.43)	1.53 (0.46-5.08)	0.64 (0.09-4.62)
	1,2,4,5,9	1.01 (0.36-2.79)	5.40 (1.20-24.31)	0.60 (0.15-2.48)	1.41 (0.41-4.84)	0.62 (0.08-4.50)
ECG LVH	1	1.17 (0.37-3.72)	3.88 (0.92-16.3)	0.48 (0.07-3.49)	1.62 (0.39-6.70)	0.76 (0.10-5.51)
Borderline T-axis	1	1.84 (1.14-2.94)	3.03 (1.41-6.50)	1.31 (0.72-2.40)	2.58 (1.27-5.08)	1.37 (0.72-2.63)
	1-3,5,9-11	1.68 (1.05-2.72)	2.75 (1.26-6.03)	1.25 (0.68-2.30)	2.30 (1.13-4.68)	1.28 (0.67-2.46)
Abnormal T-axis	1	2.70 (1.60-4.55)	4.58 (1.80-11.68)	2.14 (1.15-3.99)	3.06 (1.39-6.76)	2.50 (1.24-5.04)
	1-3,5,9-11	2.23 (1.30-3.83)	3.52 (1.29-9.58)	1.91 (1.01-3.60)	2.64 (1.13-6.18)	2.23 (1.10-4.52)

1=Age and (if applicable) sex, 2=Hypertension, 3=Body mass index, 4=ECG LVH, 5=Diabetes, 6=Smoking, 7=Alcohol, 8=Cholesterol/HDL ratio, 9= History of MI, 10=Cholesterol, 11=HDL cholesterol. The hazard ratios are given adjusted for age and gender and additionally for other potential confounders.

Table 4b: Risk factors for heart failure (continued).

Risk factor	Adjusted for	Total population HR (95% CI)	Age <70 HR (95% CI)	Age >=70 HR (95% CI)	Men HR (95% CI)	Women HR (95% CI)
Body mass index (kg/m^2)	1	1.04 (1.02-1.06)	1.04 (1.01-1.06)	1.06 (1.00-1.12)	1.03 (1.00-1.06)	1.07 (1.01-1.13)
	1,2,5	1.04 (1.01-1.06)	1.04 (1.01-1.06)	1.05 (0.99-1.11)	1.03 (1.00-1.07)	1.05 (0.99-1.11)
Smokers						
Present	1	1.49 (0.88-2.51)	1.70 (0.66-4.40)	1.32 (0.66-2.65)	1.53 (0.52-4.48)	1.44 (0.70-2.96)
Former	1	1.18 (0.74-1.89)	1.05 (0.40-2.74)	1.31 (0.76-2.25)	1.10 (0.39-3.11)	1.34 (0.77-2.33)
Alcohol (g/day)	1	1.00 (0.98-1.01)	1.00 (0.99-1.02)	0.98 (0.96-1.01)	1.01 (0.99-1.02)	0.87 (0.79-0.96)
Cholesterol (mmol/l)	1	0.91 (0.78-1.07)	0.83 (0.63-1.11)	0.94 (0.77-1.15)	0.87 (0.68-1.12)	0.94 (0.76-1.16)
HDL cholesterol (mmol/l)	1	0.63 (0.35-1.14)	0.20 (0.06-0.64)	1.05 (0.53-2.10)	0.29 (0.10-0.84)	0.97 (0.48-1.93)
	1-3,5	0.73 (0.41-1.31)	0.22 (0.07-0.72)	1.23 (0.62-2.46)	0.32 (0.11-0.93)	1.14 (0.57-2.28)
Cholesterol/HDL ratio	1	1.07 (0.96-1.19)	1.18 (1.02-1.38)	0.98 (0.84-1.14)	1.11 (0.95-1.29)	1.02 (0.87-1.20)
	1-3,5	1.04 (0.93-1.16)	1.17 (1.00-1.36)	0.95 (0.81-1.11)	1.10 (0.94-1.29)	0.99 (0.84-1.16)
Fibrinogen (g/l)	1	1.46 (1.05-2.02)	1.57 (0.80-3.06)	1.38 (0.94-2.04)	1.14 (0.66-1.97)	1.81 (1.15-2.85)
	1,6	1.43 (1.03-1.99)	1.49 (0.74-3.03)	1.37 (0.92-2.02)	1.10 (0.63-1.94)	1.78 (1.12-2.83)
Use of COPD medication	1	1.58 (0.80-3.13)	2.51 (0.98-6.42)	1.14 (0.41-3.13)	0.80 (0.25-2.56)	3.20 (1.37-7.43)

1=Age and (if applicable) sex, 2=Hypertension, 3=Body mass index, 4=ECG LVH, 5=Diabetes, 6=Smoking, 7=Alcohol, 8=Cholesterol/HDL ratio, 9= History of MI, 10=Cholesterol, 11=HDL cholesterol. The hazard ratios are given adjusted for age and gender and additionally for other potential confounders.

At the research centre, the diagnostic work-up included a standard interview and physical examination, chest X-ray, pulmonary function test (i.e. forced expiratory volume in one second (FEV1), vital capacity (VC) and peak expiratory flow rate (PEF)), ECG, echo-Doppler cardiography, symptom-limited exercise test with VO_2/VCO_2 determination, 6 minute walk test, haemoglobin measurement, thyroid function test, and pre- and post-exercise determinations of plasma neurohormone concentrations (i.e. atrial natriuretic peptide ANP, N-terminal ANP, arginine vasopressin, aldosterone, renin and norepinephrine). The chest X-rays were frontal views and were evaluated by one radiologist without knowledge of any other diagnostic information. All referred patients were followed for an additional 6 months and important clinical findings (including results from other diagnostic tests, medication use and letters from medical specialists) were collected.

Computerised registries of the GP and pharmacy data

Other potential cases of heart failure were identified through computerised registries of the general practitioners (including hospital discharge records) and the pharmacy operating in the area. The GPs classify every diagnosis according to the International Classification of Primary Care (ICPC). By searching for every patient with the code for heart failure (K77) we were able to identify additional possible cases of incident heart failure. Through the pharmacy data we identified all possible cases by selecting all new prescriptions for diuretics, digoxin, ACE-inhibitors, and intravenously administrated loop diuretics. At the GPs office all available information on the possible cases, detected by means of computerised GP and pharmacy registries, e.g indication for prescription, diagnostic tests, and letters from medical specialists, was scrutinised. As in the cases detected at the diagnostic work-up, an additional follow-up period of six months, was included.

Case definition

The definite classification of heart failure was determined during consensus meetings involving a cardiologist, internist, general practitioners and clinical epidemiologist reviewing all available information. Diagnosis of heart failure was based on consensus, using the guidelines for the diagnosis of heart failure of the Task Force on Heart Failure of the European Society of Cardiology (co-existence of symptoms and objective proof of systolic or diastolic ventricular dysfunction) complemented with information on the response to therapy for heart failure, if available from the patient's medical records.[11] The members of the panel could classify each reviewed case as; no, possible or definite heart failure. If all members agreed upon "no" or "definite" heart failure the case was

classified as such. In case of disagreement the panel tried to reach consensus. If no consensus was reached the case was classified as "possible" heart failure. In case of possible or definite heart failure the panel could also add a remark to the classification. The remark was made when the panel had little more additional information than the history and physical examination of the general practitioner, the response to therapy if present and the clinical diagnosis of the GP to establish a final panel diagnosis. In these cases, no objective measurements of ventricular function were available. Furthermore, the panel had to determine the starting date of heart failure. In the analyses of the present study emphasis is on cases classified as definite incident cases of heart failure.

Data analysis

Excluded from the cohort of 5281 Rotterdam Study participants free from heart failure at the initiation of the incidence study, were 28 persons who were lost to follow-up because they moved out of the area and could not be traced back. Age- and gender-specific incidence rates of heart failure per 10 year age-groups were calculated by dividing the number of definite incident heart failure cases by the number of person-years at risk, calculated by the sum of each participant's contribution of follow-up time per age-band. Our follow-up period started at 1-2-1996 and ended either at the onset of heart failure, at death or at the end of the follow-up period, 31-12-1997. Exact 95% confidence Intervals (95%CI) were calculated using Poisson standard errors.

Difference in baseline characteristics between participants with and without incident heart failure were examined using logistic regression analyses, adjusting for age and sex when appropriate. Cox' proportional hazards regression analysis was used to identify potential risk factors for heart failure. We separately adjusted each risk factor for potential confounders. The adjustment for potential confounders was based on pathofysiologic knowledge and prior studies. Subgroup analyses were performed to examine whether age (above and below the median age of 70 years) or gender modified the association between the potential risk factors and the occurrence of heart failure. To minimize the effect of missing data in the multivariate analysis, missing values of categorical variables were replaced by dummies. Missing values of continuous variables were replaced by the mean and a dummy was added to the model.[12] All data analyses were performed using the SPSS statistical package 7.5.2, except for the calculation of the 95% CI of the incidence rates where the STATA statistical package release 5.0 was used.

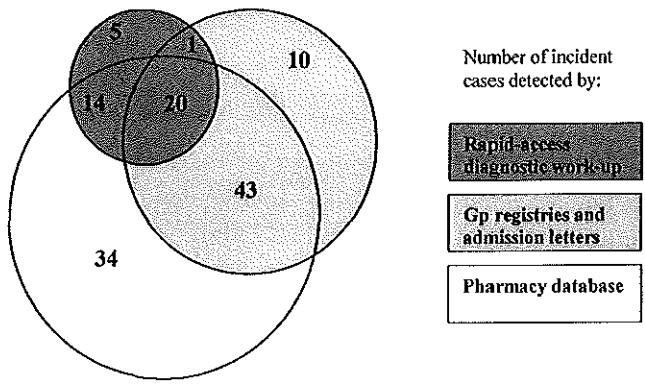

Figure 1: Number of cases detected by each of the three search strategies.

Results

Incidence of heart failure

Baseline characteristics of the 5253 participants included in this study are presented in table 2. During the follow-up period of 23 months, 127 definite new cases of heart failure were identified; 56 men and 71 women. In total 145 persons were referred for a diagnostic work-up and 40 of them were incident cases of heart failure. The remaining 87 incident cases were identified through the computerised registries and patient files (including hospital letters) of the general practitioners and the pharmacy data (figure 1). The age- and sex-specific incidence is given in table 3. The overall incidence rate of "definite" heart failure was 13.2 per 1000 person-years (95%CI 11.0-15.7); 15.4 (95%CI 11.6-20.0) in men and 11.8 (95%CI 9.2-14.9) in women. For "possible" incident heart failure these estimates were 17.2 (95%CI 14.7-20.0), 19.3 (95%CI 15.1-24.4) and 15.9 (95%CI 12.9-19.4), respectively. Figure 2 compares our age-specific incidences with those reported from a similar study in Hillingdon, London.[13] Figure 3 shows the age-specific incidences of possible and definite heart failure.

Risk factors for heart failure

Table 2 shows baseline characteristics of the participants who did and did not develop heart failure during the follow-up period. Subjects with incident heart failure were older, had a higher body mass index and fibrinogen level, more often had a low ankle-arm

blood pressure index (an indicator of peripheral arterial disease) or a history of a MI and were more often hypertensive or diabetic.

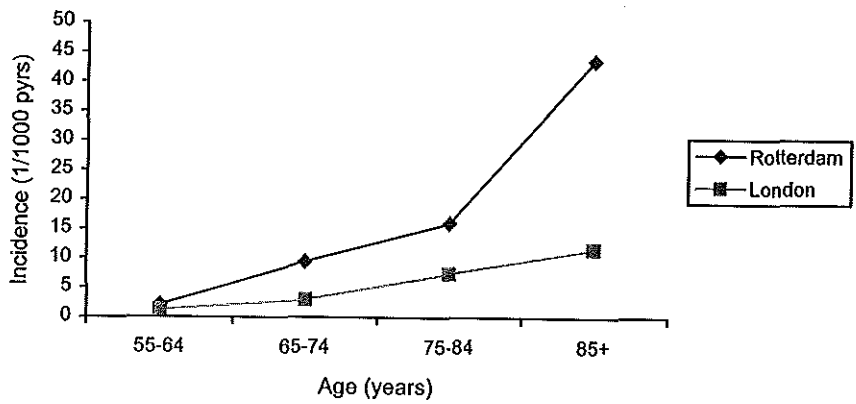

Figure 2: Estimated age- and sex-specific annual incidence rates of heart failure in the London Hillingdon Study and in the Rotterdam Study.

History

Diabetes, hypertension, peripheral arterial disease and prior myocardial infarction were independent risk factors for heart failure, and almost doubled the risk. The age- and sex-adjusted hazard ratios (HR) were 1.81 [95% CI 1.08-3.20], 1.76 [1.22-2.55], 2.09 [1.37-3.20] and 1.83 [1.15-2.93], respectively (table 4). Similar associations were found for the participants above and below the age of 70 years and for men and women. For hypertension, however, the risks appeared to be higher in women (HR 2.60 [1.60-4.22]) and for peripheral arterial disease the risk was most pronounced in those younger than 70 years of age.

ECG measures

Atrial fibrillation increased the risk for heart failure considerably (HR 5.87 [1.36-24.18]), but only in subjects younger than 70 years of age.

Participants with a borderline or an abnormal T-axis had a marked increased risk for heart failure (HR 1.84 [1.14-2.94] and 2.70 [1.60-4.55]). Electrocardiographic left ventricular hypertrophy (LVH) on ECG and heart rate were not associated with an increased risk of incident heart failure in our study.

Body mass index, smoking, and alcohol

Body mass index was associated with the risk for heart failure (HR 1.04 [1.02-1.06]). Additional adjustment for diabetes and hypertension did not change the risk estimates. Compared to never smokers, the risk of heart failure was not increased among current smokers who had a smoking history of 20 pack-years or less, but the risk was increased (HR 1.84 [1.01-3.34]) for those with more than 20 pack-years. Alcohol use was not clearly related to the occurrence of heart failure.

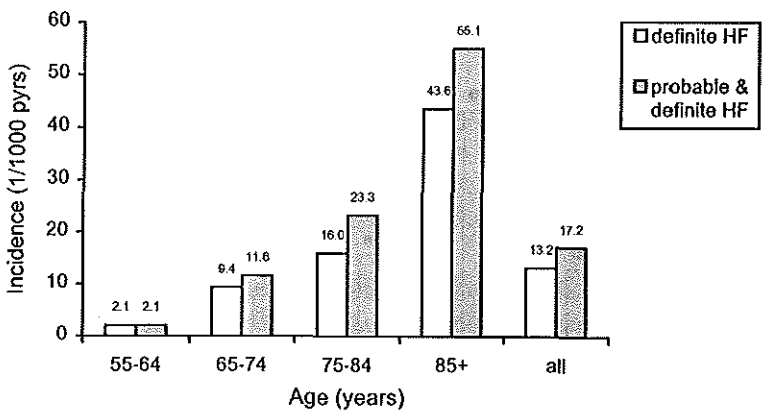

Figure 3: Estimated age-specific incidence rates of definite and probable & definite incident heart failure in the Rotterdam Study

Cholesterol, HDL cholesterol and fibrinogen

No relationship between cholesterol and incident heart failure was observed. Higher HDL cholesterol levels seemed to diminish the risk for heart failure, notably in men (HR 0.29 [0.10-0.84]) and those aged younger than 70 years of age (HR 0.20 [0.06-0.64]). Similarly, a higher cholesterol/HDL cholesterol ratio increased the risk, notably in the younger age group (HR 1.18 [1.02-1.38]). In addition higher fibrinogen levels were associated with a higher risk for heart failure (HR 1.46 [1.05-2.02]). Adjustment for smoking did not influence these findings

COPD

The risk of heart failure for subjects who used COPD medication was increased in women only HR 3.20 [1.37-7.43].

Discussion

Our study shows that the incidence of heart failure increases sharply with age in both men and women. The overall incidence rate of heart failure was estimated at 13.2 per 1000 person-years in the general population of men and women aged 55 years and over. Age, male gender, higher body mass index, history of MI, diabetes, hypertension, peripheral arterial disease, electrocardiographic T axis abnormalities and higher fibrinogen levels are risk factors for heart failure. Atrial fibrillation and the use of COPD medication are related to heart failure in, respectively, subjects younger than 70 years of age and women only.

Our study population was recruited directly from the general population and therefore provides a representative sample to assess the incidence estimates in the population at large. However, it should be emphasized that in spite of the low initial non-response rate of the baseline population (22%), it is likely that the more healthy subjects participated. Therefore, the "true" incidence in the population at large may even be somewhat higher.[14,15]

The strength of our study lies in the highly sensitive case finding of the possible incident cases. Through the computerised registries and patient files of the general practitioners and the pharmacy operating in the area in combination with our rapid access clinic we were able not only to find the cases with full blown heart failure presented to hospitals but also the mild cases and the very old who may not be send to a specialist. Through the general practitioners records we were able to follow the potential cases through time, to take the response to therapy into account and to observe whether additional new signs, symptoms or other clinical findings occurred.

Since there is no "gold standard" for the diagnosis of heart failure we used a multidisciplinary diagnostic panel to assess the diagnosis, using the guidelines for the diagnosis of heart failure of the Task Force on Heart Failure of the ESC, supplemented with response to therapy for heart failure as the best possible diagnostic tool.[11] This was also done in the Hillingdon Heart Failure Study.[13] Using the strict case definition of the ESC may, however, have led to non-recognition of very mild cases of heart failure and therefor may have led to underestimation of the rates. If we combine cases classified as possible heart failure with the definite cases, the incidence estimates increased by approximately 30%.

Although there is similarity with the methods of our study, the Hillingdon Heart Failure Study recently reported estimates that were lower in all age groups.[13] There is no a-priori reason why incidence rates in the London area would be lower than in Rotterdam. Rather, the difference might be explained by differences in case finding.

In the Hillingdon Heart Failure study new cases of heart failure were identified from hospital admissions and through a daily rapid access outpatient heart failure clinic to which GPs referred all new cases of suspected heart failure. As a consequence the cases diagnosed by the GP and not referred to the hospital, possibly because they were to old or to weak to be referred, may have been missed. Moreover cases being treated by the internist and also some outpatient cases treated for other cardiac problems by cardiologists who developed heart failure are likely to have been missed. Furthermore, in contrast to the Hillingdon study, we trained the participating GPs to use a diagnostic screening tool with maximized sensitivity to assure referral of even cases with dubious presentation and very mild symptoms. Finally, we do not think that the differences in observed incidence rates could be explained by a difference in degree of certainty in establishing a diagnosis of heart failure. In view of the amount of diagnostic information and clinical data, this seems unlikely. Even in the 34 definite cases detected by the pharmacy database detailed letters from cardiologists and from internists were available in respectively 53% and 12% of the cases in additional to information from the GP. In 35% of these cases echocardiographic data were available.

Risk factors for the development of heart failure in the population at large have been examined in the late eighties in the Study of Men Born in 1913 and in the Framingham Heart Study and might have changed over the years.[16-18] These studies used a relatively crude heart failure score to establish the diagnosis of heart failure. Nowadays more objective measurements of cardiac function, such as echocardiography are available enhancing the accuracy of heart failure detection.

Framingham reported diabetes to be a powerful risk factor especially in women and in the younger age group.[18] We also found that diabetes is a risk factor for heart failure, the risk however being higher at older age.

Hypertension is known to be a marked risk factor for heart failure, more clearly so in men and in younger patients.[16,18] Our study confirms the strong association of hypertension with heart failure risk. Left ventricular hypertrophy was the most pronounced risk factor in the Framingham Study, particularly in the younger patient group. The risk associated with LVH on ECG and the risk for heart failure was strongest in younger subjects in our study, but the association was not statistically significant. A possible explanation is that over the years the prevalence of LVH among subjects with heart failure decreased.[19]

To our knowledge, this is the first study to report that a borderline and abnormal T axis are associated with the development of heart failure. This provides further support for the view that the T axis is a solid general marker for subclinical myocardial damage.[5]

Interestingly, the use of COPD medication was associated with the incidence of heart failure, in particular in women. This might be attributable to the difficulty of diagnosing heart failure (which could lead to (mis)treatment with COPD medication) or to the fact that heart failure and COPD often coincide.

We conclude that the incidence of heart failure in an older population is high and exponentially increases with age in both men and women. Peripheral arterial disease, electrocardiographic T axis abnormalities, diabetes, hypertension, high body mass index and atrial fibrillation (the latter only in men younger then 70 years of age) are independent risk factors for the occurrence of heart failure.

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
3. World Health Organization. Diabetes mellitus: report of a WHO study group. Geneva, Switzerland: World Health Organization, 1985.
4. de Bruyne MC, Mosterd A, Hoes AW, Kors JA, Kruijssen DA, van Bemmel JH, Hofman A, Grobbee DE. Prevalence, determinants, and misclassification of myocardial infarction in the elderly. *Epidemiology* 1997;8:495-500.
5. Kors JA, de Bruyne MC, Hoes AW, van Herpen G, Hofman A, van Bemmel JH, Grobbee DE. T axis as an indicator of risk of cardiac events in elderly people. *Lancet* 1998;352:601-5.
6. Rose G, Blackburn H, Gillum R, Prineas R. Cardiovascular survey methods. Geneva, Switzerland: World Health Organization, 1982.
7. van Gent CM, van der Voort HA, de Bruyn AM, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. *Clin Chim Acta* 1977;75:243-51.
8. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. QTc dispersion predicts cardiac mortality in the elderly: the Rotterdam Study. *Circulation* 1998;97:467-72.
9. Mosterd A, Hoes AW, de Bruijne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population. The Rotterdam Study. *Eur Heart J* 1999;20:447-55.
10. Carlson KJ, Lee DC, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis* 1985;38:733-9.
11. The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741-51.
12. Miettinen OS. Theoretical epidemiology. Principles of occurrence research in medicine. New York, Crichester, Brisbane, Toronto, Singapore: John Wiley & Sons, 1985.
13. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure: a population-based study. *Eur Heart J* 1999;20:421-8.
14. Herzog AR, Rodgers WL. Age and response rates to interview sample surveys. *J Gerontol* 1988;43:S200-5.
15. Kelsey JL, O'Brien LA, Grisso JA, Hoffman S. Issues in carrying out epidemiologic research in the elderly. *Am J Epidemiol* 1989;130:857-66.
16. Eriksson H, Svardsudd K, Larsson B, Ohlson LO, Tibblin G, Welin L, Wilhelmsen L. Risk factors for heart failure in the general population: the study of men born in 1913. *Eur Heart J* 1989;10:647-56.
17. Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. *Br Heart J* 1994;72:S3-9.
18. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;22:6A-13A.

19. Mosterd A, D'Agostino RB, Silbershatz H, Sytkowski PA, Kannel WB, Grobbee DE, Levy D. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. *N Engl J Med* 1999;340:1221-27.

Chapter 6

Diagnosis in patients suspected of heart failure: importance of neurohormones

Manuscript based on chapter 6:

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Introduction

The diagnosis of heart failure is fraught with difficulties and a challenging task. This particularly applies to primary care, where the diagnosis of heart failure is mainly based on clinical judgement of the general practitioner (GP). Prior studies showed that the validity of the clinical diagnosis of heart failure is limited, particularly in women, the obese and the elderly.[1-3]

Incorrect diagnosis has major consequences for both patients and health services. Therefore, methods to improve early recognition of heart failure are required.

The diagnostic work-up in patients with clinically suspected heart failure by general practitioners consists of patient history and physical examination, possibly followed by electrocardiography (ECG) and chest X-ray. Additional diagnostic tests sometimes ordered by GPs include pulmonary function test, exercise test and haemoglobin and thyroid function determination. Currently, echocardiography is considered to be the key noninvasive diagnostic test in the diagnosis of heart failure. In the Netherlands, as in other some countries, patients have to be referred to a cardiologist for echocardiography. More recently, neurohormones e.g. atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), have been proposed as possible diagnostic indicators for heart failure.[3-5] To our knowledge, studies comparing different diagnostic strategies in patients suspected of heart failure, including assessment of the (added) value of signs and symptoms, ECG, chest X-ray or neurohormones are lacking. To address this issue, we performed a study in a cohort of 5281 men and women aged 57 years or older.

Methods

This study forms part of the Rotterdam Study, a population-based prospective cohort study on prevalence, incidence and determinants of chronic disabling diseases in the elderly. Rationale and design of the Rotterdam Study were described in detail elsewhere.[6] In short, all 10,275 inhabitants of Ommoord, a suburb of Rotterdam, who were 55 years or older were invited to participate. In total, 7,983 (78%) agreed to participate and signed informed consent. Of the 7,983 participants of the Rotterdam Study we excluded 612 participants because they were already diagnosed as cases of heart failure.

Furthermore, 979 participants of the remaining cohort died before February 1996, the starting point of the present study. For logistic reasons we included only

participants who were enlisted with the 18 general practitioners working in the Ommoord area. This resulted in a cohort of 5266 participants.

Table 1: Rotterdam Heart Failure score

History	Points	Physical examination	Points
• Rest dyspnoea	4	• Heart rate 90-110 beats/min	1
• Orthopnoea	4	> 110 beats/min	2
• Paroxysmal nocturnal dyspnoea	3		
• Dyspnoea on walking on level	2	• Raised jugular venous pressure (JVP)	2
• Dyspnoea on climbing	1	• Raised JVP & hepatomegaly or edema	3
• Paroxysmal nocturnal cough	1	• Third heart sound / gallop rhythm	3
Past history		• Crepitations basilar	1
• Myocardial infarction	2	> basilar	2
• Hypertension	1	• Rhonchi	3
• Angina pectoris	1		
• CABG or PTCA	1	If score ≥ 3, the patient was referred for diagnostic work-up.	
• Atrial fibrillation	1		
• Heart valve disease	1		
• Peripheral arterial disease	1		

Diagnostic work-up

We aimed to detect as many subjects suspected of heart failure as possible. Therefore, the 18 participating general practitioners were trained in the application of a heart failure score. The Rotterdam Heart Failure Score (table 1) was based on signs, symptoms and history of a patient corresponding with the "Boston criteria for heart failure" scoring system.[7] Several criteria (notably, history of: myocardial infarction, hypertension, angina pectoris, coronary artery bypass graft (CABG) or percutaneous transluminal angioplasty (PTCA), atrial fibrillation, heart valve disease and peripheral arterial disease) were added, based on review of the literature, to enhance referral of all subjects with possible heart failure. During the study period, the GPs were asked to determine the Heart Failure score in all Rotterdam Study participants presenting with dyspnoea, progressive fatigue/anorexia of possible cardiac origin, paroxysmal nocturnal cough, leg oedema and nocturia or any other reason for suspicion of heart failure. All Rotterdam Study participants who scored 3 or more points and those suspected by the GP of heart failure for other reasons were referred for a diagnostic work-up at the research centre before hospital referral and preferably before therapeutic interventions were initiated. A low threshold for referral was chosen to minimize non-referral of potential cases and to assure inclusion of all heart failure cases.

Table 2a: Characteristics at presentation of patients suspected of heart failure classified according to the eventual diagnosis of presence or absence of heart failure. Values are proportions (%) unless stated otherwise.

	Heart Failure present (n=44)	Heart Failure absent (n=105)	p-value
Mean age (years)	78.8	75.7	< 0.02
Women	45	67	< 0.02
Patient history			
Rest dyspnea	25	24	0.88
Orthopnea	32	16	0.04
Paroxysmal nocturnal dyspnea	34	15	0.01
Dyspnea on exertion	77	74	0.70
Nocturnal cough	27	28	0.97
Cough	23	31	0.29
Wheezing	34	42	0.37
Nocturia	34	27	0.36
Swollen legs	59	48	0.20
History of COPD	27	35	0.35
Hypertension	52	51	0.93
Diabetes	14	10	0.58
History of MI	18	9	0.10
CABG	5	3	0.60
PTCA	2	3	0.84
Hypercholesterolemia	7	12	0.32

After referral to the research centre, the diagnostic work-up included a standard interview and physical examination, chest X-ray, pulmonary function test (i.e. forced expiratory volume in one second (FEV1), vital capacity (VC) and peak expiratory flow rate (PEF)), electrocardiogram (ECG), echo-Doppler cardiography, cardiopulmonary exercise testing, 6 minute walk test, haemoglobin measurement, thyroid function test, and pre- and post-exercise blood sampling for measurement of plasma neurohormones (i.e. atrial natriuretic peptide (ANP), N-terminal ANP (NT-ANP), brain natriuretic peptide (BNP), arginine vasopressin (AVP), aldosterone, renin, norepinephrine (NE) and semicarbazide-sensitive amine oxidase (SSAO)).

Myocardial infarction (MI), chronic obstructive pulmonary disease (COPD), hypertension, diabetes, CABG, PTCA and hypercholestrerolemia were considered to be present if self reported by the participant or if reported by the referring GP. Jugular venous pressure was determined by the method described by Borst.[8] Posteroanterior chest X-rays were interpreted by one and the same radiologist without knowledge of any other diagnostic information. Thoracic and cardiac diameters were measured to calculate the cardiothoracic (CT) ratio. The chest radiograph was considered indicative for heart failure if it showed pleural effusion, redistribution, interstitial pulmonary

Table 2b: Clinical characteristics of patients suspected of heart failure classified according to the eventual diagnosis of presence or absence of heart failure. Values are proportions (%) unless stated otherwise.

	Heart Failure present (n=44)	Heart Failure absent (n=105)	p-value
Physical examination			
Jugular venous pressure			
Increased	21	10	0.07
Unable to measure	25	25	0.98
S_3	5	2	0.38
S_4	0	2	0.73
Crepitations	64	30	<0.0001
Rhonchi	11	8	0.46
Edema	5	38	0.18
Hepatomegaly			
Present	9	7	0.61
Missing	9	10	0.93
Chest X-ray			
CT-ratio	0.53	0.49	<0.001
Pleural effusion	14	0	0.58
Redistribution	7	0	0.70
Interstitial pulmonary edema	7	0	0.70
Alveolar pulmonary edema	0	0	—
Evidence of COPD	18	10	0.15
ECG			
Atrial fibrillation	30	1	< 0.001
Pacemaker rhythm	2	1	0.54
Left bundle branch block	5	3	0.60
Right bundle branch block (RBBB)	11	6	0.24
Incomplete RBBB	9	8	0.88
Left anterior fascicular block	7	3	0.28
Left posterior fascicular block	0	1	0.81
Intra ventricular conduction defect	0	1	0.81
Left ventricular hypertrophy	16	1	0.006
Right ventricular hypertrophy	2	1	0.54
Anterior MI	16	8	0.13
Inferior MI	1	3	0.12
ST-segment elevation (Stel)	2	0	0.75
ST-segment depression (Stdp)	0	0	—
Repolarization disturbances	11	1	0.02
Neurohormones (means)			
ANP (pg/ml)	517	227	< 0.0001
NT-ANP (nmol/l)	1.17	0.47	< 0.0001
BNP (pg/ml)	178	55	< 0.0001
NE (pg/ml)	485	357	0.002
SSAO (mU/l)	608	424	< 0.0001

edema or alveolar pulmonary edema. Furthermore, evidence of COPD was registered by the radiologist. ECGs were stored digitally and analyzed by the Modular ECG Analysis System (MEANS).[9] In case the MEANS program could not interpret an ECG the research physician evaluated it.

Table 3a: Results of the diagnostic models to assess the presence of heart failure in patients suspected of heart failure.

Diagnostic model	History (model A)		History + Physical (model B)		History + Physical + Chest X-ray (model C)		History + Physical + Chest X-ray + ECG (model D)	
Determinant	Coeff. (SE)	OR	Coeff. (SE)	OR	Coeff. (SE)	OR	Coeff. (SE)	OR
History								
Constant	-7.67 (2.36)		-6.48 (2.41)		-11.78 (3.00)		-12.52 (3.50)	
Age (per year)	0.09 (0.03)	1.1	0.07 (0.03)	1.1	0.03 (0.03)	1.0	0.05 (0.04)	1.1
Sex (female)	-0.97 (0.42)	0.4	-0.83 (0.43)	0.4	-1.43 (0.50)	0.2	-1.72 (0.59)	0.2
Orthopnea	1.62 (0.53)	5.1	1.65 (0.54)	5.2	1.75 (0.59)	5.7	2.08 (0.72)	8.0
History of MI	1.06 (0.60)	2.9	0.96 (0.61)	2.6	0.63 (0.66)	1.9	0.83 (0.79)	2.3
History of COPD	-0.93 (0.49)	0.4	-0.94 (0.50)	0.4	-0.87 (0.53)	0.4	-1.13 (0.67)	0.3
Physical examination								
Crepitations	—	—	1.09 (0.43)	3.0	1.28 (0.47)	3.6	1.38 (0.56)	4.0
Chest X-ray								
CT ratio	—	—	—	—	0.17 (0.04)	1.2	0.14 (0.05)	1.2
ECG								
Atrial fibrillation	—	—	—	—	—	—	4.61 (1.27)	100.8
REP	—	—	—	—	—	—	2.45 (1.32)	11.5

Coeff. = regression coefficient estimated from the multivariate model; SE = standard error; OR = odds ratio; CT ratio = cardiothoracic ratio; REP = repolarization disturbances

All referred patients were followed for an additional 6 months and important clinical findings (including results from other diagnostic tests, medication use and letters from medical specialists) were collected.

Blood sampling and neurohormone analysis

Venous blood was collected in a 10ml syringe after the participant had been supine during an ECG recording and echocardiographic investigation for at least 20 minutes. The blood from the syringe was immediately injected into prechilled tubes. Blood for measurement of ANP, NT-ANP and BNP was collected in 10-ml tubes containing

EDTA (19mg) and aprotinin (1000kIU), while for SSAO and NE measurements blood was collected in heparinized 10-ml tubes containing 12 mg of glutathione. The tubes were placed on ice and centrifuged within 30 minutes from sampling (4°C, 10 min, 3000 × g). Plasma was stored in polyethylene tubes at -20°C at the research centre before transportation to and storage at the Cardiovascular Research Laboratory, Erasmus University Medical Center, where the plasma was stored at -80°C until analyses. Plasma NE was determined by high-performance liquid chromatography with fluorimetric detection.[10] Plasma SSAO was measured as described previously.[11] Commercially available radioimmunoassay kits were used for measurement of ANP (Nichols Institute, Wijchen, The Netherlands), NT-ANP (Biotop, Oulu, Finland) and BNP (Peninsula, Belmont, CA, USA).

Table 3b: Results of the diagnostic models to assess the presence of heart failure in patients suspected of heart failure.

Diagnostic model	History + Physical + ECG (model E)		History + Physical + NT-ANP (model F)	
Determinant	Coeff. (SE)	OR	Coeff. (SE)	OR
History				
Constant	-8.83 (3.05)		-5.92 (3.09)	
Age (per year)	0.09 (0.04)	1.1	0.02 (0.04)	1.0
Sex (female)	-1.19 (0.53)	0.3	-1.06 (0.57)	0.3
Orthopnea	1.40 (0.71)	4.1	1.52 (0.74)	4.6
History of MI	1.01 (0.72)	2.8	0.21 (0.84)	1.2
History of COPD	-0.78 (0.61)	0.5	-0.67 (0.66)	0.5
Physical examination				
Crepitations	1.28 (0.53)	3.6	1.62 (0.60)	5.0
ECG				
Atrial fibrillation	4.68 (1.15)	108.0	—	—
LVH	3.10 (1.24)	22.3	—	—
Neurohormones				
NT-ANP	—	—	4.33 (0.81)	76.3

Coeff. = regression coefficient estimated from the multivariate model; SE = standard error; OR = odds ratio

Case definition

The presence of heart failure was determined six months after the initial visit during consensus meetings by an expert panel involving a cardiologist, internist, general practitioners and clinical epidemiologist reviewing all available information, except for

the neurohormones BNP and SSAO. During the consensus meetings data on these neurohormones were not yet available. Diagnosis of heart failure was based on consensus, using the guidelines for the diagnosis of heart failure of the Task Force on Heart Failure of the European Society of Cardiology (co-existence of symptoms and objective proof of systolic or diastolic ventricular dysfunction) complemented with any information on the response to therapy for heart failure during a six months follow-up period, extracted from the patient's medical records.[12] The members of the panel could classify each reviewed case as: no, possible or definite heart failure. If all members agreed upon "no" or "definite" heart failure the case was classified as such. In case of disagreement the panel tried to reach consensus. If no consensus was reached the case was classified as "possible" heart failure. In case of possible or definite heart failure the panel could also add a remark to the classification. The remark was made when the panel had little more additional information than the history and physical examination of the general practitioner, the response to therapy if present and the clinical diagnosis of the GP to establish a final panel diagnosis. In these cases, no objective measurements of ventricular function were available. In the analyses of the present study emphasis is on participants classified as definite cases of heart failure.

Data analysis

The association between each diagnostic variable and the presence of heart failure was first quantified using univariable logistic regression analysis. Variables that were associated with the presence or absence of heart failure (defined as a p-value ≤ 0.20) were included in a multivariable logistic regression model to determine their independent contribution to the prediction of heart failure. In this multivariable analysis different diagnostic strategies were considered, following the order in which diagnostic work-up of patients suspected of heart failure is commonly carried out in practice. As this work up always starts with a patient's history, we initially included all univariably associated variables from patient history in an overall multivariate model.

Of this model we first evaluated its goodness of fit (reliability) using the Hosmer & Lemeshow method.[13] If this reliability was classified as satisfactory (defined as p-value > 0.20) , the Receiver Operating Characteristic (ROC) area and its standard error were estimated.[14,15] The ROC area provides an estimate of the overall diagnostic or discriminative value of the model (i.e. ability to discriminate between patients with and without heart failure) and can range from 0.5 (no diagnostic information) to 1.0 (perfect discrimination). A value over 0.7 can be interpreted as reasonable and over 0.8 as good.[16] Subsequently, model reduction was performed by excluding variables (one by one) from the overall history model until all of the remaining regression coefficients

differed "significantly" from zero (defined as a p-value < 0.10). Each of the excluded variables as well as the univariate non-significant variables were then re-entered in the model to evaluate whether they yielded a higher ROC area. The ROC area of each reduced model was compared with the overall model, by estimating the differences in ROC area with 95% CI.[17,18] This approach yielded a reduced history model with a minimum number of determinants that did not have a statistically significant lower ROC area than the overall history model.

The ROC area reflects the overall value of a model and does not directly indicate the clinical value (i.e. ability of ruling in or out the disease) of a model. Therefore, we also estimated and compared the positive predictive value (PPV) (i.e. proportion of patients with a positive test result that was correctly diagnosed) and the negative predictive value (NPV) (i.e. the proportion of patients with a negative test result that was correctly diagnosed) obtained by the different reduced history models. In advance we decided that our threshold probabilities to calculate and compare the PPV and NPV were < 0.20 and >0.50. Less than 0.20 was chosen because we believe that this threshold reflects routine clinical practice to the extend that a subject classified with less than 20% probability of heart failure will not be treated or referred to a specialist by a GP. The upper threshold of 50% was chosen because we believe that in practice, a subject with more than 50 % probability of having heart failure is likely to be treated as such by the GP. Finally, the model with the highest ROC area as well as the best classification of patients with and without heart failure (assuming the 20% and 50% thresholds) was considered to be the "most effective'' history model.

To assess the value of physical examination in addition to the information obtained from the patient history, the same approach of model reduction and comparison was applied to all univariably significant (p-value ≤ 0.20) physical examination items after they were added to the final patient history model. This yielded a reduced history and physical examination model.

Similarly, the (univariably) significant findings from chest X-ray, ECG, and neurohormone assessment were consecutively added (one by one) to the history and physical examination model in various different orders.

Of all 149 subjects, 8 participants had missing values on one or more neurohormones. To decrease bias and increase statistical efficiency these missing neurohormone values were imputed using the expectation-maximization (EM) method.[19,20] Such imputation is based on correlation between each variable with missing values and all other variables. These correlations were estimated from the 141 set of complete subjects. All data analyses were performed using the SPSS statistical package 7.5.2.

Table 4: The distributions of subjects with and without heart failure according to the probability estimated by the different diagnostic models.

	History [A]				History & Physical examination [B]			
Estimated Probability	HF %*	Total n (%)	HF+ N (%)	HF- n (%)	HF %*	Total n (%)	HF+ n (%)	HF- n (%)
≤ 0.10	4	24 (16)	1 (2)	23 (22)	4	26 (17)	1 (2)	25 (24)
0.10-0.20	23	30 (20)	7 (16)	23 (22)	13	38 (26)	5 (11)	33 (31)
0.20-0.50	31	74 (50)	23 (52)	51 (49)	36	58 (39)	21 (48)	37 (35)
0.50-0.60	56	9 (6)	5 (11)	4 (4)	54	13 (9)	7 (16)	6 (6)
≥ 0.60	67	12 (8)	8 (18)	4 (4)	71	14 (9)	10 (23)	4 (4)
All		149	44	105		149	44	105
	History & Physical & X-ray [C]				History & Physical & X-ray & ECG [D]			
Estimated Probability	HF %*	Total n (%)	HF+ N (%)	HF- n (%)	HF %*	Total n (%)	HF+ n (%)	HF- n (%)
≤ 0.10	2	47 (32)	1 (2)	46 (44)	3	59 (40)	2 (5)	57 (54)
0.10-0.20	18	22 (15)	4 (9)	18 (17)	17	24 (16)	4 (9)	20 (19)
0.20-0.50	31	45 (30)	14 (32)	31 (30)	31	29 (20)	9 (21)	20 (19)
0.50-0.60	70	10 (7)	7 (16)	3 (3)	64	11 (7)	7 (16)	4 (4)
≥ 0.60	72	25 (18)	18 (41)	7 (7)	85	26 (17)	22 (50)	4 (4)
All		149	44	105		149	44	105
	History & Physical & ECG [E]				History & Physical & NT-ANP [F]			
Estimated Probability	HF %*	Total n (%)	HF+ N (%)	HF- n (%)	HF %*	Total n (%)	HF+ n (%)	HF- n (%)
≤ 0.10	3	61 (41)	2 (5)	59 (56)	3	68 (46)	2 (5)	66 (63)
0.10-0.20	32	19 (13)	6 (14)	13 (12)	20	20 (13)	4 (9)	16 (15)
0.20-0.50	22	36 (24)	8 (18)	28 (27)	29	21 (14)	6 (14)	15 (14)
0.50-0.60	100	5 (3)	5 (11)	0	50	8 (5)	4 (9)	4 (4)
≥ 0.60	82	28 (19)	23 (52)	5 (5)	88	32 (22)	28 (64)	4 (4)
All		149	44	105		149	44	105

HF = heart failure; + = present; - = absent; HF%* = observed prevalence (probability) of HF in that category of estimated probability.

Results

During the follow-up period of 30 months, 149 participants were referred to the research center for a diagnostic work-up. 40% was male and the age range was 61- 92 years. Of the 149 participants, 44 (29.5%) were classified during the consensus meetings as definite cases of heart failure.

Table 2a shows the associations between various patient history and clinical characteristics at presentation and the presence or absence of heart failure. Presence of heart failure was related to age, gender, orthopnea, paroxysmal nocturnal dyspnea,

edema and history of myocardial infarction (p-value ≤ 0.20). Table 2b shows these associations for the characteristics obtained from physical examination, ECG, chest X-ray and neurohormone determinations.

The overall model including all univariably associated (p ≤ 0.20) history variables had a ROC area of 0.78 (SE: 0.042). After model reduction and re-entering of excluded variables the reduced history model (model A) included age, gender, orthopnea, history of myocardial infarction and history of COPD (ROC area 0.75, SE: 0.045; fig 1 and table 3). Excluding more variables from this model significantly reduced the ROC area. Table 4 shows the actual observed prevalence of heart failure and the corresponding numbers of patients across the selected ranges of probability estimated by the derived models. Model A selected 21 subjects with a probability > 50% of which 13 actually had heart failure leading to a PPV of 0.62 (table 5). It also selected 54 subjects with a probability ≤ 0.20 of which 46 had no heart failure leading to a NPV of 0.85.

Table 5. The estimated receiver operating characteristic (ROC) area and the positive and negative predictive values defined as, respectively, the prevalence of heart failure when the model predicts a probability of >50% (positive predictive value: PPV) and the absence of heart failure when the model predicts a probability of heart failure of <20% (negative predictive value: NPV).

Model	ROC area (SE)	PPV	NPV
A	0.75 (0.05)	0.62	0.85
B	0.78 (0.04)	0.63	0.91
C	0.84 (0.03)	0.71	0.93
D	0.90 (0.03)	0.81	0.93
E	0.89 (0.03)	0.85	0.90
F	0.92 (0.02)	0.80	0.93

ROC = Receiver Operating Characteristic; SE = standard error; PPV = positive predictive value; NPV = negative predictive value.

Addition of the significant findings obtained during physical examination (i.e. increased jugular venous pressure, crepitations and edema) to model A increased the ROC area from 0.75 to 0.79 (p=0.23). The reduced model (model B) including model A and crepitations only, had a similar ROC area of 0.78 (table 3; fig 1). Although addition of crepitations to model A did not increase the ROC area, the NPV increased from 0.85 to 0.91 and the PPV from 0.62 to 0.63. Therefore, it was left in model B.

Addition of the univariably significant chest X-ray findings (cardiothoracic (CT)-ratio and signs of COPD) to model B significantly increased the ROC area from 0.78 to 0.84 (p=0.02). However, including CT ratio only yielded the same ROC area

(model C, table 3, fig. 1). Tables 4 and 5 show the increase in number of correctly classified patients and the PPV and NPV. Subsequent addition of all (univariably significant) ECG findings (i.e. atrial fibrillation, LVH, anterior and inferior myocardial infarction and repolarization disturbances (REP)) to model C significantly increased the ROC area to 0.90 (p=0.03). Excluding anterior and inferior myocardial infarction and LVH yielded the same ROC area (model D, table 3, fig. 1). Finally, separate addition of each of the neurohormones ANP, NT-ANP, BNP, SSAO and NE further increased the ROC area of model D to 0.93 (SE 0.023, p=0.08), 0.93 (SE 0.022, p=0.07), 0.92 (SE 0.024, p=0.18), 0.93 (SE 0.022; p=0.08) and 0.91 (SE 0.025, p=0.46), respectively.

Adding ECG findings before the chest X-ray to the most efficient history and physical examination model (model B), yielded a ROC area of 0.90 (SE 0.032; p=0.002). After reduction, the model (model E) including Model B, atrial fibrillation and LVH yielded a ROC area of 0.89 (SE 0.029) (table 3, fig. 1). Addition of the significant chest X-ray findings did not clearly change the ROC are, 0.90 (SE 0.025, p=0.10) and the positive and negative predictive values remained similar for both models (data not shown). Finally, the addition of one of the neurohormones ANP, NT-ANP, BNP or SSAO increased the ROC area to 0.93 (SE 0.023; p=0.01), 0.94 (SE 0.022; P=0.01), 0.92 (SE 0.024; p=0.02) and 0.92 (SE 0.023; p=0.04), respectively.

The diagnostic model E (including history, physical examination and ECG findings) had a similar area under the ROC curve (0.89) as the diagnostic models including history, physical examination (model B) and only one of the neurohormones (ANP, NT-ANP, BNP, SSAO (ROC area between 0.87 and 0.92; $p > 0.10$). The diagnostic model including model B and NT-ANP (model F) had a slightly lower PPV (0.80) compared to model E (0.85), with a slightly higher NPV (0.93 vs 0.90)(table 5).

Discussion

Our results show that addition of neurohormones to the information obtained during history taking and physical examination is as effective as the more conventional approaches (using information from chest X-ray and ECG) in determining the presence of heart failure in patients suspected of heart failure.

In the assessment of the diagnostic value of each diagnostic test in patients suspected of heart failure we evaluated each test according to the chronological order commonly applied in clinical practice. The added value of each test was evaluated conditional on the results of previous diagnostic tests. As far as we know no other studies in heart failure have so far used this approach. The few published studies

evaluating the usefulness of natriuretic peptides, studied these as a single tool for detecting left ventricular dysfunction or heart failure.[3,4]

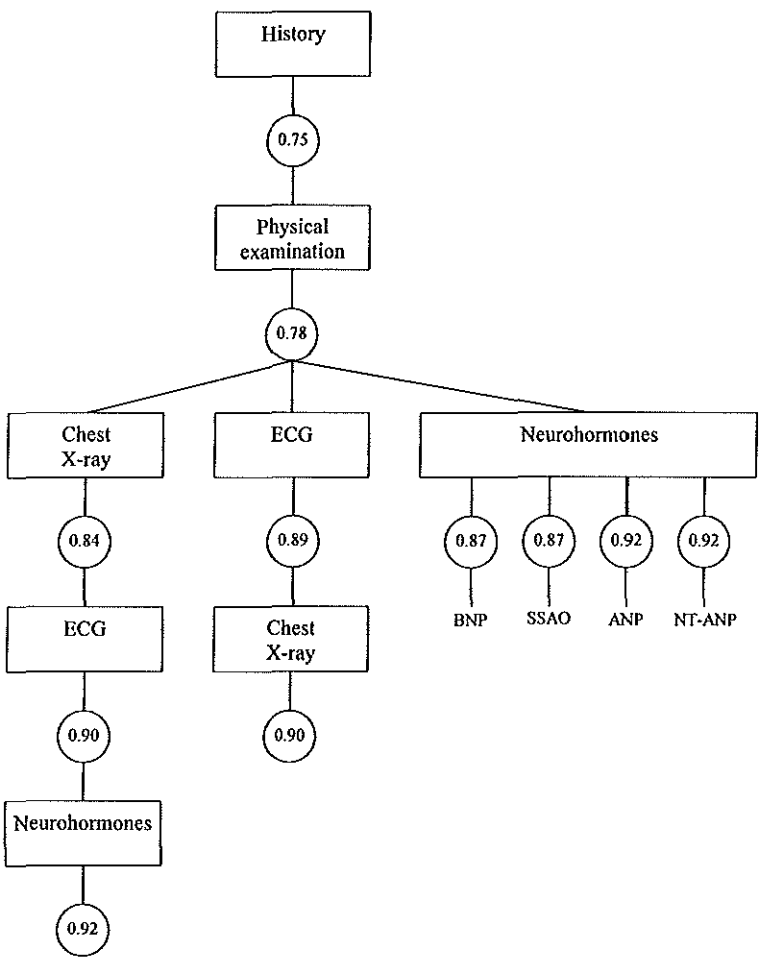

Figure 1: Flowchart for different diagnostic strategies and the corresponding ROC areas. The numbers in the circles indicate the ROC area.

Of the history variables, only age, gender, orthopnoe, history of myocardial infarction and history of COPD were independent determinants of the presence of heart failure. Except for crepitations, physical examination did not have additional diagnostic value. This is probably due to mutual dependency. The information already obtained during history taking largely overlaps the diagnostic information obtained from the physical examination. Furthermore, the information obtained from a chest X-ray does not appear to add to the diagnostic efficiency when an electrocardiogram is available.

Since there is no "gold standard" for the diagnosis of heart failure we used a multidisciplinary expert panel to classify the cases, using the guidelines for the diagnosis of heart failure of the Task Force on Heart Failure of the European Society of Cardiology, and adding the response to therapy for heart failure.[12]. When studying the diagnostic value of tests, the gold standard or 'true' diagnosis should preferably be independent from the test results that are to be studied.[21] Since there is no gold standard independent of the studied tests available for heart failure, this unavoidably leads to incorporation bias.[22] The incorporation bias might lead to overestimation of the diagnostics performance of test. However, none of the incorporated tests is perfectly related to heart failure and the classification of the panel is currently the best reference test. Furthermore, BNP and SSAO were not used in the classification procedure for heart failure but showed almost the same diagnostic results as ANP and NT-ANP. Therefore, we think incorporation bias did not materially influence our findings.

Although echocardiography currently is the most appropriate diagnostic tool to assess the diagnosis of heart failure we did not incorporate it in our diagnostic models, since echocardiography is not a readily available diagnostic tool for the general practitioner. Furthermore as our final diagnosis of heart failure was largely dependent on the demonstration of cardiac dysfunction by echocardiography, including echocardiography in the diagnostic models would have led to serious incorporation bias.

Subjects included in this study were a selected group of subjects suspected of heart failure. Most subjects with (full-blown) acute heart failure were not sent to the research center but were admitted to the hospital. This does not affect our findings because also in routine primary care these patients would not have had extensive additional testing.

We arbitrarily chose probability thresholds to estimate positive and negative predictive values. Obviously, one could use other thresholds leading to other predictive values based on personal preferences. Proper definition of such thresholds, however, requires information about acceptable costs related to these incorrect classifications.

Not only the diagnostic value of the neurohormones in important, but also the feasibility (that is handling and stability of the sample and the rapidness, price and

simplicity) of the measurement in clinical routine. Is has been shown that BNP and NT-ANP are stable in whole blood.[23-25] Furthermore, they can be measured with a rapid and simple test at a low price (€ 23).

Our findings suggest that measurement of natriuretic peptides might be useful in routine clinical (general) practice as a diagnostic tool to assess the presence of heart failure in patients suspected of heart failure, particularly as an alternative to electrocardiography. The use of natriuretic peptides may reduce the number of misdiagnoses, mistreatment an unnecessary referral to cardiologists and thereby increase cost-effectiveness.

References

1. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
2. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.
3. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
4. McDonagh TA, Rodd SD, Murdoch DR, Morton J, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1997;351:9-13.
5. Boomsma F, van Veldhuisen DJ, de Kam PJ, Man in't Veld AJ, Mosterd A, Lie KI, Schalekamp MA. Plasma semicarbazide-sensitive amine oxidase is elevated in patients with congestive heart failure. *Cardiovasc Res* 1997;33:387-91.
6. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
7. Carlson KJ, Lee DC, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis* 1985;38:733-9.
8. Borst JGG, Molhuysen JA. Exact determination of the central venous pressure. *Lancet* 1952:304-309.
9. Willems JL, Abreu-Lima C, Arnaud P, van Bemmel JH, Brohet C, Degani R, Denis B, Gehring J, Graham I, van Herpen G, et al. The diagnostic performance of computer programs for the interpretation of electrocardiograms. *N Engl J Med* 1991;325:1767-73.
10. van der Hoorn FA, Boomsma F, Man in 't Veld AJ, Schalekamp MA. Determination of catecholamines in human plasma by high-performance liquid chromatography: comparison between a new method with fluorescence detection and an established method with electrochemical detection. *J Chromatogr* 1989;487:17-28.
11. van Dijk J, Boomsma F, Alberts G, Man in 't Veld AJ, Schalekamp MA. Determination of semicarbazide-sensitive amine oxidase activity in human plasma by high-performance liquid chromatography with fluorimetric detection. *J Chromatogr B Biomed Appl* 1995;663:43-50.
12. The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741-51.
13. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons, Inc, 1989: 140-5.
14. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87.
15. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29-36.
16. Weinstein MC, Fineberg HV. Clinical Decision Analysis. Philedelphia: WB Saunders, 1980.
17. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839-43.

18. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837-45.
19. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 1995;142:1255-64.
20. Little RJA. Regression with missing X's: a review. *J Am Stat Assoc* 1992;87:1227-37.
21. Metz CE. Basic principles of ROC analysis. *Semin Nucl Med* 1978;8:283-98.
22. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978;299:926-30.
23. Davidson NC, Coutie WJ, Struthers AD. N-terminal proatrial natriuretic peptide and brain natriuretic peptide are stable for up to 6 hours in whole blood in vitro [letter]. *Circulation* 1995;91:1276-7.
24. Hall C, Aaberge L, Stokke O. In vitro stability of N-terminal proatrial natriuretic factor in unfrozen samples: an important prerequisite for its use as a biochemical parameter of atrial pressure in clinical routine [letter]. *Circulation* 1995;91:911.
25. Murdoch DR, Byrne J, Morton JJ, McDonagh TA, Robb SD, Clements S, Ford I, McMurray JJ, Dargie HJ. Brain natriuretic peptide is stable in whole blood and can be measured using a simple rapid assay: implications for clinical practice. *Heart* 1997;78:594-7.

Chapter 7

The prognosis of heart failure in the general population

The Rotterdam Study

Manuscript based on chapter 7:

A. Mosterd, B. Cost, A.W. Hoes, M.C. de Bruijne, J.W. Deckers, A. Hofman, D.E. Grobbee. The prognosis of heart failure in the general population. The Rotterdam Study (submitted).

Introduction

The transition of acute to more chronic forms of cardiac disease in the Western World is unmistakable.[1,2] The increase in hospitalization rates for heart failure, in the Netherlands as well as elsewhere in Europe, is a visible consequence of this transition.[3] Although recent papers have described the prevalence of heart failure and left ventricular systolic dysfunction as well as the incidence of heart failure,[4-7] recent information on the prognosis of heart failure in the general population is limited.[8,9]

We set out to determine the prognosis and cause of death in participants of the large population-based Rotterdam Study who were found to have heart failure at the baseline examinations.

Methods

Study population

The present investigation is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic disease in the elderly. Objectives and methods of the Rotterdam Study have been described in detail elsewhere.[10] Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the Ommoord district of Rotterdam, were invitated to participate. Of the 10275 eligible subjects, 7983 (78%) agreed to participate and signed informed consent. Participants were interviewed at home and subsequently examined at the research centre. The Rotterdam Study was approved by the Medical Ethics Committee of Erasmus University Medical School. From 1990 to 1993 baseline data were collected, including established cardiovascular risk factors, use of medications, history of cardiovascular disease, symptoms and signs attributable to heart failure and an electrocardiogram (ECG).

Hypertension was defined as systolic blood pressure above 160 mm Hg or diastolic blood pressure above 95 mm Hg or the use of antihypertensive medication for the indication hypertension. Diabetes mellitus was defined as a non-fasting blood glucose above 11.1 mmol/l or use of antidiabetic medication. Presence of angina pectoris and shortness of breath was assessed by means of the Rose and WHO questionnaires.[11] Shortness of breath was defined as WHO grade I or higher dyspnoea, reflecting shortness of breath at rest or on moderate exertion. Drug use was coded according to the Anatomical Therapeutic Chemical (ATC) classification index. Cockcroft's formula was used to estimate creatinine clearance.[12]

Table 1: Baseline characteristics of all participants and according to the presence of heart failure.

Characteristic	All (n=5255)		No Heart Failure (n=5074)		Heart Failure (n=181)		p *
Age (years)	68.9	(8.6)	68.6	(8.4)	77.3	(8.0)	<0.001
Female sex	59.3%		59.2%		60.2%		0.69
Height (cm)	167.0	(9)	167.0	(9)	165.0	(9)	0.53
Weight (kg)	73.0	(12)	73.0	(12)	73.0	(12)	0.07
Body mass index (kg/m^2)	26.4	(3.7)	26.3	(3.7)	26.9	(4.2)	0.07
Heart rate (beats/min)	74.0	(12)	74.0	(12)	72.0	(12)	0.27
Blood pressure (mm Hg)							
Systolic	139.0	(22)	139.0	(22)	139.0	(26)	0.001
Diastolic	74.0	(12)	74.0	(12)	69.0	(12)	<0.001
Total cholesterol/HDL ratio	5.3	(1.6)	5.2.0	(1.6)	5.7	(1.9)	<0.001
Current smoking	22.9%		23.1%		16.1%		0.69
Hypertension	30.5%		30.2%		40.3%		0.24
Diabetes	10.6%		10.2%		21.8%		0.01
Myocardial infarction	11.1%		9.6%		52.5%		<0.001
Atrial fibrillation	3.4%		1.8%		23.8%		<0.001
History of angina pectoris	7.1%		6.0%		38.9%		<0.001
History of PTCA	0.9%		0.7%		5.6%		<0.001
History of CABG	2.4%		2.1%		12.9%		<0.001
Use of cardiovascular medication	36.2%		34.2%		92.7%		<0.001
Serum sodium (mmol/liter)	140.0	(3)	140.0	(3)	139.0	(4)	0.02
Serum potassium (mmol/liter)	4.1	(0.3)	4.1	(0.3)	4.1	(0.4)	0.09
Serum urea (mmol/liter)	6.3	(1.9)	6.2	(18)	8.0	(3.2)	<0.001
Serum creatinine (mmol/liter)	83.0	(18)	82.0	(17)	98.0	(34)	<0.001
Creatinine clearance (ml/min)	73.0	(21)	73.0	(20)	57.0	(18)	<0.001

Values are mean values ± SD unless otherwise indicated.
P value for difference between participants with and without heart failure, adjusted for differences in age.

A 12-lead resting ECG was recorded using an ACTA electrocardiograph (ESAOTE Biomedica, Florence, Italy). All electrocardiograms were digitally stored and analysed using the Modular ECG Analysis System (MEANS) program, a standardised and validated ECG software program,[13] to assess the presence of atrial fibrillation, myocardial infarction, and left ventricular hypertrophy. In addition, if participants reported a history of myocardial infarction without electrocardiographic evidence at the time of examination, myocardial infarction was deemed present, provided that evidence of myocardial infarction was found in the patients' records (including hospital discharge letters).

Echocardiography was performed with the participant in the partial left decubitus position (Toshiba SSH-60A). 2-Dimensional imaging using parasternal long-axis views was performed to aid M-mode studies. Measurements were made according to the

recommendations of the American Society of Echocardiography using a leading edge to leading edge convention. Left ventricular internal dimension (LVIDed) was measured at end diastole, as defined by the onset of the QRS complex and at end systole (LVIDes), as determined at the nadir of septal motion. The percentage fractional shortening was calculated as 100[(LVIDed - LVIDes)/LVIDed] and used as an index of systolic function. Impaired left ventricular function was deemed to be present if fractional shortening was less than or equal to 25%, corresponding to a left ventricular ejection fraction of 42.5%.[14]

Table 2: Number of events and incidence rates according to the presence or absence of heart failure.

Endpoint	No Heart Failure (n=5074)		Heart Failure (n=181)	
	Events	Rate (95% CI) per 1000 person-years	Events	Rate (95% CI) per 1000 person-years
4 year follow-up				
Non-fatal cardiac event	167	8.3 (7.1- 9.6)	12	19.9 (10.3- 34.8)
Cardiac death	121	6.0 (5.0- 7.2)	30	49.7 (33.6- 71.0)
Sudden cardiac death	51	2.5 (1.9- 3.3)	15	24.9 (13.9- 41.0)
All-cause mortality	416	20.6 (18.7-22.7)	55	91.1 (68.7- 118.7)
6 year follow-up				
All-cause mortality	711	24.4 (22.7-26.3)	85	104.6 (83.6- 129.4)

Classification of heart failure

The prevalence of heart failure in the Rotterdam Study has been described in detail elsewhere.[6] A two-step approach was used to assess the presence of heart failure. Firstly, the presence of shortness of breath at rest or on exertion,[15] ankle edema and pulmonary crepitations was determined. If at least two of these were present in combination with evidence of cardiac disease (angina pectoris, myocardial infarction, documented coronary artery bypass surgery, documented percutaneous transluminal angioplasty, atrial fibrillation or electrocardiographic left ventricular hypertrophy), while shortness of breath could *not* be attributed to chronic obstructive pulmonary disease (as indicated by use of chronic obstructive pulmonary disease medication -ATC code r03), heart failure was considered present. This combination had a sensitivity of 80% to detect and a specificity of 98% to exclude the presence of definite heart failure as determined by a cardiologist on clinical grounds in a validation study.[16]

Secondly, the examining physician used standardised questions to verify the indication of cardiovascular medication with the participant. In case diuretics, glycosides or angiotensin converting enzyme inhibitors were used, a possible indication of heart

failure (as opposed to hypertension, arrhythmias etc.) was verified. Only participants with a definite indication for heart failure, in whom objective evidence of cardiac disease was found, were included.

As information on shortness of breath and indications for cardiovascular medication use was not obtained in the beginning of the Rotterdam Study, prevalence estimates are based on 5540 participants (age 68.9 ± 8.7 years, 2251 men).

Table 3: Hazard ratios (95% confidence intervals) for non-fatal cardiac events and death associated with heart failure.

Endpoint	All		Men	
	Crude	Age adjusted	Crude	Age adjusted
4 year follow-up				
Non-fatal cardiac event	2.8 (1.5 - 5.0)	2.6 (1.4 - 4.7)	1.6 (0.7 - 4.0)	1.5 (0.6-3.8)
Cardiac death	8.8 (5.9 - 13.2)	4.0 (2.6 - 6.0)	6.6 (3.6 - 12.0)	3.7 (2.0-6.7)
Sudden cardiac death	10.8 (6.0 - 19)	4.8 (2.6 - 8.7)	6.8 (3.0 - 15.3)	3.7 (1.6-8.5)
Total mortality	4.5 (3.4 - 6.0)	2.1 (1.6 - 2.8)	3.4 (2.1 - 5.3)	2.0 (1.2-3.1)
6 year follow-up				
Total mortality	4.4 (3.5 - 5.5)	2.1 (1.8 - 2.7)	4.2 (3.0-5.8)	2.4 (1.7-3.3)

Endpoint	Women	
	Crude	Age adjusted
4 year follow-up		
Non-fatal cardiac event	5.0 (2.3 - 10.9)	4.1 (1.8-9.3)
Cardiac death	11.5 (6.6 - 19.8)	4.3 (2.4-7.7)
Sudden cardiac death	19.6 (8.3 - 46.3)	6.6 (2.6-16.5)
Total mortality	5.7 (3.9 - 8.1)	2.2 (1.5-3.3)
6 year follow-up		
Total mortality	4.7 (3.5 - 6.4)	1.9 (1.4-2.7)

Follow-up

Information on vital status was obtained regularly from the municipal health authorities in Rotterdam. Further information on fatal as well as non-fatal endpoints for the participants enlisted with the general practitioners (GPs) working in the study district of Ommoord (85% of the cohort) was obtained from these GPs. All participating GPs have computerised records, and fatal and non-fatal events of study participants are recorded on their computer files and sent to the Rotterdam Study data-centre regularly. In April 1996 medical records (including information available at the GP office and letters of medical specialists) of participants under the care of GPs outside the Ommoord area (15% of the

cohort) were checked for possible events by research physicians from the Rotterdam Study. After notification, cause and circumstances of the events were established by questionnaire from the GPs and by the research physicians scrutinising information from hospital discharge records. Complete follow-up information was available for 95% (5255 participants) of the study population as of April 1996 (follow-up 2.8 – 6.5 years, mean 4.1 years). In addition, vital status of these 5255 persons was assessed at April 1 1998 (follow-up 4.8 – 8.5 years, mean 6.1 years).

Classification of fatal and non-fatal events was based on the 10th revision of the International Classification of Diseases (ICD-10). We defined cardiac mortality as death from myocardial infarction or other heart diseases (ICD-10: I21-28, 42, 43, 46-50), or sudden cardiac death. Sudden cardiac death was defined as death occurring within one hour after onset of symptoms, or unwitnessed death while a cardiac cause could not be excluded.[17,18] Non-fatal cardiac events were defined as myocardial infarction, or chronic ischemic heart disease (ICD-10:I21-25), coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty. All events were classified independently by two research physicians. If there was disagreement, a consensus was reached in a separate session. Finally, all events were verified by a medical expert in cardiovascular disease. If the expert disagreed with the research physicians, the expert's judgement was considered final. The research physicians and the experts based their decisions on the same data.

Table 4: Survival in participants with congestive heart failure.
Age-adjusted survival of participants without heart failure in parentheses.

	1 year	2 years	5 years
All	89% (97%)	79% (93%)	59% (85%)
Men	91% (96%)	81% (92%)	56% (84%)
Women	87% (98%)	78% (94%)	61% (86%)

Data analysis

Differences in baseline characteristics between participants with and without heart failure and between those with and without follow-up data were examined with the unpaired student's T-test (continuous variables) and binomial tests (discrete variables). Logistic regression analysis was used to test if the differences persisted upon adjustment for age. 95% confidence intervals for incidence rates were calculated assuming Poisson distribution. Cox's proportional-hazards analysis was used to determine the risk of non-fatal cardiac events, cardiac death, sudden cardiac death and all-cause mortality associated

with heart failure, taking participants without heart failure as the reference group. Kaplan-Meier survival curves were constructed for men and women having heart failure (figure 1), separately calculating survival at one, two and five years (table 4). The logrank test was used to test for differences in survival. All statistical tests were two sided.

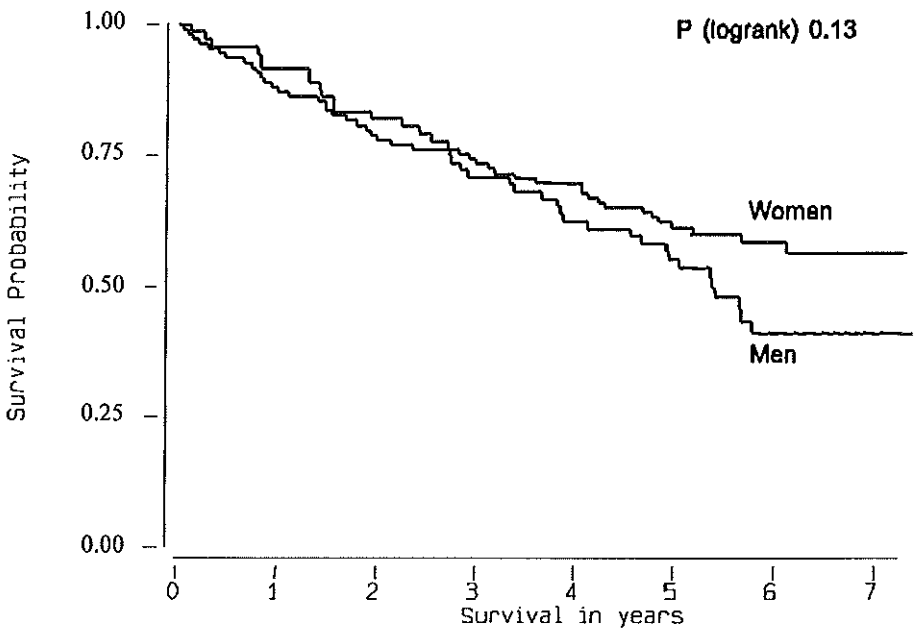

Figure 1: Kaplan Meier Survival Curves for 72 men (74.5 ± 7.4 years) and 109 women (79.2 ± 7.8) with heart failure.

Results

Table 1 provides baseline characteristics of 5255 Rotterdam Study participants aged 55 - 94 years in whom the prevalence of heart failure was determined and follow-up data were available. 181 participants (3.4%) were classified as having heart failure. The prevalence of heart failure increased with age and did not differ between men and women, as described in detail elsewhere.[6]

Table 5: Mortality in heart failure; results from hospital based studies,[20,21] placebo arms of 2 trials in patients with heart failure[24,25] and placebo arms of 2 trials in patients with asymptomatic left ventricular dysfunction.[22,23]

Study	N	Mean Age (yrs.)	Women (%)	Mean Follow-Up (months)	Total Mortality (%)	Average Mortality*	Sudden Death (% of total mortality)	Description of patients
Hospital based studies								
Madsen BK et al, 1994[20]	190	66†	28%	24.5§	60 (32%)	15,7	-	380 consecutive patients aged < 76 years admitted to hospital with heart failure. 190 excluded. Median EF 33%**
Croft JB et al, 1999[21]	154.956	77/ 80‡	58%	72¦	86% / 79%‡	13,8	33%	Medicare patients, aged >= 67 years, with 1st hospitalization for heart failure in 1986.
Trials – Heart failure								
V-HeFT II, 1991[25]	401	61	-	30	153 (38%)	15,2	63%	Mild to moderate heart failure, NYHA II-III
SOLVD treatment, 1991[24]	1284	61	20%	41	510 (40%)	11,6	22%	NYHA II - III, EF < 35%
Trials – Asymptomatic LV dysfunction								
SOLVD prevention, 1992[35]	2117	59	11%	37	334 (16%)	5,1	31%§	No symptoms of heart failure, EF <35%
SAVE, 1992[23]	1116	60	18%	42	275 (25%)	7,0	56%	No symptoms of heart failure, 3-16 days following myocardial infarction, EF <40%

* Average mortality (per 100 patient years): (total mortality / follow-up) x 12 months.
† Median age
‡ Men and women, respectively
§ Median follow-up
¦ Total follow-up 6 years
¶ Placebo arm = hydralazine & isosorbide-dinitrate
** EF = Ejection fraction.

Table 6: Prognosis of heart failure in population-based studies of incident heart failure. [8,9,29,30] Rotterdam Study results for comparison.

Study	n	Time Span	Mean Age (yrs)	Women (%)	Mean Follow-up (months)	Total Mortality (%)	Average Mortality*	Sudden Death†	Survival (%)				
										90 days	1 yr.	2 yr.	5 yr.
Framingham Heart Study Ho KL et al, 1993[29] - prospective	652	1948-1988	57±8‡ 76±10§	53	47	551 (85%)	21	50%	Men Women	73 / -¶ 72 / -	57 / 79 64 / 88	46 56	25 / 35 38 / 53
Hillingdon Heart Failure Study Cowie MR et al, 1998[8] - prospective	220	1995-1997	73/78¦	46	16	90 (41%)	31		All	71**	64		
Olmsted County, Minnesota Senni M et al, 1999[9,30] - retrospective	216	1991-1997	77±12	42					All	86 / -	76 / 88		35 / 41
Rotterdam Study - prospective	181	1990-1998	77±8	60	73	85 (47%)	7,7	27%	Men Women	99 97	91 87	81 78	56 61

* Average mortality (per 100 patient years): (total mortality / follow-up) x 12 months
† % of total mortality
‡ 1950's
§ 1980's
¦ Men and women, respectively
¶ .. / .. ; overall survival / survival in persons still alive 90 days following the diagnosis of heart failure
** 6 months.

Baseline characteristics of participants with (n = 5255) and without (n = 285) follow-up data were highly comparable, in terms of age (68.9 vs 69.0 years; p=0.83), gender (59.2% vs 61.8% female gender; p=0.43) and prevalence of heart failure (3.4% vs 3.5%; p=1.00). Differences in other baseline characteristics as described in table 1 also failed to reach statistical significance.

During the follow-up period ending April 1 1996, 471 (9.0%) participants died; 151 (3.1%) died from a cardiac-related cause, 66 (43.7%) of whom died suddenly. Non-fatal cardiac events occurred in 179 (3.7%) participants. By April 1998 an additional 325 participants had died, leading to a total mortality of 15.1%. Table 2 shows the number of events and the crude incidence rates for participants with and without heart failure. Participants with heart failure had an increased age-adjusted risk of death, including cardiac death (table 3). The risk of death in persons with heart failure did not change appreciably upon extension of follow-up from April 1996 to April 1998 (table 3). The increased risk of sudden death in persons with heart failure was particularly striking (HR 4.8, 95% CI 2.6-8.7). In addition, persons with heart failure appear to have an increased risk for non-fatal cardiac events.

Table 4 and figure 1 show survival in all 181 participants (72 men, mean age 75 ± 7 years, and 109 women, mean age 79 ± 8 years) with heart failure. Survival at one, two and five years was in the order of 90%, 80% and 60% respectively. Although crude survival did not differ between men and women (P-logrank=0.13, figure 1), age adjusted survival was higher in women than in men (hazard ratio 0.53, 95% C.I. 0.34 – 0.83), as women generally were found to have heart failure at a higher age.

Discussion

In this population-based study of 5255 persons aged 55 to 95 years the prognosis of 181 participants having heart failure was poor; age-adjusted mortality was doubled in comparison to persons without heart failure and a four- to six-fold increased risk of sudden death was observed in persons with heart failure.

The diagnosis of heart failure is fraught with difficulties.[16] In this population-based study we used a previously validated combination of signs and symptoms, that bears resemblance to the definition of heart failure proposed by the Task Force on Heart Failure of the European Society of Cardiology.[6,19] Furthermore, use of medication for heart failure was verified as symptoms and signs may be less prominent in stable patients on heart failure medication.

The potential effect of 5% losses to follow-up, mainly due to unknown addresses, is difficult to assess. Differences in baseline characteristics between participants with and without follow-up information proved to be quite small, and since a loss of 5% is quite low, we expect any bias as a result of losses to follow-up to be very limited.

The advantages of our study relate to the fact that it was population-based and included elderly participants. In addition, extensive baseline information was obtained and coding of events occurring during follow-up took place in a highly standardized manner.

Prognosis of heart failure

Studies of patients admitted to hospital with heart failure as well as clinical trials have demonstrated the poor prognosis of heart failure (table 5).[20-25] This information, however, only pertains to selected groups of heart failure patients. For example, it is obvious that clinical trials in heart failure have predominantly enrolled men and that participants in these trials tend to be younger and have less comorbidity than the typical heart failure patient in the community.

Information on the prognosis of heart failure in the community is limited; three studies addressed the prognosis in persons diagnosed as having heart failure (i.e. prevalent heart failure, not necessarily new cases of heart failure).[26-28] The Study of Men Born in 1913 reported a five year mortality rate of 26% in men with manifest heart failure.[26] NHANES reported ten year mortality rates of 72% and 60% respectively in men and women aged 65 to 75 years, in whom the presence of heart failure was assessed in 1971.[27] Lastly, the Helsinki Ageing Study found a four year mortality rate of 46% in a group of 501 persons (aged 75 to 86 years, 377 women) of whom 41 (34 women) had heart failure.[28] Age and gender adjusted risk for all cause mortality was 2.1 (95% CI 1.3 – 3.4) and 4.2 (95% CI 1.9 – 5.6) for cardiovascular mortality. Another three studies, characteristics of which are provided in table 6, assessed prognosis in patients with new onset heart failure.[8,9,29,30]

It is a reasonable assumption that heart failure mortality as observed in participants of the Rotterdam Study reflects an optimistic estimate of the prognosis in the population, as mortality was assessed in participants with prevalent heart failure. Earlier population-based studies have indicated that mortality is especially high in the first three months following the onset of heart failure (table 6).[8,9,29] It should be noted that although the response rate in our study was high (79%), non-response may have led to an overestimation of heart failure survival as response rates were lower in higher age groups and as it is conceivable that persons having severe heart failure were less likely to participate.[6]

Sudden death in heart failure

Notwithstanding the ongoing debate on the assessment of mode of death in patients with heart failure,[31] our findings that risk of sudden death in persons with heart failure is appreciable cannot easily be dismissed. Indeed, the Framingham Heart Study, the only population based study that has specifically addressed sudden death in heart failure, reported a similar fivefold increased risk for sudden death.[32] Hence, sudden death does not appear to be restricted to those having more advanced heart failure.

In conclusion, the prognosis of persons with heart failure is poor. Persons with heart failure have a fivefold increase in the risk for sudden death. To date the "typical" heart failure patient has largely been excluded from clinical trials.[33] This should change if the prognosis of heart failure in the general population is to be improved.[34]

References

1. Bonneux L, Barendregt JJ, Meeter K, Bonsel GJ, van der Maas PJ. Estimating clinical morbidity due to ischemic heart disease and congestive heart failure: the future rise of heart failure. *Am J Public Health* 1994;84:20-8.
2. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
3. Reitsma JB, Mosterd A, de Craen AJ, Koster RW, van Capelle FJ, Grobbee DE, Tijssen JG. Increase in hospital admission rates for heart failure in The Netherlands, 1980-1993. *Heart* 1996;76:388-92.
4. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure: a population-based study. *Eur Heart J* 1999;20:421-8.
5. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997;350:829-33.
6. Mosterd A, Hoes AW, de Bruijne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population. The Rotterdam Study. *Eur Heart J* 1999;20:447-55.
7. Morgan S, Smith H, Simpson I, Liddiard GS, Raphael H, Pickering RM, Mant D. Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. *BMJ* 1999;318:368-372.
8. Cowie MR, Suresh V, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Prognosis of heart failure - a population-based study of the outcome in incident cases.[Abstract]. *J Am Coll Cardiol* 1998;31:218A.
9. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med* 1999;159:29-34.
10. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
11. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. 2nd Edition. World Health Organization Geneva 1982. 1982.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
13. Willems JL, Abreu-Lima C, Arnaud P, van Bemmel JH, Brohet C, Degani R, Denis B, Gehring J, Graham I, van Herpen G, et al. The diagnostic performance of computer programs for the interpretation of electrocardiograms. *N Engl J Med* 1991;325:1767-73.
14. Quinones MA, Pickering E, Alexander JK. Percentage of shortening of the echocardiographic left ventricular dimension. Its use in determining ejection fraction and stroke volume. *Chest* 1978;74:59-65.
15. Rose GA, Blackburn H. Cardiovascular survey methods. *Monogr Ser World Health Organ* 1968;56:1-188.
16. Mosterd A, Deckers JW, Hoes AW, Nederpel A, Smeets A, Linker DT, Grobbee DE. Classification of heart failure in population based research: an assessment of six heart failure scores. *Eur J Epidemiol* 1997;13:491-502.
17. Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. *Circulation* 1992;85:I11-8.

18. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992;85:I2-10.
19. The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741-51.
20. Madsen BK, Hansen JF, Stokholm KH, Brons J, Husum D, Mortensen LS. Chronic congestive heart failure. Description and survival of 190 consecutive patients with a diagnosis of chronic congestive heart failure based on clinical signs and symptoms. *Eur Heart J* 1994;15:303-10.
21. Croft JB, Giles WH, Pollard RA, Keenan NL, Casper ML, Anda RF. Heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the Medicare population. *Arch Intern Med* 1999;159:505-10.
22. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
23. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
24. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
25. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-10.
26. Eriksson H, Wilhelmsen L, Caidahl K, Svardsudd K. Epidemiology and prognosis of heart failure. *Z Kardiol* 1991;80:1-6.
27. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992;20:301-6.
28. Kupari M, Lindroos M, Iivanainen AM, Heikkila J, Tilvis R. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. *J Intern Med* 1997;241:387-94.
29. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.
30. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;98:2282-9.
31. Cleland JG, Habib F. Assessment and diagnosis of heart failure. *J Intern Med* 1996;239:317-25.
32. Kannel WB, Plehn JF, Cupples LA. Cardiac failure and sudden death in the Framingham Study. *Am Heart J* 1988;115:869-75.
33. Massie BM. 15 years of heart-failure trials: what have we learned? *Lancet* 1998;352:SI29-33.
34. Erhardt LR, Cline CM. Organisation of the care of patients with heart failure. *Lancet* 1998;352:SI15-8.
35. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.

Chapter 8

Prognostic value of left ventricular dysfunction: a population-based study

Manuscript based on chapter 8:

B. Cost, A.W. Hoes, A. Mosterd, A. Hofman, D.E. Grobbee. Prognostic value of left ventricular dysfunction: a population-based study (submitted).

Introduction

Heart failure is a growing health problem in western societies. The increase in the occurrence of heart failure is mainly attributable to the ageing of the population and improvement in prevention and treatment of cardiovascular disorders, including ischemic heart disease.[1] The prognosis of patients with heart failure is poor; within 5 years of a diagnosis of heart failure in the Framingham Heart Study, 75% of the men and 62% of the women had died.[2] One third to one half of all deaths in patients with heart failure occur sudden.[3,4]

Heart failure is attributable to systolic dysfunction, diastolic dysfunction or both. Left ventricular systolic dysfunction is relatively common with about half of the cases being asymptomatic.[5,6] It is known that impaired systolic function is associated with a poorer prognosis in patients with myocardial infarction or congestive heart failure. Little is known about the prognosis of left ventricular dysfunction in the population at large.

The objective of this study was to determine whether left ventricular systolic dysfunction in the general population is associated with a higher risk for all cause mortality, cardiac death and sudden cardiac death.

Methods

This study forms part of the Rotterdam Study, a prospective follow-up study of subjects aged 55 years or over to investigate the prevalence, incidence, and risk factors for chronic disabling diseases of the elderly. The study was approved by the Medical Ethics Committee of the Erasmus University. Rationale and design of the Rotterdam Study were described in detail elsewhere.[7] In short, all 10,275 inhabitants of Ommoord, a suburb of Rotterdam, who were 55 years or older were invited to participate. In total, 7,983 (78%) agreed to participate and signed informed consent. Between 1990 and 1993 all subjects were interviewed at home and invited to visit the research centre twice for clinical measurements. The data collected at baseline included history, height, weight, blood pressure levels and an electrocardiogram (ECG). For logistic reasons, echocardiographic facilities were not available in the beginning of the Rotterdam Study and in several short periods thereafter.

Subjects were categorized in groups of current smokers, former smokers and those who never smoked. Body mass index was calculated as weight/length^2 in kg/m^2. Blood pressure was calculated as the mean of two consecutive measurements with a

random-zero sphygmomanometer. Hypertension was defined as systolic blood pressure above 160 mmHg or diastolic blood pressure above 95 mmHg or use of antihypertensive medication for the indication hypertension. Diabetes mellitus was defined as a non-fasting blood glucose above 11.0 mmol/l or the current use of an antidiabetic drug.[8] History of myocardial infarction (MI) was defined as self-reported MI confirmed by a physician, or MI on the ECG.[9] Presence of angina pectoris was diagnosed using the Rose questionnaire.[10] Serum total cholesterol was determined with an automated enzymatic procedure.[11]

Table 1: Baseline characteristics of the 2823 elderly participants in the Rotterdam Study, in whom echocardiography was performed. Groups are classified according to presence or absence of a technically adequate echocardiographic recording allowing assessment of left ventricular systolic function (LVSF).

	LVSF assessed (n=2270)	LVSF not assessable (n=553)	p-Value*
Age (years)†	65.7 (0.16)	70.2 (0.35)	<0.001
Women (%)	54.7	51.5	0.18
Body mass index (kg/m^2)†	26.0 (0.09)	26.9 (0.17)	<0.001
Hypertension (%)	25.0	32.7	0.03
Angina pectoris (%)	8.1	10.1	0.33
History of MI (%)	9.7	15.2	0.05
Diabetes mellitus (%)	5.5	9.0	0.10
Use of COPD medication (%)	3.5	6.3	0.01
Current smokers (%)	21.8	25.4	0.001
Former smokers (%)	45.3	42.0	0.05
Never smokers (%)	32.9	32.5	0.32
Cholesterol (mmol/l)†	6.6 (0.02)	6.6 (0.05)	0.45

LVSF = left ventricular systolic function, MI = myocardial infarction, COPD = chronic obstructive pulmonary disease. *Adjusted for age and gender when appropriate. † Values are means (SEM).

Echocardiography was performed with the participant in the left lateral position (Toshiba SSH-60A). Standard two-dimensional imaging using parasternal long axis views was performed to aid M-mode studies. All measurements were made according to the recommendations of the American Society of Echocardiography, using a leading edge to leading edge method.[12] Left ventricular internal dimension at end-diastole (LVIDed) was determined at the end of diastole as defined by the onset of the QRS-complex. Left ventricular internal dimension at end-systole (LVIDes) was measured at

the nadir of septal motion. Left ventricular fractional shortening (FS) was calculated as the percentage difference between LVIDed and LVIDes: (LVIDed – LVIDes)/ LVIDed *100%. Fractional shortening is often used as an index of systolic function. Systolic function was considered to be impaired if fractional shortening was less than 25%, corresponding to a left ventricular ejection fraction of 42.5%.[13]

In the present analysis the follow-up period of the population lasted until January 1996. Clinical follow-up data on fatal and non-fatal endpoints were obtained from the general practitioners (GPs) working in the study district of Ommoord through linkage of the general practitioner's automated medical record system to the data base of the Rotterdam Study on a regular basis. From the municipal health service in Rotterdam information was obtained on the vital status of the participants. Study physicians regularly evaluated all events, including deaths, reported by the GPs by reviewing the medical records and hospital letters available at the GP's office. In case of death of a participant the GP filled in a questionnaire on the cause and circumstances of death of the participant. Study physicians checked follow-up data from participants with a GP outside the Ommoord area (15% of the cohort) by reviewing the complete patient chart and correspondence from medical specialists of these participants. All events were classified according to the International Classification of Diseases, 10th version (ICD-10). The events were classified independently by two research physicians from the Rotterdam Study. In case of disagreement between the two, a consensus was sought in a separate session. A medical expert in the field of cardiovascular disease checked all classified events. If no consensus was reached, this expert's judgement was considered final. Cardiac mortality was defined as death from myocardial infarction, chronic ischemic disease, pulmonary embolism or other pulmonary heart disease, cardiomyopathy, cardiac arrest, arrhythmia, heart failure (all defined according to ICD-10: I 21-28, I42-43, I46-I50), or sudden cardiac death. Sudden cardiac death was defined as death occurring instantaneously or within one hour after onset of symptoms or unwitnessed death, in which a cardiac cause could not be excluded.[14,15]

Subjects living in nursing homes (n=897) were excluded from ultrasound examination because of technical limitations in the transport of the ultrasound equipment. Of the remaining 7,086 participants 6,494 visited the research centre. As mentioned before echocardiographic facilities were not available during certain periods, this resulted in 2,823 echocardiograms being performed. We excluded 553 participants (20%) whose echocardiographic registrations were deemed inadequate to reliably measure fractional shortening. Of the remaining 2,270 participants, data on the vital status was missing in 315 and on cause specific mortality in 318 participants. Subjects without follow-up data (mainly because they moved to unknown addresses or no data

could be gathered about the vital status or time of death) were excluded from the survival analyses. Overall, complete follow-up information was available for 86% (i.e.1,955/2,270) of the participants.

Table 2: Characteristics of subjects with impaired* and with normal left ventricular systolic function (LVSF).

	Impaired LVSF (n=73)	Normal LVSF (n=2197)	p-Value†
Age (years)‡	68.3 (0.87)	65.6 (0.16)	0.002
Women (%)	34.2	55.4	<0.001
Body mass index (kg/m^2)‡	25.9 (0.36)	26.0 (0.09)	0.80
Hypertension (%)	27.4	24.9	0.75
Angina pectoris (%)	26.0	7.5	<0.001
History of MI (%)	30.9	8.9	<0.001
Diabetes mellitus (%)	5.5	5.5	0.62
Use of COPD medication (%)	9.6	3.3	0.01
Current smokers (%)	15.1	22.0	0.16
Former smokers (%)	65.8	44.7	0.02
Never smokers (%)	19.2	33.3	0.15
Cholesterol (mmol/l)‡	6.5 (0.13)	6.6 (0.02)	0.89
Fractional shortening‡	20.9 (0.39)	40.1 (0.15)	

LVSF = left ventricular systolic function, MI = myocardial infarction, COPD = chronic obstructive pulmonary disease. * impaired = fractional shortening <25%, † Adjusted for age and gender when appropriate. ‡ Values are means (SEM).

Means and proportions of baseline characteristics between subjects with and without an echocardiography and between subjects with an echocardiography with a normal and impaired left ventricular systolic function were compared using logistic regression, adjusting for age and gender when appropriate.

Kaplan-Meier survival curves were plotted to describe the trend in mortality over time for subjects with normal and impaired left ventricular systolic function. Differences between the curves were compared with the logrank test.

The risk for all-cause death, cardiac death or sudden death associated with impaired fractional shortening was calculated using Cox' proportional hazards model, and presented with a 95% confidence interval (95% CI). To adjust for age and gender, these were added to the model (model A). Next, adjustments were made for other

prognostic factors such as body mass index, diabetes mellitus, use of COPD medication, smoking and cholesterol level and these were added to a subsequent model (model B). Finally, cardiovascular risk factors potentially included in the causal pathway of left ventricular dysfunction, e.g. hypertension, angina pectoris and history of MI were added to model B (model C). All analyses were also done with fractional shortening as a continuous variable. Subgroup analyses were performed to examine whether age (above and below the median age (70)) or gender modified the relationship between systolic dysfunction and (cardiovascular) mortality.

Table 3: Left ventricular systolic (dys)function and risk for all cause mortality, cardiac death and sudden death. Hazard ratios with 95% confidence intervals are given for left ventricular dysfunction defined as a fractional shortening <25% and for fractional shortening as a continuous variable.

Fractional Shortening		All cause mortality	Cardiac death	Sudden death
<25%				
	Crude	3.3 (1.6-6.9)	6.3 (2.2-18.6)	8.1 (1.7-38.5)
	Model A	2.5 (1.2-5.2)	4.7 (1.6-13.9)	5.6 (1.2-27.2)
	Model B	2.9 (1.4-6.0)	5.4 (1.8-16.5)	4.7 (0.9-23.8)
	Model C	2.4 (1.1-5.2)	3.9 (1.2-12.9)	3.3 (0.6-19.3)
Continuous (per %)				
	Crude	0.95 (0.93-0.98)	0.93 (0.89-0.98)	0.93 (0.86-1.00)
	Model A	0.96 (0.94-0.99)	0.94 (0.90-0.99)	0.95 (0.88-1.02)
	Model B	0.96 (0.94-0.99)	0.94 (0.90-0.98)	0.95 (0.88-1.02)
	Model C	0.96 (0.94-0.99)	0.96 (0.91-1.00)	0.98 (0.91-1.06)

Model A: adjusted for age and sex; Model B: adjusted for age, sex, body mass index, diabetes mellitus, use of COPD medication, smoking and cholesterol level; Model C: adjusted for age, sex, body mass index, diabetes mellitus, use of COPD medication, smoking, cholesterol level and hypertension, angina pectoris, history of myocardial infarction. COPD = chronic obstructive pulmonary disease.

Results

Table 1 shows the characteristics of the participants in the Rotterdam Study who underwent echocardiography. The participants with a technically inadequate echocardiographic recording were more likely to be older, had a higher body mass index and more often were hypertensive, smokers or used medication for chronic obstructive pulmonary disease (ATC-code R03). Of the 2270 participants with an adequate echocardiogram 73 (3.2% (95%CI 2.5-3.9)) had impaired systolic function, i.e. a fractional shortening less than 25%. Compared to those with normal fractional

shortening, those with reduced fractional shortening were older and a larger proportion was male. In addition, they had a higher prevalence of a positive history of MI and angina pectoris and more often used COPD medication (Table 2).

During the mean follow-up period of 3 years (maximum 6 years), 85 (4.3%) participants died; 24 (1.2%) died from a cardiac cause and 10 (0.5%) died suddenly.

Figure 1 shows the Kaplan-Meier survival rates for all cause mortality for subjects with normal and impaired left ventricular systolic function. The mortality rate in the group with impaired left ventricular systolic function was significantly higher (p=0.0007).

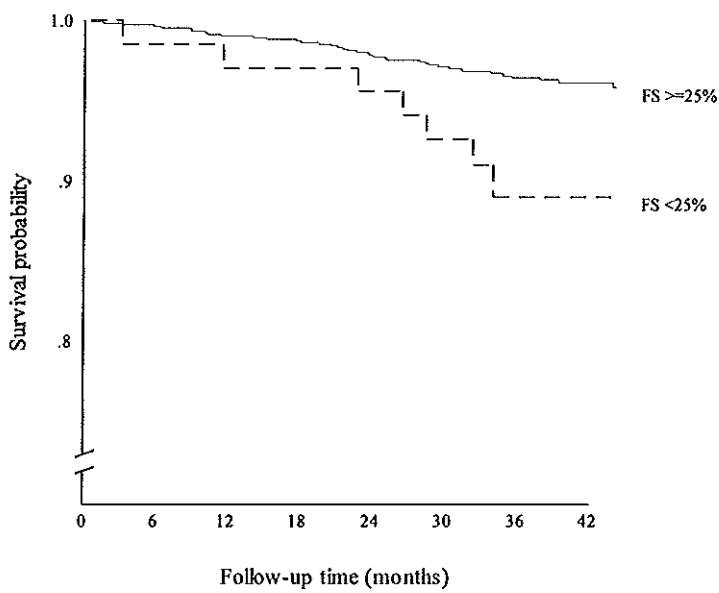

Figure 1: Kaplan-Meier survival curves for all cause mortality in participants with normal and impaired systolic function. FS = fractional shortening.

Participants with an impaired ventricular systolic function had an increased crude relative risk for all cause mortality (hazard ratio (HR) 3.3; 95%CI 1.6-6.9), cardiac death (HR 6.3; 95%CI 2.2-18.6) and sudden death (HR 8.1; 95%CI 1.7-38.5), compared to those with a normal systolic function (table 3). For the population as a whole, for each percentage increase in fractional shortening the crude relative risk was reduced by 5% (HR 0.95; 95%CI 0.93-0.98) for all cause mortality, 7% (HR 0.93;

95%CI 0.89-0.98) for cardiac death and 7% (HR 0.93; 95%CI 0.86-1.00) for sudden death.

Adjustment for (other) cardiovascular risk factors lowered the hazard ratio estimates but, except for sudden death, the hazard ratios remained statistically significant. Subgroup analyses did not indicate that the risk was modified by gender and age (data not shown).

Discussion

Our study shows that left ventricular function, measured as the fractional shortening, is a strong predictor of all cause mortality, cardiac death and sudden death in the elderly population at large. This increased risk is only partly attributable to other cardiovascular risk indicators.

The overall response and completeness of follow-up of our study was high. Nevertheless, non-response and loss to follow-up may have led to an underestimation of the risks. Notably a lower response rate in diseased people with poorer prognoses could be of influence.

2823 participants of the Rotterdam study underwent echocardiography, e.g. 35% of the total population. This was largely due to the absence of echocardiographic facilities during certain periods, and is unlikely to have influenced our risk estimates. In addition, certain participants who did not undergo echocardiography when the device was available were not able to come to the research centre due to physical inability and comorbidity. This most likely led to underestimations of the risks.

Due to the size of our study population, left ventricular dysfunction was estimated by fractional shortening, rather than by determining the ejection fraction. In the absence of wall motion abnormalities fractional shortening can be assumed to reliably reflect left ventricular systolic function.[13] The cardiovascular risk profile of participants in whom the echocardiographic recordings were deemed inadequate was less beneficial than in those with available echocardiographic interpretations. The risks for all cause mortality, cardiac death and sudden death in this group was lower than the risks of the participants with an impaired left ventricular dysfunction, but higher than in participants with normal systolic function (data not shown). Thus, inability to measure the left ventricular function also seems of prognostic importance.

One could argue whether adjustment for cardiovascular risk indicators that are causally related to systolic dysfunction (such as hypertension and prior MI) is adequate.

However, although the risk estimates alternated after adjustment, the value of left ventricular systolic dysfunction in predicting cardiac mortality persisted.

Previous studies established the prognostic importance of an impaired systolic function in patients with severe heart failure, survivors of a myocardial infarction or patients with other cardiovascular risk factors.[16-18] These studies were all based on selected patient populations of, usually symptomatic, treated patients. To our knowledge this is the first study to assess the prognostic importance of left ventricular dysfunction the elderly population at large.

We conclude that left ventricular dysfunction is a strong and independent predictor of mortality in the elderly. Prevention and early detection and treatment of systolic dysfunction might lead to a significant reduction of mortality in the elderly.

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107-15.
3. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-10.
4. Kannel WB, Plehn JF, Cupples LA. Cardiac failure and sudden death in the Framingham Study. *Am Heart J* 1988;115:869-75.
5. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997;350:829-33.
6. Mosterd A, Hoes AW, de Bruijne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population. The Rotterdam Study. *Eur Heart J* 1999;20:447-55.
7. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
8. World Health Organization. Diabetes mellitus: report of a WHO study group. Geneva, Switzerland: World Health Organization, 1985.
9. de Bruyne MC, Mosterd A, Hoes AW, Kors JA, Kruijssen DA, van Bemmel JH, Hofman A, Grobbee DE. Prevalence, determinants, and misclassification of myocardial infarction in the elderly. *Epidemiology* 1997;8:495-500.
10. Rose G, Blackburn H, Gillum R, Prineas R. Cardiovascular survey methods. Geneva, Switzerland: World Health Organization, 1982.
11. van Gent CM, van der Voort HA, de Bruyn AM, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. *Clin Chim Acta* 1977;75:243-51.
12. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-83.
13. Quinones MA, Pickering E, Alexander JK. Percentage of shortening of the echocardiographic left ventricular dimension. Its use in determining ejection fraction and stroke volume. *Chest* 1978;74:59-65.
14. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992;85:I2-10.
15. Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. *Circulation* 1992;85:I11-8.
16. Aronow WS, Ahn C, Kronzon I, Nanna M. Prognosis of patients with heart failure and unoperated severe aortic valvular regurgitation and relation to ejection fraction. *Am J Cardiol* 1994;74:286-8.
17. Scrutinio D, Lagioia R, Ricci A, Clemente M, Boni L, Rizzon P. Prediction of mortality in mild to moderately symptomatic patients with left ventricular dysfunction. The role of the New York Heart Association classification, cardiopulmonary exercise testing, two-dimensional echocardiography and Holter monitoring. *Eur Heart J* 1994;15:1089-95.

18. Pernenkil R, Vinson JM, Shah AS, Beckham V, Wittenberg C, Rich MW. Course and prognosis in patients > or = 70 years of age with congestive heart failure and normal versus abnormal left ventricular ejection fraction. *Am J Cardiol* 1997;79:216-9.

Chapter 9

General discussion

Background

Heart failure is a multifactorial clinical syndrome for which no universally accepted definition exists.[1] Heart failure is attributable to systolic and/or diastolic cardiac dysfunction (i.e. inability to contract normally and expel sufficient blood (systolic failure) and/or inability to relax and fill normally (diastolic failure)). Although heart failure is a disabling and invalidating condition, which carries a very poor prognosis and requires frequent hospital (re)admissions, data on its epidemiology are relatively scarce.[1] In this thesis various epidemiologic aspects of heart failure in the population at large, such as diagnosis, risk factors, incidence and prognosis were discussed. Most chapters are based on studies performed as part of the Rotterdam Study, a prospective follow-up study among all inhabitants of 55 years and older, living in the suburb Ommoord of Rotterdam.[2] This final chapter will address the epidemiology of heart failure in view of our major findings, discuss the consequences of our findings for medical practice and will give suggestions for future research.

Occurrence

Estimates of the prevalence of asymptomatic and symptomatic left systolic ventricular dysfunction (i.e. heart failure) based on population-based studies using echocardiography were recently reported.[3-7] Although discrepancies between the studies exist, all studies indicate that the prevalence of left ventricular systolic dysfunction (LVSD) and heart failure is high and increases with age. Furthermore, the majority of persons with LVSD is asymptomatic.[4,5] No data on the occurrence of left ventricular diastolic dysfunction (LVDD) in the population at large are available.

To reliably assess the incidence of heart failure, each person with signs and symptoms suggestive of heart failure should undergo a complete comprehensive cardiovascular work-up. This approach was used in the Hillingdon Heart Failure Study and in chapter 4 by our own group.[8]

Our study yielded higher incidence estimates than those reported in the Hillingdon Heart Failure Study, but probably provides the most representative incidence estimates in the population at large. The Hillingdon Heart Failure Study identified all their cases from hospital admissions and from referrals to an outpatient heart failure clinic whereas we also identified the ones who where not admitted to the hospital or to the clinic. Furthermore, we tried to maximise sensitivity of case finding by training the GPs in the use of diagnostic screening tools. However, it should be emphasized that the

true incidence may even be somewhat higher in the population at large due to a higher non-response rates in unhealthy participants in the Rotterdam Study and also because we used a rather strict case definition.[9,10]

Our age and gender specific incidence estimates of heart failure can be useful in estimating the magnitude of the health impact of heart failure in the elderly and could aid in future planning. Furthermore, our estimates show that, the "typical" heart failure patient (men and women, older than 70 years, usually with comorbidity and not all referred to secondary health care) has largely been excluded from clinical trials.[11]

Diagnosis

The diagnosis of heart failure is difficult and represents a challenge to physicians, notably it's early stages. Correctly diagnosing heart failure is the basis of optimal clinical care for heart failure patients as it facilitates approaches to adequately treat and improve prognosis in these patients.

As there is no gold standard for the diagnosis of heart failure, there is considerable variation in the methods to its diagnosis. Often the diagnosis of heart failure is primarily based on signs and symptoms. The validity of the clinical diagnosis of patients with heart failure is poor, however, especially in a primary care.[12-14] The use of additional tests, preferably rapid, non-expensive and non-invasive, should be explored. For example, the additional diagnostic value of a test-treatment with furosemide, although recommended in two Dutch guidelines on management of heart failure, remains uncertain.[15,16] Since such a test treatment is often applied in medical practice, studies exploring its value are warranted.

Neurohormones have recently been put forward as a potential diagnostic tool. It is known that, in order to maintain circulatory homeostasis, complex neuroendocrine and haemodynamic mechanisms are activated to compensate the loss of cardiac function.[17] The neuroendocrine responses include activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone (RAAS) system and release of natriuretic and vasoactive peptides. The activation of the sympathetic nervous system (norepinephrine) was first discovered in 1962 and since 1984 it has been known that the prognosis in patients with heart failure is inversely related to norepinephrine levels.[18] The RAAS system is also activated and related to the prognosis in most patients with severe heart failure.[19] Because plasma concentrations of natriuretic peptides are increased in early stages of heart failure, circulating levels of natriuretic peptides may be sensitive diagnostic markers of heart failure.[20-23] The determination of

neurohormones used to be time consuming and expensive. Currently, rapid and relatively inexpensive (€ 23) assays for humoral measurements have become available, but these are still not widely used. Furthermore, it should be emphasized that measurement of neurohormones merely indicates the presence or absence of heart failure and provides no objective measurement of the cardiac function nor indicates the presence of treatable underlying causes of heart failure.We observed that neurohormones are of considerable diagnostic value when added to the findings of history and physical examination (chapter 6). Therefore, the results of our study suggests that (until echocardiography is easily and immediately available and affordable) measurement of natriuretic peptides provides a useful alternative in routine clinical (general) practice in patients suspected of heart failure. It may also be useful in deciding whether or not to opt for echocardiographic investigation.

In recent years Doppler echocardiographic has emerged as an important non-invasive tool to diagnose heart failure, also in a non-hospital setting.[22-25] According to the diagnostic of the Task Force on Heart Failure of the European Society of Cardiology objective evidence of cardiac dysfunction has to be present in addition to clinical symptoms to establish a diagnosis of heart failure.[26] Echocardiography is recommended as the key diagnostic tool to assess the presence of cardiac impairment. Therefore, ideally every patient suspected of heart failure should be screened by echocardiography to confirm the diagnosis. However, Doppler echocardiographic is not readily available for primary care physicians. Currently, in the Netherlands patients suspected of heart failure by the GP have to be referred to a cardiologist for echocardiographic investigation. This leads to a considerable time delay because of limited availability of rapid cardiologic consultation and also because of limited availability of echocardiographic resources. Furthermore, the patients referred frequently remain in secondary care for quite some time, often, unnecessarily, leading to higher costs.

If echocardiograpy is to be used in all heart failure patients a more rapid, easily available and inexpensive echocardiographic service is needed such as the open access echocardiography operating in some places in the UK.[24,25] There is, however, much debate on how this service should be delivered, as indicated by the number of comments and articles on the echocardiography in recent years.[24,25,27-39]

It is now been recognized that a proportion of the patients with heart failure have normal systolic function, especially the elderly. In these patients ventricular diastolic function is decreased. Diastolic dysfunction prevents the ventricles from being filled adequately at normal atrial pressure.[40] Until recently, no standardized method existed to diagnose left ventricular diastolic dysfunction. The European Study Group on Diastolic Heart Failure of the European Society of Cardiology has now proposed guidelines for

the diagnosis of diastolic heart failure in 1998.[41] Still criteria used in the guideline were based on highly selected patient groups. Application of these criteria in the general population needs further study. A better understanding of the nature and implications of diastolic dysfunction is to be expected in the near future.

Etiology

Risk factors for the development of heart failure in the population at large have been examined in the late eighties using relatively non-sensitive methods to establish the diagnosis of heart failure.[42-44] We used more objective measurements of cardiac function, enhancing the accuracy of the heart failure diagnosis and confirmed the role of several established risk factors for heart failure such as history of myocardial infarction, diabetes, hypertension, peripheral arterial disease and obesity. In addition, an electrocardiographic T axis abnormality was a strong risk factor of heart failure. Since abnormal T axis is a marker of ischaemic myocardial damage (i.e. abnormalities due to ischaemic changes), this again indicates that coronary artery disease clearly increases the risk of heart failure. By calculation of etiologic fractions (proportion of exposed cases * (RR-1)/RR * 100) one can estimate the proportion of disease that is attributable to risk factors. The proportion of heart failure that may be attributed to the strongest risk factors (history of myocardial infarction, diabetes, hypertension, peripheral arterial disease and electrocardiographic T axis abnormalities) is estimated to be as high as 70%.

Prognosis

Information on the prognosis of asymptomatic left ventricular systolic and diastolic dysfunction and of heart failure in unselected patients is limited.
To our knowledge our studies are amongst the first to show that the prognosis of persons with heart failure or with left ventricular systolic dysfunction in the population at large is poor. Several studies have demonstrated the prognostic benefits of treatment of symptomatic left ventricular dysfunction (i.e. heart failure).[45-50] Asymptomatic systolic left ventricular dysfunction is increasingly being recognized as an important precursor of heart failure; 30% of the participants in the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial with asymptomatic impaired systolic function developed symptoms within three years.[47] Theoretically, prevention and early detection and

treatment of asymptomatic systolic dysfunction might lead to a significant reduction in mortality.

Management

The development of heart failure can be delayed or prevented by a number of interventions that reduce the risk of developing left ventricular dysfunction and decrease it's progression. Interventions should be directed at modifiable risk factors of heart failure (i.e. coronary heart disease, hypertension, diabetes) and at limiting myocardial injury (i.e. thrombolytic therapy, PTCA, CABG). However, paradoxically, the success of treatment of acute coronary artery disease, valvular diseases and hypertension, creates a growing group of older people who are at risk of developing heart failure and a clear increase in the prevalence of heart failure.[51]

Treatment strategies in heart failure have changed markedly in recent decades, and the currently available treatment options have unequivocally been shown to reduce morbidity and mortality.[45,47,52] This, however, further contributes to the increasing prevalence of heart failure. Currently, improved diagnostic tools such Doppler echocardiography, ultrafast magnetic resonance imaging (MRI), electron-beam computed tomography (EBCT) scanning and neurohormones are available to diagnose heart failure and its precursor left ventricular dysfunction and the view that there are opportunities for preventive therapeutic interventions have fuelled discussions regarding the possibility of screening for heart failure and/or asymptomatic LVSD.

However, to justify screening for heart failure or asymptomatic left ventricular systolic function to be worthwhile, several criteria must be fulfilled as suggested by Wilson (table 1).[53] Currently, the most important criteria, such as knowledge on natural history, efficacy and the cost-effectiveness are still unknown. The natural history of asymptomatic left ventricular dysfunction is still not fully understood. Consequently, a detailed strategy (frequency of screening, at which age the screening be should initiated and who should be screened, e.g., all people or high risk subjects, how the echocardiographic service is to be organised and the number of echocardiographic facilities needed) cannot be developed. The efficacy of the drug treatment (i.e. ACE-inhibition) in asymptomatic LVSD has not been studied in the most relevant patient groups (men and women above the age of 70 years men and women, usually with comorbidity). Furthermore, the cost-effectiveness of detecting and treating asymptomatic LVSD is unknown. Therefore, research aimed at comparing the effect of screening and early treatment of asymptomatic LVSD to a strategy involving initiating

treatment when symptoms develop is needed. For screening for heart failure almost the same is true; there is no screening strategy and the cost-effectiveness of screening has not been evaluated.

In theory the prognosis of heart failure can be improved by early detection of and optimal treatment of heart failure. In the Netherlands, and in some other countries, most heart failure patients are diagnosed and treated by GPs.[13] As mentioned above, optimisation of detection of heart failure by GPs can be established by providing adequate resources for diagnosis, such as open-access echocardiography or neurohumoral measurements. Although there are several guidelines recommending the use of ACE inhibitors, these drugs are still under-utilized and prescribed in sub-optimal dosage, in both primary care and secondary care.[54-58] Implementation of recommendations in clinical practice is important. Furthermore, since heart failure is a disease of the elderly, clinical trials should also include the elderly heart failure patients, especially those managed in primary care. As heart failure progresses, hospital admission and readmission is almost inevitable. Presently, the number of hospital (re)admissions is high and rising, hospital admissions are expensive and that there is a decreased availability of hospital beds.[59] Non-compliance with management (such as with drug treatment and diet) is among the most important problems in patients with heart failure.[60] Several small studies evaluating the effect of non-pharmacological management programs, have been published recently and they suggest that a nurse-directed, multidisciplinary treatment strategy can improve quality of life and reduce hospital readmissions in patients with heart failure.[61-64] The benefit in terms of readmissions and quality of life of these studies should be evaluated further in larger studies.

Conclusions

Heart failure is a major health problem and its magnitude is expected to increase considerably in the near future. Current knowledge of heart failure and of asymptomatic left ventricular systolic function is increasing but much progress can be made in the diagnosis and management of the disease.

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
3. Morgan S, Smith H, Simpson I, Liddiard GS, Raphael H, Pickering RM, Mant D. Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. *BMJ* 1999;318:368-372.
4. Mosterd A, Hoes AW, de Bruijne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population. The Rotterdam Study. *Eur Heart J* 1999;20:447-55.
5. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997;350:829-33.
6. Gardin JM, Siscovick D, Anton-Culver H, Lynch JC, Smith VE, Klopfenstein HS, Bommer WJ, Fried L, O'Leary D, Manolio TA. Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly. The Cardiovascular Health Study. *Circulation* 1995;91:1739-48.
7. Lauer MS, Evans JC, Levy D. Prognostic implications of subclinical left ventricular dilatation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). *Am J Cardiol* 1992;70:1180-4.
8. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure: a population-based study. *Eur Heart J* 1999;20:421-8.
9. Herzog AR, Rodgers WL. Age and response rates to interview sample surveys. *J Gerontol* 1988;43:S200-5.
10. Kelsey JL, O'Brien LA, Grisso JA, Hoffman S. Issues in carrying out epidemiologic research in the elderly. *Am J Epidemiol* 1989;130:857-66.
11. Massie BM. 15 years of heart-failure trials: what have we learned? *Lancet* 1998;352:SI29-33.
12. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
13. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.
14. Cowie M, Struthers A, Wood D, Coats A, Thompson S, Poole-Wilson P, Sutton G. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
15. Anonymous. Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (CBO). Consensus hartfalen [In Dutch]. Utrecht: CBO, 1994.
16. Walma EP, Bakx HCA, Besselink RAM, Hamstra PWJ, Hendrick JMA, Kootte JHA, Veelen van AWC, Vink R, Geijer RMM. NHG standaard hartfalen [In Dutch]. *Huisarts en Wetenschap* 1995;38:471-87.
17. Packer M. Pathophysiology of chronic heart failure. *Lancet* 1992;340:88-92.
18. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819-23.

19. Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49:1659-66.
20. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, Kubo SH, Rudin-Toretsky E, Yusuf S. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation* 1990;82:1724-9.
21. Lerman A, Gibbons RJ, Rodeheffer RJ, Bailey KR, McKinley LJ, Heublein DM, Burnett J, Jr. Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left-ventricular dysfunction. *Lancet* 1993;341:1105-9.
22. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
23. McDonagh TA, Rodd SD, Murdoch DR, Morton J, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1997;351:9-13.
24. Francis CM, Caruana L, Kearney P, Love M, Sutherland GR, Starkey IR, Shaw TR, McMurray JJ. Open access echocardiography in management of heart failure in the community. *BMJ* 1995;310:634-6.
25. Murphy JJ, Frain JP, Ramesh P, Siddiqui RN, Bossingham CM. Open-access echocardiography to general practitioners for suspected heart failure. *Br J Gen Pract* 1996;46:475-6.
26. The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741-51.
27. Colquhoun MC, Waine C, Monaghan MJ, Struthers AD, Mills PG. Investigation in general practice of patients with suspected heart failure. How should the essential echocardiographic service be delivered?. *Br Heart J* 1995;74:335-6.
28. Murphy JJ, Bossingham CM. Open access echocardiography. General practitioners use echocardiography approximately. *BMJ* 1995;311:325.
29. Willenheimer RB, Israelsson BA, Cline CM, Erhardt LR. Simplified echocardiography in the diagnosis of heart failure. *Scand Cardiovasc J* 1997;31:9-16.
30. Inglesfield JW. Open-access echocardiography. *Lancet* 1996;348:1386-7; discussion 1387-8.
31. Rimington H, Adam G, Chambers J. Open-access echocardiography. *Lancet* 1996; 348: 555-6.
32. Davie A, McMurray J. Open-access echocardiography. *Lancet* 1996;348:1387-8.
33. Wong PS, Doshi S. Open access echocardiography. Service is valuable for evaluating murmurs too. *BMJ* 1995;311:326.
34. Zarifis J, Beevers DG, Lip GY. Open access echocardiography. Hospital patients need open access echocardiography. *BMJ* 1995;311:326.
35. O'Toole L, Oates A, Channer KS. Open access echocardiography. Open access to specialist opinion is preferable. *BMJ* 1995;311:326; discussion 327-8.
36. Wallace M, Levy M. Open access echocardiography. Study's conclusion is misleading and cannot be generalised. *BMJ* 1995;311:326-7; discussion 327-8.
37. Slovick DI. Open access echocardiography. Service should be reserved for equivocal cases. *BMJ* 1995;311:327; discussion 327-8.

38. MacFadyen RJ, MacDonald TM, Clarkson P, Wheeldon NM. Open access echocardiography. Single assessment may be dangerous. *BMJ* 1995;311:327; discussion 327-8.
39. Kirby PJ, Strang JR. Open access echocardiography. Study's design leaves cost effectiveness and "therapeutic impact" in doubt. *BMJ* 1995;311:327; discussion 327-8.
40. Wheeldon NM, Clarkson P, MacDonald TM. Diastolic heart failure. *Eur Heart J* 1994;15:1689-97.
41. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998;19:990-1003.
42. Eriksson H, Svardsudd K, Larsson B, Ohlson LO, Tibblin G, Welin L, Wilhelmsen L. Risk factors for heart failure in the general population: the study of men born in 1913. *Eur Heart J* 1989;10:647-56.
43. Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. *Br Heart J* 1994;72:S3-9.
44. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;22:6A-13A.
45. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
46. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
47. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
48. Anonymous. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol* 1996;78:902-7.
49. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184-91.
50. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669-77.
51. Yusuf S, Thom T, Abbott RD. Changes in hypertension treatment and in congestive heart failure mortality in the United States. *Hypertension* 1989;13:I74-9.
52. Carson P, Johnson G, Fletcher R, Cohn J. Mild systolic dysfunction in heart failure (left ventricular ejection fraction >35%): baseline characteristics, prognosis and response to therapy in the Vasodilator in Heart Failure Trials (V-HeFT). *J Am Coll Cardiol* 1996;27:642-9.
53. Wilson JMG. Screening criteria. London: OHE, 1965.
54. Parameshwar J, Shackell MM, Richardson A, Poole-Wilson PA, Sutton GC. Prevalence of heart failure in three general practices in north west London. *Br J Gen Pract* 1992;42:287-9.

55. Clarke KW, Gray D, Hampton JR. Evidence of inadequate investigation and treatment of patients with heart failure. *Br Heart J* 1994;71:584-7.
56. Mair FS, Crowley TS, Bundred PE. Prevalence, aetiology and management of heart failure in general practice. *Br J Gen Pract* 1996;46:77-9.
57. Hillis GS, Trent RJ, Winton P, MacLeod AM, Jennings KP. Angiotensin-converting-enzyme inhibitors in the management of cardiac failure: are we ignoring the evidence? *Qjm* 1996;89:145-50.
58. Hillis GS, Al-Mohammad A, Wood M, Jennings KP. Changing patterns of investigation and treatment of cardiac failure in hospital. *Heart* 1996;76:427-9.
59. Reitsma JB, Mosterd A, de Craen AJ, Koster RW, van Capelle FJ, Grobbee DE, Tijssen JG. Increase in hospital admission rates for heart failure in The Netherlands, 1980-1993. *Heart* 1996;76:388-92.
60. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Avorn J. Noncompliance with congestive heart failure therapy in the elderly. *Arch Intern Med* 1994;154:433-7.
61. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995;333:1190-5.
62. Kornowski R, Zeeli D, Averbuch M, Finkelstein A, Schwartz D, Moshkovitz M, Weinreb B, Hershkovitz R, Eyal D, Miller M, et al. Intensive home-care surveillance prevents hospitalization and improves morbidity rates among elderly patients with severe congestive heart failure. *Am Heart J* 1995;129:762-6.
63. Fonarow GC, Stevenson LW, Walden JA, Livingston NA, Steimle AE, Hamilton MA, Moriguchi J, Tillisch JH, Woo MA. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. *J Am Coll Cardiol* 1997;30:725-32.
64. West JA, Miller NH, Parker KM, Senneca D, Ghandour G, Clark M, Greenwald G, Heller RS, Fowler MB, DeBusk RF. A comprehensive management system for heart failure improves clinical outcomes and reduces medical resource utilization. *Am J Cardiol* 1997;79:58-63.

Chapter 10

Summary

Summary

Heart failure is one of the commonest cardiovascular disorders in Western Society, especially in the elderly, and is still a growing major public health problem due to the expected increase in the number of elderly. Despite the fact that heart failure and its precursor left ventricular systolic dysfunction are increasingly being recognised as important causes for morbidity and mortality, epidemiologic data are scarce. In this thesis, various epidemiologic aspects of heart failure and its precursor left ventricular systolic function are described.

Chapter 2 presents an overview on the current epidemiological knowledge about asymptomatic left ventricular systolic function in the population at large, based on literature data. An important reason for the lack of epidemiologic data is that echocardiography, currently recommended as the diagnostic tool to assess the left ventricular systolic function (LVSD), has only recently been used in population-based studies. LVSD is common, more frequent with age and is higher in men than in women. About half of the LVSD patients are asymptomatic. Data on incidence, etiology, prognosis and management of LVSD is scarce and urgently needed.

The diagnosis of heart failure is difficult, especially in primary care. A heart failure score might be a useful screening test to identify possible heart failure cases. In **chapter 3** the interobserver variation among general practitioners in the use of a scoring system to detect possible heart failure is studied. Five GPs and one cardiologist were asked to examine 15 patients and fill in a heart failure score. Intraclass correlation coefficients were calculated to determine the reproducibility of the score. The interobserver agreement on the presence of heart failure and on signs and symptoms of heart failure was low and agreement on referral was good and correct. We concluded that when the aim is referral of those with possible heart failure a heart failure score appears to be a useful tool.

In **chapter 4** the incidence and management of heart failure in general practice in the Netherlands is described. We used data from the Dutch National Survey of Morbidity and Interventions in General Practice (NIVEL) carried out in 1987 and 1988 and data of the Rotterdam General Practitioners Project (ROHAPRO)-database from 1991-1997. In 1987-88 the overall incidence rate of heart failure in those aged 55 years or over was 11.3 per 1000 person years (95% CI 9.8-12.9). The incidence rate increased from 2.7 per 1000 person years in men aged 55-64 to 27.8 per 1000 person years in men

aged >75 years and for women in the same age-categories from 1.7 per 1000 person years to 33.3 per 1000 person years, respectively. Of the 210 incident cases of heart failure, 45 (21%) were referred to a specialist. In 1987-1988 drugs were prescribed by the GP in 162 of the incident cases (77%); 90 patients received a loop diuretic, 48 another diuretic while only seven patients received an ACE-inhibitor. In 86% of patients diagnosed with heart failure from 1991 till 1997, medication was prescribed; notably a diuretic (93%), ACE-inhibitors (51%) and digoxin (40%). About half was referred to a cardiologist. We conclude that the incidence rate of heart failure in general practice is high in both men and women and clearly increases with age. In contrast to most current clinical guidelines only a minority of the heart failure patients was referred to a specialist and many patients with heart failure do not receive ACE-inhibition.

In **chapter 5** the incidence of heart failure and the risk factors for heart failure in an elderly general population sample were studied. During 23 months of follow-up, all new cases of heart failure were identified among 5281 participants of the Rotterdam Study. Three methods to detect possible cases were used; diagnostic work-up at a rapid-access clinic of possible heart failure cases referred by GPs, computerised GP registries, and pharmacy data. The diagnostic work-up included echocardiography, exercise testing and neurohumoral measurements. Of all possible cases additional data were collected from the patients' medical records. A panel of a cardiologist, internist, general practitioner and clinical epidemiologist reviewed all collected data to classify the cases. Cox' proportional hazards regression analysis was used to identify potential risk factors for heart failure. The overall incidence was 13.2 per 1000 patient years (95% CI 11.6-20). The incidence rate increased from 2.1 per 1000 person-years in those aged 55-64 to 43.4 in those aged 85 years and over. Increased age, male gender, higher body mass index, history of myocardial infarction, diabetes, hypertension, peripheral arterial disease, electrocardiographic T axis abnormalities and higher fibrinogen levels appeared to be independent risk factors for heart failure. Thus the incidence of heart failure in the elderly is high and exponentially increases with age. Insight in risk factors enables targeted preventive strategies.

As mentioned above the diagnosis of heart failure is difficult, particularly in general practice where the diagnosis is primarily based on signs and symptoms. Additional diagnostic tests (including measurement of neurohormones) might improve the accuracy of the diagnosis of heart failure in the absence of echocardiography. In **chapter 6** we evaluated and compared the performance of different diagnostic strategies in primary care patients suspected of heart failure. 149 patients in whom the GP

suspected heart failure were referred to a research centre for a diagnostic work-up. The work-up consisted of history taking, physical examination, ECG, chest X-ray, echocardiography and measurement of neurohormones. An expert panel reviewed all data and decided on the presence or absence of heart failure. Multivariate logistic regression analyses were used to construct diagnostic models. To compare the diagnostic performance of the different diagnostic strategies we used ROC areas and subsequently the positive and negative predictive values of the models were compared. The diagnostic model including history variables only yielded a ROC area of 0.75. The consecutive addition of physical examination, chest X-ray and ECG increased the ROC area to 0.78, 0.84 and 0.90, respectively. The model with history, physical examination and ECG had a ROC area of 0.89. Addition of the chest X-ray findings yielded a higher ROC area but the predictive values did not improve. Neurohormones further increased the ROC areas. Compared to the history, physical examination and ECG model the models containing one of the studied neurohormones and history and physical examination alone produced similar ROC areas. In addition, the history, physical examination and ANP model classified the patients better than the history, physical examination and ECG model. The data suggest that neurohormone levels can improve diagnostic accuracy in patients suspected of heart failure.

Chapter 7 describes a study on the prognosis of heart failure in the general population. In 5255 Rotterdam Study participants (age 68.9 ± 8.6 years, 3113 women) the presence of heart failure was determined and baseline variables were obtained at the first examination taking place from 1990 to 1993. Information on vital status, fatal and non-fatal endpoints was obtained from the municipal health authorities, general practitioners and hospital records. 181 participants (age 77.3 ± 7.9 years, 109 women) had heart failure. Of these 85 (47%) persons died during the 4.8 – 8.5 (mean 6.1) years of follow-up. One, two and five years' survival was 89%, 79%, and 59%, representing an age-adjusted mortality twice (hazard ratio 2.1, 95% CI 1.8-2.7) that of persons without heart failure. The hazard ratio for sudden death was even more pronounced: 4.8, (95% CI 2.6-8.7). Heart failure generally afflicts older persons in the community and carries a poor prognosis. Having heart failure confers a fivefold increase in the risk of sudden death.

In **chapter 8** we investigated the prognostic value of left ventricular systolic dysfunction in the population at large. 2823 echocardiograms were available in the population-based Rotterdam Study, among men and women aged 55 years and older. Fractional shortening (FS) was determined in 2270 and used as an index for systolic

function. Follow-up data was available for 86%. The association between systolic dysfunction (FS <25%) and all cause mortality, cardiac death and sudden death was examined using Cox' proportional hazards model. During a mean follow-up period of 3 years (maximum 6 years), 85 (4.3%) participants died; 24 (1.2%) died from a cardiac cause and 10 (0.5%) died suddenly. Subjects with an impaired ventricular systolic function had a crude increased relative risk (hazard ratios) of 3.3 (95%CI 1.6-6.9) for all cause mortality, 6.3 (95%CI 2.2-18.6) for cardiac death and 8.1 (95%CI 1.7-38.5) for sudden death. Adjustment for (other) cardiovascular risk factors reduced the risk estimates but these remained statistically significant, except for sudden death. Analyses using fractional shortening as a continuous variable showed that with each percentage increase in fractional shortening risks of cardiac death reduced by approximately 7% (95%CI 2-11). Left ventricular systolic dysfunction is a strong independent predictor of mortality in the general population.

Finally, in **chapter 9**, the general discussion the implications of the studies described in this thesis are discussed and recommendations for future research are given.

Chapter 11

Samenvatting

Samenvatting

Hartfalen is, met name bij ouderen, een van de meest voorkomende hart- en vaatziekten in de westerse landen en zal, met name door de veroudering van de bevolking een steeds belangrijker volksgezondheidsprobleem worden. Ondanks het feit dat hartfalen en systolische linker ventrikel disfunctie (de voorloper van hartfalen) steeds vaker erkend worden als belangrijke oorzaken van morbiditeit (ziekte) en mortaliteit (sterfte), zijn epidemiologische gegevens schaars. In dit proefschrift worden verschillende epidemiologische aspecten van hartfalen en systolische linker ventrikel disfunctie beschreven.

In **hoofdstuk 2** wordt een overzicht gegeven van de huidige epidemiologische kennis op het gebied van asymptomatische systolische linker ventrikel disfunctie in de algemene populatie, aan de hand van een literatuuroverzicht. Tot voorkort waren weinig epidemiologische gegevens beschikbaar. Een belangrijke oorzaak voor het ontbreken van epidemiologische gegevens is het feit dat de echocardiografie, die momenteel beschouwd wordt als de standaard om systolische linker ventrikel disfunctie te diagnosticeren, pas recent toegepast wordt bij bevolkingsonderzoek. Uit deze onderzoekingen blijkt dat systolische linker ventrikel disfunctie frequent voorkomt, dat de prevalentie stijgt met het toenemen van de leeftijd en hoger is bij mannen dan bij vrouwen. Ongeveer de helft van de patiënten met systolische linker ventrikel disfunctie heeft geen klachten passend bij hartfalen. Additionele epidemiologische gegevens over de incidentie, de etiologie, de prognose en het beleid bij systolische linker ventrikel disfunctie zijn nodig.

Het stellen van de diagnose hartfalen is niet eenvoudig, met name in de eerste lijn. Een hartfalen scorelijst zou een nuttig hulpmiddel kunnen zijn om mogelijk hartfalen op te sporen. In **hoofdstuk 3** wordt een onderzoek naar de onderlinge overeenstemming van huisartsen bij het gebruik van een hartfalen scorelijst beschreven. Vijf huisartsen en een cardioloog werd gevraagd 15 patiënten te onderzoeken en een hartfalen scorelijst in te vullen. Intra class correlatie coëfficiënten werden berekend om de reproduceerbaarheid van de score te bepalen. Hieruit bleek dat de "tussen persoon" overeenstemming over de aanwezigheid van hartfalen en de bevindingen bij anamnese en lichamelijk onderzoek laag was. De "tussen persoon" overeenstemming over het wel of niet verwijzen van een van hartfalen verdachte patiënt daarentegen was goed. Een scorelijst met als doel de selectie voor het verwijzen van mogelijke hartfalen patiënten te ondersteunen lijkt dus een nuttig hulpmiddel te zijn.

In **hoofdstuk 4** wordt de incidentie en het beleid van hartfalen in de huisartsenpraktijk beschreven. Wij maakten daarbij gebruik van gegevens van de Nationale Studie naar ziekten en verrichtingen in de huisartsenpraktijk (NIVEL) uitgevoerd tussen 1987 en 1988 en van gegevens van het Rotterdams Huisartsen Project (ROHAPRO) verzameld tussen 1991 en 1997. In 1987-88 was de incidentie van hartfalen bij personen van 55 jaar en ouder 11,3 per 1000 persoonsjaren (pj) (95% betrouwbaarheidsinterval (BI) 9,8-12,9). De incidentie nam toe van 2,7 per 1000 pj bij mannen in de leeftijd van 55-64 jaar tot 27,8 per 1000 pj bij mannen van 75 jaar en ouder en bij vrouwen in dezelfde leeftijdscategorieën van 1,7 per 1000 pj tot respectievelijk 33,3 per 1000 pj. Van de 210 incidente gevallen van hartfalen werden er 45 (21%) verwezen naar een specialist. In 1987-1988 werd bij 162 (77%) patiënten een medicijn voorgeschreven: 90 kregen een lis-diureticum, 48 een ander diureticum en maar 7 patiënten kregen een ACE-remmer. In de periode tussen 1991 en 1997 werd bij 86% van de hartfalen patiënten medicatie voorgeschreven, dit betrof diuretica (93%), ACE-remmers (51%) en digoxine (40%). Ongeveer de helft van de hartfalen patiënten was ooit verwezen naar een cardioloog. Deze resultaten laten zien dat de incidentie van hartfalen in de huisartsenpraktijk hoog is bij zowel mannen als vrouwen en stijgt met het toenemen van de leeftijd. In tegenstelling tot de meeste beschikbare richtlijnen over hartfalen, wordt een minderheid van de hartfalen patiënten verwezen wordt naar een specialist en wordt bij veel hartfalen patiënten geen ACE-remmer voorgeschreven.

In **hoofdstuk 5** wordt een onderzoek naar de incidentie en de risicofactoren van hartfalen in de algemene bevolking beschreven. Gedurende een follow-up periode van 23 maanden werden 5281 deelnemers van het Erasmus Rotterdam, Gezondheid en Ouderen (ERGO) onderzoek gevolgd om alle nieuwe gevallen van hartfalen op te speren. Er werden 3 methoden gebruikt om mogelijke nieuwe gevallen van hartfalen op te sporen: een snel toegankelijke diagnostische hartfalen polikliniek waarnaar huisartsen potentiële hartfalen patiënten konden verwijzen, gegevens uit een geautomatiseerd huisartsen informatiesysteem en informatie uit een geautomatiseerd apothekersbestand. Het diagnostisch onderzoek op de diagnostische polikliniek bestond onder andere uit echocardiografie, inspanningstesten en het meten van de neurohumorale parameters in het bloed. Verder werd van alle mogelijke incidente patiënten additionele informatie uit de medische status bij de huisarts verkregen. Aan de hand van alle verzamelde gegevens bepaalde een panel (bestaande uit een cardioloog, een internist, een huisarts en een klinisch epidemioloog) of er wel of niet sprake was van incident hartfalen. Cox' proportional hazard regressie analyses werden gebruikt om risicofactoren voor hartfalen op te sporen. De incidentie van hartfalen was 13,2 per 1000 pj (95% BI 11,6-20,0). De

incidentie nam toe van 2,1 per 1000 pj bij patiënten in de leeftijd van 55-64 jaren tot 43,4 per 1000 pj bij patiënten van 85 jaar en ouder. Dit laat zien dat de incidentie van hartfalen bij ouderen hoog is en exponentieel stijgt met het toenemen van de leeftijd. Onafhankelijk risicofactoren voor het optreden voor hartfalen waren oudere leeftijd, mannelijk geslacht, obesitas, een myocard infarct in de voorgeschiedenis, diabetes mellitus, hypertensie, perifeer arterieel vaatlijden, abnormale T-as op het electrocardiogram en hogere serum fibrinogeen concentraties. Verder inzicht in de rol van risicofactoren bij het ontstaan van hartfalen kan gebruikt worden bij de ontwikkeling van maatregelen ter voorkoming van hartfalen.

Zoals hierboven reeds vermeld, is hartfalen moeilijk te diagnosticeren, met name in de huisartsenpraktijk. De huisarts stelt zijn diagnose hartfalen met name op grond van de bevindingen bij anamnese en lichamelijk onderzoek. Aanvullend onderzoek (onder andere het meten van de neurohormoon concentraties in het bloed) zou indien echocardiografie niet beschikbaar is de betrouwbaarheid van de diagnose hartfalen kunnen verbeteren. In **hoofdstuk 6** wordt de nauwkeurigheid van verschillende diagnostische strategieën zoals die toegepast zouden kunnen worden in de huisartsenpraktijk bij patiënten verdacht van hartfalen vergeleken. Door huisartsen werden 149 patiënten met de verdenking hartfalen doorgestuurd naar onze hartfalenpolikliniek voor verdere diagnostiek. De diagnostiek bestond uit anamnese, lichamelijk onderzoek, elektrocardiogram, thoraxfoto, echocardiogram en het meten van de neurohormonen. Een expert panel bekeek alle informatie en besliste of hartfalen wel of niet aanwezig was. Multivariabele regressie analyses werden gebruikt om diagnostische modellen te maken. Voor het vergelijken van de nauwkeurigheid van de verschillende diagnostische modellen gebruikten we Receiver Operating Characteristics (ROC) curven en de positieve en negatieve voorspellende waarde van de modellen vergeleken. Het model met alleen de anamnese variabelen had een oppervlakte onder de ROC curve van 0,75. Het achtereenvolgens toevoegen van lichamelijk onderzoek-, thoraxfoto- en ECG variabelen verhoogde de oppervlakten onder de ROC curven naar respectievelijk 0,78, 0,84 en 0,90. Het model met anamnese-, lichamelijk onderzoek- en ECG variabelen had een oppervlakte onder de ROC curve van 0,89. Het toevoegen van de thoraxfoto variabelen vergrootte de oppervlakte onder de ROC curve weliswaar enigszins, maar de positieve en negatieve voorspellende waarde van het diagnostische model verbeterde niet. Toevoeging van neurohormonen vergrootte de oppervlakte onder de ROC curve verder. In vergelijking met een diagnostisch model met anamnese-, lichamelijk onderzoek- en ECG variabelen had een model met anamnese-, lichamelijk onderzoek variabelen en een van de neurohormonen een vergelijkbare oppervlakte

onder de ROC curve. Het model met anamnese, lichamelijk onderzoek en het neurohormoon ANP classificeerde de patiënten beter dan het model met anamnese-, lichamelijk onderzoek- en ECG variabelen. Uit onze gegevens kan worden afgeleid dat het bepalen van neurohormonen de accuratesse van de diagnostiek van patiënten verdacht van hartfalen kan verbeteren.

In **hoofdstuk 7** wordt de prognose van hartfalen in de algemene bevolking onderzocht. Bij 5255 deelnemers van het ERGO onderzoek (gemiddelde leeftijd 68,9 ± 8,6 jaar, 3133 vrouwen) werden tijdens de eerste onderzoeksronde van ERGO (1990-1993) verschillende variabelen gemeten en de aanwezigheid van hartfalen vastgesteld. Uit gegevens van de gemeente, de huisartsendossiers en brieven afkomstig van specialisten, werd informatie verkregen over het eventuele overlijden van de deelnemer en het optreden van hart- en vaatziekten. Bij het eerste ERGO bezoek hadden 181 deelnemers (gemiddelde leeftijd 77,3 ± 7,9 jaar, 109 vrouwen) hartfalen. Hiervan overleden er 85 (47%) gedurende de follow-up periode. De 1-, 2- en 5 jaars overleving waren respectievelijk 89%, 79% en 59%, overeenkomend met een twee maal zo groot risico (gecorrigeerd voor leeftijd) op sterfte (hazard ratio HR 2,1: 95% BI 1,8-2,7) ten opzichte van deelnemers zonder hartfalen. Het risico te overlijden aan een plotselinge hartdood was nog hoger: ruim 4,8 (95% BI 2,6-8,7) keer zo hoog. Deze resultaten illustreren dat hartfalen optreedt op hogere leeftijd en een slechte prognose heeft.

In **hoofdstuk 8** wordt de prognostische waarde van systolische linker ventrikel disfunctie in de algemene bevolking beschreven. Cardiale echografieën waren beschikbaar van 2823 ERGO-deelnemers van 55 jaar en ouder. Fractional shortening (FS) werd gebruikt als maat voor de systolische functie en deze kon worden bepaald bij 2270 deelnemers. Complete follow-up gegevens waren beschikbaar van 86% van deze deelnemers. De relatie tussen systolische disfunctie (FS<25%) en sterfte (ongeacht de oorzaak), sterfte ten gevolge van cardiale oorzaken en plotselinge dood werd bestudeerd met behulp van Cox' proportional hazards modellen. Gedurende een gemiddelde follow-up periode van 3 jaar (maximaal 6 jaar) overleden 85 deelnemers (4.3%), 24 ten gevolge van cardiale aandoeningen en bij 10 was er sprake van een plotselinge hartdood. Deelnemers met een verminderde linker ventrikel functie hadden (ongecorrigeerd) een 3,3 (95% BI 1,6-6,9) maal verhoogd risico op sterfte, een 6,3 (95%BI 2,2-18,6) maal verhoogd risico op cardiale sterfte en een 8,1 (95%BI 1,7-35,5) maal verhoogd risico op plotselinge dood. Correctie voor (andere) cardiovasculaire risicofactoren verkleinde deze relatieve risico's maar deze bleven statistisch significant verhoogd, behalve het risico op plotselinge dood. Analyses met fractional shortening als

continue variabele lieten zien dat met iedere procent stijging van de fractional shortening het risico van sterfte afneemt met ongeveer 7 %. Hieruit blijkt dat de systolische linker ventrikel disfunctie een sterke en onafhankelijke risico-indicator is voor sterfte in de algemene bevolking.

Tenslotte worden in **hoofdstuk 9** worden de resultaten van de verschillende in het proefschrift beschreven onderzoekingen bediscussieerd en worden aanbevelingen voor toekomstig onderzoek gegeven.

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Curriculum Vitae

Ben Cost was born on November 21, 1964 in The Hague, The Netherlands. He attended secondary school at the 'Anne-Frank MAVO' and thereafter at the Sint-Jans College (HAVO,VWO) in The Hague. Subsequently, he studied physics for a year at the University of Leiden. In 1986, he started his medical studies, also in Leiden, and he obtained his medical degree in 1993. During his study, he did research on the analysis of plasma lipoproteins by fast protein liquid chromatography at the TNO-IVVO, Gaubius location and at the department of Internal Medicine of the University Hospital Leiden (under the supervision of Prof. dr. ir. L.M. Havekes and Dr. A.H.M. Smelt). From 1993 till 1995 he worked as a resident in Internal Medicine at the Leyenburg Hospital in The Hague (head: Dr. J.C.M. van der Vijver). In 1995, he started to work on this thesis at the department of General Practice (head: Prof. dr. A. Prins, in 1997 succeeded by Prof. dr. S. Thomas) and at the Department of Epidemiology & Biostatistics (head: Prof. dr. A. Hofman) of the Erasmus University Medical School. In 1998 he obtained a Master of Science degree in Clinical Epidemiology. Presently, he is working as a resident at the department of Internal Medicine I (head: Prof. dr. M.A.D.H. Schalekamp), University Hospital 'Dijkzigt' Rotterdam.