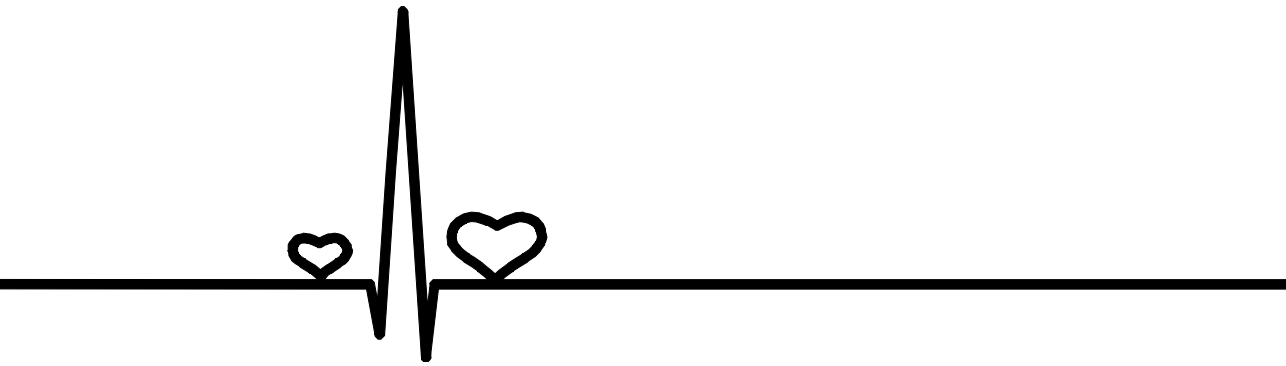
HEART FAILURE IN GERIATRIC OUTPATIENTS

Diagnosis, prognosis and treatment

Irène Oudejans



Heart failure in geriatric outpatients. Diagnosis, prognosis and treatment.
Thesis Utrecht University, The Netherlands. With a summary in Dutch.

ISBN 978-90-76525-00-6
Author Irène Oudejans
Cover, Layout Luuk Oudejans
Uitgeverij APPR bv, Naarden

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Hartfalen in geriatrische patiënten

Diagnose, prognose en behandeling
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
donderdag 10 mei 2012 des ochtends te 10.30 uur
door
Irène Oudejans-Mooijaart
geboren op 5 juli 1969 te Zaandam

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The author gratefully acknowledges financial support for publication of this thesis by the ‘Stichting Vrienden van het Hart, Zuid-oost Brabant’, the ‘Stichting Wetenschappelijk Onderzoek Hart- en Vaatziekten Amersfoort’ and the Elkerliek Hospital, Helmond.
Additional support was received from Roche Diagnostics Nederland BV, Almere.

Voor Luuk

Contents

Chapter 1

General introduction

Background

The ageing of the population and improved survival following acute cardiac events leads to an increased prevalence of heart failure, especially in the elderly (roughly defined as those aged 75 years or older).[1-3] Nevertheless current heart failure research is largely ignoring elderly persons. The typical participant of large clinical trials in heart failure is a man in his mid sixties with prior coronary artery disease, rather than an elderly woman with a history of hypertension, diabetes and/or chronic obstructive pulmonary disease.[4]

Accurate recognition of heart failure is important since appropriate management improves prognosis, also in elderly patients.[5] Unfortunately, diagnosing heart failure in elderly patients suspected of new, slow onset heart failure, who often first present themselves to geriatricians or general practitioners, rather than to cardiologists, is notoriously difficult.[4] In these patients, a wide range of (both cardiovascular and non-cardiovascular) comorbidity in combination with limited access to echocardiography,[6-8] often leads to an assessment of the presence or absence of heart failure merely based on symptoms and signs, which frequently results in an incorrect diagnosis.[9-11] The management of elderly patients with heart failure is lacking a solid scientific base,[12] and is complicated by multiple comorbidity, that also influences prognosis.

Echocardiography is considered the most important diagnostic test in the evaluation of patients suspected of heart failure, as it confirms the diagnosis of heart failure, and helps to ascertain the cause of heart failure.[13] Unfortunately, echocardiography is the exception rather than the rule, in the evaluation of (elderly) patients suspected of new, slow onset heart failure by physicians other than cardiologists.[4,13,14] The introduction of natriuretic peptides has revolutionized the assessment of heart failure, also in settings with limited access to echocardiography.[9,13] Although serum levels of natriuretic peptides rise with age, cut-off values to rule out the presence of heart failure are not available for elderly patients suspected of new, slow onset heart failure.[15,16] Apart from diagnostic tests, clinicians can be supported by diagnostic algorithms and rules in the evaluation of patients suspected of heart failure but none of these have been derived in geriatric patients, nor have they been validated in these patients.[17,18] Also, information on the prognosis of elderly patients diagnosed with slow onset heart failure is scarce and the impact of concomitant diseases on prognosis is poorly quantified.[1,19] The aim of the studies presented in this thesis is to fill several of the knowledge gaps in elderly (suspected) heart failure patients mentioned above.

Purpose and outline of the thesis

The focus of this thesis is on heart failure in elderly patients. We set out to study diagnosis, prognosis and impact of both cardiovascular and non-cardiovascular comorbidity in geriatric outpatients suspected of new, slow onset heart failure. In **chapter 2** we describe the proportion of geriatric patients suspected of having heart failure in whom the presence or absence of heart failure is correctly diagnosed by geriatricians and general practitioners based on diagnostic tests readily available in daily practice, such as symptoms and signs, electrocardiography, chest X-ray and N-terminal pro B-type Natriuretic Peptide. In **chapter 3** the applicability of current diagnostic algorithms is evaluated in geriatric patients suspected of new, slow onset heart failure. In **chapter 4** we validate the currently available diagnostic rules for suspected heart failure to geriatric patients. In **chapter 5** the value of symptoms, signs and additional tests in diagnosing heart failure in geriatric patients suspected of new, slow onset heart failure is determined. This includes the derivation of a diagnostic rule based on symptoms, signs and readily available tests (e.g. natriuretic peptides), to predict the probability of the presence or absence of heart failure in an individual patient suspected of heart failure. As geriatric patients have a wide range of comorbidity, we evaluate the impact of comorbidity (assessed by the Charlson Comorbidity Index) on three-year mortality of geriatric patients with newly diagnosed, slow onset heart failure in **chapter 6**. The potential of Galectin-3, a novel biomarker, in the diagnosis of heart failure and to determine the three-year mortality in geriatric patients with heart failure, is studied in **chapter 7**. In **chapter 8** we determine the representation of elderly patients in clinical trials that have evaluated the effect of the drug therapies that constitute the cornerstone of heart failure treatment. Finally, the implications of the studies presented in this thesis are discussed and recommendations for future research are provided (**chapter 9)**.

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Chapter 2

Diagnosing heart failure without echocardiography: how often are general practitioners and geriatricians correct?

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submitted

Abstract

Aim

Diagnosing heart failure in general practice and geriatric out-patient clinics is difficult due to comorbidity and limited access to echocardiography. We determined the ability of general practitioners (GPs) and geriatricians to establish heart failure in elderly outpatients using diagnostics readily available in daily practice (e.g. symptoms, signs, electrocardiography and natriuretic peptides).

Setting

Two expert panels of three GPs and three geriatricians respectively, in the Netherlands.

Methods

The expert panels established the presence or absence of heart failure based on all available diagnostic information, except echocardiography, in 90 elderly outpatients (age 81.7 ± 5.6 years, 71% female) suspected of new, slow onset heart failure. The assessment of an expert panel (provided with echocardiography and follow-up information) was used as the reference standard.

Results

Forty two (47%) patients had heart failure according to the expert panel. The GPs considered heart failure present in 25 (28%) patients, heart failure absent in 33 (37%) patients and possible in the remaining 32 patients (36%). The prevalence of heart failure in these groups was 96%, 6% and 50%, respectively, and three patients were diagnosed incorrectly. The geriatricians considered heart failure present in 33 (37%) patients, heart failure absent in 31 (34%) patients and possible in 26 (29%) patients, the prevalence of heart failure being 85%, 0% and 54%, respectively; incorrectly diagnosing five.

Conclusions

Using readily available diagnostics GPs and geriatricians can establish the presence or absence of heart failure in two thirds of elderly patients suspected of new, slow onset heart failure, incorrectly diagnosing only a few patients. Echocardiography to confirm or exclude heart failure can be targeted at those in whom the diagnosis is uncertain.

Introduction

The ageing of the population and improved survival following acute cardiac events leads to an increased prevalence of heart failure, especially in the elderly.[1,2] Recognition of heart failure is important since appropriate management improves prognosis, also in elderly patients.[3] Unfortunately, diagnosing heart failure in elderly patients suspected of new, slow onset heart failure, who usually present themselves to general practitioners (GPs) and geriatricians, rather than cardiologists, is notoriously difficult.[4] In these patients, a wide range of (both cardiovascular and non-cardiovascular) comorbidity in combination with limited access to echocardiography, may interfere with optimal diagnostic procedures.[5-7] Notwithstanding guidelines stressing the importance of echocardiography in diagnosing heart failure,[8,9] echocardiography is the exception rather than the rule in the evaluation of patients suspected of new, slow onset heart failure by physicians other than cardiologists.[4,10] We set out to determine the ability of GPs and geriatricians to correctly establish the presence or absence of heart failure in elderly patients suspected of new, slow onset heart failure using symptoms, signs, and tests that are readily available to them in daily practice, such as electrocardiography (ECG), chest X-ray, and (N-terminal pro) B-type Natriuretic Peptide ((NT-pro)BNP).

Methods

Study population

This study was part of a larger study of 206 elderly patients referred, for a variety of reasons, to the geriatric outpatient clinic of two regional hospitals in the Netherlands (Elkerliek Hospital, Helmond and Meander Medical Center, Amersfoort) presenting with symptoms suggestive of new, slow onset heart failure (i.e. breathlessness, fatigue, and ankle swelling).[11] In short, all participants underwent a standardized diagnostic work-up including clinical history taking, physical examination, ECG, chest X-ray, laboratory tests (including NT-proBNP), echocardiography and pulmonary function tests. An expert panel including a cardiologist, general practitioner, pulmonologist and geriatrician, established the presence or absence of heart failure, based on all available information - including six months follow-up -, according to the diagnostic criteria for heart failure of the European Society of Cardiology (ESC).[12] The diagnosis established by this expert panel is referred to as the ‘reference standard’. All participants or their

representatives, in case of impaired cognitive functioning, gave written consent. The study was approved by the Medical Ethical Committees of both participating hospitals. Patients were recruited between July 2003 and July 2007. For the current study a random sample of 90 patients (71% female, mean age 81.7 years (Standard Deviation (SD) 5.6)) was drawn and presented to two additional panels.

Physician panels

Case descriptions of a random sample of 90 patients were provided to two physician panels, consisting of three GPs and three geriatricians respectively. The GPs were working in different family practices and the geriatricians in different hospitals. The panels were asked to indicate whether heart failure was present, possibly present (in cases consensus was not reached or when the panel was in doubt), or absent, based on all the information provided. This information included signs, symptoms, ECG, chest X-ray, laboratory tests (including NT-proBNP), and pulmonary function tests. No information on echocardiographic findings was given. Thresholds for NT-proBNP values were taken from studies performed in elderly patients and the latest guidelines.[9,13,14] The reproducibility (intrarater agreement) of the diagnoses made by these panels was evaluated by re-testing a random sample of nine cases (10%) per panel. In addition, the panels were asked to write down their anticipated management of the patients, e.g. referral echocardiography in case of possible heart failure.

Data analysis

The diagnoses established by the GPs and geriatricians panels were compared to the diagnoses established by the expert panel of the original study ('reference standard'). First, the proportion of patients in whom GPs and geriatricians were certain about the presence or absence of heart failure and the proportion in whom the panels remained uncertain were determined. In addition, the proportions of patients with a 'certain' diagnosis in whom the panels incorrectly classified heart failure as absent (false negative) or present (false positive) were calculated. The reproducibility per panel was assessed using Cohen's κ. Data were analyzed using the SPSS software (version 17.0 for Windows SPSS Inc., Chicago, IL, USA).

Table 1. Clinical characteristics of 90 elderly patients suspected of new, slow onset heart failure*

Characteristic	All n = 90	HF present n = 42	HF absent n = 48
Clinical history			
Age, years	81.7 ± 5.6	83.0 ± 5.1	80.5 ± 5.8
Male sex	26 (29)	14 (33)	12 (25)
Breathlessness during exertion	85 (94)	40 (95)	45 (94)
Fatigue	77 (86)	34 (81)	43 (90)
Nocturnal dyspnea/ orthopnea	31 (34)	19 (45)	12 (25)
Loss of appetite	28 (31)	17 (40)	11 (23)
Cardiovascular co-morbidities and risk factors			
Ischaemic heart disease	18 (20)	11 (26)	7 (15)
Myocardial infarction	10 (11)	7 (17)	3 (6)
Vascular comorbidity	57 (63)	26 (62)	31 (65)
Hypertension	33 (37)	18 (43)	15 (31)
Diabetes mellitus	29 (32)	12 (29)	17 (35)
CVA or TIA	21 (23)	11 (26)	10 (21)
Atrial fibrillation	18 (20)	16 (38)	2 (4)
Current smoker	15 (17)	8 (19)	7 (15)
Non-cardiovascular comorbidity			
Visual impairment	48 (53)	23 (55)	25 (52)
Hearing impairment	31 (34)	13 (31)	18 (38)
COPD	30 (33)	13 (31)	17 (35)
Cognitive disorder	27 (30)	14 (33)	13 (27)
Osteoarthritis	27 (30)	13 (31)	14 (29)
Mood disorders	21 (23)	8 (19)	13 (27)
Osteoporosis	13 (14)	5 (12)	8 (17)
Physical examination			
Body Mass Index, kg/m^2	25.8 ± 4.6	24.6 ± 3.6	26.7 ± 5.1
Elevated JVP	7 (8)	5 (12)	2 (4)
Pulmonary crepitations	6 (7)	4 (10)	2 (4)
Bilateral ankle swelling	32 (36)	18 (43)	14 (29)
No signs of heart failure	38 (42)	13 (31)	25 (52)
Additional tests			
Atrial fibrillation at ECG	14 (16)	14 (35)	0 (0)
Normal ECG	28 (32)	4 (10)	24 (50)
NT-proBNP, pg/ml	492 (193-2441)	2441 (686-7365)	207 (105-345)
CTR > 0.50	60 (67)	35 (83)	25 (53)

* Data are presented as mean ± standard deviation, median (Inter Quartile Range: 25^{th} - 75^{th} percentiles), or number (%) of patients. Heart failure determined by expert panel ('reference standard'). COPD, chronic obstructive pulmonary disease; CTR, cardio thoracic ratio on chest X-ray; CVA, cerebro vascular accident; ECG, electrocardiography; Ischaemic heart disease includes prior myocardial infarction, angina pectoris, coronary artery bypass grafting, and percutaneous coronary intervention; HF, heart failure; JVP, jugular venous pressure; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; TIA, transient ischaemic attack; Vascular comorbidity includes hypertension, diabetes mellitus, stroke, and peripheral artery disease; Signs of heart failure includes tachycardia, tachypnoea, pulmonary rales, pleural effusion, elevated JVP, peripheral oedema, and hepatomegaly.

Results

In 42 (47%) of the 90 patients suspected of new, slow onset heart failure (mean age 82 years, 71% female) heart failure was diagnosed by the expert panel. The baseline characteristics of these 90 patients with a wide range of both vascular and non-vascular comorbidity are shown in Table 1.

The GPs panel diagnosed 25 (28%) patients with heart failure, 33 (37%) patients without heart failure, and considered heart failure “possible” in the remaining 32 (36%) patients (Table 2). According to the expert panel the prevalence of heart failure in these groups was 96%, 6% and 50%, respectively. The GPs panel established an incorrect diagnosis in three patients (3%; one false positive and two false negatives; Table 3). The geriatricians panel diagnosed 33 (37%) patients with heart failure, 31 (34%) patients without heart failure, and considered heart failure possible in the remaining 26 (29%) patients. The prevalence of heart failure in these groups was 85%, 0% and 54%, respectively. The geriatrician panel established an incorrect diagnosis in five patients (6%; all false positive).

The GPs and geriatricians reached the same diagnosis in 77% (69 of 90 patients) of the patients. In 22% (20 of 90 patients) one panel was in doubt while the other panel was certain about the presence or absence of heart failure. Only in one patient, who according to the expert panel did not have heart failure, GPs and geriatricians established opposite diagnoses (patient 7 in Table 3). The GPs more often were uncertain about the diagnosis than the geriatricians were (32 and 26 patients, respectively), but the number of false positive patients were lower than for the geriatricians (1 and 5 patients, respectively). In the latter panel, the number of false negatives was lower (0 versus 2 patients).

Half of the patients (50% in the GPs and 54% in the geriatricians panel) in whom the panels were uncertain about the presence or absence of heart failure, were diagnosed with heart failure by the expert panel. The majority of patients with possible heart failure according to either the GP or geriatrician panel would have been referred for echocardiography as an additional test: 29 of 32 (91%) patients and 21 of 26 (81%) patients, respectively. In the remaining patients, the effects of treatment of hypertension or chronic obstructive pulmonary disease (COPD), or results of recent pacemaker implantation would have been awaited. Both panels would have referred all patients for echocardiography when clinical improvement was lacking.

Table 2. Assessment of heart failure (HF) by general practitioners and geriatricians panels in numbers

	Diagnosis according to 'reference standard'		
Panel	**HF present (n = 42)**	**HF absent (n = 48)**	**Proportion with HF**
General practitioners			
HF present (n = 25)	24	1	96% (24/25)
HF possible (n = 32)	16	16	50% (16/32)
HF absent (n = 33)	2	31	6% (2/33)
Geriatricians			
HF present (n = 33)	28	5	85% (28/33)
HF possible (n = 26)	14	12	54% (14/26)
HF absent (n = 31)	0	31	0% (0/31)

The reproducibility of the diagnoses was good (Cohen's kappa: κ = 0.82 for GPs panel, and κ = 1.0 for geriatricians panel). On re-evaluation the GPs considered one patient (without heart failure according to the expert panel), initially as not having heart failure, as possibly heart failure.

Discussion

Using diagnostic tests readily available in daily practice, GPs and geriatricians are able to establish the presence or absence of heart failure in the majority (64% and 71% for the GPs and geriatricians panel, respectively) of elderly patients (mean age 81.7 years) with a wide range of comorbidity who are suspected of new, slow onset heart failure. In only 3% (GPs) and 6% (geriatricians) of all patients an incorrect diagnosis was established.

To our knowledge, this is the first study to determine the ability of GPs and geriatricians to establish the presence or absence of heart failure using diagnostic tests (symptoms, signs, ECG, chest X-ray, natriuretic peptides) available to them in daily practice. The elderly patients (mean age 81.7 ± 5.6 years) in this study reflect patients frequently encountered in day-to-day practice, but who are typically excluded from clinical trials.[15,16] One of the inherent limitations of our study is that a gold standard for diagnosing heart failure is lacking. We used an expert panel to determine the presence or absence of heart failure, in accordance with recent diagnostic studies in suspected heart failure.[17,18] As guidelines recommend cut-off values of NT-proBNP levels to rule out heart failure have not been validated in elderly patients,[9] thresholds of NT-proBNP levels from studies performed in elderly

Table 3. Characteristics of individual misdiagnosed patients per panel*

Patient	FP/FN	Gender, age	Comorbidity	Patient history	Physical examination	ECG	CTR	NT-proBNP	Other	Echocardiography
General practitioners panel										
1	FP	m, 79	MI, COPD, CKD	orthopnea	oedema	prior MI	> 0.50	> 2000	Hb 5.7 MDRD 19	normal
2	FN	f, 90	-	breathlessness AP	rales, oedema	LBTB	≤ 0.50	514		LVEF 40%
3	FN	f, 88	COPD, DM	breathlessness	oedema	LBTB	≤ 0.50	523		impaired diastolic function mitral insufficiency
Geriatricians panel										
4	FP	f, 79	COPD, Hypertension	breathlessness	-	normal	> 0.50	338		normal
5	FP	m, 89	PAD, Hypertension	breathlessness	-	RBTB	> 0.50	492		normal
6	FP	f, 92	DM	breathlessness nocturia	cardiac murmur	total AV block	> 0.50	155		normal
7	FP	f, 89	-	breathlessness	-	normal	≤ 0.50	491		normal
8	FP	f, 81	CABG, DM	breathlessness	rales, oedema, displaced apex	LVH ST-depression	> 0.50	207		normal

* Age in years; AP, angina pectoris; AV, atrioventricular; CKD, chronic kidney disease; Comorbidity, relevant (cardiovascular) comorbidity; COPD, chronic obstructive pulmonary disease; CTR, cardio thoracic ratio on chest X-ray; displaced apex, laterally displaced apex beat; ECG, electrocardiography; f, female; FN, false negative; FP, false positive; Hb, haemoglobin in mmol/l (9.2 g/dL); LBTB, left bundle branch block; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; m, man; MI, myocardial infarction; MDRD, estimated Glomerular Filtration Rate according to the Modification of Diet in Renal Disease study group equation in ml/min/1.73 m^2; NT-proBNP, N-terminal pro B-type Natriuretic Peptide in pg/ml; PAD, peripheral arterial disease; RBTB, right bundle branch block; ST, ST segment.

patients were handed to both panels.[13,14] Panel members discussed case descriptions of patients rather than seeing actual patients, which may reduce the ability to establish a correct diagnosis. On the other hand, physicians are used to discuss patients with colleagues without actually examining the patient and the reproducibility of the diagnoses established by both panels was good.

General practitioners and geriatricians are frequently confronted with patients they suspect of heart failure because of symptoms or signs (e.g. shortness of breath, fatigue, oedema), that are known to be only moderately predictive of heart failure.[19-22] In the absence of direct access to echocardiography other diagnostic tests (in addition to signs and symptoms), such as electrocardiography and natriuretic peptides are important tools in primary care and geriatric practice.[4,9,10]

Only in one of 90 patients the panels established an opposite diagnosis. In all other patients the panels established the same diagnoses or decided that additional tests were needed to obtain certainty about the presence or absence of heart failure.

If a patient is incorrectly diagnosed with heart failure (false positive patient), treatment will not result in clinical improvement, but may result in adverse drug effects or drug interactions that may be especially harmful in fragile, elderly patients. On the other hand, withholding treatment to a patient incorrectly diagnosed as not having heart failure (false negative patient), will result in deterioration of symptoms and signs of heart failure. In both scenarios the initial diagnosis is likely to be reconsidered. In elderly patients with a wide range of comorbidity, an uncertain diagnosis with referral for echocardiography is probably preferable to an incorrect diagnosis of heart failure followed by deteriorating symptoms and signs or by developing side effects due to an inappropriate treatment. The observation that heart failure was present in half (50% in the GPs and 54% in the geriatricians panel) of patients in whom the panels were uncertain about the diagnosis indicates that both GPs and geriatricians are able to correctly identify patients, most likely to benefit from additional investigations.

Applying diagnostic tests readily available in daily practice - notably natriuretic peptides - (in addition to signs and symptoms, but not including information from echocardiography) GPs and geriatricians can establish the presence or absence of heart failure in two thirds of elderly patients suspected of new, slow onset heart failure. Echocardiography to confirm or exclude heart failure can be targeted at those in whom the diagnosis remains uncertain (about one third of patients), because the number of false-positives and false-negatives in the other two thirds of patients in whom the GPs and geriatricians consider heart failure to be present or absent, respectively, is low.

Acknowledgements

We wish to thank the following physicians for participation in the physician panels: general practitioners E. Plum, MD, Helmond; A.P.A. Pril-Hes, MD, Helmond; R.M.P. Verouden, MD, Helmond; and geriatricians J.A.M. Bloemen, MD, Elkerliek Hospital, Helmond; C.M.J. van der Linden, clinical pharmacologist, MD, Catharina Hospital, Eindhoven; R.W. Vingerhoets, MD, Tweesteden Hospital, Tilburg, The Netherlands.

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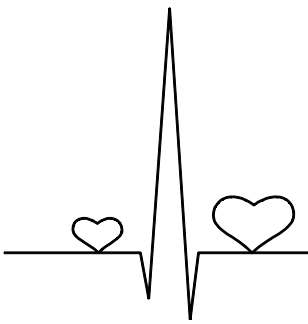
Chapter 3

Applicability of current diagnostic algorithms in geriatric patients suspected of new, slow onset heart failure



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Age Ageing. 2012 jan 17. [Epub ahead of print]

Abstract

Background

Referral for echocardiography for all geriatric outpatients suspected of heart failure is not feasible. Diagnostic algorithms could be helpful.

Objective

To investigate whether available diagnostic algorithms accurately identify (older) patients (aged 70 years or over) eligible for echocardiography, with acceptable numbers of false-negatives.

Methods

Algorithms (European Society of Cardiology (ESC) guideline, National Institute for Health and Clinical Excellence (NICE) guideline, multidisciplinary guideline the Netherlands (NL), and algorithm by Mant *et al*) were validated in 203 geriatric patients (mean age 82 ± 6 years, 30% men) suspected of new, slow onset heart failure. Heart failure was adjudicated by an expert panel. Applicability of algorithms was evaluated by calculating proportion of patients (i) referred for echocardiography, (ii) with heart failure among referred patients, and (iii) without heart failure in the non-referred.

Results

Ninety two (45%) patients had heart failure. Applying algorithms resulted in referral for echocardiography in 52% (normal NT-proBNP; ESC), 72% (normal ECG; ESC), 56% (NICE), 93% (NL) and 70% (Mant) of all patients, diagnosing heart failure in 78%, 56%, 76%, 49% and 62% of those referred, respectively. In patients not referred for echocardiography heart failure was absent in 90%, 82%, 93%, 100% and 95%, respectively.

Conclusions

The ESC NT-proBNP (< 400 pg/ml) based algorithm combines the lowest number of referrals for echocardiography (of whom 78% has heart failure) with a limited number (10%) of false negatives in the non-referred.

Introduction

Ageing of the population and improved survival following acute cardiac events has led to an increased prevalence of heart failure, especially in the elderly.[1,2] Diagnosing heart failure is important for patient management, because of beneficial effects on both morbidity and mortality of targeted interventions.[3-5] Unfortunately, detecting heart failure in the elderly with a wide range of comorbidity is notoriously difficult, particularly in the early stages and in a setting without direct access to echocardiography, such as in primary care or geriatric practice.[6] Clinicians, other than cardiologists, do not routinely use echocardiography in the diagnostic work-up of heart failure.[7] Natriuretic peptides are increasingly used in the diagnostic assessment of heart failure. Although serum levels of natriuretic peptides rise with age, specific cut-off values to rule out the presence of heart failure are not available for elderly patients suspected of new, slow onset heart failure.[8,9] Diagnostic algorithms can support clinicians in the evaluation of patients suspected of heart failure. Available algorithms are generally aimed at excluding heart failure and identifying patients that require referral for additional diagnostic investigations (in particular echocardiography) to establish the presence and cause of heart failure. The latter will guide treatment.[3] Unfortunately these algorithms are generally derived and validated in populations that include few elderly patients. We set out to assess the applicability of existing diagnostic algorithms to geriatric outpatients (aged 70 years or over) suspected of new, slow onset heart failure.

Methods

Search

In December 2010 the MEDLINE database was searched for publications on diagnostic algorithms to diagnose new, slow onset heart failure (see Appendix). To identify relevant publications missed by the search reference lists of all manuscripts identified and those of relevant review articles were scrutinized. Only algorithms based on diagnostic tests available to geriatricians (thus excluding echocardiography) were included and the diagnosis of heart failure should have been based on an adequate reference (“gold”) standard (i.e. clinical or echocardiographic evaluation). Only the latest versions of the algorithms were included.

Validation sample

The validation sample consisted of patients aged 70 years or older referred for a variety of reasons to the geriatric outpatient clinic of two regional hospitals in the Netherlands (Elkerliek Hospital, Helmond and Meander Medical Center, Amersfoort). When the geriatrician had a suspicion of heart failure because of breathlessness, fatigue, ankle swelling, or any combination of these, patients were eligible for this study as detailed previously.[10] Patients were excluded when ankle swelling was the single sign present and was evidently caused by venous insufficiency, emergency admission for heart failure was needed, or when a diagnosis of heart failure had already been established by a cardiologist. Participants underwent a standardized diagnostic work-up (including clinical history, physical examination, chest X-ray, electrocardiography (ECG), laboratory tests and echocardiography). None of the patients had previously undergone echocardiography. Information on comorbidity was obtained from the general practitioner's referral letter and letters of other specialists retrieved from the hospital information system. Diagnoses established by the geriatricians during a complete geriatric assessment and within two months after the initial visit were used to complete information on comorbidity. An expert panel consisting of a cardiologist, general practitioner, pulmonologist and geriatrician established the presence or absence of heart failure according to the prevailing diagnostic criteria for heart failure of the European Society of Cardiology (ESC), using all available diagnostic information including N-Terminal pro B-type Natriuretic Peptide (NT-proBNP), echocardiography, and clinical course (e.g. response to therapy) during a six month follow-up period.[11] Heart failure was considered present when symptoms and signs suggestive of heart failure (such as breathlessness, ankle swelling, fatigue, pulmonary rales, elevated jugular venous pressure) were present combined with objective echocardiographic evidence of cardiac dysfunction at rest. Patients with heart failure were further classified as having systolic heart failure (left ventricular ejection fraction (LVEF) less than 45%), and heart failure with preserved ejection fraction (HFPEF; echocardiographic evidence of diastolic dysfunction (abnormal left ventricular relaxation or diastolic stiffness) in combination with LVEF $\geq$ 45%). To prevent incorporation bias, which is an important issue in this type of diagnostic research, NT-proBNP values were only provided to the expert panel, after the presence or absence of heart failure had been established based on all other diagnostic information (including echocardiography).[12] Only in three (1%) patients knowledge of NT-proBNP values led to reconsideration of the initial diagnosis.

All participants or their representatives, in case of impaired cognition, gave written consent. The inclusion started July 2003 and ended July 2007. The study was approved by the Medical Ethical Committees of both participating hospitals.

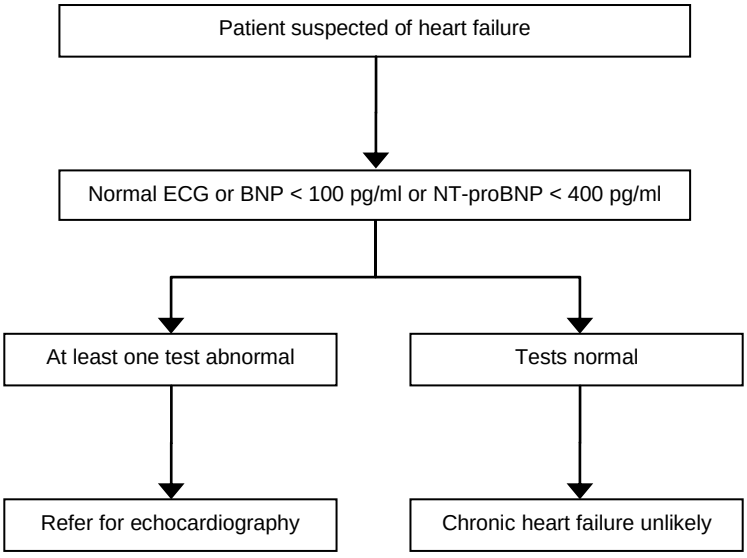
Data analysis

Univariate analyses were performed using *t*-tests for continuous variables, and χ^2 -tests for differences in proportions. The diagnostic algorithms were evaluated by applying the algorithms to each patient in the validation sample and comparing the results to the observed outcome, i.e. whether the patient actually had heart failure according to the expert panel. Applicability of diagnostic algorithms was evaluated by calculating the following measures: (i) proportion of suspected patients in whom the algorithm recommends referral for echocardiography (% referred patients), (ii) proportion of patients in whom the algorithm recommends referral for echocardiography, that indeed has heart failure (positive predictive value) and (iii) proportion of patients in whom heart failure is excluded according to the algorithm, that indeed does not have heart failure (negative predictive values). Predictive values were presented with 95% confidence intervals.

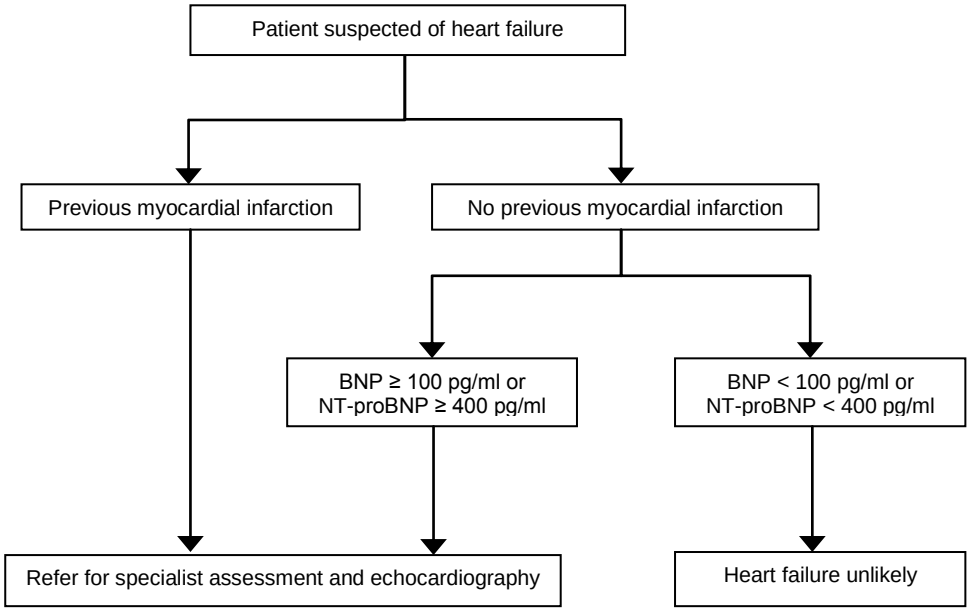
Overall, the number of missing variables was less than 1% (range 0-2%). Prior to analysis we imputed values by using a regression method.[13] Data were analyzed using the SPSS software (version 17.0 for Windows SPSS Inc., Chicago, IL, USA).

Figure 1. Diagnostic algorithms for suspected heart failure

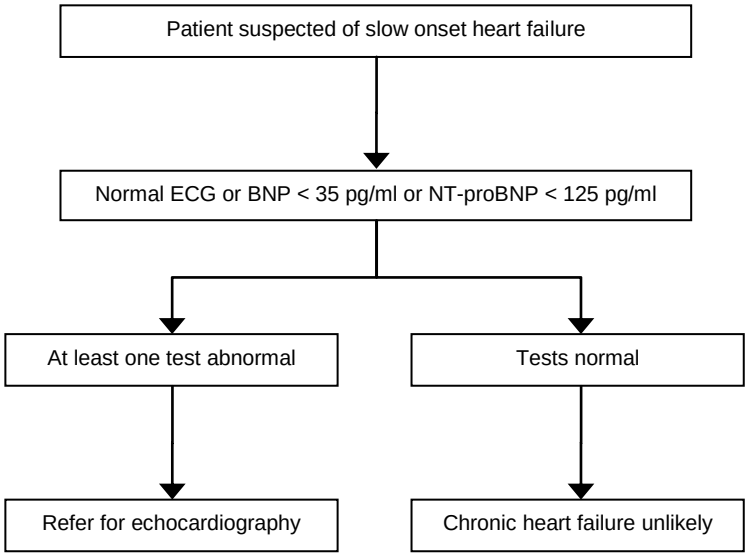
1a. Guideline of the European Society of Cardiology (ESC)



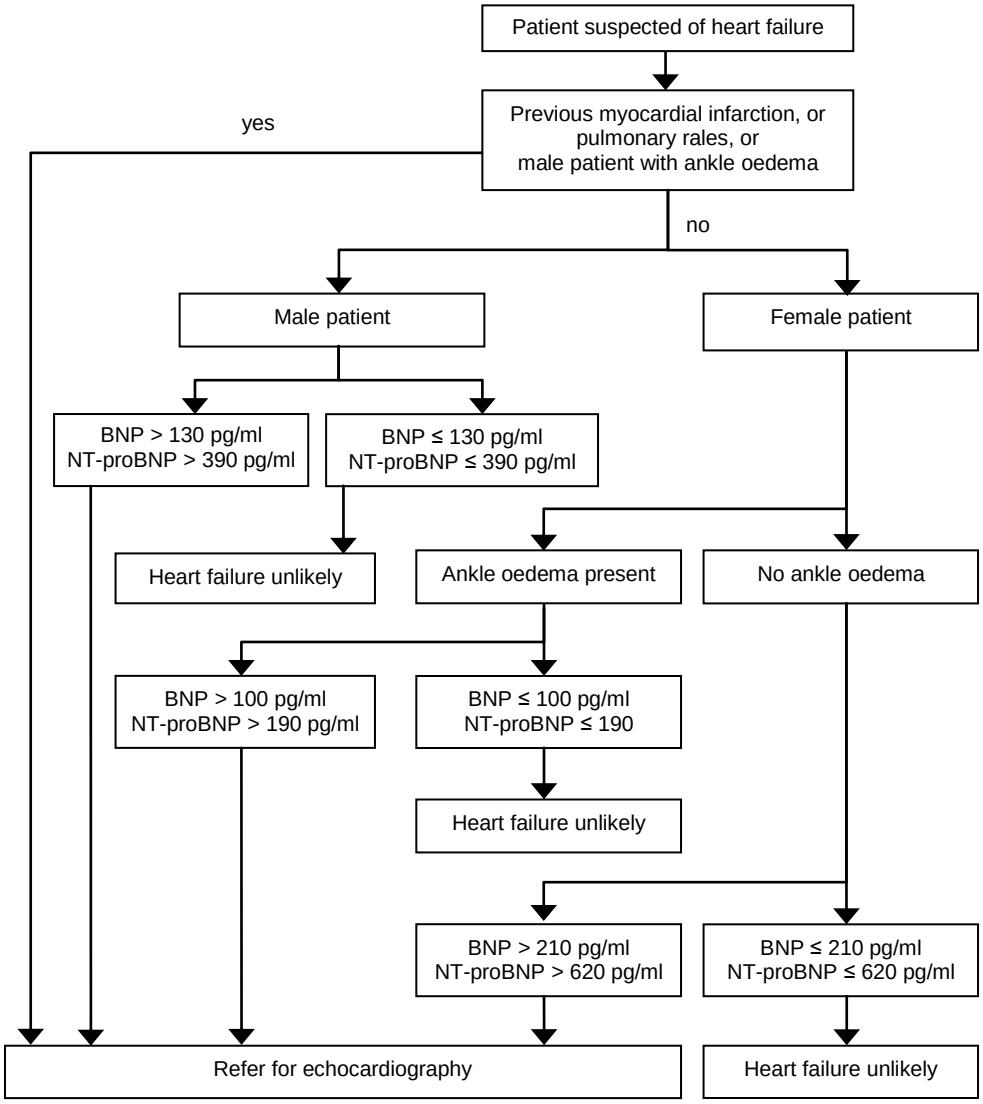
1b. Guideline of the National Institute for Health and Clinical Excellence, United Kingdom (NICE)



1c. Multidisciplinary Guideline for Heart Failure 2010, The Netherlands (NL)



1d. Study by Mant *et al**



* Cutoff values of BNP/NT-proBNP according to post-test disease probability (i.e. the proportion of patients testing positive who truly have the disease) of respectively 20%, 25% and 30%: female patient without ankle oedema: 210/620, 280/820 and 360/1060 pg/ml; male patient without ankle oedema: 130/390, 170/510 and 220/660 pg/ml; female patient with ankle oedema: 100/190, 140/410 and 180/520 pg/ml. A post-test probability of 20% indicates that all patients in that category need referral for echocardiography, with heart failure present in at least 20% of these patients.

Results

Algorithms

The MEDLINE search identified four algorithms to potentially apply to geriatric outpatients suspected of new, slow onset heart failure (Figure 1): algorithms from the 'Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008' of the ESC; from 'Chronic Heart Failure, National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care' of the National Institute for Health and Clinical Excellence (NICE), United Kingdom; from the 'Multidisciplinary Guidelines for Heart Failure 2010', The Netherlands (NL) and from the study performed by Mant *et al.* [3,14-16]

Mant performed a systematic review of the diagnosis of heart failure based on clinical features and investigations available in a primary care setting.[15] The prediction rule was developed in the dataset of the United Kingdom Natriuretic Peptide (UKNP) study of Zaphiriou et al, that confirmed the ability of natriuretic peptides to 'rule-out' heart failure in 306 patients (104 (34%) with heart failure) suspected of heart failure by their general practitioner.[17] The prediction rule was externally validated in five other datasets, and converted to an algorithm.

Validation

The mean age of the 203 geriatric patients in the validation sample was 82 years (range 70-98 years), 30% were male, and according to the expert panel, new, slow onset heart failure was present in 92 (45%) patients (Table 1). The main reasons for referral were functional impairment (39%), breathlessness (35%), cognitive impairment (31%) and mobility disorders (29%). Forty nine (53%) patients had 'systolic' heart failure (median LVEF 35% (Inter Quartile Range (IQR) 27.5 - 40.0)) and 39 (42%) had HFPEF (median LVEF 50% (IQR 45 - 60)). In four patients left ventricular function was normal but heart failure was present due to right-sided heart failure (two patients), severe mitral regurgitation (one patient) and aortic stenosis (one patient). Patients with heart failure were older (83 and 81 years, respectively; $p = 0.01$), more often male (37% and 24%; $p = 0.05$), and more frequently had a history of myocardial infarction (18% and 5%; $p < 0.01$) and atrial fibrillation (39% and 5%; $p < 0.01$), compared to patients without heart failure. The median number of drugs used per patient was six.

Other than heart failure, the most common diagnoses newly established by the geriatricians were cognitive disorders (23% and 30%, $p = 0.27$), vitamin deficiency (23% and 20%, $p = 0.60$), orthostatic hypotension (14% and 18%, $p = 0.46$), mood disorders (14% and 16%, $p = 0.68$), and chronic obstructive pulmonary disease

Table 1. Characteristics of 203 geriatric patients suspected of heart failure*

Characteristic	All n = 203	HF present n = 92	HF absent n = 111	p-value
Age, years	82 ± 6	83 ± 5	81 ± 6	0.01
Female	142 (70)	58 (63)	84 (76)	0.05
Cardiovascular comorbidities and risk factors				
Ischaemic heart disease	41 (20)	25 (27)	16 (14)	0.02
Myocardial infarction	23 (11)	17 (18)	6 (5)	< 0.01
Vascular comorbidity	122 (60)	54 (59)	68 (61)	0.71
Hypertension	87 (43)	38 (41)	49 (44)	0.68
Diabetes mellitus	56 (28)	25 (27)	31 (28)	0.91
CVA or TIA	41 (20)	20 (22)	21 (19)	0.62
Atrial fibrillation	42 (21)	36 (39)	6 (5)	< 0.01
Current smoker	28 (14)	17 (18)	11 (10)	0.08
Non-cardiovascular comorbidities				
Visual impairment	98 (48)	49 (53)	49 (44)	0.20
Hearing impairment	75 (37)	33 (36)	42 (38)	0.77
Cognitive disorder	63 (31)	25 (27)	38 (34)	0.28
Osteoarthritis	60 (30)	26 (28)	34 (31)	0.71
COPD	53 (26)	25 (27)	28 (25)	0.75
Mood disorders	45 (22)	22 (24)	23 (21)	0.59
Vitamin deficiency	43 (21)	21 (23)	22 (20)	0.60
Osteoporosis	34 (17)	14 (15)	20 (18)	0.60
Drugs				
Loop diuretic	72 (35)	38 (41)	34 (31)	0.11
ACE-i/ARBs	66 (33)	34 (37)	32 (29)	0.22
β-Blockers	45 (22)	25 (27)	20 (18)	0.12
Digitalis	25 (12)	22 (24)	3 (3)	< 0.01
Aldosterone antagonists	17 (8)	10 (11)	7 (6)	0.24
Oral anticoagulants	26 (13)	19 (21)	7 (6)	< 0.01
Antiplatelets	82 (40)	38 (41)	44 (40)	0.81
Drugs, number	6 ± 3	6 ± 3	6 ± 4	0.68
Physical examination				
Systolic blood pressure, mm Hg	156 ± 26	156 ± 28	156 ± 24	0.92
Diastolic blood pressure, mm Hg	82 ± 11	82 ± 12	81 ± 11	0.73
Heart rate, bpm	76 (70-80)	76 (70-82)	76 (70-80)	0.56
Body Mass Index, kg/m^2	26 (23-29)	24 (21-28)	27 (24-30)	< 0.01
Pulmonary rales	57 (28)	28 (30)	29 (26)	0.50
Oedema	78 (38)	39 (42)	39 (35)	0.29
Diagnostic tests				
NT-proBNP, pg/ml	485 (195-1946)	2136 (789-5785)	210 (113-338)	< 0.01
NT-proBNP < 400 pg/ml	98 (48)	10 (11)	88 (79)	< 0.01
Normal ECG	56 (28)	10 (11)	46 (41)	< 0.01

* Data are presented as mean ± standard deviation, median (Inter Quartile Range: 25th - 75th percentiles), or number (%) of patients. ACE-i, angiotensin-converting enzyme-inhibitor; ARBs, angiotensin II receptor blockers; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CVA, cerebro vascular accident; ECG, electrocardiography; HF, heart failure; Ischaemic heart disease includes prior myocardial infarction, angina pectoris, coronary artery bypass grafting, and percutaneous coronary intervention; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; TIA, transient ischaemic attack; Vascular comorbidity includes hypertension, diabetes mellitus, stroke, and peripheral artery disease. Information on comorbidities was obtained from the general practitioner's referral letter and letters of other specialists retrieved from the hospital information system. Diagnoses established by the geriatricians during a complete geriatric assessment and within two months after the initial visit were used to complete information on comorbidity.

(COPD; 12% and 14%, p = 0.74) in patients with and without heart failure, respectively.
The results of applying the diagnostic algorithms to the geriatric validation sample are provided in Table 2. Thresholds below which the prevalence of heart failure was less than 20% were chosen in the diagnostic algorithm of Mant. Applying the diagnostic algorithms resulted in referral for echocardiography in 52% (normal NT-proBNP; ESC), 72% (normal ECG; ESC), 56% (NICE), 93% (NL) and 70% (Mant) of all patients, leading to a diagnosis of heart failure (positive predictive values) in 78%, 56%, 76%, 49% and 62% of those referred, respectively. In patients not referred for echocardiography heart failure was absent (negative predictive values) in 90%, 82%, 93%, 100% and 95%, respectively.

Discussion

Available diagnostic algorithms (ESC, NICE, NL and Mant) reliably exclude the presence of heart failure in elderly outpatients suspected of new, slow onset heart failure by their geriatrician. The prevalence of heart failure in patients not referred for additional investigations, notably echocardiography, ranges from 0% to 18%. Strict application of these algorithms, however, also leads to a significant proportion (range 52% to 93%) of patients undergoing further evaluation, in particular echocardiography.
The validation sample consisted of elderly patients (mean age 82 years, 70% women) with a wide range of both cardiovascular and non-cardiovascular comorbidity (e.g. hypertension, atrial fibrillation, COPD, cognitive disorders), using a median of six medications, who were suspected of new, slow onset heart failure by their geriatrician because of the presence of symptoms and signs suggestive of heart failure. The prevalence of heart failure (45%) was in line with findings from earlier studies.[8,9] Although none of the participants had a prior diagnosis of heart failure, in one third a loop diuretic was prescribed. Loop diuretics are commonly used as part of antihypertensive treatment in the Netherlands (although thiazide diuretics are recommended) and loop diuretic are also known to be prescribed in patients with ankle swelling or dyspnoea without first confirming or excluding the presence of heart failure.[18]
The ESC NT-proBNP (< 400 pg/ml) based algorithm combines the lowest number of referrals for echocardiography (of whom 78% has heart failure) with a limited number (10%) of false negatives in the non-referred. Although earlier studies showed that NT-proBNP safely excluded the presence of heart failure in primary

Table 2. Performance of diagnostic algorithms in 203 geriatric patients*

		Non-referral			Referral		
			HF absent	NPV		HF present	PPV
Algorithm	**Determinant**	**n (%)**	**n**	**% (95% CI)**	**n (%)**	**n**	**% (95% CI)**
ESC	NT-proBNP < 400 pg/ml	98 (48)	88	90 (87-93)	105 (52)	82	78 (74-82)
	Normal ECG	56 (28)	46	82 (77-87)	147 (72)	82	56 (52-60)
NICE	No previous MI and NT-proBNP < 400 pg/ml	90 (44)	84	93 (90-96)	113 (56)	86	76 (72-80)
NL	Normal ECG and NT-proBNP < 125 pg/ml	15 (7)	15	100 (92-100)	188 (93)	92	49 (45-53)
Mant	HF unlikely	60 (30)	57	95 (92-98)	143 (70)	89	62 (58-66)

* CI, confidence interval; ESC, guideline of the European Society of Cardiology; HF, heart failure; MI, myocardial infarction; NICE, guideline of the National Institute for Health and Clinical Excellence; NL, Dutch guideline; Non-referral, number of patients not referred for echocardiography (proportion of all 203 patients); NPV, negative predictive value: proportion of non-referred patients without HF; PPV, positive predictive value: proportion of referred patients with HF; Referral, number of patients referred for echocardiography (proportion of all 203 patients). Algorithm of Mant HF unlikely: cutoff values of NT-proBNP below which the presence of HF is less than 20% (see footnote figure 1d)

care patients and nursing home residents at first sight the finding that an algorithm that merely uses NT-proBNP (ESC) performs better than algorithms that combine NT-proBNP and clinical variables, may come as a surprise.[19,20] It is, however, known that classic features of heart failure may have limited value in geriatric patients: pulmonary rales and oedema are frequently present even in the absence of cardiac dysfunction.[21] The algorithm of Mant contains both items (pulmonary rales and oedema) explaining at least partially its limited use in excluding heart failure in this geriatric cohort. Adding the presence of a previous myocardial infarction to the 400 pg/ml NT-proBNP cutoff value, as done in the algorithm of the NICE guideline, did not lead to more adequate referrals or less false negatives compared to ESC NT-proBNP based algorithm. The algorithm of the Dutch multidisciplinary guideline, combining a normal ECG with a NT-proBNP level below 125 pg/ml, may be useful to exclude heart failure in general practice, but results in a 93% referral rate in geriatric patients suspected of heart failure. Similarly, combining a normal ECG with NT-proBNP levels below 400 pg/ml (as suggested by the ESC) would have resulted in a high referral rate as well: 160 (79%) patients would have to undergo echocardiography (87 (54%) patients having heart failure; data not shown) with heart failure being absent in 38 (88%) of the 43 non-referred patients. Thus, adding a normal ECG to various NT-proBNP cutoff levels, does not improve diagnostic accuracy in geriatric patients. This is probably due to the limited amount of patients without heart failure that have a normal ECG in our geriatric cohort (59% of patients without heart failure).

The ESC guideline also states that the presence of heart failure is likely when NT-proBNP levels exceed 2000 pg/ml mandating referral for echocardiography. Fifty patients (25%) of our geriatric cohort had NT-proBNP values above 2000 pg/ml, with only one of them ultimately being diagnosed as not having heart failure (positive predictive value 98%). Our findings indicate that in geriatric patients suspected of new, slow onset heart failure NT-proBNP values below 400 pg/ml safely exclude heart failure (heart failure treatment can be withheld), whereas NT-proBNP values higher than 2000 pg/ml adequately confirm the presence of heart failure, and (symptomatic) treatment should be started. In the remaining patients (n = 55, 27%) with equivocal NT-proBNP values (400 - 2000 pg/ml) uncertainty about the presence or absence of heart failure could lead to a strategy of watchful waiting, and initiation of treatment if symptoms worsen. Unfortunately, accessibility of natriuretic peptides may be limited, complicating implementation of the studied algorithms.[22]

In patients in whom algorithms incorrectly concluded heart failure to be absent (false negatives), the proportion of patients with systolic heart failure (LVEF < 45%)

and heart failure with preserved ejection fraction (diastolic dysfunction in combination with LVEF ≥ 45%) was the same (data not shown). Physicians will always consider the trade-off between the yield of additional investigations and the burden these investigations impose on their patients. Echocardiography, key to determine the presence and cause of heart failure, is generally considered a patient friendly, easy to perform test that has no side effects. Nevertheless, for elderly patients, who are likely to have multiple comorbidities, a hospital visit to undergo echocardiography is a considerable effort.[23,24] Current daily practice shows that performing echocardiography in all patients suspected of heart failure by non-cardiologists is a non-realistic option.[7] In geriatric practice the aim of medical care is to improve quality of life by reducing symptoms, rather than merely improving survival. As such the management of heart failure in geriatric patients will generally consist of lifestyle advices and medications. The proportion of patients receiving more advanced treatment for heart failure, e.g. device therapy, percutaneous interventions or open heart surgery, is negligible.[25,26] It follows that there is a need for strategies to reliably rule in or out the presence of heart failure in this specific patient group, using easily obtainable information from medical history, physical examination, electrocardiography and laboratory testing (such as natriuretic peptides) and reserving additional investigations only for those in whom the presence of heart failure remains uncertain or for the few geriatric patients that may benefit from advanced treatment options (e.g. valve replacement). Handheld echocardiography may lower the threshold to perform echocardiography in the near future, but we are not aware of studies assessing the cost-effectiveness of these devices in elderly patients suspected of heart failure.

Management of heart failure in elderly patients with a wide range of comorbidity is complicated by the lack of evidence based guidance as they are often excluded from participation in trials.[27,28] No therapeutic interventions have been proven to improve outcome in HFPEF, which is present in half of the elderly patients with heart failure.[29] The therapeutic management of elderly patients with systolic heart failure is largely based on extrapolating findings from studies performed in younger patients with less comorbidity.[27] This said, a few studies performed in elderly patients, show benefit of beta-blockers and angiotensin converting enzyme (ACE)-inhibitors.[4,5] Despite the scarcity of evidence for treatment benefits, establishing a correct diagnosis in elderly patients with a wide range of comorbidity remains essential, not only for those who are found to have heart failure, but also to prevent potential side effects in those not having heart failure.

The present study, the largest in geriatric patients suspected of new, slow onset heart failure to date, provides information on a specific group of patients largely

ignored in previous (diagnostic) heart failure studies. Another strength of our study is that, to reflect daily practice, only algorithms using diagnostic tests generally available to geriatricians were included. Limitations, inherent to the nature of our diagnostic study, need to be discussed. Establishing the diagnosis heart failure is difficult because a gold standard is lacking. This mandated the use of an expert panel to attribute a final diagnosis of heart failure, of which the consensus diagnosis was highly reproducible, as in previous studies.[30,31] The introduction of natriuretic peptides has revolutionized the assessment of heart failure, but limited information is available regarding reference values in elderly patients.[3,30] The first study to derive NT-proBNP reference values for heart failure in patients aged 70 years and older was performed in patients with acute onset of heart failure.[8] Levels of natriuretic peptides will be lower in the type of patients included in our study, i.e. those with slow onset heart failure.[17,30] The 2005 ESC heart failure guidelines used by the expert panel to diagnose the presence or absence of heart failure in the validation sample, did not specify NT-proBNP cut off values.[11] In combination with the absence of reference values for elderly patients with slow onset heart failure, this meant that echocardiography was of main importance in the final diagnosis of heart failure by the expert panel in our study.

In conclusion, existing diagnostic algorithms accurately rule out heart failure in geriatric outpatients suspected of new, slow onset heart failure by their geriatrician. Unfortunately these algorithms refer a significant amount (52 to 93%) of patients for additional investigations, notably echocardiography. The NT-proBNP based ESC algorithm appears to be the current algorithm of choice for geriatric outpatients, combining the lowest number of referrals (52%) for echocardiography (of whom the majority has heart failure) with a few false negatives (10%) in the non-referred. There remains a need for better diagnostic algorithms in geriatric patients suspected of heart failure, that combine low false negative rates with fewer referrals for echocardiography.

Acknowledgements

We wish to thank the participating patients and geriatricians. We also thank Professor M.R. Cowie, Department of Clinical Cardiology, National Heart & Lung Institute, Imperial College, Royal Brompton Campus, London, United Kingdom for allowing us to use the United Kingdom Natriuretic Peptide (UKNP) study data.

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Appendix

Appendix 1. Search strategy

Search	Limits
"practice guideline"[Publication Type] AND "heart failure"[MeSH]	English
"clinical prediction models heart failure"	English
"heart failure"[MeSH] AND "prediction models"	English
"multivariate analysis"[MeSH] AND "heart failure/diagnosis"[MeSH]	English
"models, statistical"[MeSH] AND "heart failure/diagnosis"[MeSH]	English
"heart failure/diagnosis"[MeSH] AND ("algorithm" OR "multivariate analysis" OR "logistic model" OR "biological model" OR "statistical model" OR "mathematics" OR "regression analysis" OR "risk factor" OR "risk assessment" OR "predictive value" OR "area under curve" OR "evaluation study" OR "evaluation" OR "reproducibility" OR "prediction" OR "prediction rule" OR "predict")	English, clinical trial and review

Chapter 4

Diagnostic prediction rules in heart failure: validation in geriatric outpatients

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submitted

Abstract

Background

Heart failure is difficult to establish based on symptoms, signs, and easily accessible additional tests, especially in elderly patients. Diagnostic prediction rules, combining such diagnostic items, help physicians in the early assessment of patients suspected of slow onset heart failure. We set out to investigate the applicability of existing diagnostic prediction rules to geriatric outpatients suspected of new, slow onset heart failure.

Methods

The MEDLINE database was searched for publications on diagnostic prediction rules for slow onset heart failure. The validation cohort consisted of 203 geriatric outpatients (aged 70 years or older) suspected of new, slow onset heart failure. An expert panel established the presence of heart failure. Prediction rules were evaluated using measures of calibration and discrimination.

Results

Two diagnostic prediction rules providing an absolute probability of heart failure in individual patients were identified: by Mant *et al* (five items) and by Kelder *et al* (ten items). In the validation cohort (203 geriatric outpatients (median age 82 years, 30% men)) 92 (45%) patients had heart failure. Both rules showed good calibration (Mant: slope 1.22, intercept 0.39; Kelder: slope 1.45, intercept -0.10) and discrimination (c-statistic Mant: 0.90 (95% CI 0.86 - 0.95); c-statistic Kelder: 0.89 (95% CI 0.85 - 0.94)) in the geriatric validation cohort.

Conclusions

Existing diagnostic rules accurately predict the presence of heart failure in geriatric outpatients suspected of new, slow onset heart failure. The applicability of these rules is, however, hampered by the complexity of calculation of the probability of heart failure. More easily applicable rules, preferably derived in elderly patients, may improve implementation.

Introduction

The ageing of the population and improved survival following acute cardiac events leads to an increased prevalence of heart failure in the elderly.[1,2] Diagnosing or excluding heart failure in suspected patients is difficult based on symptoms, signs, and easily accessible tests (such as electrocardiography (ECG)), especially in elderly patients with multiple comorbidity.[3] Diagnostic prediction rules provide an absolute probability that heart failure is present in individual patients based on a combination of diagnostic items.[4] Such a rule can be helpful in guiding management decisions, for example exclusion of heart failure or referral for additional investigations, typically echocardiography. Especially in elderly patients such a rule could be important because symptoms and signs suggestive of heart failure may be attributable to comorbidity and routine referral for echocardiography in all suspected patients is unrealistic and would lead to unnecessary increased costs and patient burden. The validity of currently available diagnostic rules in elderly patients is, however, unknown. We assessed the applicability of existing diagnostic prediction rules to geriatric outpatients suspected of slow onset heart failure.

Methods

Search

In November 2011 the MEDLINE database was searched for publications on prediction rules, to diagnose new, slow onset heart failure (see Appendix 1 for search algorithm).[5] The main search terms used were “heart failure” in combination with the terms “prediction models” and “multivariate analysis”. To identify studies missed by the search reference lists of all manuscripts identified and those of relevant review articles were scrutinized. Only rules based on diagnostic tests readily available to physicians (thus excluding echocardiography) involved in the early assessment of patients suspected of slow onset heart failure were included. In addition, only studies in which the assessment of heart failure, necessary to develop these rules, was based on adequate reference standards (i.e. including clinical and echocardiographic criteria according to prevailing guidelines) were included. Corresponding authors of included diagnostic prediction rules were contacted to ask permission to use the logistic regression equations of their diagnostic prediction rules.

Validation cohort

The validation cohort existed of patients aged 70 years or older referred to the geriatric outpatient clinic for a variety of reasons (mainly functional impairment, breathlessness, cognitive impairment and mobility disorders) of two regional hospitals in the Netherlands (Elkerliek Hospital, Helmond and Meander Medical Center, Amersfoort) as detailed previously.[6] When the geriatrician had a suspicion of heart failure because of breathlessness, fatigue, ankle swelling, or any combination of these, patients were eligible for this study. Patients were excluded when ankle swelling was the single sign present and was evidently caused by venous insufficiency, when emergency admission for heart failure was needed, or when a diagnosis of heart failure had already been established by a cardiologist. Participants underwent a standardized diagnostic work-up (including clinical history, physical examination, ECG, chest X-ray, laboratory tests, pulmonary function tests, and echocardiography). An expert panel consisting of a cardiologist, general practitioner, pulmonologist and geriatrician established the presence or absence of heart failure according to the diagnostic criteria for heart failure of the European Society of Cardiology (ESC), using all available diagnostic findings including information from history taking and physical examination, N-Terminal pro B-type Natriuretic Peptide (NT-proBNP), echocardiography, information from six months follow-up (including additional diagnoses and response to therapy).[7] All participants or their representatives, in case of impaired cognition, provided written consent. The inclusion started July 2003 and ended July 2007. The study was approved by the Medical Ethics Committees of both participating hospitals.

Data analysis

To evaluate the predictive performance of the diagnostic prediction rules, the risk of heart failure was calculated for each geriatric patient in the validation cohort applying the formulas of the diagnostic prediction rules and compared to the observed outcome (i.e. the presence or absence of heart failure according to the expert panel). This was quantified using measures of calibration and discrimination. Calibration refers to the agreement between the predicted probability and observed prevalence of heart failure in the validation dataset.[8] This was graphically assessed with a calibration plot depicting a calibration line between the observed and predicted outcomes.[9] For both diagnostic prediction rules the slope and intercept of the calibration line were calculated. If a model shows perfect calibration the actual slope and intercept should be 1 and 0, respectively.[9] Calibration was further tested with the Hosmer-Lemeshow statistic, where an insignificant (p-value > 0.05) test indicates good model fit [10]. The calibration performance of a rule in an independent

dataset (external validation set) is commonly influenced by the prevalence of the outcome in the validation set. To allow for a fair comparison of the diagnostic prediction rules, we adjusted the intercept of each model before applying it to the data, such that the mean predicted probability was equal to the observed outcome frequency.[11,12]

Table 1. Baseline characteristics, determinants of heart failure and outcome in the derivation and validation cohorts*

	Derivation cohorts		Validation cohort
	UKNP patients	Kelder	Geriatric patients
Characteristic	N = 306	N = 721	N = 203
Age, years	74 (66-80)	73 (64-80)	82 (78-86)
Female	176 (58)	466 (65)	142 (70)
Previous MI	42 (14)	43 (6)	23 (11)
Previous MI, CABG or PCI	51 (17)	48 (7)	30 (15)
Loop diuretic	148 (48)	233 (32)	72 (35)
Oedema	142 (46)	197 (27)	78 (38)
Heart rate, bpm	72 (62-85)	76 (68-87)	76 (70-80)
Irregularly irregular pulse	56 (18)	72 (10)	56 (28)
Pulmonary rales	88 (29)	99 (14)	57 (28)
Displaced apex beat	21 (7)	70 (10)	9 (4)
Heart murmur suggesting MR	-	77 (11)	13 (6)†
Any heart murmur	-	189 (26)	33 (16)
Elevated JVP	52 (17)	56 (8)	22 (11)
NT-proBNP, pg/ml	382 (135-1215)	23 (9-81)	485 (195-1946)
Heart failure	104 (34)	207 (29)	92 (45)
Heart failure with reduced LVEF, n (% of HF)	79 (76)	131 (63)	49 (53.3)

* Data are presented as median (Inter Quartile Range: 25th - 75th percentiles), or number (%) of patients. CABG, coronary artery bypass grafting; HF, heart failure; HF with reduced LVEF, Heart Failure with reduced left ventricular ejection fraction, according to guidelines of the ESC, 2002[13] (Mant) and guidelines of the ESC, 2005[6] (Kelder and validation cohort); JVP, jugular venous pressure; MI, myocardial infarction; MR, mitral regurgitation; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; PCI, percutaneous coronary intervention; UKNP, United Kingdom Natriuretic Peptide study, dataset of the UKNP study in which Mant developed the prediction rule. '-' not described.

† As this determinant was not observed in the validation cohort, this value is imputed (see discussion paragraph).

Discrimination, which is the ability of the rule to distinguish between patients with and without heart failure, was quantified with the c-statistic which is the same as the area under the Receiver Operating Characteristic curve (ROC area).[8] Theoretically, a c-statistic ranges from 0.5 (discrimination equivalent to that of chance) to 1.0 (perfect discrimination).[9,14] To illustrate the capacity of the diagnostic rules in diagnosing and ruling out heart failure, numbers of false-positive and false-negative diagnoses were calculated assuming that in case the calculated probability of heart failure exceeds 80%, heart failure is considered present, while probabilities below 20% are considered to indicate ruling out heart failure. Overall, the proportion of missings per variable was less than 1% (range 0-2%). Prior to analysis we applied single imputation of missings.[15] Data were analyzed using the SPSS software (version 17.0 for Windows SPSS Inc., Chicago, IL, USA) and 'R' (version 2.8.1; R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org).

Figure 1. Diagnostic prediction rules

Diagnostic prediction rule of Mant et al[16]

Probability of heart failure:
1/(1 + exp-(-7.54 + logpreodds + 0.81 x male gender + 1.30 x myocardial infaction + 0.38 x ankle oedema + 1.40 x pulmonary rales + 0.99 x log(NT-proBNP + 1))).

The expression '(-7.54 + log preodds + 0.81 x male gender + 1.30 x myocardial infaction + 0.38 x ankle oedema + 1.40 x pulmonary rales + 0.99 x log (NT-proBNP + 1)' is called the linear predictor. In this expression, '-7.54 + log preodds' represents the intercept and the other numbers represent the regression coefficients (weights) of each corresponding predictor. Prevalence of heart failure in the validation cohort was 45.3% resulting in log preodds of -0.19. The formula '1/(1 + exp-(-7.54 + logpreodds….))' represents individual patient baseline risk increased by the presence of any of the other factors.

Diagnostic prediction rule of Kelder et al[17]

Probability of heart failure:
1/(1 + exp-(-7.42 + 0.02 x age + 0.95 x history of coronary disease + 0.57 x the use of a loop diuretic + 0.73 x irregular pulse + 0.02 x heart rate + 1.34 x displaced apex beat + 0.56 x heart murmur suggesting mitral regurgitation + 0.81 x pulmonary rales + 0.68 x elevated jugular venous pressure + 0.49 x log NT-proBNP)).

In this expression '-7.42' includes baseline prevalence of heart failure (-6.62) according to Kelder and adjustment (-0.80) for validation cohort.

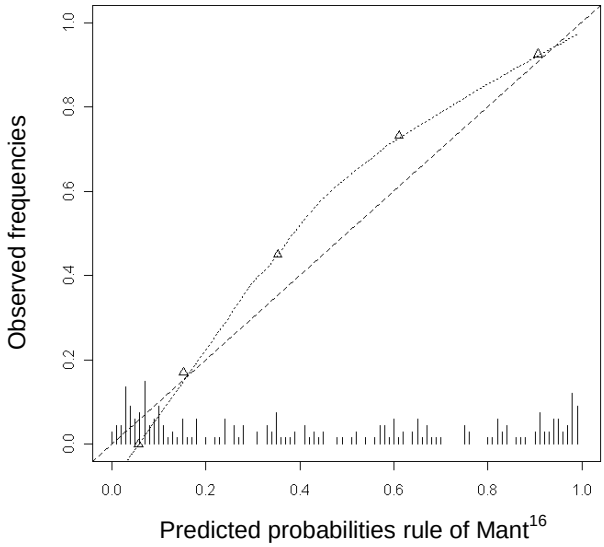
Results

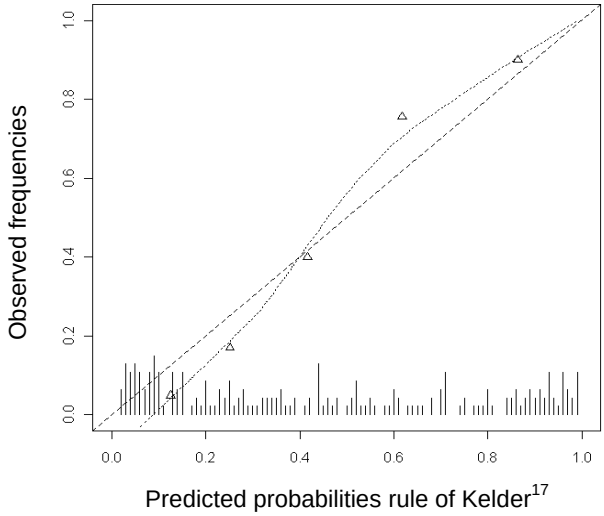
The MEDLINE search identified two diagnostic prediction rules providing an absolute probability of heart failure in individual patients suspected of new, slow onset heart failure: one by Mant *et al*[16] and one by Kelder *et al.*[17] The characteristics of the patients in the derivation cohorts described in the Mant study (participants of the United Kingdom Natriuretic Peptide (UKNP) study[18]; median age 74 years, 58% women), and in the Kelder study (73 years, 65% women) and of the 203 patients of the validation cohort (82 years, 70% women), are presented in Table 1.

Mant developed a diagnostic prediction rule (Figure 1) based on the dataset of the UKNP study, that confirmed the ability of natriuretic peptides to 'rule-out' heart failure in 306 patients (104 (34%) with heart failure) suspected of heart failure by their general practitioner, and was externally validated in five other datasets of patients with possible heart failure.[19-23] The diagnostic prediction rule derived by Kelder predicts the presence or absence of heart failure in primary care patients suspected of heart failure.[17] In this study all patients were referred to a specially equipped rapid access outpatient clinic. The rule was validated in two other datasets of patients suspected of heart failure in primary care.[18,19]

Both diagnostic prediction rules showed good calibration in the geriatric patient cohort for all probabilities (Mant: slope 1.22, intercept 0.39; Kelder: slope 1.45, intercept -0.10; Figure 2) as was confirmed by the Hosmer-Lemeshow tests (both: $p > 0.05$). Discriminative ability of both rules in geriatric patients was good. The c-statistic in the Mant study was 0.90 (95% Confidence Interval (CI) 0.86 - 0.95) in our geriatric population and similar to the c-statistic in the derivation cohort 0.90 (0.86 - 0.93); In the Kelder study the c-statistic in the geriatric cohort was 0.89 (95% CI 0.85 - 0.94), while this was 0.85 (0.82 - 0.88) in the derivation cohort). Thirty five out of 38 (92%) patients with a high probability (> 80%) of heart failure according to the Mant rule actually had heart failure; for the Kelder rule this was the case in 48 out of 54 (90%). In patients with a low predicted probability (< 20%) of heart failure according to the Mant and Kelder rules, 97% (71 out of 73) and 91% (67 out of 74) did not have heart failure respectively. The Mant rule incorrectly diagnosed five (2%) patients (two false positives and three false negatives), and the Kelder rule incorrectly diagnosed 13 (6%) patients (seven false positives and six false negatives).

Figure 2. Calibration of diagnostic prediction rules in 203 geriatric outpatients*





* Agreement between the predicted risks of heart failure according to the diagnostic model and the observed proportions. The smoothed line indicates the agreement between predicted risks of heart failure and observed proportions. The dotted line indicates ideal calibration. The triangles indicate the observed proportions of heart failure with similar predicted risks grouped in quintiles. The vertical lines just above the horizontal axis show the distribution of the predicted risks.

Discussion

Available diagnostic rules for predicting the presence of heart failure (rules by Mant *et al*[16] and by Kelder *et al*[17]) accurately predict the probability of heart failure in geriatric outpatients suspected of new, slow onset heart failure: both rules show good calibration (Mant: slope 1.22, intercept 0.39; Kelder: slope 1.45, intercept -0.10) and discrimination (c-statistic Mant 0.90 (95% CI 0.86 - 0.95); c-statistic Kelder 0.89 (95% CI 0.85 - 0.94)) in our geriatric validation cohort.

Some limitations of our study need to be discussed. The determinant 'heart murmur suggesting mitral regurgitation' of the diagnostic rule of Kelder was not measured in our geriatric cohort. Because a proxy variable was lacking, and the prevalence of this variable in geriatric patients with an undefined heart murmur is not reported in previous studies, we randomly assigned the prevalence of this determinant as observed in the derivation study (41%: 77 of 189 patients with any heart murmur) to the geriatric patient cohort (13 of 33 patients). This option could be applied because the weight of this determinant in the diagnostic rule was relatively low. Otherwise this option could have had a tempering effect on the predictive ability of the rule. An expert panel established the presence or absence of heart failure in the validation cohort based on all diagnostic information including NT-proBNP as recommended by the ESC guidelines of 2005, which at that time did not propose cutoff values for normal levels of NT-proBNP.[7] Because normal values for elderly with slow onset heart failure were unknown and echocardiography is of main importance in the final diagnosis, levels of NT-proBNP were of minor importance for diagnosing heart failure in our study. The first study exploring normal levels of NT-proBNP in diagnosing heart failure in elderly patients was derived in 2006 by Berdagué *et al*.[24] However this study was performed in patients with acute symptoms of heart failure, whereas levels of natriuretic peptides tend to be lower in patients with slow onset heart failure.[18,19] The present cutoff values of the ESC guidelines of 2008 were not part of the diagnostic process in the validation cohort.

A major strength of the present study is that it studies the largest group of geriatric patients suspected of new, slow onset heart failure to date. As previous diagnostic studies have not specifically addressed geriatric populations we set out to apply diagnostic prediction rules for establishing the presence or absence of new, slow onset heart failure to this population frequently excluded to participate in clinical studies.[25] Another strength is that to ascertain applicability in daily practice for geriatricians, only studies were included which evaluated the performance of diagnostic tests available for geriatricians.

The complexity of the two prediction rules studied limits their applicability in daily practice. The number of items included in the Kelder rule is ten. In addition, some items may not be obtained easily (the item 'heart murmur suggesting mitral regurgitation' was not routinely available in the elderly validation cohort and in the population of the UKNP-study), or may have a large inter and intra observer variability. Furthermore, calculating the probability of heart failure with these diagnostic rules is complex due to the mathematical equations. Although an algorithm based on a diagnostic rule is more easy to implement, the algorithm based on Mants rule, including gender, myocardial infarction, ankle oedema, pulmonary rales and NT-proBNP, performed suboptimal.[5] We believe that, despite the good performance of these two rules in geriatric outpatients, simpler diagnostic rules could improve implementation in daily practice. Such a rule should be derived from studies performed in the domain of elderly patients suspected of heart failure, since diagnostic items or their weight may differ in the elderly.
In conclusion, existing diagnostic prediction rules accurately predict the presence or absence of heart failure in geriatric outpatients suspected of new, slow onset heart failure by the geriatrician. These rules may help physicians in their decisions to rule out heart failure, refer for additional diagnostic investigations or initiate targeted therapy. As the use of these rules in daily clinical practice may be limited due to the number and type of items included and complicated equations, alternative, simpler rules or algorithms could be helpful.

Acknowledgements

We wish to thank the participating patients and geriatricians. We also thank Professor M.R. Cowie, Department of Clinical Cardiology, National Heart & Lung Institute, Imperial College, Royal Brompton Campus, London, United Kingdom for allowing us to use the United Kingdom Natriuretic Peptide (UKNP) study data, and Professor J. Mant, General Practice and Primary Care Research Unit, University of Cambridge, United Kingdom, for allowing us to use the logistic regression equation for the clinical model of his diagnostic prediction rule.

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Appendix

Appendix 1. Search strategy

Search	**Limits**
“practice guideline”[Publication Type] AND “heart failure”[MeSH]	English
“clinical prediction models heart failure”	English
“heart failure”[MeSH] AND “prediction models”	English
“multivariate analysis”[MeSH] AND “heart failure/diagnosis”[MeSH]	English
“models, statistical”[MeSH] AND “heart failure/diagnosis”[MeSH]	English
“heart failure/diagnosis”[MeSH] AND (“algorithm” OR “multivariate analysis” OR “logistic model” OR “biological model” OR “statistical model” OR “mathematics” OR “regression analysis” OR “risk factor” OR “risk assessment” OR “predictive value” OR “area under curve” OR “evaluation study” OR “evaluation” OR “reproducibility” OR “prediction” OR “prediction rule” OR “predict”)	English, clinical trial and review

Chapter 5

Clinical evaluation of geriatric outpatients with suspected heart failure: value of symptoms, signs and additional tests

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Johanna A.M. Bloemen
Mark J.M. Valk
Edwin van Velzen
Jos P.M. Wielders
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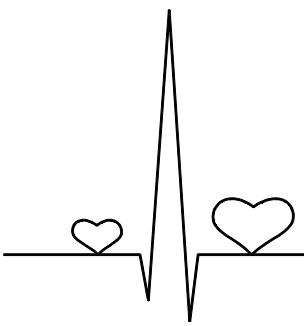


Eur J Heart Fail 2011;13:518-527

Abstract

Aims

Heart failure is common in geriatric patients. Clinicians face diagnostic challenges primarily due to comorbidity and limited access to echocardiography. The purpose of this study was to identify independent determinants of the presence of heart failure in geriatric outpatients and to determine the optimal diagnostic strategy.

Methods and Results

Geriatric outpatients (mean age 82 (± 6) years, 30% men) with suspected heart failure underwent an extensive standardized diagnostic work-up. An expert consensus panel determined the presence of heart failure. Heart failure was present in 94 of 206 participants (46%). Male sex (Odds Ratio (OR) 2.0), age per 10 years (OR 1.6), nocturnal dyspnoea (OR 1.7), absence of wheezing (OR 2.1), loss of appetite (OR 1.7), and lower body mass index (BMI; OR 0.9) were independently associated with the presence of heart failure: the c-statistic of the model containing these items was 0.75. Of all additional tests, N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) improved the diagnostic accuracy the most (OR ln NT-proBNP 2.8; c-statistic 0.92). A diagnostic rule, consisting of six clinical variables and NT-proBNP, showed good negative and positive predictive values.

Conclusions

Half of geriatric patients suspected of heart failure actually have heart failure. Apart from age, gender and nocturnal dyspnoea, absence of wheezing, loss of appetite and lower BMI were independently associated with the presence of heart failure. Symptoms and signs in combination with NT-proBNP reliably identified the presence or absence of heart failure in the vast majority of patients. Additional diagnostic tests, in particular echocardiography, can be targeted at those in whom the presence of heart failure remains uncertain and to ascertain the cause of heart failure.

Introduction

The ageing of the population and improved survival following acute cardiac events has led to an increased prevalence of heart failure, especially in the elderly.[1,2] Early detection of heart failure is notoriously difficult, particularly in patients with a wide range of (both cardiovascular and non-cardiovascular) comorbidities and in a setting without direct access to echocardiography, such as in primary care or geriatric practice.[3] In the elderly, comorbid conditions such as chronic obstructive pulmonary disease, obesity, chronic venous insufficiency, cognitive impairment or hearing problems are frequently present, hampering clinical assessment.[4,5] Assessing the presence or absence of heart failure merely based on symptoms and signs, often leads to an incorrect diagnosis, but this approach is frequently taken in general practice.[6-8] The diagnostic work-up (e.g. electrocardiography (ECG), chest X-ray, echocardiography) in suspected heart failure in geriatric patients is further complicated by immobility and comorbidity.[3] The introduction of natriuretic peptides has revolutionized the assessment of heart failure, even in settings with limited access to echocardiography.[6,9]

No study to date has specifically assessed the diagnostic value of symptoms, signs and additional tests (notably natriuretic peptides, ECG and chest X-ray) in geriatric patients suspected of heart failure. The aim of this study was to identify independent determinants of the presence of heart failure in geriatric patients suspected of new, slow onset heart failure. In addition, we set out to develop an easily applicable diagnostic rule to predict the probability of heart failure in these patients.

Methods

Study population

Patients referred to the geriatric outpatient clinic - for a variety of reasons notably functional impairment, breathlessness, cognitive impairment, and mobility disorders - of two regional hospitals in the Netherlands (Elkerliek Hospital, Helmond and Meander Medical Center, Amersfoort) who presented with symptoms of breathlessness, fatigue, ankle swelling, or any combination of these were eligible. Patients were excluded when (i) ankle swelling was the single sign present and was evidently caused by venous insufficiency, (ii) emergency admission for heart failure was needed, (iii) a diagnosis of heart failure had already been established earlier by a cardiologist or (iv) when written consent was not obtained.

All participants or their representatives, in case of impaired cognition, gave written consent. Patient recruitment started in July 2003 and ended in July 2007. The study was approved by the Medical Ethical Committees of both participating hospitals.

Diagnostic work-up

All participants underwent a diagnostic work-up including standardized clinical history, physical examination, ECG, chest X-ray, laboratory tests, echocardiography and pulmonary function tests. Data on comorbidities were obtained from discussions with the patient and his or her family, from the general practitioner referral letter, from letters written by other specialists retrieved from the hospital information system and as established by the geriatrician. Information on symptoms and medication use was obtained using a standardized questionnaire. The physical examination performed by the geriatrician, included blood pressure measurements with a sphygmomanometer, palpation of the apical impulse in decubital position, auscultation of the heart, pulmonary and abdominal examination, and assessment of the jugular venous pressure (JVP) and peripheral oedema. Height and weight were measured without shoes and with light clothing.

A standard 12-lead ECG was recorded and classified by a trained geriatrician (IO) together with a cardiologist (AM). An abnormal ECG was defined as an ECG showing atrial fibrillation, complete or incomplete left bundle branch block, prior myocardial infarction, left ventricular hypertrophy, ST and/or T-wave abnormalities, sinus tachycardia, pacemaker rhythm or second degree or complete atrio-ventricular block. Posterior-anterior and lateral plane chest X-rays were taken in the standing position and classified by a radiologist and a pulmonologist (EV). Laboratory tests consisted of complete blood count, electrolytes, renal function (estimated glomerular filtration rate according to the Modification of Diet in Renal Disease study group equation (eGFR MDRD)), urea, glucose, hepatic enzymes, C-reactive protein (CRP), thyroid stimulating hormone (TSH) and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels.[10] Pulmonary function tests consisted of spirometric measurements and were done on a Jaeger Masterscreen MS Body (Cardinal Health Netherlands 214 B.V., Kleve, Germany). Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured before and after bronchodilation. The presence of chronic obstructive pulmonary disease (COPD) was based on patient history and clinical symptoms in accordance with the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria.[11] Trained pulmonary function technicians performed all measurements and the quality of the

flow-volume curves was assessed by a pulmonologist (EV) and a trained geriatrician (IO).
In both hospitals, routine echocardiograms were made using a Philips Ultrasound-HP Sonos 5500 Echocardiography System (Philips Healthcare Nederland B.V., Eindhoven, The Netherlands) by trained cardiosonographers. Images were interpreted by a cardiologist and reviewed by the cardiologist involved in the present study (AM). Left ventricular ejection fraction (LVEF) was measured quantitatively by the two-dimensional method and semiquantatively with the visual estimate method ('eyeballing').[12] (Doppler) Measurements included left atrial dimension, pulmonary vein flow velocity, E- and A-wave velocity as well as E-deceleration time. E/A velocity ratio was calculated. Tissue Doppler Imaging was not available. Images were stored for off-line assessments.
After the diagnostic assessment, the patient's own geriatrician started treatment with care as usual. In case of heart failure, patients were treated according to the guidelines of the European Society of Cardiology (ESC).[13]

Diagnostic outcome (reference standard)
The primary outcome of the study was the presence of heart failure at the time of initial presentation. An expert panel consisting of a cardiologist, general practitioner, pulmonologist and geriatrician used all available diagnostic information, including echocardiography, response to treatment, relevant clinical information and six months follow up. The expert panel was blinded to serum NT-proBNP levels.[14]
The diagnostic criteria for heart failure of the ESC were applied.[13] Heart failure was considered present when symptoms and signs indicative of heart failure (such as breathlessness, ankle swelling, fatigue, pulmonary rales, elevated JVP) were present combined with objective echocardiographic evidence of cardiac dysfunction at rest. Heart failure was classified as present or absent. In cases when the expert panel was in doubt heart failure was considered absent.
Patients with heart failure were further classified as having systolic heart failure, heart failure with preserved ejection fraction (HFPEF), isolated right sided heart failure, or heart failure due to valvular dysfunction. Systolic heart failure was present when LVEF was less than 45%. Echocardiographic evidence of diastolic dysfunction (abnormal left ventricular relaxation or diastolic stiffness) in combination with LVEF $\geq$ 45% was necessary to diagnose HFPEF.[13] Isolated right sided heart failure was defined as increased right atrial pressure, estimated from the respiratory variation in diameter of the caval vein or right ventricular dysfunction assessed semi quantitatively by the two dimensional visual estimate method, or

both, and LVEF ≥ 45%. Heart failure was attributed to valvular dysfunction in case of severe valvular stenosis or regurgitation in combination with normal left ventricular function.
The reproducibility of the diagnoses made by the expert panel was evaluated by re-testing a random sample of 10% (n = 21) by the same expert panel.

Data analysis

We first quantified the association of all individual potential diagnostic determinants with the presence or absence of heart failure using univariable logistic regression analysis. Subsequently, variables with a p-value < 0.15 in the univariate analyses were included in the multivariable logistic regression analysis to determine which diagnostic items were independently associated with the presence of heart failure. Since diagnostic work-up in daily medical practice starts with patient history followed by physical examination and finally additional diagnostic tests, variables were included in the multivariable model in this hierarchical way.[15] First, the multivariate model was built with variables from history taking and physical examination. Model reduction was performed by excluding variables (one by one) with a p-value > 0.10 based on the likelihood ratio test (stepwise backwards). The discriminative ability of this clinical model was quantified by the c-statistic (also known as area under the Receiver Operating Characteristic curve), while the calibration was tested with the Hosmer-Lemeshow statistic.[16] Calibration, which is the agreement between the observed proportions of heart failure and the predicted risks, was studied with a calibration plot.[16] To correct for over-fitting and over-optimism (i.e. to assure that the model would be as realistic as possible when applied in new patients) the model was internally validated with bootstrapping techniques, where in each bootstrap sample the entire modelling process was repeated.[16] This technique resulted in a shrinkage factor for the regression coefficients and a c-statistic corrected for over-optimism.[17] Subsequently, univariate variables from ECG, chest X-ray and laboratory tests were added one by one, to judge whether they yielded independent diagnostic value beyond the clinical model. Additional tests were added until there was no further improvement in the model. Discriminative ability was quantified, calibration was tested and bootstrapping techniques were applied for this diagnostic model.
To construct an easily applicable diagnostic rule or points score we transformed the original regression coefficients of the variables in the final model to integers according to their relative contributions to the risk estimation. Afterwards continuous variables were clustered into groups with similar predictive probabilities of the presence of heart failure. Score thresholds for ruling in and ruling out heart

failure were introduced based on clinically acceptable probabilities of false positive (20%) and false negative (20%) diagnoses. After calculating the diagnostic score for each patient, the observed percentages of correctly diagnosed patients across score categories were estimated.

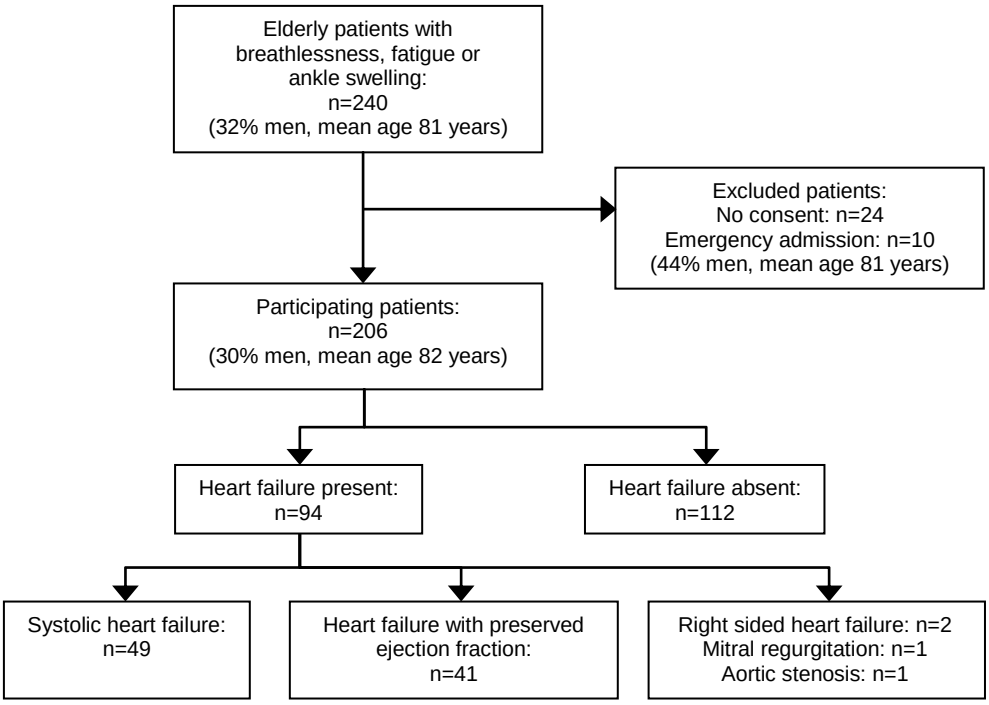
Overall the number of missing values was low with less than 1% (range 0-4%) missing per variable with the exception of spirometric measurements. Spirometric measurements were performed in 157 (76%) patients. Because spirometry is not needed for diagnosing heart failure, it was not included in the diagnostic models.[9] To prevent biased results due to incomplete data, instead of performing a complete case analysis, we imputed values prior to regression analysis, by using a regression method with the addition of a random error term.[18] NT-proBNP values were logarithmically transformed to obtain normal distributions. Thresholds of NT-proBNP levels were taken from the latest guidelines.[9] Data were analyzed using the SPSS software (version 15.0 for Windows SPSS Inc., Chicago, IL, USA) and S-plus (version 6.1, 2002; Insightful Corp., Seattle, Washington).

Results

Of the 240 eligible patients, 206 (86%) were included in the study (Figure 1). Twenty-four patients did not consent to participate. Ten patients were excluded because of emergency admission for heart failure. Heart failure was present in 94 (46%) of the 206 participating geriatric outpatients suspected of heart failure by the geriatrician, of whom the majority was female (70%), and the average age was 82 (Standard Deviation (SD) 6) years (Table 1). Forty nine patients (52%) had 'systolic' heart failure (median LVEF 35% (Inter Quartile Range (IQR) 27.5 - 40.0)) and 41 (44%) had HFPEF (median LVEF 50% (IQR 45.0 - 60.0)). In four patients left ventricular function was normal but heart failure was present due to right-sided heart failure (two patients), mitral regurgitation (one patient) and aortic stenosis (one patient). Twenty-eight (68%) patients with HFPEF had a LVEF between 45% to 55%, and 13 (32%) a LVEF above 55%.

The main reasons for referral were functional impairment (40%) and breathlessness (35%), followed by cognitive impairment (31%) and mobility disorders (29%). Half of the patients were referred for two or more reasons (51%). The median number of drugs per patient was six. Patients who were found to have heart failure more frequently used digitalis (22% and 4% respectively; $p < 0.01$) and oral anticoagulants (21% and 6% respectively; $p < 0.01$; Table 1) than those

Figure 1. Flow chart of patient participation*



* Excluded and participating patients did not differ regarding gender and age (p-values 0.11 and 0.37, respectively).

without heart failure. The use of other medications did not differ between the two groups. There was a wide range of cardiovascular and non-cardiovascular comorbidity, the average number of comorbidities per patient was six (Table 2). Male sex, age, nocturnal dyspnoea, absence of wheezing, nocturia, loss of appetite, ischaemic heart disease, lower body mass index (BMI), elevated JVP, and pulmonary rales were more prevalent in patients with heart failure (Tables 1 and 2). In 32% of patients with heart failure no classic signs (i.e. presence of tachypnoea, pulmonary rales, pleural effusion, elevated JVP, peripheral oedema or hepatomegaly) of heart failure were present. Independent determinants of the presence of heart failure were male sex, age, nocturnal dyspnoea, absence of wheezing, loss of appetite and lower BMI (clinical model, c-statistic 0.75 (95% CI 0.69 - 0.82, Table 3). Of all additional diagnostic tests, atrial fibrillation on ECG, abnormal ECG, cardiothoracic ratio (CTR) > 0.50, pleural effusion on chest X-ray, eGFR MDRD and NT-proBNP were univariate determinants of heart failure (Table 4). Of these tests, NT-proBNP had the largest added value, i.e. it had the most

Table 1. Clinical characteristics of 206 geriatric patients with suspected heart failure, according to the presence or absence of new, slow onset heart failure*

Characteristic	All n = 206	HF present n = 94	HF absent n = 112	p-value
Age, years	82 ± 6	83 ± 5	80 ± 6	< 0.01
Male sex	62 (30)	35 (37)	27 (24)	0.04
Clinical history				
Breathlessness during exertion	190 (92)	87 (93)	103 (92)	0.88
Fatigue	176 (85)	79 (84)	97 (87)	0.60
Nocturnal dyspnoea or orthopnea	63 (31)	35 (37)	28 (25)	0.06
Absence of wheezing	153 (74)	77 (82)	76 (68)	0.02
Nocturia twice or more per night	100 (49)	51 (54)	49 (44)	0.13
Loss of appetite	61 (30)	40 (43)	21 (19)	< 0.01
Drugs				
Loop diuretic	72 (35)	37 (39)	35 (31)	0.22
ACE-i/ARBs	68 (33)	33 (35)	35 (31)	0.56
Beta-blockers	47 (23)	25 (27)	22 (20)	0.24
Digitalis	25 (12)	21 (22)	4 (4)	< 0.01
Aldosterone antagonists	17 (8)	9 (10)	8 (7)	0.53
Oral anticoagulants	27 (13)	20 (21)	7 (6)	< 0.01
Antiplatelets	83 (40)	39 (42)	44 (39)	0.75
NSAID	17 (8)	8 (9)	9 (8)	0.90
Antidiabetic drugs	50 (24)	21 (22)	29 (26)	0.55
Treatment for COPD	54 (26)	27 (29)	27 (24)	0.45
Drugs, number	6 (4-8)	6 (5-8)	5 (4-9)	0.97
Physical examination				
Systolic blood pressure, mm Hg	156 (27)	156 (28)	156 (25)	0.93
Diastolic blood pressure, mm Hg	82 (12)	82 (12)	81 (11)	0.42
Heart rate, bpm	76 (70-80)	76 (70-81)	76 (70-80)	0.68
Irregular pulse	56 (27)	41 (44)	15 (13)	< 0.01
Body Mass Index, kg/m^2	26 (23-29)	25 (21-28)	27 (24-31)	< 0.01
Laterally displaced apex beat	9 (4)	6 (6)	3 (3)	0.31
Elevated JVP	22 (11)	15 (16)	7 (6)	0.03
Pulmonary rales more than basal	14 (7)	10 (11)	4 (4)	0.05
Rhonchi	14 (7)	6 (6)	8 (7)	0.83
Bilateral ankle swelling	80 (39)	40 (43)	40 (36)	0.32
No classic signs of heart failure	79 (39)	30 (32)	49 (44)	0.08

* Data are presented as mean ± standard deviation, median (Inter Quartile Range: 25^{th} - 75^{th} percentiles), or number (%) of patients. ACE-i, angiotensin-converting enzyme-inhibitor; Antidiabetic drugs, both oral and parenteral drugs; ARBs, angiotensin II receptor blockers; bpm, beats per minute; classic signs of heart failure, including tachycardia, tachypnoea, pulmonary rales, pleural effusion, elevated JVP, peripheral oedema, and hepatomegaly; COPD, chronic obstructive pulmonary disease; HF, heart failure; JVP, jugular venous pressure; NSAID, non-steroidal anti-inflammatory drugs.

Table 2. Comorbidities and risk factors of 206 geriatric patients with suspected heart failure, according to the presence or absence of new, slow onset heart failure*

	All n = 206	HF present n = 94	HF absent n = 112	p-value
Cardiovascular comorbidities and risk factors				
Ischaemic heart disease	41 (20)	24 (26)	17 (15)	0.06
Myocardial infarction	23 (11)	16 (17)	7 (6)	0.01
Angina pectoris	17 (8)	7 (7)	10 (9)	0.70
Vascular comorbidity	124 (60)	55 (59)	69 (62)	0.65
Hypertension	89 (43)	39 (41)	50 (45)	0.65
Diabetes mellitus	57 (28)	25 (27)	32 (29)	0.75
CVA or TIA	41 (20)	20 (21)	21 (19)	0.65
Valvular disorders	18 (9)	13 (14)	5 (4)	0.02
Atrial fibrillation	43 (21)	36 (38)	7 (6)	< 0.01
Overweight	82 (40)	34 (36)	48 (43)	0.33
Obesity	36 (17)	8 (9)	28 (25)	< 0.01
Current smoker	30 (15)	17 (18)	13 (12)	0.20
Non-cardiovascular comorbidity				
Visual impairment	99 (48)	48 (51)	51 (46)	0.43
Hearing impairment	75 (36)	32 (34)	43 (38)	0.52
Cognitive disorder	63 (31)	25 (27)	38 (34)	0.26
Osteoarthritis	61 (30)	25 (27)	36 (32)	0.39
COPD	55 (27)	26 (28)	29 (26)	0.78
Mood disorders	48 (23)	23 (24)	25 (22)	0.72
Urinary tract problems	46 (22)	19 (20)	27 (24)	0.50
Vitamin deficiency	44 (21)	21 (22)	23 (21)	0.75
Orthostatic hypotension	34 (17)	14 (15)	20 (18)	0.57
Osteoporosis	34 (17)	13 (14)	21 (19)	0.34
Malignancies	31 (15)	16 (17)	15 (13)	0.47
Constipation	31 (15)	18 (19)	13 (12)	0.13
Anaemia	22 (11)	8 (9)	14 (13)	0.36
Renal insufficiency	17 (8)	9 (10)	8 (7)	0.53
Gastritis	12 (6)	5 (5)	7 (6)	0.78
Thyroid dysfunction	5 (2)	4 (4)	1 (1)	0.18

* Data are presented as number (%) of patients. CVA, cerebro vascular accident; TIA, transient ischaemic attack; Ischaemic heart disease includes prior myocardial infarction, angina pectoris, coronary artery bypass grafting, and percutaneous coronary intervention; Overweight, body mass index (BMI) 25 - 30 kg/m^2; Obesity, BMI > 30 kg/m^2; Vascular comorbidity includes hypertension, diabetes mellitus, stroke, and peripheral artery disease; Visual impairment includes cataract, blindness or glaucoma; other abbreviations as in Table 1.

profound effect on the c-statistic, with an increase from 0.75 (95% CI 0.69 - 0.82) to 0.92 (95% CI 0.88 - 0.95; diagnostic model, Table 5). Using the diagnostic model, we formulated the diagnostic rule (Table 6) with a c-statistic of 0.90 (95% CI 0.86 - 0.94), after correction for over-optimism (shrinkage factor of 0.70). Both the Hosmer-Lemeshow test (p-value > 0.05) and the calibration plot indicated good calibration (Figure 2). Scores in the diagnostic rule ranged from 1 to 67 points. Applying 16 and 32 points as cut-off values, 96 patients (47% of total study group) were in the low risk group (sensitivity 0.88; specificity 0.76; positive predictive value (PPV) 0.75; negative predictive value (NPV) 0.89) and 78 patients (38%) were in the high risk group (sensitivity 0.73; specificity 0.92; PPV 0.88; NPV 0.80). The remaining 32 patients (16% of the study group) were in the medium risk group.

Table 3. Determinants of the presence of heart failure from clinical history and physical examination*

	Unadjusted	Multivariate model	Clinical model
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Clinical history			
Male sex	1.9 (1.0-3.4)	2.2 (1.1-4.7)	2.7 (1.3-5.5)
Age (per 10 years)	2.3 (1.4-3.9)	2.0 (1.1-3.7)	1.9 (1.1-3.6)
Nocturnal dyspnoea or orthopnea	1.8 (1.0-3.2)	2.0 (0.9-4.1)	2.2 (1.1-4.5)
Absence of wheezing	2.1 (1.1-4.1)	2.4 (1.1-5.1)	2.6 (1.2-5.5)
Nocturia twice per night or more	1.6 (0.9-2.8)	1.4 (0.8-2.7)	
Loss of appetite	3.2 (1.7-6.0)	2.1 (1.0-4.4)	2.2 (1.1-4.5)
Current smoker	1.7 (0.8-3.7)		
Comorbidity			
Myocardial infarction	3.1 (1.2-7.8)	3.0 (1.1-8.6)	
Vascular comorbidity	0.9 (0.5-1.5)		
Physical examination			
Heart rate (per beat/min)	1.0 (0.9-1.0)		
Body Mass Index (per kg/m^2)	0.9 (0.8-0.9)	0.9 (0.9-1.0)	0.9 (0.9-1.0)
Elevated JVP	2.8 (1.1-7.3)	1.6 (0.6-4.7)	
Pulmonary rales more than basal	3.2 (1.0-10.6)	2.1 (0.5-9.0)	
Bilateral ankle swelling	1.3 (0.8-2.3)		
c-statistic			0.75 (0.69-0.82)

* CI, confidence interval; OR, odds ratio; other abbreviations as in Table 1.

Table 4. Unadjusted values of different diagnostic tests in predicting heart failure in geriatric patients with suspected heart failure*

	HF present n = 94	HF absent n = 112	OR (95% CI)
ECG			
Atrial fibrillation	34 (36)	3 (3)	20.6 (6.1-69.9)
Abnormal ECG	82 (87)	65 (58)	4.9 (2.4-10.1)
Chest X-ray			
CTR > 0.50	70 (74)	55 (49)	3.3 (1.8-6.0)
Pleural effusion	19 (20)	1 (1)	28.1 (3.7-214)
Laboratory tests			
eGFR MDRD, ml/min/1.73 m^{2} †	58 (45-73)	67 (53-77)	0.9 (0.7-1.0)
NT-proBNP, pg/ml‡	2162 (727-5302)	213 (109-340)	4.5 (3.1-6.8)

* CTR, cardio thoracic ratio; eGFR MDRD, estimated glomerular filtration rate according to the modification of diet in renal disease study group equation; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; other abbreviations as in Tables 1 and 3.
† OR: per 10 ml/min/1.73m^2 increase.
‡ OR: per ln pg/ml increase.

The reproducibility of the expert panel diagnosis of heart failure, which was re-evaluated in 10% of the participants by the same expert panel, was good (Cohen's kappa: κ = 0.90). In one case, initially classified as no heart failure, HFPEF was classified during the re-evaluation. This woman with hypertension, dyspnoea during light exercise, oedema, nocturia and recent weight gain had a normal ECG and an enlarged CTR at chest X-ray. Echocardiography showed a normal LVEF, with a decreased E/A ratio indicative of impaired relaxation of the left ventricle. Her NT-proBNP turned out to be 86 pg/ml.

Discussion

New, slow onset heart failure was found to be present in 94 (46%) of 206 geriatric outpatients referred for various reasons (including functional impairment, breathlessness, cognitive impairment and mobility disorders) who were suspected of heart failure by the geriatrician because of the presence of breathlessness, fatigue or ankle swelling. Male sex (OR 2.0), age (OR per 10 years 1.6), nocturnal dyspnoea (OR 1.7), absence of wheezing at history taking (OR 2.1), loss of appetite (OR 1.7), and lower BMI (OR 0.9) were independent determinants of the presence of heart failure: the c-statistic of the model containing these items was

0.75. The diagnostic accuracy of this model improved most by adding NT-proBNP (OR ln NT-proBNP 2.8; c-statistic 0.92).

This is the first study to identify determinants of heart failure in elderly outpatients suspected of heart failure by the geriatrician with a wide range of cardiovascular and non-cardiovascular comorbidity, whose primary reason for referral was not heart failure, but rather a variety of reasons that warranted geriatric evaluation. The prevalence of heart failure in these patients was high (46%), in line with findings from an earlier study.[19] Apart from factors generally known to be associated with heart failure (age, male sex and nocturnal dyspnoea), we found new symptoms and signs (loss of appetite, absence of wheezing at history taking and lower BMI)

Table 5. Multivariable models predicting the presence of heart failure in geriatric patients with suspected heart failure*

Model	OR (95% CI)	p-value	c-statistic (95% CI)	p-value likelihood ratio test
Clinical model:			0.75 (0.69-0.82)	
Male sex	2.0 (1.0-4.1)	0.10		
Age, per 10 years	1.6 (1.5-1.7)	0.14		
Nocturnal dyspnoea or orthopnea	1.7 (0.8-3.5)	0.15		
Absence of wheezing	2.0 (0.9-4.2)	0.11		
Loss of appetite	1.7 (0.9-3.6)	0.14		
BMI, kg/m^2	0.9 (0.9-1.0)	0.13		
Clinical model +				
Atrial fibrillation	9.0 (2.3-35.6)	0.04	0.81 (0.75-0.87)	< 0.01
Abnormal ECG	2.8 (1.3-6.1)	0.05	0.79 (0.73-0.85)	< 0.01
CTR > 0.50	2.4 (1.2-4.8)	0.06	0.78 (0.72-0.84)	< 0.01
Pleural effusion	7.8 (1.0-61.5)	0.10	0.78 (0.72-0.85)	< 0.01
ln NT-proBNP	2.8 (1.8-4.2)	0.01	0.92 (0.88-0.95)	< 0.01
Clinical model + ln NT-proBNP +				
Atrial fibrillation	2.7 (0.6-11.6)	0.17	0.92 (0.88-0.95)	< 0.01
Abnormal ECG	1.4 (0.5-3.6)	0.32	0.91 (0.88-0.95)	< 0.01
CTR > 0.50	1.4 (0.6-3.3)	0.32	0.91 (0.88-0.95)	< 0.01
Pleural effusion	6.6 (0.6-75.0)	0.14	0.92 (0.89-0.96)	< 0.01

* ln NT-proBNP, natural logarithm of N-Terminal pro B-type Natriuretic Peptide; other abbreviations as in previous tables. All models are corrected for over-fitting and over-optimism resulting in slightly different odds ratios compared to odds ratios presented in Table 3.

related to heart failure in geriatric outpatients suspected of heart failure.[14,20] Our findings confirm and extend the notion that the presentation of heart failure in elderly patients is often atypical because comorbid conditions can mimic or mask symptoms and signs of heart failure.[3,21] Loss of appetite and a lower BMI may be caused by prolonged hepatic congestion or malnutrition, suggesting cardiac cachexia, which often complicates terminal stages of heart failure.[22] In geriatric patients suspected of heart failure, physicians should enquire about loss of appetite and estimate BMI. Both heart failure and COPD are important - and not necessarily mutually exclusive - differential diagnostic considerations in patients complaining of shortness of breath.[14,23] In patients complaining of wheezing, compared to those without these symptoms, COPD was more prevalent (53% and 18% respectively; $p < 0.01$, data not shown). Our study, despite being one of the

Table 6. Summary of points scores in the diagnostic rule*

Characteristic		Points
Male sex		6
Age (years)	≤ 70	0
	71-75	1
	76-80	2
	81-85	3
	86-90	4
	≥ 91	5
Nocturnal dyspnoea or orthopnea		6
Wheezing		-3
Loss of appetite		3
Body Mass Index (kg/m^2)	< 20.0	8
	20.0-24.9	6
	25.0-29.9	4
	30.0-34.9	2
	≥ 35.0	0
NT-proBNP (pg/ml)	< 400	0
	400-2000	20
	> 2000	40
c-statistic		0.90 (0.86-0.94)

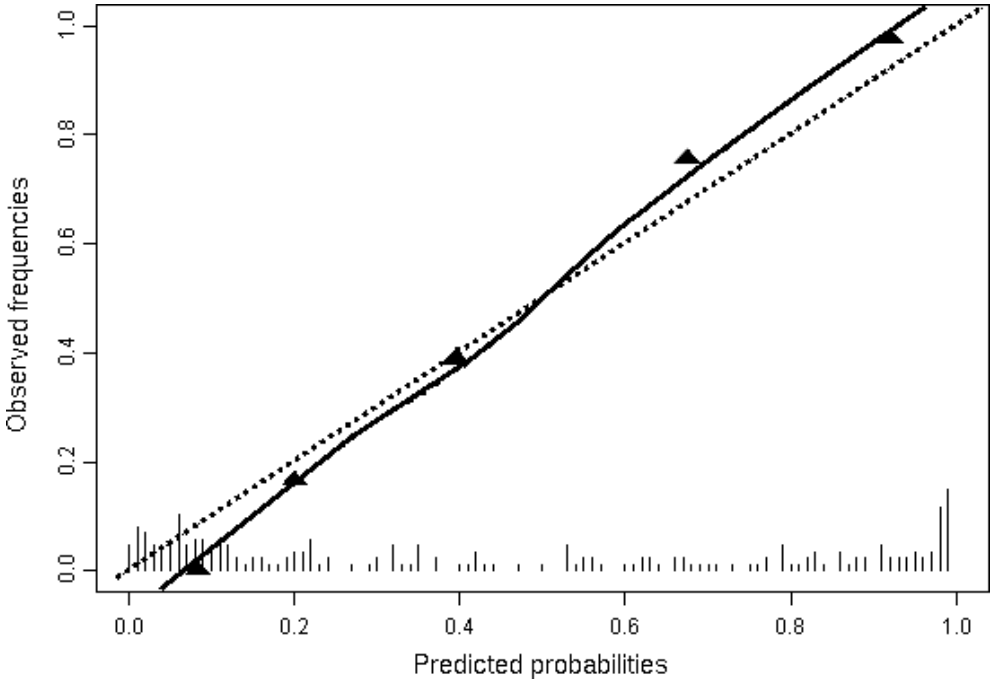
* The clinical model in combination with NT-proBNP is called the diagnostic model. Probability of heart failure as estimated by this model = 1/(1+exp-(-11.09 + 0.61*male gender + 0.02*age per year + 0.60*nocturnal dyspnoea or orthopnea – 0.32*wheezing at history taking + 0.34*loss of appetite – 0.03*BMI + 1.01*ln NT-proBNP)) in which -11.09 is the intercept and other numbers are regression coefficients (relative weights or log odds ratios) of the diagnostic tests, adjusted for over-fitting. If a geriatric patient with suspected new, slow onset heart failure has a score of 16 points or less according to the diagnostic rule, heart failure is unlikely to be the cause. If a patient has a score of 32 points or more, heart failure is likely to be present. In all other patients the diagnosis is unclear and further diagnostic tests are warranted.

largest available diagnostic studies in heart failure, lacked power to perform full subgroup analyses according to the main reason for referral (functional impairment, breathlessness, cognitive impairment and mobility disorders). Importantly, however, the differences in the presence of the three cornerstone signs and symptoms of heart failure (breathlessness, fatigue and ankle oedema) according to the reason for referral were limited, although fatigue was observed more frequently in those referred because of functional impairment and less frequently in those referred because of cognitive impairment (data not shown). This underscores the atypical presentation of new, slow onset heart failure in geriatric outpatients. Apart from cardiac and pulmonary disease, breathlessness can be caused by multiple other causes, such as neurological or muscular disorders, poor physical condition, obesity, severe kyphoscoliosis or anxiety. This is especially important in the elderly. Elderly patients in whom shortness of breath is not readily attributable to cardiac or pulmonary disease – typically resulting in referral to a cardiologist or pulmonologist – are frequently referred to a geriatric outpatient clinic and, as shown in our study, for a variety of reasons. Digitalis and oral anticoagulants were used more frequently in patients with heart failure, very likely reflecting the high prevalence of atrial fibrillation in heart failure patients. The use of other medications known to improve symptoms and/or prognosis of heart failure, notably loop diuretics, angiotensin-converting enzyme-inhibitors and beta-blockers, did not differ between patients with and without heart failure.

Another finding of interest is that in almost one third of patients with heart failure no classic signs of heart failure were present on physical examination. Signs may be present less often in elderly patients compared to adult patients, or may be more difficult to detect due to the wide range of comorbidities present.[24] Interestingly, the proportion of oedema in patients with or without heart failure was similar. This could be explained by the presence of alternative causes of oedema.[25]

Levels of NT-proBNP are lowest in patients screened for heart failure, higher in patients suspected of slow onset heart failure (e.g. as in primary care), and highest in patients with acute heart failure.[14,26-29] In our study, levels of NT-proBNP were high despite the fact that these patients had slow onset heart failure. It is well known that NT-proBNP levels, even in the absence of heart failure, are higher in women, the elderly, and in those with renal insufficiency or a lower BMI.[30-32] These were all characteristics of our study group, which at least partially explains the higher levels of NT-proBNP. Diagnostic delay may also play a role, resulting in more severe disease and higher levels of NT-proBNP at initial presentation.[30]

Figure 2. Agreement between the predicted risk of heart failure according to the diagnostic model and the observed proportions – calibration of the diagnostic model*



* Smoothed line indicates agreement between predicted risks of heart failure and observed proportions. Diagonal line indicates ideal calibration (line of identity). Triangles indicate the observed proportions of heart failure with similar predicted risks grouped in quintiles. Lower part of the figure: histogram of the predicted probabilities.

Correctly diagnosing heart failure in geriatric outpatients suspected of having heart failure by the geriatrician improved considerably when adding NT-proBNP to signs and symptoms. The resulting diagnostic rule, consisting of six clinical variables and NT-proBNP, identified three groups of patients: patients without (47% of total population), with (38%), and with possible (16%) heart failure. In the first two groups, geriatricians can exclude heart failure safely or start treatment for heart failure, respectively. Thus the diagnosis remains uncertain in only a minority of patients and additional tests are needed to establish a correct diagnosis. Cut-off points were chosen with high negative and positive predicted values to prevent an incorrect heart failure diagnosis as much as possible. In case of false negative findings untreated heart failure will deteriorate resulting in reconsideration of the initial diagnosis. In patients with an incorrect (false positive) diagnosis of heart

failure treatment can lead to adverse drug effects or drug interactions without improvement of symptoms and signs.

Some limitations of our study need to be discussed. Tissue Doppler imaging was not available at the time of the study (2003 - 2007) but echocardiography was performed according to the prevailing guidelines and HFPEF was assessed by measuring LVEF in combination with conventional diastolic function parameters.[13] Although the proportion of patients with HFPEF (44%) might be considered low, a similar estimate was reported in a previous study of geriatric patients with suspected heart failure.[19] The expert panel based its conclusion on all available diagnostic findings, except for NT-proBNP levels. This could have resulted in some incorporation bias, which is an important issue in this type of diagnostic research.[15] However, information about symptoms, signs, ECG, chest X-ray and echocardiography is crucial for the expert panel to prevent misclassification in the final diagnosis.[14] Moreover, variables that were shown to be independently related to heart failure (BMI, loss of appetite, absence of wheezing) in our study are not generally seen as important diagnostic markers. Importantly, levels of NT-proBNP were not available to the expert panel, and therefore incorporation bias did not apply to NT-proBNP. Furthermore incorporation bias for all other tests, including signs and symptoms, is probably limited due to the importance of echocardiography in the final diagnosis of the expert panel. Another limitation is the lack of external validation of our diagnostic rule. Although we did adjust for over-fitting and over-optimism (i.e. 'internal validation'), the accuracy of our diagnostic rule awaits further testing in other elderly patient groups suspected of heart failure (external validation). We are not aware of any geriatric cohorts available for this analysis. A final limitation concerns data collection in our study, which was completed before publication of the current heart failure guidelines in 2008. However, since the diagnostic presentation or referral pattern in elderly patients with suspected heart is unlikely to have changed in the last few years, we feel that our findings can be applied to current clinical practice.

A gold standard for diagnosing heart failure is lacking, mandating the use of an expert panel to attribute a final diagnosis of heart failure.[2] In our study, as in previous studies, the consensus diagnosis of the expert panel was highly reproducible.[6,14] Another strength is the limited number of eligible patients that did not consent to participate (10%). We believe our study population to be representative of, and our study results to be generalisable to, geriatric outpatients suspected of new, slow onset heart failure, (i.e. a population characterized by a mean age of 82 years, predominantly female, with a wide range of comorbidities and on multiple pharmaceutical therapies, with symptoms and signs suggesting

heart failure). Our diagnostic rule is likely to be applicable to geriatric outpatients suspected of new, slow onset heart failure.
In conclusion, in a large group of elderly outpatients who were referred to a geriatrician for a variety of reasons, up to half of those suspected of new, slow onset heart failure by the geriatrician actually had heart failure. Loss of appetite, lower BMI and absence of wheezing were specific features of heart failure in these elderly patients. Classic signs of heart failure were absent in one third of patients with heart failure. These observations underline the often atypical presentation of heart failure in elderly patients and the need for a high index of suspicion to diagnose heart failure in this specific patient group. The ability to reliably identify the presence or absence of heart failure based on symptoms and signs improved considerably when NT-proBNP levels were used. In the vast majority of geriatric outpatients with suspected heart failure, no further additional diagnostic tests were needed for a correct diagnosis. Additional tests were only needed in patients in whom the diagnosis was in doubt or to determine the cause of heart failure.

Acknowledgements

We wish to thank the participating patients and geriatricians.

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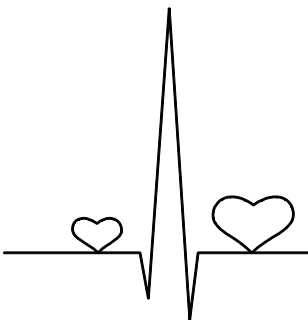
Chapter 6

Comorbidity drives mortality in newly diagnosed heart failure: a study among geriatric outpatients



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J Card Fail 2012;18:47-52

Abstract

Background

Elderly heart failure patients frequently have multiple comorbidities. The prognostic impact of multiple comorbidities combined is poorly quantified in these patients. We assessed the impact of comorbidities on three-year mortality in geriatric outpatients with newly diagnosed heart failure.

Methods and Results

Of 93 geriatric outpatients with heart failure (mean age 82.7 years, 37% men), 52 (56%) patients died within three years after heart failure was diagnosed. Comorbidity was measured with the Charlson Comorbidity Index (CCI). Age and gender adjusted hazard ratio (HR) for three-year mortality was 1.6 (95% confidence interval (CI) 0.9 - 3.2) for patients with 3 - 4 CCI points and 3.2 (95% CI 1.5 - 6.8) for those with more than 4 CCI points, compared to 1 - 2 CCI points. After adjustment for age, gender, left ventricular ejection fraction (LVEF), and N-Terminal pro B-type Natriuretic Peptide (NT-proBNP), CCI remained predictive of death (CCI 3 - 4: HR 1.5 (0.7 - 2.9); CCI > 4: HR 4.0 (1.9 - 8.8)). In addition to age and gender the c-statistics for CCI and LVEF were similar (0.63 (95% CI 0.55 - 0.70) and (0.64 (95% CI 0.56 - 0.72), respectively).

Conclusions

The majority of geriatric outpatients with new heart failure die within three years. Comorbidity, summarized in the Charlson Comorbidity Index, is the strongest independent predictor of mortality.

Introduction

The ageing of the population and improved survival following acute cardiac events leads to an increased prevalence of heart failure, especially in the elderly.[1,2] Survival in geriatric patients with heart failure is generally poor. Elderly heart failure patients have a wide range of both cardiovascular and non-cardiovascular comorbidities, that may influence prognosis.[3,4] Although the impact of several diseases on prognosis in heart failure patients has been established, predominantly in hospitalized patients, the impact of combinations of concomitant diseases in geriatric patients is largely unknown, especially in the large group of geriatric outpatients with newly diagnosed heart failure not requiring hospital admission.[1,5,6] The Charlson Comorbidity Index (CCI) is an extensively studied and validated instrument to assess comorbidity, that has been shown to predict prognosis in a variety of patient groups (e.g. patients with cancer, pneumonia, or admitted to internal wards).[7-9] In elderly heart failure patients, other than two studies, addressing short-term (one year) or long-term (twelve-year) mortality, the effect of comorbidity, as measured with the CCI, on the prognosis of heart failure has not been addressed.[10,11] We determined the impact of comorbidity, measured with the CCI, on three-year mortality in geriatric outpatients with newly diagnosed heart failure.

Methods

Study population

Patients referred, for a variety of reasons, to the geriatric outpatient clinic of two regional hospitals in the Netherlands (Elkerliek Hospital, Helmond and Meander Medical Center, Amersfoort) who presented with symptoms of breathlessness, fatigue, ankle swelling, or any combination of these were eligible, as described in detail elsewhere.[12] Only patients with newly diagnosed heart failure in whom the symptoms had increased gradually before the diagnosis (so called “slow onset” heart failure) were included. Patients with acute onset heart failure requiring emergency admission were excluded. Briefly, 206 geriatric outpatients suspected of new heart failure by a geriatrician, underwent a comprehensive, standardized diagnostic work-up. The presence or absence of heart failure was established by an expert panel according to the diagnostic criteria for heart failure of the European Society of Cardiology (ESC), using all available diagnostic information.[13] All participants or their representatives, in case of impaired cognition, gave written

consent. Patients were recruited between July 2003 and July 2007. The study was approved by the Medical Ethical Committees of both participating hospitals.

Comorbidity

We used the CCI, that assigns points for several medical conditions, to evaluate the severity of comorbidity, with a score ranging from 1 (only heart failure present) to 30 (extensive comorbidity).[7] All diagnoses obtained from the general practitioner's referral letter, letters of other specialists retrieved from the hospital information system and diagnoses established by the geriatricians within two months after the initial visit were regarded as comorbidity. The presence or absence of heart failure according to the expert panel was established before calculating the CCI.

Outcome

Outcome of the study was all-cause mortality within three years after heart failure was diagnosed. Information on vital status was obtained from the hospital information system or from the patients' general practitioners. Follow-up data were collected between July 2003 and July 2010. One patient without heart failure was lost to follow-up after the first year and was considered withdrawn alive as of the last date of follow-up.

Data analysis

Data with a normal distribution were summarized as means with standard deviation (SD). Data with a skewed distribution were summarized as medians with interquartile ranges (25^{th} - 75^{th} percentile). To obtain a normal distribution, N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) values were logarithmically transformed. Left ventricular ejection fraction (LVEF) was categorized in patients with LVEF ≤ 35%, 35 - 45%, and ≥ 45%. Charlson Comorbidity Index score was categorized in subjects with a CCI score of 1 - 2, 3 - 4 and above 4 points.[14] A Cox proportional hazards analysis was performed to calculate differences in survival between patients with and without heart failure and differences between patients with heart failure due to impaired (n = 49) and preserved LVEF (n = 44), after adjusting for age and gender. The ability of 'established' determinants (i.e. age, gender, LVEF, and NT-proBNP) and CCI to discriminate between patients who died and who remained alive was estimated using the c-statistic which reflects the area under the receiver operating characteristic curve (ROC-area).[15] The c-statistic can range from 0.5 (no discrimination, like flipping a coin) to 1.0 (perfect discrimination).[16] Multivariate proportional hazards analysis was performed to

Table 1. Baseline characteristics of geriatric outpatients with heart failure*

Variable	All n = 93
Age, years	82.7 ± 5.3
Male sex	34 (37)
Cardiovascular comorbidity and risk factors	
Ischaemic heart disease	25 (27)
Myocardial infarction	17 (18)
Angina pectoris	8 (9)
Vascular comorbidity	55 (59)
Hypertension	39 (42)
Diabetes mellitus	25 (27)
CVA or TIA	20 (22)
Atrial fibrillation	36 (39)
Overweight	31 (36)
Current smoker	18 (19)
Non-cardiovascular comorbidity	
COPD	25 (27)
Cognitive impairment	25 (27)
Malignancies	15 (16)
Drugs	
Loop diuretic	38 (41)
ACE-i/ARB	35 (38)
β-Blocker	26 (28)
Digitalis	22 (24)
MRA	10 (11)
Drugs, number	6 (5-8)
Additional tests	
NT-proBNP, pg/ml	2295 (791-5543)
eGFR MDRD, ml/min/1.73 m^2	58 ± 20
CCI, points	3 (2-4)
LVEF, %	43 ± 14

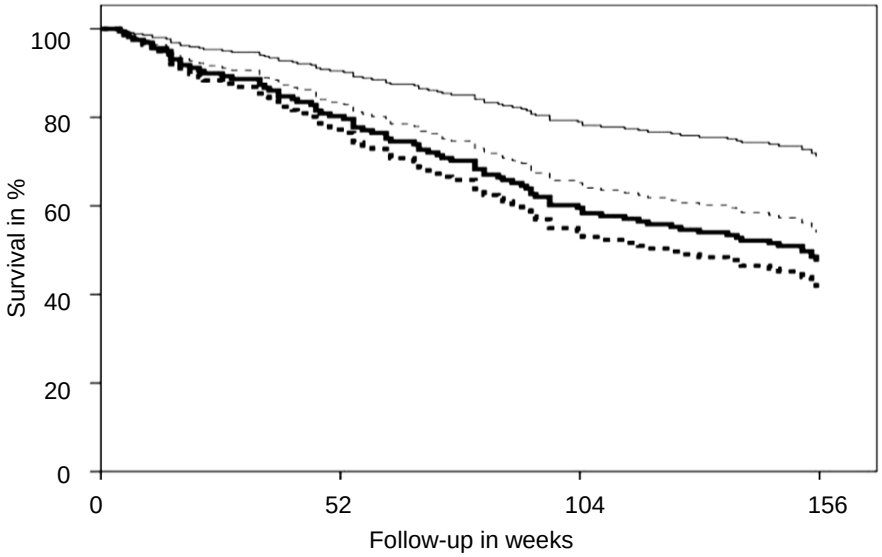
* Data are presented as number (%) of patients, mean ± SD, or median (25^{th} - 75^{th} percentiles). ACE-i, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CVA, cerebro vascular accident; eGFR MDRD, estimated glomerular filtration rate according to the modification of diet in renal disease study group equation; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; TIA, transient ischaemic attack. Ischemic heart disease, presence of myocardial infarction, angina pectoris, coronary artery bypass grafting or percutaneous coronary intervention; Overweight, body mass index (BMI) 25 - 30 kg/m^2; Vascular comorbidity, including hypertension, diabetes mellitus, stroke, and peripheral artery disease.

determine the independent value of comorbidity after adjusting for 'established' determinants of mortality in heart failure. For continuous variables, the assumption of linearity was assessed using restrictive cubic splines.[15]
The reproducibility (intrarater agreement) of the CCI, evaluated by re-testing 21 cases (10% of total population), was good with an intraclass correlation coefficient of 0.95 (95% Confidence Interval (CI) 0.89-0.98). None of the predictors had missing values. Data were analyzed using the SPSS software (version 17.0 for Windows SPSS Inc., Chicago, IL, USA), and 'R' (version 2.8.1; R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org).

Results

Ninety three geriatric outpatients with newly diagnosed, "slow onset" heart failure (63% female; mean age 82.7 years, ± 5.3) were included (Table 1). Three-year all-cause mortality was much higher (56%) in geriatric patients with newly diagnosed heart failure than those without (28%; crude Hazard Ratio (HR) 2.6 (95% CI 1.7 - 4.1; age and gender adjusted HR 2.2 (95% CI 1.4 - 3.4)); Figure 1). Three-year mortality did not differ between patients with systolic heart failure - left ventricular ejection fraction < 45% - (59%) and those with heart failure with preserved ejection fraction (HFPEF; 52%; crude HR 1.3 (95% CI 0.7 - 2.2); HR adjusted for age and gender 1.3 (0.7 - 2.3)).
Mortality increased with higher CCI score, from 43% in the 35 patients with a CCI of 1-2, to 57% in those (n = 42) with CCI 3 - 4, and 81% in those (n = 16) with CCI above four points. Compared to CCI 1 - 2, HR for death within three years was 1.6 (95% CI 0.8 - 3.0) for patients with CCI score 3 - 4 and 3.3 (95% CI 1.5 - 6.9) for patients with CCI score above four points (Table 2). The CCI remained predictive of mortality after adjustment for age and gender (CCI 3 - 4: HR 1.6 (0.9 - 3.2); CCI > 4: HR 3.2 (1.5 - 6.8) Figure 2). In addition to age and gender the c-statistic for CCI was 0.63 (95% CI 0.55 - 0.70), 0.64 (95% CI 0.56 - 0.72) for LVEF, and 0.59 (95% CI 0.50 - 0.67) for NT-proBNP. Combining these determinants improved the c-statistic to 0.69 (95% CI 0.62 - 0.76). The CCI remained predictive of mortality after adjustment for age, gender, LVEF, and NT-proBNP (CCI 3 - 4: HR 1.5 (0.7 - 2.9); CCI > 4: HR 4.0 (1.9 - 8.8)).

Figure 1. Cox survival curves for geriatric patients according to the presence and type of heart failure, adjusted for age and gender*



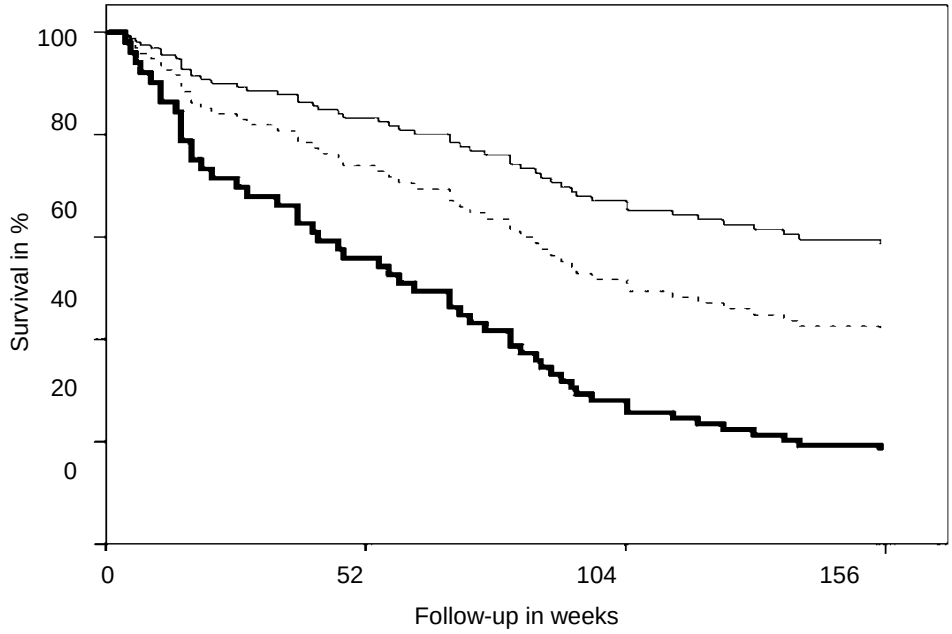
* Heart failure absent; Heart failure present;
Heart failure with preserved ejection fraction; Systolic failure

Table 2. Three-year mortality in 93 geriatric outpatients with heart failure in relation to 'established' determinants and Charlson Comorbidity Index*

Variable	Alive n = 41	Deceased n = 52	Crude HR (95% CI)	Adjusted for age and gender HR (95% CI)	Adjusted for age, gender, LVEF, NT-proBNP, and CCI HR (95% CI)
Age, years	82.4 ± 5.7	82.9 ± 5.1	1.1 (0.7-1.9)	1.2 (0.7-2.1)	1.3 (0.7-2.4)
Male sex	13 (32)	21 (40)	1.3 (0.8-2.3)	1.4 (0.8-2.4)	1.3 (0.7-2.4)
LVEF					
LVEF ≥ 45%	21 (51)	23 (44)	-	-	-
LVEF 35 – 45%	14 (34)	9 (17)	0.7 (0.3-1.5)	0.7 (0.3-1.5)	0.6 (0.2-1.3)
LVEF ≤ 35%	6 (15)	20 (38)	2.0 (1.1-3.7)	2.2 (1.1-4.1)	2.1 (1.0-4.7)
NT-proBNP, pg/ml	1883 (760-3507)	2925 (851-7500)	1.2 (0.9-1.5)	1.2 (1.0-1.6)	1.1 (0.8-1.4)
CCI					
CCI 1-2 points	20 (49)	15 (29)	-	-	-
CCI 3-4 points	18 (44)	24 (46)	1.6 (0.8-3.0)	1.6 (0.9-3.2)	1.5 (0.7-2.9)
CCI > 4 points	3 (7)	13 (25)	3.3 (1.5-6.9)	3.2 (1.5-6.8)	4.0 (1.9-8.8)

* HR of CCI 3-4 and > 4 points, compared to CCI 1-2 points; HR of LVEF 35-45% and ≤ 35%, compared to LVEF ≥ 45%; CI, Confidence Interval; HR, Hazard Ratio; other abbreviations as in Table 1. HR increases per 10 years of age, and per ln NT-proBNP.

Figure 2. Cox survival curves for geriatric patients with heart failure according to Charlson Comorbidity Index, adjusted for age and gender*



* Charlson Comorbidity Index: ——— 1-2 points; - - - - - 3-4 points; ▬▬ > 4 points

Discussion

More than half of 93 (52 (56%)) geriatric outpatients with newly diagnosed, “slow onset” heart failure (i.e. gradually increasing symptoms of heart failure not requiring hospital admission) died within three years after establishing the diagnosis. Mortality increased with more extensive comorbidity, as assessed with the CCI; three-year mortality being 81% in heart failure patients with a CCI score above four points. The CCI was the strongest independent predictor of mortality.

Three-year mortality in our group of geriatric outpatients with new heart failure, being twice as high compared to those without heart failure, reflects the poor prognosis of heart failure as demonstrated previously in the general population and in elderly hospitalized patients.[17,18] As elderly heart failure patients are likely to have multiple, cardiovascular and non-cardiovascular comorbidities, that influence prognosis, we intended to determine the prognostic value of comorbidity ‘as a

whole' rather than focusing on the impact of individual concomitant diseases (e.g. renal failure, chronic obstructive pulmonary disease (COPD), stroke, or dementia).[4,19] To this goal we used the CCI, a validated instrument that has been shown to predict non-sudden death in heart failure, mortality or lung transplantation within the first year after admission for right sided heart failure in pulmonary arterial hypertension, and in-hospital mortality among elderly patients admitted to an internal medicine ward.[9,20,21] The strong relation between CCI and mortality testifies to the importance of various comorbidities in geriatric outpatients with heart failure. Our patient population (mean age 82.7 years, median drugs used six) differed from that in the study of 125 heart failure patients, that failed to demonstrate an impact of CCI on twelve-years mortality.[11] The mean age of those patients was 74 years and the fact that they were using only two medications on average suggests limited comorbidity. Furthermore it is possible that the CCI does not predict twelve-year mortality very well because less than 50% of heart failure patients tend to survive five years, irrespective of the extent of their comorbidities.[1]

Several risk models to help physicians in estimating prognosis in heart failure patients (e.g. the Seattle Heart Failure Model (SHFM), and the scoring systems of the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study, and the Acute Decompensated Heart Failure Registry (ADHERE)) exist.[6,22,23] The SHFM predicts 5-year mortality based on information obtained from participants with severe systolic heart failure (median age 65 years, 24% women) of the Prospective Randomized Amlodipine Survival Evaluation (PRAISE1) study.[24] The EFFECT study included patients (mean age 76.3 years, 51% women) admitted with acute heart failure to determine 30-day and 3-year mortality and the ADHERE registry determined in-hospital mortality in patients (mean age 72.4 years, 52% women) admitted with acute heart failure.[25] Ours is the first study to determine the prognostic impact of comorbidity in elderly heart failure outpatients (mean age 82.7 years, 63% women) not requiring hospitalization, including both systolic heart failure and HFPEF. In contrast to the three established risk models we included measurements of natriuretic peptides, that are known to be important predictors in heart failure. Renal function is important in determining the prognosis of heart failure.[1,5] In our patient group, all seven patients with an estimated glomerular filtration rate below 30 ml/min/1.73m^2, died within 86 weeks after heart failure was diagnosed (data not shown). Unfortunately, the CCI uses serum creatinine to estimate renal function, rather than the Glomerular Filtration Rate according to the Modification of Diet in Renal Disease study group equation (eGFR MDRD), which is more accurate in elderly patients.[26] The CCI defines moderate or severe renal disease as serum creatinine of at least 3 mg/dl (265 µmol/L) which was only

present in one patient, who died within 12 weeks. It is imaginable that the CCI underestimates the severity of renal dysfunction in elderly patients.

Numerous determinants of the prognosis of heart failure have been identified, of which age, gender, and severity of heart failure (reflected in LVEF and NT-proBNP) are generally considered the 'established' determinants.[1,27] Of these four 'established' determinants only an ejection fraction less than 35% influenced prognosis. The observation that male gender does not predict mortality in geriatric patients with heart failure patients is consistent with previous studies in the elderly.[28] In contrast with earlier studies, neither age nor NT-proBNP predicted three-year mortality in this group of elderly heart failure patients (mean age 82.7 years) with high NT-proBNP levels (median 2295 pg/ml). The impact of ejection fraction was modest; mortality rates did not differ between patients with systolic heart failure - left ventricular ejection fraction < 45% - and those with HFPEF. The observation that mortality was higher in patients with LVEF ≤ 35% is in line with the results of the recently published report of the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC).[29]

Most prognostic studies in heart failure to date were performed in patients with known heart failure, e.g. when admitted for decompensated heart failure, and in general population samples screened for the prevalence of heart failure.[10,11,17-19] In these studies the actual duration of heart failure can vary appreciably. In daily practice, however, physicians establish a diagnosis, directly followed by an assessment (implicitly or explicitly) of the prognosis of the individual patient, to determine the optimal treatment strategy, taking into account both life expectancy and quality of life. The major strength of our study is that we determined prognosis in patients with newly diagnosed heart failure, reflecting everyday practice, which only few studies have done before.[30,31] Another strength is that we studied elderly outpatients with a wide range of comorbidity who are generally excluded from clinical trials, but who are frequently treated by general practitioners, geriatricians, internists, and cardiologists.[32,33] As such this is the first prognostic study of geriatric outpatients with newly diagnosed heart failure (mean age 82.7 years, 63% female) with a wide range of both cardiovascular and non-cardiovascular comorbidity. Although the results in our study may not come as a surprise, they have not been established before in this population. The main limitation of our study relates to the small number of patients (n = 93) with heart failure resulting in a lack of power to analyze multiple determinants of prognosis. Elderly patients with multiple comorbidity and with newly detected heart failure had a poor prognosis. This raises the question whether this is attributable to an inherent poor prognosis in these patients or, at least partly, to poor adherence to evidence-based heart failure

medication following the diagnosis; albeit that evidence from randomized trials on the efficacy of heart failure therapy in these patients is very limited. However, no detailed information on the use of heart failure medication following the diagnosis was available in our study.

Our study shows that the prognosis of geriatric outpatients with newly diagnosed heart failure is determined to a large extent by (the severity of) concomitant diseases. Explicitly taking comorbidity into consideration (e.g. by means of the CCI) will facilitate treatment decisions and discussing the various options with elderly heart failure patients and their caregivers. In those with a high CCI (and thus with a limited life expectancy) the focus is likely to be on symptom relief per se (e.g. by diuretics), whereas in those with a low CCI - in addition to relief of symptoms – aiming to improve prognosis, for example by initiating and up titrating beta-blockers and angiotensin converting enzyme-inhibitors, could be a treatment goal.

In conclusion, the majority of geriatric outpatients with newly diagnosed heart failure not requiring hospital admission, die within three years after establishing the diagnosis. Comorbidity, as summarized in the CCI, is the strongest, independent predictor of three-year mortality. It follows that routine application of the CCI may be of help in adequately managing this group of patients.

Acknowledgements

We wish to thank the participating patients and geriatricians.

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Appendix

Appendix 1. Charlson Comorbidity Index*

Comorbidity	Points
Myocardial infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end organ damage	2
Any tumour	2
Leukaemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumour	6
AIDS	6

* The total equals the score. Example: congestive heart failure (1) and diabetes with end organ damage (2) = total score (3). The total score is classified into four categories as a prognostic variable for mortality: 0, 1-2, 3-4, > 4 points. According to Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.

Chapter 7

Galectin-3 is a marker for diagnosis and prognosis of heart failure in geriatric outpatients

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Submitted

Abstract

Background

Galectin-3, a galactosidase-binding lectin which is linked to tumour growth, is emerging as a potentially useful biomarker in the development and progression of heart failure. Data in elderly patients, the vast majority of heart failure patients, are absent. We determined the diagnostic and prognostic potential of galectin-3 in geriatric outpatients.

Methods

Geriatric patients suspected of heart failure underwent an extensive standardized diagnostic work-up. An expert panel determined the presence of heart failure based on all diagnostic information except for plasma galectin-3 levels, which were measured with a commercially available galectin-3 assay (ELISA). The diagnostic value of galectin-3 was determined by comparing patients with and without heart failure. Cox proportional hazards analysis was used to determine the value of galectin-3 in predicting three-year mortality in heart failure.

Results

Heart failure was present in 28 (40%) of 70 geriatric patients (mean age 80.8 years, 20% man). Mean galectin-3 levels were higher in patients with heart failure than in those without (21.8 and 15.6 ng/ml, respectively; $p = 0.04$). In heart failure patients three-year mortality was higher when galectin-3 levels were higher than the recently proposed cut-off value of 17.8 ng/ml: 74% and 33%, respectively; age-adjusted hazard ratio 3.7 (95% CI 1.0 - 13.2).

Conclusions

In geriatric patients suspected of heart failure galectin-3 may be helpful in diagnosing heart failure. Elevated galectin-3 levels in elderly heart failure patients are associated with higher mortality rates.

Introduction

Heart failure is a clinical syndrome with signs and symptoms attributable to cardiac dysfunction at rest.[1] The prevalence of heart failure is increasing, especially in the elderly.[2] Galectin-3, a galactosidase-binding lectin with an established role in tumour growth, progression and metastasis, is emerging as an important biomarker in the development and progression of heart failure.[3] Galectin-3 is up-regulated in hypertrophied hearts, and secreted by myocardial macrophages and activates quiescent fibroblasts into activated myofibroblasts, that secrete extracellular matrix protein leading to myocardial fibrosis and adverse remodelling which is associated with the development of heart failure.[3] Galectin-3 levels are elevated in patients with heart failure and higher galectin-3 levels are associated with a poor outcome in both acute heart failure and chronic heart failure.[4] Therefore, it has been suggested that galectin-3 may be used as a diagnostic and prognostic biomarker in heart failure. However, data on galectin-3 biology are lacking in the elderly, who constitute the majority of heart failure patients. We determined the diagnostic and prognostic value of galectin-3 in geriatric outpatients.

Methods

Patients referred to the geriatric outpatient clinic who were suspected of heart failure by the geriatrician, typically because of shortness of breath, increasing fatigue or exercise intolerance, underwent an extensive standardized diagnostic work-up including history taking, physical examination, electrocardiogram (ECG), chest X-ray, laboratory tests (including N-terminal pro B-type Natriuretic Peptide (NT-proBNP)) and echocardiography, as previously detailed.[5] Patients with acute symptoms requiring immediate treatment were excluded. None of the patients had a prior diagnosis of heart failure established by a cardiologist. An expert panel determined the presence of heart failure according to the guidelines of the European Society of Cardiology based on all diagnostic information except for serum galectin-3 levels.[6] Heart failure was considered present when symptoms and signs suggestive of heart failure (such as shortness of breath, peripheral oedema, fatigue, pulmonary rales, elevated jugular venous pressure) were present combined with objective echocardiographic evidence of cardiac dysfunction at rest.[6] Patients with heart failure were further classified as having systolic heart failure or heart failure with preserved ejection fraction (HFPEF). Systolic heart failure was considered present when left ventricular ejection fraction (LVEF) was

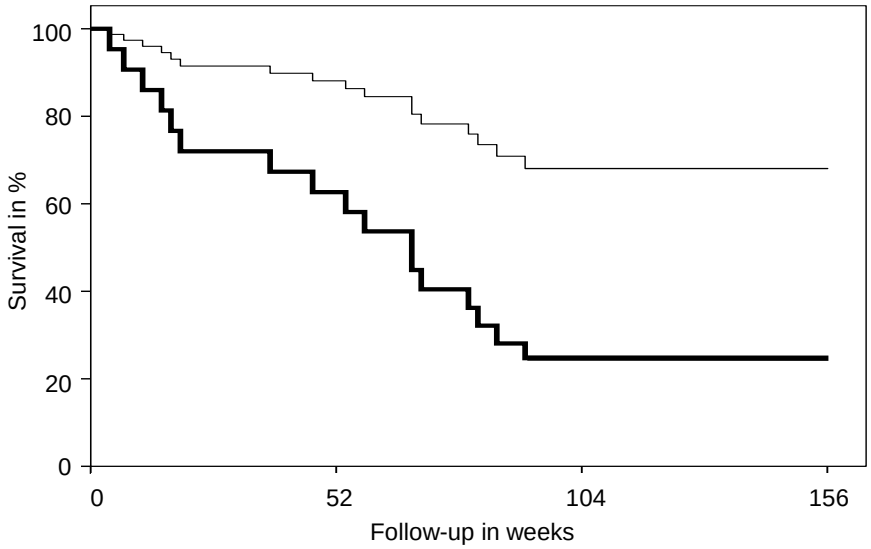
less than 45%. Echocardiographic evidence of diastolic dysfunction (abnormal left ventricular relaxation or diastolic stiffness) in combination with LVEF ≥ 45% were required to diagnose HFPEF.[6] Follow-up information on vital status was obtained from the hospital information system or from the patients' general practitioner. All participants or, in case of impaired cognition, their representatives provided written informed consent. Patients were recruited between July 2003 and July 2007. The study was approved by the Medical Ethical Committees of both participating hospitals (Elkerliek Hospital, Helmond and Meander Medical Center, Amersfoort, the Netherlands). For the present study galectin-3 levels were measured in a subset of 70 patients of the overall cohort (n = 206; due to logistical problems in both hospitals, plasma was not stored for the remaining 136 patients), of whom plasma was archived, using an enzyme-linked immunosorbent assay (ELISA) developed by BG Medicine (BG Medicine, Inc., Waltham, MA, USA. www.bg-medicine.com).[7] This assay quantitatively measures the concentration of human galectin-3 levels in EDTA plasma or serum with high sensitivity (lower limit of detection 1.13 ng/ml) and exhibits no cross-reactivity with collagens or other members of the galectin family. There is no interference from medications commonly prescribed in heart failure, icterus or lipemia.[7] Prior to assaying EDTA plasma was stored frozen at - 80° Celsius. Continuous variables with a normal distribution are presented as means with standard deviation (SD). Variables with a skewed distribution are presented as medians with interquartile range (IQR; 25^{th} - 75^{th} percentile). N-terminal pro B-type Natriuretic Peptide values were logarithmically transformed to obtain a normal distribution. In addition to analyzing galectin-3 as a continuous variable, we also used a dichotome variable with a cut-off value of 17.8 ng/ml: the value recently introduced to indicate increased risk of adverse outcome in patients with chronic heart failure.[8] Another study showed that the 90^{th} percentile of galectin-3 levels in 1092 healthy persons was 17.6 ng/ml.[7] The diagnostic value of galectin-3 was determined by comparing patients with and without heart failure. Cox proportional hazards analysis was used to calculate the value of galectin-3 in predicting three-year mortality in heart failure, both crude and after adjusting for age and gender. For galectin-3 the assumption of linearity was assessed using restrictive cubic splines. Data were analyzed using the SPSS software (version 17.0 for Windows SPSS Inc., Chicago, IL, USA).

Table 1. Characteristics of geriatric patients*

Variable	All n = 70	HF present n = 28	HF absent n = 42	p-value
Age, years	80.8 ± 5.5	81.5 ± 5.1	80.3 ± 5.8	0.36
Male sex	14 (20)	6 (21)	8 (19)	0.81
Cardiovascular comorbidities and risk factors				
Ischemic heart disease	11 (16)	7 (25)	4 (10)	0.10
Myocardial infarction	6 (9)	5 (18)	1 (2)	0.03
Vascular comorbidity	44 (63)	19 (68)	25 (60)	0.48
Hypertension	30 (43)	11 (39)	19 (45)	0.62
Diabetes Mellitus	17 (24)	10 (36)	7 (17)	0.07
Atrial fibrillation	14 (20)	8 (29)	6 (14)	0.14
COPD	19 (27)	6 (21)	13 (31)	0.38
Current smoker	10 (14)	4 (14)	6 (14)	1.00
Drugs, number	7 (3)	7 (3)	7 (4)	1.00
Physical examination				
Systolic blood pressure, mm Hg	151 ± 26	155 ± 27	147 ± 25	0.20
Diastolic blood pressure, mm Hg	81 ± 12	85 ± 14	78 ± 10	0.02
Heart rate, beats/min	77 (15)	80 (20)	75 (11)	0.26
Irregularly irregular pulse	20 (29)	14 (50)	6 (14)	< 0.01
Additional tests				
Atrial fibrillation at ECG	12 (17)	10 (36)	2 (5)	< 0.01
LVH at ECG	11 (16)	8 (29)	3 (7)	0.02
CTR at chest X-ray > 0.50	44 (63)	23 (82)	21 (50)	< 0.01
Creatinine clearance, ml/min/1.73 m^2	65 (54-77)	58 (43-74)	69 (56-78)	0.02
C-reactive protein, mg/l	7 (4-16)	9 (5-42)	6 (2-10)	0.05
NT-proBNP, pg/ml	396 (156-1836)	2171 (1277-4092)	200 (99-259)	< 0.01
Galectin-3, ng/ml	16.7 (12.9-22.7)	21.8 (16.2-26.8)	15.6 (12.3-19.3)	0.04
Galectin-3 > 17.8 ng/ml	31 (44)	19 (68)	12 (29)	< 0.01
Death within three years	30 (43)	17 (61)	13 (31)	< 0.01

* Data are presented as number (%) of patients, mean ± standard deviation or median (25^{th} - 75^{th} percentiles). COPD, chronic obstructive pulmonary disease; Creatinine clearance, estimated glomerular filtration rate according to the modification of diet in renal disease study group equation (eGFR MDRD); CTR, cardio thoracic ratio; HF, heart failure; LVH, left ventricular hypertrophy; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide. Ischemic heart disease, including prior myocardial infarction, angina pectoris, coronary artery bypass grafting, and percutaneous coronary intervention. Vascular comorbidity, including hypertension, diabetes mellitus, stroke, and peripheral artery disease.

Figure 1. Cox regression survival curve in geriatric heart failure patients according to Galectin-3 level, corrected for age*



* Legend: Galectin-3 ≤ 17.8 ng/ml; Galectin-3 > 17.8 ng/ml

Results

Heart failure was present in 28 (40%) of 70 geriatric patients suspected of heart failure (Table 1). Eleven (39%) patients had 'systolic' heart failure (defined as LVEF < 45%) with a mean LVEF of 28% (SD 8) and 17 (61%) patients had HFPEF with a mean LVEF of 57% (SD 11). Galectin-3 was higher in patients found to have heart failure than in those without (21.8 and 15.6 ng/ml, respectively; p = 0.04). Galectin-3 levels were similar in patients with systolic heart failure and those with HFPEF (21.1 (IQR 15.4 - 24.5) and 24.0 (IQR 16.4 - 31.0) ng/ml, respectively; p = 0.42). In contrast, NT-proBNP levels were higher in those with systolic heart failure than in those with HFPEF (median 4262 and 1883 pg/ml, respectively; p = 0.02). In patients with heart failure elevated galectin-3 levels were associated with an increased risk of death within three years (Hazard Ratio (HR) 1.3 per 10 ng/ml increase (95% Confidence Interval (CI) 1.05 – 1.50)). Three-year mortality was higher when galectin-3 levels were higher than 17.8 ng/ml (74% and 33%, respectively, HR 3.7 (95% CI 1.1 - 12.9)). This prognostic value remained similar after adjustment for age (HR 3.69 (95% CI 1.0 - 13.2) Figure 1), and age and gender (HR 3.4 (95% CI 0.9 - 12.4)).

Discussion

Our study extends the observations from previous studies on the diagnostic and prognostic value of galectin-3 in chronic heart failure to large group of elderly patients with (suspected) heart failure.[4,8,9] We found no difference in galectin-3 levels between patients with systolic heart failure and those with HFPEF. This observation is in line with results from a substudy of the Coordinating study evaluating outcomes of Advising and Counseling in Heart failure (COACH) trial, that found similar increases in galectin-3 levels carried more prognostic information in heart failure patients with preserved left ventricular ejection fraction.[4] As galectin-3 levels rise with myocardial fibrosis, that contributes to the development of HFPEF, galectin may be more useful in the diagnosis and management of patients with HFPEF, than the natriuretic peptides that increase in response to the volume overload and elevated wall pressures commonly observed in systolic heart failure. The limited number of patients in this study precludes a full assessment of the diagnostic and prognostic value of galectin-3 beyond information that is usually routinely available in heart failure patients, e.g. NT-proBNP levels. Nevertheless, this is the first study to assess the potential diagnostic and prognostic role of galectin-3 in the elderly patients (mean age 82 years). Our patients reflect the group of “real world” elderly patients with considerable comorbidity in whom heart failure is regularly diagnosed and managed by non-cardiologists (e.g. general practitioners and geriatricians).[10] The need for more insight into this group of heart failure patients, who are frequently excluded from clinical trials, is increasingly appreciated.[11]

In conclusion, in elderly patients with a wide range of comorbidity, suspected of new heart failure, galectin-3 may play a role in establishing the presence or absence of heart failure. Elevated galectin-3 levels indicate an increased risk of three-year mortality in elderly heart failure patients.

Acknowledgements

We wish to thank the participating patients. Also we thank clinical chemists Dr. Ir. J.P.M. Wielders, Meander Medical Hospital, Amersfoort, The Netherlands, Dr. C.H.H. Schoenmakers, Elkerliek Hospital, Helmond, The Netherlands, and Dr. M. Dokter (University Medical Center, Groningen, The Netherlands) for facilitating collection and storage of all blood samples, and for performing galectin-3 assays.

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Chapter 8

Drug treatment in the elderly with chronic heart failure: Where is the evidence?

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Submitted

Abstract

Most patients with heart failure are older than 75 years. Unfortunately little evidence based information is available to guide drug treatment in elderly patients. We performed a systematic review to investigate to what extent patients (aged 75 years and older) are included in clinical trials of drugs considered the cornerstone of heart failure treatment. All randomised controlled trials assessing the effects of diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, or mineralocorticoid receptor antagonists in chronic heart failure included in the MEDLINE and Embase databases, were eligible when they evaluated either the effect on mortality and hospitalizations ("hard" endpoints) or quality of life ("soft" endpoint) or both. Seventy two different trials including a total of 72,164 patients (mean age 65 years, 27% female) fulfilled the inclusion criteria; 43 trials evaluated mortality/hospitalization (67,528 patients, mean age 65 years, 27% female) and 33 trials evaluated quality of life (14,539 patients, 66 years, 34% female). Four trials evaluated both endpoint categories. None of these studies exclusively included patients of at least 75 years. In only three (3,128 (4.6%) patients) studies evaluating the effect on mortality/hospitalization and two (314 (2.2%) patients) studies evaluating the effect on quality of life the mean age of the participants was at least 75 years. Subgroup analyses in elderly patients were only reported in a minority: 16 mortality trials, 10 hospitalization trials, and 1 quality of life trial. The mean age of patients included in heart failure trials increased slightly from 62 years before 1990 to 66 years between 2000 and 2010. Although the majority of chronic heart failure patients are older than 75 years they remain largely underrepresented in clinical trials evaluating essential heart failure drugs.

Introduction

The ageing of the population and improved survival following acute cardiac events has led to an increased prevalence of heart failure, especially in the elderly.[1,2] The majority of patients who are diagnosed with heart failure are older than 75 years.[3-5] Older patients are more likely to have heart failure with preserved left ventricular ejection fraction.[6] Initial management of chronic heart failure consists of lifestyle measures and drug treatment, predominantly with diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers and mineralocorticoid receptor antagonists.[6] More advanced treatment options (e.g. device therapy (both cardiac resynchronisation therapy (CRT) and implantation of cardioverter-defibrillators (ICD)), coronary revascularization or open heart surgery) are usually reserved for younger patients.[7,8] In geriatric practice the aim of medical care is to improve quality of life by reducing symptoms, rather than merely improving survival. As such, the management of heart failure in geriatric patients will generally consist of lifestyle advices and medications. Unfortunately, little evidence based information is available to guide heart failure drug therapy in elderly patients.[9,10] We set out to investigate to what extent elderly patients (defined as those aged 75 years or older) are included in clinical trials of the abovementioned cornerstone heart failure medications. For this we studied both “hard” (mortality, hospitalization) and “soft” (quality of life assessed by validated heart failure questionnaires) endpoints, the latter being particularly relevant for elderly patients.

Methods

The MEDLINE and Embase databases were searched from inception to September 2011 using the search term “heart failure” in combination with the terms “drug therapy” and “randomised controlled trial”. To identify relevant publications missed by the search, reference lists of all manuscripts identified and those of relevant review articles and guidelines were scrutinized. All randomised controlled trials of diuretics, ACE-inhibitors, ARBs, beta-blockers, or mineralocorticoid receptor antagonists in the treatment of chronic heart failure included in the MEDLINE and Embase databases were eligible when they evaluated the endpoints mortality, hospitalization or quality of life. Substudies of original studies were excluded, as were studies that did not use generally accepted, validated quality of

life questionnaires. Only studies published in English, French, Italian, Spanish, German, and Dutch were considered.
For each trial included in the analysis the following information was extracted: inclusion criteria (age, New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF)), the number of participants, age (mean, standard deviation, median, interquartile range, when available), gender, and outcome parameters. The absolute number of patients aged 75 years or older was noted for each trial, when available. The mean age weighed according to trial size (by the absolute number of participants) was calculated per drug category and for all trials combined. In addition the mean age of the participants per decade of publication was calculated. Data were analysed using SPSS (version 17.0 for Windows SPSS Inc., Chicago, IL, USA).

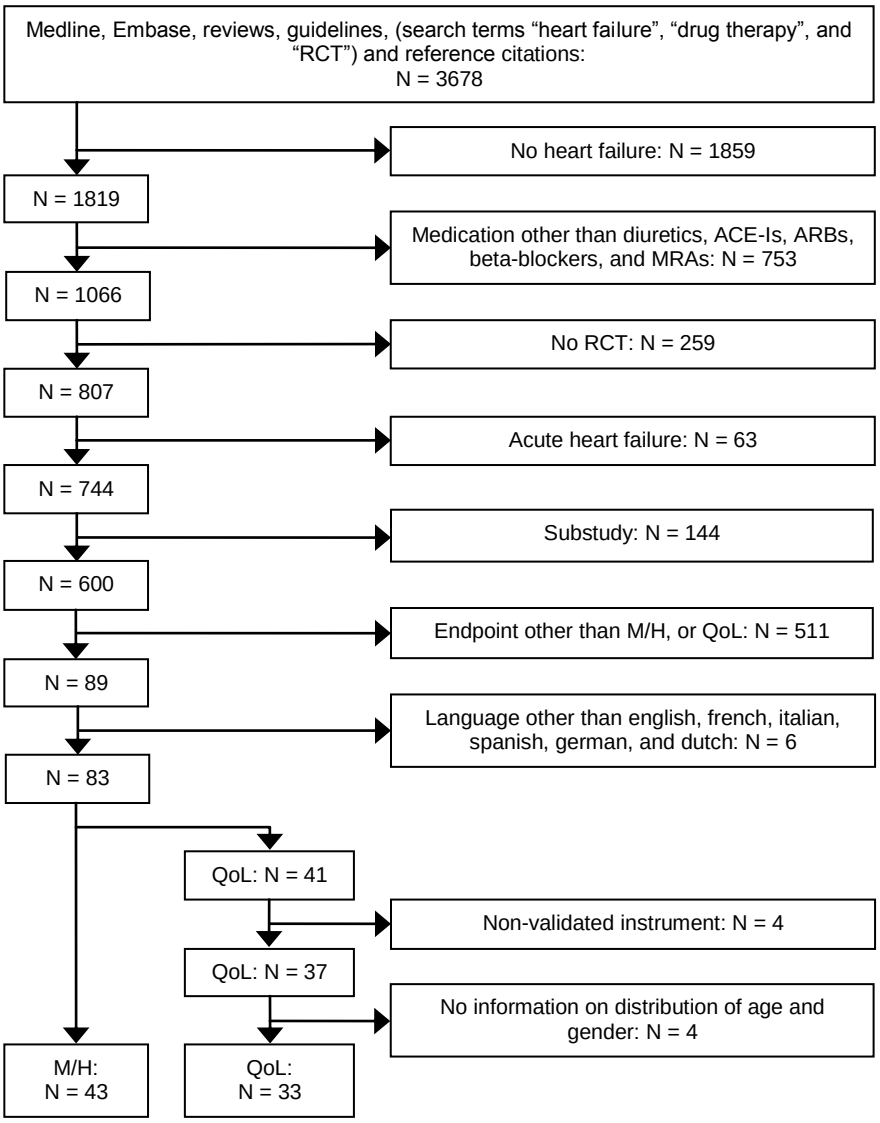
Results

Of 3678 publications reviewed, 75 fulfilled all inclusion criteria (Figure 1). These 75 publications reported 72 different trials and included a total of 72,164 patients with a mean age of 65 years and 27% of the participants were female (Table 1). Of the 72 trials, 39 different trials evaluated the effect on mortality/hospitalization only, 29 evaluated the effect on quality of life, and four trials evaluated both mortality/hospitalization and quality of life (SOLVD, I-PRESERVE, ELITE, Val-HeFT). Not one study exclusively included patients 75 years or over. The number of patients aged 75 years or older included in the trials was only described in eight trials (5577 patients out of 20150 (28%)). Patients aged 75 years or older were excluded from participation in eight trials. Table 2 summarizes age and gender characteristics per category of drug therapy.

Mortality and hospitalization

The 43 trials reporting mortality or hospitalization, including a total of 67,528 patients (mean age 65 years, 27% female), are described in more detail in the Appendix. In three trials (a total of 3,128 (4.6%) patients, 43% women) the mean age of the participants exceeded 75 years (PEP-CHF; SENIORS; and Barabino, et al).[11-13] In 16 studies, modification by age of the effect of the drug on mortality was specifically addressed (44,097 patients, 66 years, 28% women). All 16 studies reported a similar effect across age categories; ten studies showed no effect of treatment in any age groups (29,294 patients, 67 years, 31 % women), six studies

Figure 1. Flow chart of included trials searched in september 2011*



* ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; H, hospitalization; M, mortality; MRA, mineralocorticoid receptor antagonist; QoL, quality of life; RCT, randomised controlled trial. In one study all endpoints (mortality, hospitalization, and quality of life) were evaluated.

Table 1. Age and gender distribution in heart failure studies according to endpoint*

				Participants			Age groups	
Study	**Year**	**Drug**	**Inclusion age**	**N**	**Age**	**Female n (%)**	**Age: n (%)**	**Endpoint**
Diuretic								
PEACH[14]	1999	furosemide	-	240	75	107 (45)	-	Q
Muller, et al.[15]	2003	furosemide	≥ 18	237	74	135 (57)	-	M/H
Gupta, et al.[16]	2010	torasemide	-	28	59	3 (11)	-	Q
Angiotensin converting enzyme inhibitor								
Captopril-Digoxin Multicenter Research Group[17]	1988	captopril	< 75	300	57	51 (17)	-	M/H
Barabino, et al.[13]	1991	captopril	≥ 65	150	75	77 (51)	-	M/H
Munich Mild HF trial[18]	1992	captopril	≥ 18	170	62	42 (25)	-	M
Cowley, et al.[19]	1994	captopril	-	209	64	57 (27)	-	M
CHIPS[20]	2000	captopril	18-80	298	65	92 (31)	-	M/H
Cilazapril-Captopril Multicentre Group[21]	1998	cilazapril	≥ 18	367	63	132 (36)	-	Q
CONSENSUS[22]	1987	enalapril	-	253	71	75 (30)	-	M
SOLVD[23]	1991	enalapril	< 80	2,569	61	505 (20)	-	M/H
SOLVD[24]	1994	enalapril	21-80	2,465	61	478 (19)	-	Q
V-HeFT II[25]	1991	enalapril	18-75	804	61	0 (0)	≥ 65: 225 (28)	M/H
de Vries, et al.[26]	1995	enalapril	18-75	46	65	7 (15)	-	Q
Pacher, et al.[27]	1996	enalapril	-	83	56	14 (17)	-	M
NETWORK[28]	1998	enalapril	18-85	1,532	70	556 (36)	-	M/H
Guazzi, et al.[29]	1999	enalapril	-	20	58	4 (20)	-	Q
HEDS[30]	2000	enalapril	-	248	56	37 (15)	-	M/H
Kitzman, et al.[31]	2010	enalapril	-	71	70	60 (85)	-	Q
FEST[32]	1995	fosinopril	18-75	308	63	79 (26)	-	M/H
Fosinopril HF Study group[33]	1995	fosinopril	18-75	241	62	49 (20)	-	M/H
Multicenter Lisinopril-Captopril Congestive HF Study Group[34]	1989	lisinopril	-	189	60	41 (22)	-	Q
ATLAS[35]	1999	lisinopril	-	3,164	64	648 (20)	-	M/H
IMPRESS[36]	2000	lisinopril	≥ 18	573	64	122 (21)	-	M/H

Study	Year	Drug	Inclusion age	Participants N	Participants Age	Participants Female n (%)	Age groups Age: n (%)	Endpoint
Gundersen, et al.[37]	1995	ramipril	-	223	64	63 (28)	-	Q
CASSIS[38]	1995	spirapril	-	248	58	42 (17)	-	Q
OVERTURE[39]	2002	omapratilat	-	5,770	63	1,212 (21)	-	M/H
PEP-CHF[11]	2002	perindopril	≥ 70	850	76	468 (55)	> 75: 385 (45)	M/H
Zi, et al.[40]	2003	quinapril	> 65	74	78	48 (65)	-	Q
Angiotensin receptor blocker								
RESOLVD[41]	1999	candesartan	-	768	63	127 (17)	-	Q
CHARM-added[42]	2003	candesartan	≥ 18	2,548	64	542 (21)	≥ 75: 457 (18)	M/H
CHARM-preserved[43]	2003	candesartan	≥ 18	3,023	67	1,212 (40)	≥ 75: 807 (27)	M/H
CHARM-alternative[44]	2003	candesartan	≥ 18	2,028	67	646 (32)	≥ 75: 472 (23)	M/H
I-PRESERVE[45]	2008	irbesartan	≥ 60	4,128	72	2,491 (60)	≥ 75: 1,413 (34)	M/H/Q
Hong Kong diastolic HF study[46]	2008	irbesartan	≥ 18	151	74	93 (62)	-	Q
Kum, et al.[47]	2008	irbesartan	-	50	67	14 (28)	-	Q
Brack, et al.[48]	2008	irbesartan	-	89	67	22 (25)	-	Q
ELITE[49]	1997	losartan	≥ 65	722	73	240 (33)	≥ 70: 508 (70)	M/H
ELITE[50]	2000	losartan	≥ 65	300	73	71 (24)	-	Q
Losartan pilot exercise study investigators[51]	1997	losartan	-	116	58	26 (22)	-	Q
Houghton, et al.[52]	2000	losartan	≥ 18	20	66	1 (5)	-	Q
HEAAL[53]	2009	losartan	≥ 18	3,834	66	1,143 (30)	-	M/H
ELITE-II[54]	2000	losartan	≥ 60	3,152	71	967 (31)	≥ 70: 1,813 (58)	M/H
REPLACE[55]	2001	telmisartan	≥ 21	378	64	41 (11)	-	Q
Cice, et al.[56]	2010	telmisartan	≥ 18	332	63	153 (46)		M/H
Val-HeFT[57]	2001	valsartan	≥ 18	5,010	63	1,005 (20)	≥ 65: 2,350 (47)	M/H
Val-HeFT[58]	2005	valsartan	≥ 18	3,010	63	630 (21)	≥ 65: 1,408 (47)	Q
Parthasarathy, et al.[59]	2009	valsartan	≥ 21	150	62	75 (50)	≥ 65: 67 (45)	Q
Beta-blocker								
Sturm, et al.[60]	2000	atenolol	18-75	100	51	12 (12)	-	M/H
BETACAR[61]	2006	betaxolol	18-75	255	57	36 (14)	-	Q
Hawkins, et al.[62]	2009	bisoprolol	-	27	71	8 (30)	-	Q

				Participants			Age groups	
Study	**Year**	**Drug**	**Inclusion age**	**N**	**Age**	**Female n (%)**	**Age: n (%)**	**Endpoint**
CIBIS-I[63]	1994	bisoprolol	18-75	641	60	112 (17)	-	M/H
CIBIS-II[64]	1999	bisoprolol	18-80	2,647	61	515 (19)	-	M/H
CIBIS-III[65]	2005	bisoprolol	≥ 65	1,010	74	321 (32)	-	M/H
Pollock, et al.[66]	1990	bucindolol	-	19	54	4 (21)	-	Q
BEST[67]	2001	bucindolol	≥ 18	2,708	60	593 (22)	≥ 75: 322 (12)	M/H
CASPER[68]	2009	carvedilol	-	405	65	109 (27)	-	Q
CARVIVA HF trial[69]	2011	carvedilol	18-90	121	67	39 (32)	-	Q
US Carvedilol HF study group[70]	1996	carvedilol	-	1,094	58	256 (23)	≥ 59: 554 (51)	M/H
Metra, et al.[71]	2000	carvedilol	-	150	57	14 (9)	-	Q
Sanderson, et al.[72]	1999	carvedilol	-	51	60	11 (22)	-	Q
COPERNICUS[73]	2002	carvedilol	-	2,289	63	458 (20)	-	M/H
COMET[74]	2003	carvedilol	-	3,029	62	612 (20)	≥ 65: 1,392 (46)	M/H
MUCHA[75]	2004	carvedilol	20-80	173	60	40 (23)	≥ 65: 74 (43)	M/H
CARMEN[76]	2004	carvedilol	-	572	62	110 (19)	-	M/H
Sanderson, et al.[77]	1997	celiprolol	-	50	62	12 (24)	-	Q
Fisher, et al.[78]	1994	metoprolol	-	50	63	2 (4)	-	H
MERIT-HF[79]	2000	metoprolol	40-80	3,991	64	898 (23)	≥ 70: 1,245 (31)	M/H
ENECA[80]	2005	nebivolol	≥ 65	260	72	69 (27)	> 70: 104 (40)	Q
SENIORS[12]	2005	nebivolol	≥ 70	2,128	76	785 (37)	≥ 75: 1,064 (50)	M/H
Marazzi, et al.[81]	2011	nebivolol	-	160	66	62 (39)	-	M/H
Mineralocorticoid receptor antagonist								
RALES[82]	1999	eplerenone	≥ 55	2,737	69	446 (27)	≥ 75: 657 (24)	M/H
Agostoni, et al.[83]	2005	spironolactone	-	30	59	8 (27)	-	Q
Berry, et al.[84]	2007	spironolactone	-	40	62	9 (23)	-	Q
EMPHASIS-HF[85]	2011	spironolactone	-	1,663	65	610 (22)	-	M/H

* Age, age in years; Age groups, number of patients above the cutoff age described in the mentioned trial; H, hospitalization; M, mortality; Q, quality of life; Year, year of publication; '-', not described.

reported a beneficial effect of treatment on mortality in all age groups (14,803 patients, 64 years, 22% women)). In ten studies (25,321 patients, 67 years, 31% women) modification by age of the effect of the drug on hospitalization rates was specifically addressed. Four studies showed no effect of treatment in any of the age groups studied (12,274 patients, 68 years, 37% women), while six studies reported increased survival following drug therapy in all age groups (13,047 patients, 66 years, 26% women)). In mortality/hospitalization trials the mean age of included patients increased slightly from 63 years before 1990 to 66 years between 2000 and 2010 (Table 3).

Table 2. Age and gender of participants according to drug category in included studies*

Drug category	Studies	Patients	Age	Female
	N	N	years	n (%)
Mortality/hospitalization				
Diuretic	1	237	74	135 (57)
ACE-i	21	22,978	66	5,722 (25)
ARB	9	24,777	67	8,399 (34)
Beta-blocker	14	20,592	64	4,776 (23)
MRA	2	4,400	67	1,056 (24)
Total†	43	67,528	65	18,450 (27)
Quality of life				
Diuretic	2	268	73	110 (41)
ACE-i	14	5,127	63	1,214 (24)
ARB	12	9,180	68	3,595 (39)
Beta-blocker	9	1,338	64	302 (23)
MRA	2	70	61	17 (24)
Total‡	33	14,539	66	4,895 (34)

* ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist. Standard deviation could not be calculated due to missing data in the included trials.

† Total numbers represent different studies: four studies compared drugs from two different drug categories (ELITE[49] and ELITE-II[54]: losartan compared to captopril; CARMEN[76], carvedilol compared to enalapril; and CIBIS-III[65], bisoprolol compared to enalapril).

‡ Total numbers represent different studies: six studies compared drugs from two different drug categories (Guazzi, et al[29], enalapril compared to losartan; Losartan pilot exercise study investigators[51], losartan compared to enalapril; RESOLVD[41], candesartan compared to enalapril; ELITE[50], losartan compared to captopril; Hong Kong diastolic heart failure study[46], irbesartan compared to ramipril; and Brack, et al[48], irbesartan compared to uptitrating various ACE-is).

Table 3. Mean age of participants (in years) per decade of publication of the study per endpoint*

	All endpoints		Mortality/Hospitalization		Quality of life	
Year of publication	Number of patients	Age	Number of patients	Age	Number of patients	Age
-1990	761	62	553	63	208	59
1991-2000	29,473	64	24,409	64	5,064	63
2001-2010	48,815	66	39,669	66	9,146	68
2011-	3,018	69	2,897	69	121	67
All	72,164†	65	67,528	65	14,539	66

* Standard deviation could not be calculated due to missing data in the included trials.
† As in four studies (SOLVD, I-PRESERVE, ELITE, and Val-HeFT) all endpoints were determined, patients were only counted once in the overall number of patients.

Quality of life

The 33 trials reporting quality of life included a total of 14,539 patients (mean age 66 years, 34% female). In two studies (314 patients in total, 49% women) the mean age of the participants was at least 75 years (PEACH; and Zi, et al).[14,40] Only one study evaluated the effect of drug therapy across age categories (Val-HeFT, 3010 patients, 63 years, 21% women).[58] In this study treatment improved quality of life irrespective of age. In quality of life trials the mean age of the participants increased from 59 years before 1990 to 68 years between 2000 and 2010.

Discussion

The cornerstone of the drug treatment in chronic heart failure consists of diuretics, ACE-inhibitors/ARBs, beta-blockers and mineralocorticoid receptor antagonists. These drugs have been evaluated in 43 randomised controlled trials with mortality/hospitalization as endpoint, including a total of 67,528 participants with a mean age of 65 years, 27% of whom were women. The mean age of the 14,539 participants in the 33 studies with quality of life as endpoint was 66 years (34% female). Only four studies evaluated both mortality/hospitalization and quality of life. None of the 72 different studies exclusively focused on patients aged 75 years or over. In eight trials age above 75 years was an exclusion criterium. Only in three (3,128 (4.6%) patients) of the mortality/hospitalization and two (314 (2.2%) patients) of the quality of life heart failure studies, the mean age of the participants was at least 75 years. In the last 35 years the mean age of the included patients in

heart failure trials increased from 62 years before 1990 to 66 years between 2000 and 2010.

Drug trials in chronic heart failure have predominantly been carried out in patients (usually men) with a mean age of 65 years, whereas the mean age of onset of heart failure in the population at large exceeds 75 years,[3-5] and the mean age of hospitalized heart failure patients is 73 years.[86] The majority of elderly heart failure patients are female, have a wide range of co-morbidities and more often have preserved left ventricular systolic function, while the available trials almost exclusively included patients with reduced ejection fraction. In our review patients included in trials for systolic heart failure were younger than patients included for trials for heart failure with preserved ejection fraction (64 and 71 years, respectively, 23% and 53% women; appendix).

Only 17 of 72 trials reported treatment effects according to age, all found similar results across age categories. It should be noted, however, that the power of such subgroup analyses is limited, the confidence limits of the subgroup effects tend to be very large, especially when there was no overall beneficial treatment effect (7 of these 17 trials). Furthermore, most trials excluded patients with various comorbidity (i.e. elderly patients), in whom concomitant diseases (e.g. COPD, renal failure, dementia), are likely to complicate heart failure treatment and result in higher mortality and hospitalization rates.[9,87-89] Heart failure with preserved ejection fraction is more prevalent in elderly patients but there is little evidence of effective treatments.[6]

Most elderly heart failure patients are managed by generalists (general practitioners, internists, and geriatricians), and not by cardiologists (who tend to treat younger male patients with systolic heart failure due to ischemic events with limited comorbidity).[89,90] Our review shows that there is a limited amount of evidence in the elderly, as has been established before.[91] Although the average age of participants of heart failure trials increased over the last decades, on-going heart failure trials still have a minimal representation of elderly patients.[9] Comorbidity (e.g. renal failure, cancer, chronic obstructive pulmonary disease) often leads to exclusion from participation in clinical trials. In a recent Dutch study of geriatric heart failure patients (mean age 83 years, 63% women) the prevalence of (non cardiovascular) comorbidity was high,[92] confirming results from an earlier study in general practice from the Netherlands (mean 79 years, 57% women),[89] and comorbidity per se (assessed with the Charlson Comorbidity Index) was the single strongest predictor of mortality.[93] Cardiovascular comorbidity (e.g. diabetes, atrial fibrillation) seems less prevalent in the very old (≥ 85 years) than in younger patients (possibly because of the so-called “depletion of susceptibles”) and is of

less prognostic importance.[94] Notwithstanding its relevance (especially for elderly heart failure patients) quality of life was evaluated as an endpoint in less than a quarter of the number of patients in whom the effect on mortality/hospitalization was evaluated.

Some limitations of this review need to be discussed. As the scope of this systematic review was to evaluate the participation of elderly patients in trials that assessed the effect of current "standard" medication (i.e. diuretics, ACE-inhibitors, ARBs, beta-blockers, and mineralocorticoid receptor antagonists) in chronic heart failure, we did not include other heart failure drugs, such as ivabradine[95] that was reported to be beneficial in a recent study whose participants had a mean age of 60 years. We chose not to perform an individual patient data meta-analysis as many of the included trials (18 out of 43 (42%) mortality/hospitalization, and 13 out of 33 (39%) quality of life) were performed in the previous century, which is likely to pose difficulties to obtain source information. The main strength of the current review is that it provides a comprehensive, complete and up-to-date assessment of the inclusion of elderly patients in clinical trials of essential heart failure drugs, not only taking into account the effects on mortality and hospitalizations but also on quality of life. Previous reviews on the treatment of chronic heart failure provided an overview of both randomised controlled trials in combination with retrospective studies and population based studies,[96] explored treatment and side effects instead of determining the participation of elderly persons,[97] or did not specifically address elderly patients.[98]

Implications for the future

As most evidence for treatment of chronic heart failure is obtained from clinical trials in men in their mid-sixties, physicians treating elderly patients with chronic heart failure must take into account that they treat their patients on the assumption that *'therapies (especially drugs) found to be beneficial in a narrow range of patients generally have broader application in actual practice.'*, as concluded in the CONSORT statement.[99] As evidence of the generalizability of trial results to patients that differ from those enrolled in the trial is scarce, we believe that guidelines should also alert physicians to which patient group the recommendations are applicable.[100] It is self-evident that trials should include patients likely to be treated in daily practice. For heart failure, this implies that also chronic heart failure patients treated by generalists (i.e. general practitioners, internists, and geriatricians) should be recruited. Special attention in future heart failure trials should be paid to quality of life as an outcome measure, as this is particularly relevant for elderly patients. The influence of age on the effect of drug

treatment in heart failure should be determined in future trials in patients of at least 75 years or older. Furthermore, all heart failure trials should specifically report on the absolute number of elderly participants.

In conclusion, although chronic heart failure has a high prevalence in elderly patients, these patients remain largely underrepresented in clinical trials evaluating cornerstone drug therapy. This complicates the management of older patients with heart failure in daily practice. Because the “natural history” of the trials in the past decades reveals only a small increase in the mean age of included patients, other measures (e.g. directives from registration authorities such as the European Medicines Agency (EMA) to include enough elderly patients in heart failure trials) could be considered.

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Appendix

Appendix 1. Characteristics in heart failure studies according to endpoint*

Study	Year	Drug	Compared to	Inclusion			Participants			Age groups	QoL tests	Effect drug on		
				Age	NYHA	LVEF	N	Age	Female n (%)	Age: n (%)		M	H	QoL
Diuretic														
PEACH[14]	1999	furosemide	torasemide	-	II-III	-	240	75	107 (45)	-	MLHFQ	-	-	no
Muller, et al.[15]	2003	furosemide	torasemide	≥ 18	≥ II	-	237	74	135 (57)	-	-	=	=	-
Gupta, et al.[16]	2010	torasemide	placebo, crossover	-	-	≤ 45%	28	59	3 (11)	-	MLHFQ	-	-	no
Angiotensin converting enzyme inhibitor														
Captopril-Digoxin Multicenter Research Group[17]	1988	captopril	digoxin, placebo	< 75	-	≤ 40%	300	57	51 (17)	-	-	no	captopril and digoxin better	-
Barabino, et al.[13]	1991	captopril	ibopamine, placebo	≥ 65	≥ II	-	150	75	77 (51)	-	-	no	+	-
Munich Mild HF trial[18]	1992	captopril	placebo	≥ 18	I-III	-	170	62	42 (25)	-	-	no	-	-
Cowley, et al.[19]	1994	captopril	flosequinan	-	III-IV	-	209	64	57 (27)	-	-	=	-	-
CHIPS[20]	2000	captopril	D	18-80	I-III	< 45%	298	65	92 (31)	-	-	=	=	-
Cilazapril-Captopril Multicentre Group[21]	1998	cilazapril	captopril, placebo	≥ 18	≥ II	-	367	63	132 (36)	-	SIP, POMS, DFI, HSI	-	-	no
CONSENSUS[22]	1987	enalapril	placebo	-	IV	-	253	71	75 (30)	-	-	+	-	-
SOLVD[23]	1991	enalapril	placebo	< 80	-	≤ 35%	2,569	61	505 (20)	-	-	+	+	-
SOLVD[24]	1994	enalapril	placebo	21-80	-	≤ 35%	2,465	61	478 (19)	-	various	-	-	+
V-HeFT II[25]	1991	enalapril	H+ISDN	18-75	-	< 45%	804	61	0 (0)	≥ 65: 225 (28)	-	+	=	-

Study	Year	Drug	Compared to	Inclusion			Participants			Age groups	QoL tests	Effect drug on		
				Age	NYHA	LVEF	N	Age	Female n (%)	Age: n (%)		M	H	QoL
de Vries, et al.[26]	1995	enalapril	felodipine	18-75	II-III	< 40%	46	65	7 (15)	-	SHFQ, PGWB, SDS			no
Pacher, et al.[27]	1996	enalapril	D	-	III-IV	-	83	56	14 (17)	-	-	=	-	-
NETWORK[28]	1998	enalapril	D	18-85	≥ II	all	1,532	70	556 (36)	-	-	composite endpoint: =		-
Guazzi, et al.[29]	1999	enalapril	losartan, placebo	-	II-III	< 40%	20	58	4 (20)	-	MLHFQ	-	-	no
HEDS[30]	2000	enalapril	D	-	≥ II	≤ 35%	248	56	37 (15)	-	-	=	=	-
Kitzman, et al.[31]	2010	enalapril	placebo	-	-	≥ 50%	71	70	60 (85)	-	MLHFQ			no
FEST[32]	1995	fosinopril	placebo	18-75	II-III	≤ 35%	308	63	79 (26)	-	-	no	+	-
Fosinopril HF Study group[33]	1995	fosinopril	placebo	18-75	II-III	≤ 35%	241	62	49 (20)	-	-	no	no	-
Multicenter Lisinopril-Captopril Congestive HF Study Group[34]	1989	lisinopril	captopril	-	≥ II	< 45%	189	60	41 (22)	-	DFI	-	-	lisinopril better
ATLAS[35]	1999	lisinopril	D	-	≥ II	≤ 30%	3,164	64	648 (20)	-	-	=	higher dosage better	-
IMPRESS[36]	2000	lisinopril	omapratilat	≥ 18	≥ II	≤ 40%	573	64	122 (21)	-	-	composite endpoint: =		-
Gundersen, et al.[37]	1995	ramipril	placebo	-	II-III	≤ 40%	223	64	63 (28)	-	SHFQ, PGWB, SDS	-	-	no
CASSIS[38]	1995	spirapril	enalapril, placebo, D	-	≥ II	< 40%	248	58	42 (17)	-	MLHFQ	-	-	lowest dosage spirapril: +
OVERTURE[39]	2002	omapratilat	omapratilat	-	≥ II	≤ 30%	5,770	63	1,212 (21)	-	-	=	=	-
PEP-CHF[11]	2002	perindopril	placebo	≥ 70	-	≥ 40%	850	76	468 (55)	> 75: 385 (45)	-	no	+	-
Zi, et al.[40]	2003	quinapril	placebo	> 65	II-III	≥ 40%	74	78	48 (65)	-	OTE	-	-	no

Study	Year	Drug	Compared to	Inclusion			Participants			Age groups	QoL tests	Effect drug on		
				Age	NYHA	LVEF	N	Age	Female n (%)	Age: n (%)		M	H	QoL
Angiotensin receptor blocker														
RESOLVD[41]	1999	candesartan	enalapril, and candesartan with enalapril	-	≥ II	< 40%	768	63	127 (17)	-	MLHFQ			no
CHARM-added[42]	2003	candesartan	placebo	≥ 18	≥ II	≤ 40%	2,548	64	542 (21)	≥ 75: 457 (18)	-	+	+	-
CHARM-preserved[43]	2003	candesartan	placebo	≥ 18	≥ II	> 40%	3,023	67	1,212 (40)	≥ 75: 807 (27)	-	no	+	-
CHARM-alternative[44]	2003	candesartan	placebo	≥ 18	≥ II	≤ 40%	2,028	67	646 (32)	≥ 75: 472 (23)	-	+	+	-
I-PRESERVE[45]	2008	irbesartan	placebo	≥ 60	≥ II	≥ 45%	4,128	72	2,491 (60)	≥ 75: 1,413 (34)	MLHFQ	no	no	no
Hong Kong diastolic HF study[46]	2008	irbesartan	ramipril, care as usual	≥ 18	≥ II	> 45%	151	74	93 (62)	-	MLHFQ	-	-	no
Kum, et al.[47]	2008	irbesartan	care as usual	-	II-III	< 50%	50	67	14 (28)	-	MLHFQ	-	-	+
Brack, et al.[48]	2008	irbesartan	ACE-i[†]	-	II-III	< 40%	89	67	22 (25)	-	MLHFQ	-	-	both drugs: +
ELITE[49]	1997	losartan	captopril	≥ 65	≥ II	≤ 40%	722	73	240 (33)	≥ 70: 508 (70)	-	losartan better	=	-
ELITE[50]	2000	losartan	captopril	≥ 65	≥ II	≤ 40%	300	73	71 (24)	-	MLHFQ, SIP	-	-	both drugs: +
Losartan pilot exercise study investigators[51]	1997	losartan	enalapril, D	-	≥ II	≤ 45%	116	58	26 (22)	-	DFI	-	-	lowest dosage losartan: +
Houghton, et al.[52]	2000	losartan	placebo	≥ 18	II-III	< 40%	20	66	1 (5)	-	DSQ	-	-	no
HEAAL[53]	2009	losartan	D	≥ 18	≥ II	≤ 40%	3,834	66	1,143 (30)	-	-	composite endpoint: higher dosage better		-
ELITE-II[54]	2000	losartan	captopril	≥ 60	≥ II	≤ 40%	3,152	71	967 (31)	≥ 70: 1,813 (58)	-	=	=	-
REPLACE[55]	2001	telmisartan	care as usual	≥ 21	II-III	≤ 40%	378	64	41 (11)	-	MLHFQ	-	-	no

Study	Year	Drug	Compared to	Inclusion			Participants			Age groups	QoL tests	Effect drug on		
				Age	NYHA	LVEF	N	Age	Female n (%)	Age: n (%)		M	H	QoL
Cice, et al.[56]	2010	telmisartan	placebo	≥ 18	II-III	≤ 40%	332	63	153 (46)		-	+	+	-
Val-HeFT[57]	2001	valsartan	placebo	≥ 18	≥ II	< 40%	5,010	63	1,005 (20)	≥ 65: 2,350 (47)	-	no	+	-
Val-HeFT[58]	2005	valsartan	placebo	≥ 18	≥ II	< 40%	3,010	63	630 (21)	≥ 65: 1,408 (47)	MLHFQ	-	-	+
Parthasarathy, et al.[59]	2009	valsartan	placebo	≥ 21	-	≥ 40%	150	62	75 (50)	≥ 65: 67 (45)	MLHFQ, EuroQol	-	-	no
Beta-blocker														
Sturm, et al.[60]	2000	atenolol	placebo	18-75	-	≤ 25%	100	51	12 (12)	-	-	+	+	-
BETACAR[61]	2006	betaxolol	carvedilol	18-75	II-III	≤ 35%	255	57	36 (14)	-	MLHFQ	-	-	both drugs: +
Hawkins, et al.[62]	2009	bisoprolol	placebo	-	-	< 40%	27	71	8 (30)	-	MLHFQ, SF-36, CRQ	-	-	no
CIBIS-I[63]	1994	bisoprolol	placebo	18-75	III-IV	< 40%	641	60	112 (17)	-	-	no	+	-
CIBIS-II[64]	1999	bisoprolol	placebo	18-80	III-IV	≤ 35%	2,647	61	515 (19)	-	-	+	+	-
CIBIS-III[65]	2005	bisoprolol	enalapril	≥ 65	II-III	< 35%	1,010	74	321 (32)	-	-	=	=	-
Pollock, et al.[66]	1990	bucindolol	placebo	-	-	< 40%	19	54	4 (21)	-	MLHFQ			+
BEST[67]	2001	bucindolol	placebo	≥ 18	III-IV	≤ 35%	2,708	60	593 (22)	≥ 75: 322 (12)	-	no	no	-
US Carvedilol HF study group[70]	1996	carvedilol	placebo	-	≥ II	≤ 35%	1,094	58	256 (23)	≥ 59: 554 (51)	-	+	+	-
Sanderson, et al.[72]	1999	carvedilol	metoprolol	-	-	< 45%	51	60	11 (22)	-	MLHFQ	-	-	both drugs: +
Metra, et al.[71]	2000	carvedilol	metoprolol	-	≥ II	≤ 35%	150	57	14 (9)	-	MLHFQ	-	-	both drugs: +
COPERNICUS[73]	2002	carvedilol	placebo	-	III-IV	< 25%	2,289	63	458 (20)	-	-	+	+	
COMET[74]	2003	carvedilol	metoprolol	-	≥ II	< 35%	3,029	62	612 (20)	≥ 65: 1,392 (46)	-	carvedilol better	composite endpoint: =	-

Study	Year	Drug	Compared to	Inclusion			Participants			Age groups	QoL tests	Effect drug on		
				Age	NYHA	LVEF	N	Age	Female n (%)	Age: n (%)		M	H	QoL
MUCHA[75]	2004	carvedilol	placebo, D	20-80	II-III	≤ 40%	173	60	40 (23)	≥ 65: 74 (43)	-	+	+	-
CARMEN[76]	2004	carvedilol	enalapril, and carvedilol with enalapril	-	-	< 40%	572	62	110 (19)	-	-	=	=	-
CASPER[68]	2009	carvedilol	placebo	-	-	≤ 40%	405	65	109 (27)	-	KCCQ, PHQ-8, TSQM	-	-	no
CARVIVA HF trial[69]	2011	carvedilol	ivabradine, and carvedilol with ivabradine	18-90	II-III	-	121	67	39 (32)	-	QLMI	-	-	no
Sanderson, et al.[77]	1997	celiprolol	metoprolol, placebo	-	≥ II	< 45%	50	62	12 (24)	-	MLHFQ	-	-	metoprolol better
Fisher, et al.[78]	1994	metoprolol	placebo	-	-	≤ 40%	50	63	2 (4)	-	-	-	+	-
MERIT-HF[79]	2000	metoprolol	placebo	40-80	≥ II	≤ 40%	3,991	64	898 (23)	≥ 70: 1,245 (31)	-	+	+	-
ENECA[80]	2005	nebivolol	placebo	≥ 65	≥ II	≤ 35%	260	72	69 (27)	> 70: 104 (40)	MLHFQ	-	-	no
SENIORS[12]	2005	nebivolol	placebo	≥ 70	-	≤ 35%	2,128	76	785 (37)	≥ 75: 1,064 (50)	-	no	composite endpoint: +	-
Marazzi, et al.[81]	2011	nebivolol	carvedilol	-	I-III	< 40%	160	66	62 (39)	-	-	=	=	-
Mineralocorticoid receptor antagonist														
RALES[82]	1999	eplerenone	placebo	≥ 55	III-IV	≤ 35%	2,737	69	446 (27)	≥ 75: 657 (24)	-	+	+	-
Agostoni, et al.[83]	2005	spironolactone	placebo	-	II-III	-	30	59	8 (27)	-	MLHFQ	-	-	no
Berry, et al.[84]	2007	spironolactone	placebo	-	I-III	< 40%	40	62	9 (23)	-	VAS	-	-	↓
EMPHASIS-HF[85]	2011	spironolactone	placebo	-	II	≤ 30%	1,663	65	610 (22)	-	-	+	+	-

* Age, age in years; Age groups, number of patients above the cutoff age described in the mentioned trial; crossover, after randomisation patients were initial treated with one drug and later treated with the other drug; CRQ, Chronic Respiratory Questionnaire; D, various dosages of the drug; DFI, Dyspnea Fatigue Index; DSQ, Disease Specific Questionnaire; EuroQol, EuroQol questionnaires; H+ISDN, hydralazine and isosorbidedinitrate; H, hospitalization; HSI, Health Status Index; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; M, mortality; MLHFQ, Minnesota Living with Heart Failure Questionnaire; no, no effect of treatment on outcome; NYHA, New York Heart Association functional class; OTE, McMaster Overall Treatment Evaluation questionnaire; PGWB, Psychological General Well Being index; PHQ-8, Depressive Symptoms Questionnaire; POMS, Profile Of Mood States; QLMI, MacNew Quality of Life after Myocardial Infarction questionnaire; QoL, quality of life; SDS, Sleep Dysfunction Scale; SF-36, Medical Outcomes Study Short Form-36 Questionnaire; SHFQ, Severe Heart Failure Questionnaire; SIP, Sickness Impact Profile; TSQM, Treatment Satisfaction Questionnaire with Medication; various, scales excerpted from previously validated instruments; VAS, Visual Analogue Scale (www.euroqol.org); Year, year of publication; '-', not described; '+', treatment improved outcome; '=', both drugs showed the same outcome, or outcome was the same regardless of dosage; '↓', treatment worsens outcome.

† Brack, et al.: ACE-inhibitor already received was uptitrated, irrespective of which ACE-inhibitor was used.

Chapter 9

General discussion

Case report

A 82-year-old woman was referred to the geriatrician because of weight loss, cognitive decline and depression. She was known with both cardiovascular (hypertension, atrial fibrillation, and transient ischemic attack) and non-cardiovascular (osteoarthritis, visual impairment, and frequent urinary tract infections) comorbidity. She used the following medications: digoxin, acenocoumarol, diclofenac, furosemide, lactulose, and eye drops (not specified further). Her daughter mentioned that her mother lost weight and was tired, had swollen legs and sat in a chair all day. The daughter considered her mother to be depressed and suffering from cognitive impairment. There were doubts about medication compliance. The patient herself did not seem to be aware of any memory or mood problems, nor of the weight loss. She was more concerned about her visual impairment and painful knees that limited her activities. Although she said to be able to walk half a mile with a walker, she hardly ever went outside. During walking she had to stop because of breathlessness, which both patient and her daughter attributed to poor physical condition. Wheezing was not observed by her daughter. Nocturnal dyspnoea was possibly present as her daughter thought her mother to wander around her apartment at night for no apparent reason. She was disoriented, but she denied this ('there is no need for me to know which day it is') and an impairment of her short term memory was noted. Initially nervous and reluctant to cooperate, she later was more at ease. The mini mental state examination (MMSE) showed 19 out of 30 points, suggestive of possible dementia. The patient preferred no additional investigations but was prepared to cooperate as soon as she realised her daughter was worried. Physical examination revealed high blood pressure (185/100 mmHg) with an irregular pulse (80 beats per minute), and a trace of pitting oedema. Her skin was pale. Auscultation of heart and lungs showed no abnormalities. Her body mass index (BMI) was 23.3 kg/m^2. She was dyspnoeic during the physical examination.

The geriatrician considered the following diagnoses: malignancy, dementia, depression, heart failure, digoxin intoxication, anaemia, and gastritis. After deliberation with the patient, she agreed to carry out additional tests that could be performed immediately (electrocardiography (ECG), chest X-ray and laboratory tests). Abnormal findings included an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP, 792 pg/ml), impaired renal function (creatinine clearance 46 ml/min/1.73 m^2), and anaemia (haemoglobin 6.9 mmol/l). Acenocoumarol was not adequately dosed (INR 1.5) and there was no digoxin intoxication (digoxin 0.8 ng/ml). Inspiration at the chest X-ray was inadequate, the cardiothoracic ratio was

0.54. Electrocardiography showed atrial fibrillation with a heart rate of 92/min and left ventricular hypertrophy, similar to an ECG made years earlier. Based on the available information the geriatrician considered heart failure likely and initiated treatment with a loop diuretic (furosemide 40 mg once daily) and advised the patient and her daughter on the importance of salt and fluid restriction, as well as daily weighing. Digoxin was replaced by a beta-blocker, an angiotensin converting enzyme (ACE) inhibitor was to be started at a later stage. Doubts remained about the compliance of the patient given her impaired cognitive functioning. Echocardiography, had it been performed, would most likely have shown preserved left ventricular systolic function and diastolic dysfunction in the setting of left ventricular hypertrophy.

This case illustrates the diagnostic and therapeutic challenges facing health care professionals managing elderly patients. Although there are numerous questions outside the scope of heart failure in this example (such as: Should targeted tests to detect a malignancy be performed?) there are many clinically relevant questions for the geriatrician related to the diagnosis and management of heart failure alone. These include: Does this patient have heart failure? Should the patient be referred for echocardiography (which she will probably refuse)? Are geriatricians able to diagnose heart failure without echocardiography? If the patient, on the other hand, wants to be referred to a cardiologist, what will be the added value? What evidence is available to guide treatment of heart failure in geriatric patients? What is the impact of comorbidity on prognosis? Some of these questions were answered by the studies performed in this thesis.

Main outcomes of this thesis

The ageing of the population and improved survival following acute cardiac events have led to an increased prevalence of heart failure, especially in the elderly.[1,2] Early detection of heart failure is notoriously difficult, particularly in patients with a wide range of (both cardiovascular and non-cardiovascular) comorbidity and in a setting without direct access to echocardiography, such as in primary care or geriatric practice.[3] The management of those found to have heart failure is hampered by the lack of evidence based guidance for heart failure patients aged 75 years or older, who represent more than 50% of persons developing heart failure.[4-6] This thesis addressed the diagnosis, prognosis and treatment of heart failure in geriatric outpatients. The main results of the studies described in this thesis are:

Diagnosis

- Half of geriatric patients suspected of heart failure actually have heart failure (chapter 5).
- Classic signs of heart failure (such as tachypnoea, pulmonary rales, or peripheral oedema) are absent in one third of geriatric patients with new, slow onset heart failure (chapter 5).
- Loss of appetite, lower BMI and absence of wheezing are specific features of heart failure in geriatric outpatients suspected of heart failure (chapter 5).
- Geriatricians and general practitioners correctly establish the presence or absence of heart failure in two thirds of geriatric patients suspected of new, slow onset heart failure, using simple diagnostic tests (ECG, chest X-ray, laboratory tests) readily available to them (chapter 2).
- Existing diagnostic algorithms accurately rule out heart failure in geriatric outpatients suspected of new, slow onset heart failure (chapter 3).
- Current diagnostic prediction rules accurately predict the presence or absence of heart failure in geriatric outpatients suspected of new, slow onset heart failure, although they were not derived in elderly patients (chapter 4). The complexity of these prediction rules may limit their use in daily practice.
- A diagnostic prediction rule based on findings from patient history and physical examination in combination with NT-proBNP reliably predicts the presence or absence of heart failure in the vast majority of geriatric outpatients suspected of having heart failure (chapter 5).
- In geriatric patients suspected of new, slow onset heart failure, galectin-3 may play a role in establishing the presence or absence of heart failure (chapter 7).

Prognosis

- The majority of geriatric patients with newly diagnosed, slow onset heart failure dies within three years after the diagnosis is established (chapter 6).
- Comorbidity, as summarized in the Charlson Comorbidity Index (CCI), is the strongest predictor of three-year mortality, independent of the severity of heart failure, as reflected in left ventricular ejection fraction (LVEF) and NT-proBNP (chapter 6).
- Elevated galectin-3 levels indicate an increased risk for three-year mortality in geriatric heart failure patients (chapter 7).

Treatment

- The mean age of participants in clinical trials evaluating essential heart failure medications (diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists) is 65 years (chapter 8). The mean age of participants increased only slightly over the last 35 years.
- No trials have been exclusively designed to evaluate the effect of drug treatment on mortality, hospitalization or quality of life in patients 75 years or older (chapter 8).

Implications for daily clinical practice

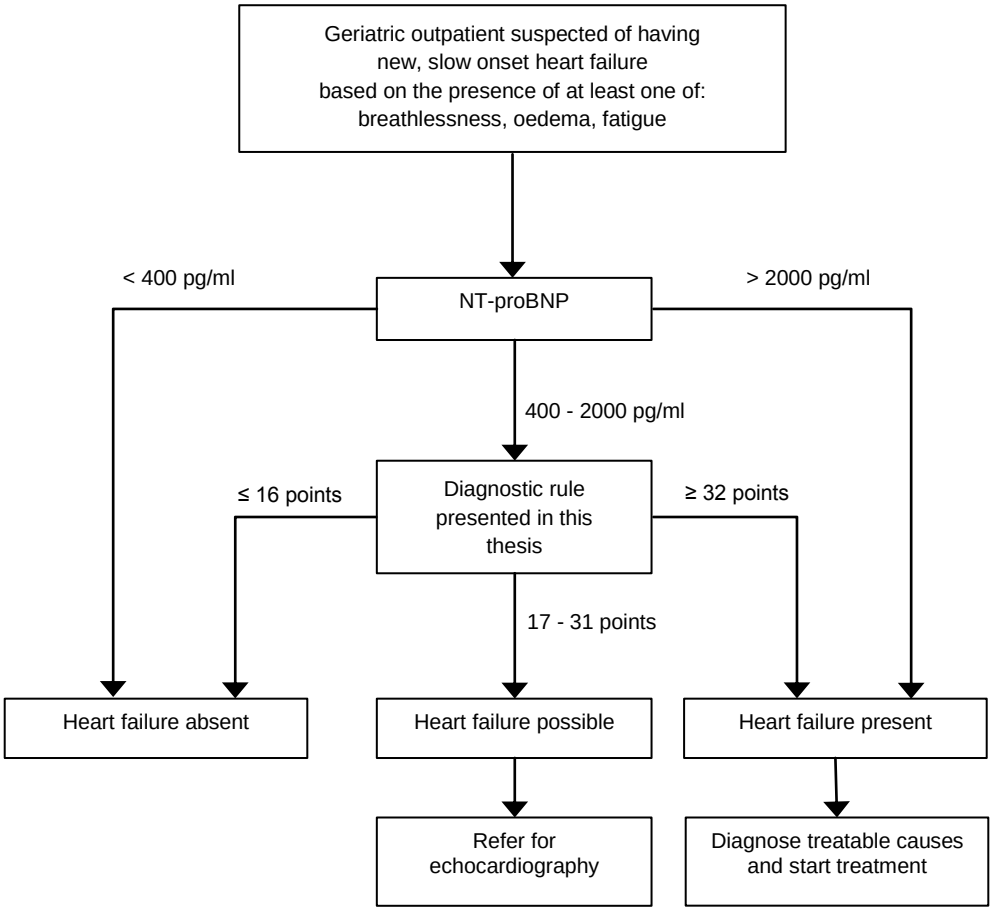
Geriatric patients are characterised by high (biological) age, atypical presentation of symptoms and multiple comorbidity, frequently rooted in a combination of physical, mental, social and functional problems. As this all may compromise daily living the emphasis of medical care in geriatric practice is to maintain or improve quality of life and independence of the patient. For geriatric patients suspected of heart failure a diagnostic strategy that leads to accurately establishing the presence or absence of heart failure with as little additional tests as possible is particularly desirable.

The findings in this thesis confirm and extend the notion that clinical characteristics of heart failure in elderly patients often differ from those in younger patients.[7] Breathlessness, fatigue or oedema, especially in patients with known cardiovascular diseases (e.g. hypertension, myocardial infarction, atrial fibrillation) should raise the suspicion of new, slow onset heart failure,[8] but weight loss, depressive mood, cognitive dysfunction, mobility disorders, or loss of independence may also be caused by heart failure. Consequently, physicians need a high index of suspicion to diagnose heart failure in this specific patient group. In elderly patients the absence of typical signs of heart failure should not be interpreted as absence of heart failure; signs may simply be absent or more difficult to detect due to comorbidity (e.g. chronic obstructive pulmonary disease (COPD)).[9]

When symptoms and signs have raised the possibility of heart failure, determination of (NT-pro)BNP is warranted based on the results of studies described in this thesis: heart failure can safely be excluded when NT-proBNP levels are below 400 pg/ml and can be deemed present when levels are above 2000 pg/ml (Figure 1). In those with NT-proBNP levels between 400 and 2000 pg/ml application of the diagnostic rule developed in this thesis can be helpful. This

diagnostic strategy will result in exclusion of heart failure in 48%, diagnosing heart failure in 38%, and referral for echocardiography of 15% of all patients. Half of those referred for echocardiography will have heart failure. In only 9% of all patients an incorrect diagnosis will be established when this strategy is applied (4% false positives and 5% false negatives).

Figure 1. Flow chart of diagnosing heart failure in geriatric outpatients suspected of new, slow onset heart failure*



* Diagnostic rule presented in this thesis: see chapter 5.

Current guidelines mandate additional investigations (particularly echocardiography) once heart failure has been established to determine the cause of heart failure and to guide management (e.g. device therapy in patients with systolic heart failure and prolongation of the QRS interval). As care in geriatric practice is aimed at improving quality of life by reducing symptoms rather than merely improving survival, the management of heart failure in geriatric patients will generally consist of lifestyle advices and medications. The proportion of patients receiving more advanced treatment for heart failure, e.g. device therapy, percutaneous interventions or open heart surgery, is negligible.[10,11] Potential causes or factors contributing to the occurrence of heart failure can often be identified from patient history (e.g. COPD, alcohol abuse, use of non-steroidal anti-inflammatory drugs or corticosteroids), physical examination (hypertension, valvular heart disease), ECG (atrial fibrillation, prior myocardial infarction, left ventricular hypertrophy) and laboratory tests (anaemia, impaired renal function, thyroid dysfunction). Current daily practice shows that echocardiography in all patients suspected of heart failure by non-cardiologists is not a realistic option.[12] Referral for echocardiography of geriatric patients can probably be limited to patients in whom the diagnosis remains unclear (e.g. patients with an intermediate score on the diagnostic rule presented in this thesis), or who show no clinical improvement following targeted heart failure treatment or who are potential candidates for invasive therapies.

Left ventricular ejection fraction is an important determinant of prognosis in patients with heart failure. In geriatric heart failure patients, however, comorbidity reflected in the CCI[13] is the strongest predictor of three year mortality, regardless of LVEF. Assessment of comorbidity therefore should be an integral part of the evaluation of heart failure in geriatric patients.

The paucity of evidence based information regarding the treatment of elderly heart failure patients, particularly in the presence of comorbidity, should be taken into account when caring for these patients. This not only concerns the initiation and uptitration of heart failure medications such as ACE-inhibitors and beta-blockers that have been shown to be effective in younger heart failure patients, but also includes lifestyle measures and more advanced treatment options.

Future clinical research

Diagnosis

Elderly patients reflect the group of “real world” patients with considerable comorbidity in whom heart failure is usually diagnosed and managed by non-cardiologists (e.g. geriatricians and general practitioners).[14] The need for more insight into this group of heart failure patients, who are frequently excluded from clinical trials, is increasingly appreciated.[15] As establishing a diagnosis starts with suspicion of that diagnosis, research should be performed to determine which initial symptoms or signs (e.g. weight loss, depression) in elderly patients may alert physicians to the possible presence of heart failure. As both geriatricians and general practitioners are retrospectively able to accurately diagnose the presence or absence of heart failure using symptoms, signs, ECG, chest X-ray, laboratory tests and spirometry, this should be prospectively tested in daily practice. Our diagnostic rule is designed to establish the presence or absence of heart failure in geriatric patients suspected of heart failure with only findings from history taking, physical examination and laboratory tests (NT-proBNP). External validation in other elderly patient groups (for example other geriatric outpatients suspected of new, slow onset heart failure, or elderly patients suspected of acute heart failure) is warranted. When echocardiographic findings in geriatric heart failure patients do not alter treatment options, the added value of echocardiography seems limited. Future studies should formally assess the added value of echocardiography in the elderly. In the Netherlands it is easier for a geriatric patient to have laboratory tests than to be referred to a cardiologist for echocardiography. Research for the added value of novel biomarkers, such as galectin-3, in the diagnosis and prognostication may be especially important in these patients.

Prognosis and treatment

Little evidence based information is available to guide heart failure treatment in elderly patients as they are underrepresented in randomised clinical trials.[15,16] In more advanced treatment options, recent, but retrospective, studies show that neither implantable cardioverter defibrillators (ICDs)[17] nor percutaneous coronary intervention (PCI)[18] improve mortality in elderly patients. In elderly patients with extensive comorbidity, further prospective studies are warranted, to quantify the effects of the available treatment modalities (including lifestyle measures, drug therapy, and more advanced treatment options, e.g. device therapy, coronary revascularization or valve surgery). These studies should not only explore the impact on mortality or hospitalization, but should also include measures of quality

of life, the latter being particularly relevant for elderly patients. Increasing life span without taking quality of life into account is no option in geriatric practice.

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Summary

Summary

The ageing of the population and improved survival following acute cardiac events have led to an increased prevalence of heart failure, especially in the elderly. When a physician notes that a patient has symptoms or signs suggestive of heart failure, typically breathlessness, fatigue, or ankle swelling, additional investigations are necessary. Assessing the presence or absence of heart failure merely based on symptoms and signs only, may lead to an incorrect diagnosis (in around 25-30% of patients), but understandably, this approach is frequently taken. Early detection of heart failure is particularly difficult in patients with a wide range of (both cardiovascular and non-cardiovascular) comorbidity and in a setting without direct access to echocardiography, such as in geriatric practice or primary care. For geriatric patients suspected of heart failure a diagnostic strategy that most accurately identifies patients with and without heart failure with as little additional testing is desirable. The main focus of this thesis is to optimize the diagnostic management of geriatric patients suspected of heart failure. In addition, the prognosis and evidence-based drug treatment of geriatric patients with established heart failure is studied.

The pivotal study population in this thesis consisted of 206 patients (mean age 82 years, 70% women) referred to the geriatric outpatient clinic - for a variety of reasons notably functional impairment, breathlessness, cognitive impairment, and mobility disorders - of two regional hospitals in the Netherlands (Elkerliek Hospital, Helmond and Meander Medical Center, Amersfoort) who presented with symptoms of breathlessness, fatigue, ankle swelling, or any combination of these. All participants underwent a diagnostic work-up including standardized clinical history, physical examination, electrocardiography (ECG), chest X-ray, laboratory tests, pulmonary function tests and echocardiography. In case of heart failure, patients were treated according to the guidelines of the European Society of Cardiology (ESC). An expert panel consisting of a cardiologist, general practitioner, pulmonologist and geriatrician determined the presence of heart failure applying the diagnostic criteria for heart failure of the ESC of 2005, using all available diagnostic information, including echocardiography (except serum N-terminal pro B-type Natriuretic Peptide (NT-proBNP) levels) as well as 6-months follow-up data on response to treatment, and other clinically relevant information. Heart failure was present in 94 of 206 participants (46%). All patients were followed for the occurrence of clinical events.

Chapter 1 provides the general introduction of the thesis. As both geriatricians and general practitioners are frequently confronted with patients with symptoms or

signs suggestive of heart failure, but have limited access to echocardiography, we explored their ability to diagnose the presence or absence of heart failure based on diagnostic tests more readily available in daily practice (e.g. symptoms, signs, ECG, chest X-ray, laboratory tests (including natriuretic peptides), and spirometry) in **chapter 2.** Two panels of three geriatricians and three general practitioners, respectively, were asked to establish the presence or absence of heart failure in elderly patients. They correctly identified the presence or absence of heart failure in two thirds of elderly patients. Consequently, echocardiography to confirm or exclude heart failure could be targeted at those in whom the diagnosis remains uncertain. In **chapter 3** a MEDLINE search identified four algorithms to potentially apply to geriatric outpatients suspected of new, slow onset heart failure: algorithms from the 'Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008' of the ESC; from the 'Chronic Heart Failure, National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care' of the National Institute for Health and Clinical Excellence (NICE), United Kingdom; from the 'Multidisciplinary Guidelines for Heart Failure 2010', The Netherlands (NL) and from the study performed by Mant *et al.* Applicability of these algorithms in our geriatric cohort was evaluated by calculating proportion of patients (i) referred for echocardiography, (ii) with heart failure among referred patients, and (iii) without heart failure in the non-referred. Applying algorithms resulted in referral for echocardiography in 52% (normal NT-proBNP; ESC), 72% (normal ECG; ESC), 56% (NICE), 93% (NL) and 70% (Mant) of all patients, diagnosing heart failure in 78%, 56%, 76%, 49% and 62% of those referred, respectively. In patients not referred for echocardiography heart failure was absent in 90%, 82%, 93%, 100% and 95%, respectively. The ESC NT-proBNP (< 400 pg/ml) based algorithm combined the lowest number of referrals for echocardiography (of whom 78% has heart failure) with a limited number (10%) of false negatives in the non-referred. In addition to diagnostic algorithms, diagnostic prediction rules (or diagnostic scores) have been developed to estimate the probability of heart failure in an individual patient. These rules not only help in excluding heart failure but also in establishing a high probability of heart failure. Current available diagnostic rules for suspected heart failure (Mant, *et al* and Kelder, *et al*) were validated in our geriatric patients in **chapter 4**. Both rules showed good calibration (Mant: slope 1.22, intercept 0.39; Kelder: slope 1.45, intercept -0.10) and discrimination (area under the Receiver Operating Characteristic (ROC) curve (c-statistic) Mant: 0.90 (95% confidence interval (CI) 0.86 - 0.95); c-statistic Kelder: 0.89 (95% CI 0.85 - 0.94)) in the geriatric validation cohort. Although both diagnostic rules accurately predict the presence of heart failure in geriatric outpatients, the applicability of these rules

may, however, be hampered by the large number of items included in the rule and the complexity of calculation of the probability of heart failure. In **chapter 5** we determined that apart from age, gender and nocturnal dyspnoea, absence of wheezing, loss of appetite and lower body mass index were independently associated with the presence of heart failure in geriatric patients suspected of new, slow onset heart failure. Of all additional diagnostic tests (ECG, chest X-ray and laboratory tests) NT-proBNP had the largest added value, i.e. had the most profound effect on the c-statistic, with an increase from 0.75 (95% CI 0.69 - 0.82) to 0.92 (95% CI 0.88 - 0.95). We developed a diagnostic rule consisting of these six clinical variables in combination with NT-proBNP. Scores in the diagnostic rule ranged from 1 to 67 points. Applying 16 and 32 points as cut-off values, 96 patients (47% of total study group) were in the low risk group (negative predictive value (NPV) 0.89) and 78 patients (38%) were in the high risk group (positive predictive value (PPV) 0.88). The remaining 32 patients (16% of the study group) were in the medium risk group. The score we developed accurately classifies most geriatric patients suspected of heart failure with little additional testing (apart from patient history and physical examination only NT-proBNP levels are required), while only 16% of the patients require referral for echocardiography to establish the diagnosis. As the proportion of elderly patients receiving more advanced treatment for heart failure (e.g. device therapy, percutaneous interventions or open heart surgery) is negligible, echocardiography in geriatric patients is primarily performed to determine the presence or absence of heart failure. Our diagnostic rule may partially take over this role of echocardiography in geriatric patients suspected of new, slow onset heart failure.

In **chapter 6** we determined that half of geriatric patients with heart failure died within three years. Comorbidity, summarized in the Charlson Comorbidity Index (CCI), was the strongest predictor of mortality, independent of severity of heart failure, as reflected in left ventricular ejection fraction and NT-proBNP. It follows that routine application of the CCI may be of help in adequately managing this group of patients. Biomarkers are increasingly applied in the evaluation of heart failure. We determined that among geriatric patients suspected of heart failure galectin-3 levels are higher in patients with heart failure than in those without heart failure (21.8 and 15.6 ng/ml, respectively; p = 0.04; **chapter 7**). In patients with heart failure three-year mortality was higher when galectin-3 levels were higher than the recently proposed cut-off value of 17.8 ng/ml: 74% and 33%, respectively; age-adjusted Hazard Ratio 3.7 (95% CI 1.0 - 13.2). Prognosis of heart failure can be improved by a range of drugs but evidence in elderly patients is scarce as we determined in **chapter 8**. In this systemic review the mean age of the participants

of the randomised controlled trials in the cornerstone heart failure treatment (diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists) was 65 years in trials with mortality/hospitalization as the outcome parameter and 66 years in trials with quality of life at the endpoint. In the last 35 years the mean age of the included patients increased only slightly. We recommend including patients in trials that more closely resemble patients treated in daily practice; i.e. older patients (with more comorbidity). In **chapter 9** the implications of the studies presented in this thesis are discussed and recommendations for future research are provided. A diagnostic algorithm is suggested based on findings from history taking, physical examination and levels of NT-proBNP, which accurately establishes the presence or absence of heart failure in geriatric patients suspected of slow onset heart failure, referring only 15% of all patients for echocardiography. Future research should especially be performed in these patients determining optimal treatment strategies (concerning lifestyle measures, drug treatment, and more advanced treatment options, e.g. device therapy, coronary revascularization or valve surgery). These studies should explore both “hard” endpoints (mortality, hospitalization) and “softer” endpoints (quality of life), the latter being particularly relevant for elderly patients.

Samenvatting

Samenvatting

De vergrijzing van de bevolking en een betere overlevingskans na acute cardiale aandoeningen hebben geleid tot een verhoogde prevalentie van hartfalen, vooral bij ouderen. Als een arts opmerkt dat een patiënt symptomen of verschijnselen heeft die wijzen op hartfalen, meestal kortademigheid, vermoeidheid of enkeloedeem, zijn aanvullende onderzoeken nodig. Het enkel op basis van symptomen en verschijnselen beoordelen van de aanwezigheid of afwezigheid van hartfalen kan leiden tot een onjuiste diagnose (bij ongeveer 25-30% van de patiënten), maar begrijpelijkerwijze wordt deze benadering vaak gekozen. Het vroeg opsporen van hartfalen is in het bijzonder moeilijk bij patiënten met een breed scala aan (zowel cardiovasculaire als niet-cardiovasculaire) comorbiditeit en in een omgeving zonder directe toegang tot echocardiografie, zoals in de geriatrische praktijk of de eerstelijnsgezondheidszorg. Bij geriatrische patiënten bij wie een vermoeden van hartfalen bestaat, is een diagnostische strategie gewenst die patiënten met en zonder hartfalen zo nauwkeurig mogelijk identificeert met zo weinig mogelijk aanvullende onderzoeken. Het belangrijkste aandachtspunt van dit proefschrift is het optimaliseren van de diagnostiek van geriatrische patiënten bij wie hartfalen wordt vermoed. Bovendien wordt de prognose en de empirische basis bestudeerd voor de medicatie van geriatrische patiënten bij wie hartfalen is vastgesteld.

De populatie van de hoofdstudie in dit proefschrift bestond uit 206 patiënten (gemiddelde leeftijd 82 jaar, 70% vrouwen) die, wegens een verscheidenheid aan redenen, met name functionele achteruitgang, kortademigheid, cognitieve stoornissen en mobiliteitsstoornissen, zijn verwezen naar de geriatrische polikliniek van twee regionale ziekenhuizen in Nederland (Elkerliek Ziekenhuis, Helmond en Meander Medisch Centrum, Amersfoort) en die symptomen vertoonden van kortademigheid, vermoeidheid, enkeloedeem of een combinatie hiervan. Alle deelnemers ondergingen gestandaardiseerde diagnostische onderzoeken, te weten anamnese, lichamelijk onderzoek, elektrocardiografie (ECG), thoraxfoto, laboratoriumtests, longfunctietests en echocardiografie. In geval van hartfalen werden patiënten behandeld volgens de richtlijnen van de European Society of Cardiology (ESC). Een panel van deskundigen, bestaande uit een cardioloog, een huisarts, een longarts en een geriater, stelde de aanwezigheid van hartfalen vast door de diagnostische criteria voor hartfalen van de ESC uit 2005 toe te passen met alle beschikbare diagnostische informatie, met inbegrip van echocardiografie (maar zonder kennis van de N-terminaal pro B-type natriuretisch peptide (NT-proBNP) waarden) en vervolggegevens van zes maanden, zoals de reactie op de ingestelde behandeling en andere klinisch relevante informatie. Hartfalen was

aanwezig in 94 van de 206 deelnemers (46%). Het optreden van klinische gebeurtenissen is gevolgd bij alle patiënten.

Hoofdstuk 1 bevat de algemene introductie van het proefschrift. Omdat zowel geriaters als huisartsen vaak worden geconfronteerd met patiënten met symptomen of verschijnselen die wijzen op hartfalen, maar beperkte toegang hebben tot echocardiografie, hebben we in **hoofdstuk 2** onderzocht in hoeverre zij in staat waren de aanwezigheid of afwezigheid van hartfalen vast te stellen op basis van diagnostische tests die in de dagelijkse praktijk gemakkelijker te verkrijgen zijn (bijv. symptomen, verschijnselen, ECG, thoraxfoto, laboratoriumtests (inclusief natriuretische peptiden) en spirometrie). Aan twee panels van respectievelijk drie geriaters en drie huisartsen is gevraagd de aanwezigheid of afwezigheid van hartfalen bij oudere patiënten vast te stellen. Ze hebben de aanwezigheid of afwezigheid van hartfalen bij twee derde van de oudere patiënten correct geïdentificeerd. Bijgevolg kan echocardiografie om hartfalen te bevestigen of uit te sluiten worden gericht op degenen bij wie de diagnose onzeker blijft. In **hoofdstuk 3** heeft een MEDLINE-onderzoek vier algoritmen geïdentificeerd om mogelijk toe te passen op geriatrische poliklinische patiënten bij wie een nieuw, langzaam begin van hartfalen vermoed wordt: algoritmen uit de 'Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008' van de ESC; uit 'Chronic Heart Failure, National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care' van het National Institute for Health and Clinical Excellence (NICE), Verenigd Koninkrijk; uit de 'Multidisciplinary Guidelines for Heart Failure 2010', Nederland (NL) en uit de door Mant, *et al.* uitgevoerde studie. De toepasbaarheid van deze algoritmen in ons geriatrische cohort werd geëvalueerd door het aantal patiënten te berekenen (i), dat is verwezen voor echocardiografie, (ii) met hartfalen onder verwezen patiënten en (iii) zonder hartfalen bij de niet-verwezen patiënten. Het toepassen van algoritmen heeft geresulteerd in verwijzing voor echocardiografie bij 52% (normaal NT-proBNP, ESC), 72% (normale ECG, ESC), 56% (NICE), 93% (NL) en 70% (Mant) van alle patiënten, waarbij een diagnose van hartfalen is vastgesteld in respectievelijk 78%, 56%, 76%, 49% en 62% van de verwezen patiënten. Bij patiënten die niet verwezen zijn voor echocardiografie, was hartfalen afwezig in respectievelijk 90%, 82%, 93%, 100% en 95%. Het op NT-proBNP (<400 pg/ml) van de ESC gebaseerde algoritme combineerde het laagste aantal verwijzingen voor echocardiografie (van wie 78% hartfalen heeft) met een beperkt aantal (10%) valse negatieven bij de niet-verwezen patiënten. Naast diagnostische algoritmen zijn er diagnostische voorspellingsregels (of diagnostische scores) ontwikkeld om de kans op hartfalen bij een individuele patiënt in te schatten. Deze regels helpen niet

alleen bij het uitsluiten van hartfalen, maar ook bij het vaststellen van een grote kans op hartfalen. De momenteel beschikbare diagnostische regels voor hartfalen (Mant, *et al.* en Kelder, *et al.*) zijn gevalideerd bij onze geriatrische patiënten in **hoofdstuk 4**. Beide regels vertoonden een goede calibratie (Mant: richtingscoëfficiënt 1,22, constante 0,39; Kelder: richtingscoëfficiënt 1,45, constante -0,10) en discriminatie (oppervlakte onder de Receiver Operating Characteristic (ROC) curve (*c-statistic*) Mant: 0,90 (95% betrouwbaarheidsinterval (BI) 0,86 - 0,95); *c-statistic* Kelder: 0,89 (95% BI 0,85 - 0,94)) in het geriatrische validatiecohort. Hoewel beide diagnostische regels de aanwezigheid van hartfalen bij geriatrische poliklinische patiënten nauwkeurig voorspellen, wordt de toepasbaarheid van deze regels gehinderd door het grote aantal items en de complexiteit van de berekening van de kans op hartfalen. In **hoofdstuk 5** hebben we vastgesteld dat de afwezigheid van een piepende ademhaling, verlies van eetlust en een lagere Body Mass Index (BMI), afgezien van leeftijd, geslacht en nachtelijke kortademigheid, onafhankelijk van elkaar verband houden met de aanwezigheid van hartfalen bij geriatrische patiënten bij wie een nieuw, langzaam begin van hartfalen werd vermoed. Van alle aanvullende diagnostische tests (ECG, thoraxfoto en laboratoriumtests) had NT-proBNP de grootste toegevoegde waarde, dat wil zeggen: had de grootste invloed op de *c-statistic*, met een stijging van 0,75 (95% BI 0,69 - 0,82) tot 0,92 (95% BI 0,88 - 0,95). Wij hebben een diagnostische regel ontwikkeld die bestaat uit deze zes klinische variabelen in combinatie met NT-proBNP. Scores in de diagnostische regel lagen tussen 1 en 67 punten. Met het toepassen van 16 en 32 punten als afkapwaarden zaten 96 patiënten (47% van de totale studiegroep) in de laag-risicogroep (negatieve voorspellende waarde (NPV) 0,89) en 78 patiënten (38%) in de hoog-risicogroep (positieve voorspellende waarde (PPV) 0,88). De overige 32 patiënten (16% van de studiegroep) zaten in de middelste risicogroep. Met de score die wij ontwikkeld hebben, worden de meeste geriatrische patiënten bij wie hartfalen vermoed wordt correct geclassificeerd met beperkt onderzoek (naast anamnese en lichamelijk onderzoek is alleen de NT-proBNP waarde nodig), terwijl slechts 16% van de patiënten een verwijzing voor echocardiografie nodig hebben om de diagnose vast te stellen. Omdat het aantal oudere patiënten dat een geavanceerde behandeling voor hartfalen krijgt (bijv. implantatie van een pacemaker of inwendige defibrillator, percutane interventies of een openhartoperatie) te verwaarlozen is, is echocardiografie bij geriatrische patiënten in de eerste plaats bedoeld om de aanwezigheid of afwezigheid van hartfalen vast te stellen. Onze diagnostische regel kan de rol van echocardiografie gedeeltelijk overnemen bij geriatrische patiënten bij wie een nieuw, langzaam begin van hartfalen vermoed wordt.

In **hoofdstuk 6** hebben we vastgesteld dat de helft van de geriatrische patiënten met hartfalen binnen drie jaar is overleden. Comorbiditeit, samengevat in de Charlson Comorbidity Index (CCI), kon de sterfte onafhankelijk van de ernst van het hartfalen (als vastgesteld met ejectiefractie van de linkerhartkamer en NT-proBNP) het best voorspellen. Hieruit volgt dat routinematige toepassing van de CCI van hulp kan zijn bij het begeleiden van deze groep patiënten. Biomarkers worden steeds meer toegepast bij de evaluatie van hartfalen. We hebben vastgesteld dat galectine-3 waarden bij geriatrische patiënten bij wie een vermoeden van hartfalen bestaat hoger zijn bij patiënten met hartfalen dan bij patiënten zonder hartfalen (respectievelijk 21,8 en 15,6 ng/ml, p = 0,04; **hoofdstuk 7**). Bij patiënten met hartfalen lag de sterfte binnen drie jaar hoger wanneer de galectine-3 waarde hoger lag dan de onlangs voorgestelde afkapwaarde van 17,8 ng/ml: respectievelijk 74% en 33%; naar leeftijd gewogen Hazard Ratio 3,7 (95% BI 1,0 - 13,2). De prognose van hartfalen kan worden verbeterd door een reeks medicijnen, maar bewijs bij oudere patiënten is schaars, zoals wij in **hoofdstuk 8** hebben vastgesteld. In dit systematische review was de gemiddelde leeftijd van de deelnemers aan de gerandomiseerde gecontroleerde onderzoeken naar de fundamentele behandeling van hartfalen (diuretica, ACE-remmers, angiotensine-receptorblokkers, betablokkers en mineraalcorticoïde receptorantagonisten) 65 jaar voor onderzoeken met sterfte/ziekenhuisopname als uitkomstparameter en 66 jaar voor onderzoeken met levenskwaliteit als eindpunt. De afgelopen 35 jaar is de gemiddelde leeftijd van de onderzochte patiënten slechts licht gestegen. Wij raden aan patiënten in onderzoeken op te nemen die meer lijken op patiënten die in de dagelijkse praktijk werden behandeld, dat wil zeggen oudere patiënten (met meer comorbiditeit). In **hoofdstuk 9** worden de implicaties van het onderzoek in dit proefschrift besproken en worden aanbevelingen gedaan voor toekomstig onderzoek. Er wordt een diagnostisch algoritme gesuggereerd op basis van de bevindingen uit anamnese, lichamelijk onderzoek en de NT-proBNP waarden, waarmee nauwkeurig de aanwezigheid of afwezigheid wordt bepaald van hartfalen bij geriatrische patiënten bij wie een vermoeden van een langzaam begin van hartfalen bestaat, waarbij slechts 15% van alle patiënten voor echocardiografie verwezen wordt. Toekomstig onderzoek moet vooral bij deze patiënten worden uitgevoerd, waarbij optimale behandelingsstrategieën worden bepaald (met betrekking tot maatregelen op het gebied van de levensstijl, medicamenteuze behandeling en meer geavanceerde behandelingsopties, zoals een inwendige defibrillator, coronaire revascularisatie of klepoperaties). Hierin moeten zowel de 'harde' (sterfte, ziekenhuisopname) als de 'zachtere' eindpunten (levenskwaliteit) worden verkend, waarbij met name de laatste relevant zijn voor oudere patiënten.

Co-authors

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Dankwoord

Dankwoord

Ooit las ik een artikel waarvan ik dacht dat geriatrische patiënten er voordeel van zouden kunnen hebben als iets dergelijks voor hen beschikbaar zou zijn. Nu schrijf ik het dankwoord van mijn proefschrift waarin ik aantoon dat het inderdaad voor de geriatrische patiënt nuttig is. Ongelooflijk dat dit echt gelukt is. Wat is er veel gebeurd om dit mogelijk te maken. Graag wil ik jullie dan ook allemaal bedanken.

Allereerst wil ik de patiënten en hun mantelzorgers bedanken voor hun medewerking aan mijn onderzoek. Zonder hen was dit onderzoek niet mogelijk geweest.
Prof. dr. A.W. Hoes, beste Arno, aanvankelijk was het mijn bedoeling om een klein onderzoekje te verrichten met maximaal 20 patiënten. Natuurlijk vond jij dat erg weinig, en uiteindelijk is de teller op 206 patiënten blijven steken. Ik blijf onder de indruk van jouw overzicht over mijn proefschrift. Daar waar ik door de bomen het bos niet meer zag, kon jij heel helder en beknopt de route uitstippelen. Hartelijk bedankt voor je bijdrage aan mijn groei als onderzoeker.
Dr. A. Mosterd, beste Arend, wat heb je veel tijd gestoken in mijn begeleiding. Was het aanvankelijk niet duidelijk of het doel promoveren was, in de loop van het traject werd dat wel duidelijk en werden we daar beiden steeds gemotiveerder van. Ik heb ontzettend veel van je geleerd en kan me bijna niet voorstellen dat onze wekelijkse telefoontjes een keer zullen eindigen. Elk overleg gaf mij weer hernieuwde energie en richting, waarvoor ik je hartelijk wil bedanken. Fijn ook dat je mijn onderzoeks ups en downs begreep en me altijd van goede raad wist te voorzien.
Beste Peter Zuithoff, ‘mijn statisticus’, wat kan je alles goed en rustig uitleggen. En nog prettiger is dat je dat best meerdere keren wilt doen. Ik heb erg genoten van onze samenwerking en je droge humor. Dr. F.H. Rutten, beste Frans, je opbouwende en kritische adviezen waren zeer waardevol voor mij. Hans Kelder, dank voor inzage in je database. Dr. R.A. de Boer, beste Rudolf, dank voor de prettige samenwerking. Prof. dr. A.A. Voors, beste Adriaan, hartelijk dank voor het meedenken over en het meeschrijven van het stuk over de behandeling van hartfalen bij ouderen.

De leden van de beoordelingscommissie wil ik hartelijk bedanken dat ze de tijd namen om mijn proefschrift te beoordelen en te opponeren: prof. dr. M.J. Schuurmans, prof. dr. A. de Boer en prof. dr. M.G.M. Olde Rikkert. Dear prof. dr.

J.J.V. McMurray, I am honoured to have you in Utrecht on this special occasion. Thank you for reading, assessing and approving my thesis.

In het Meander Medisch Centrum Amersfoort is mijn onderzoek ontstaan. Met dr. ir. J.P.M. Wielders, klinisch chemicus, had ik het eerst contact over de mogelijkheden van het laboratorium om aan mijn projectje (dat was het destijds) mee te werken. Beste Jos, jij bracht mij in contact met Arend. Hartelijk dank voor je mogelijkheden om het NT-proBNP van alle patiënten te bepalen. Aan het eind van de patiëntbesprekingen wist je altijd de spanning op te bouwen als je de uitslag van het NT-proBNP mocht onthullen. Tijdens deze patiëntenbesprekingen heb ik me altijd vereerd gevoeld dat jullie, Edwin van Velzen, longarts, en Mark Valk, huisarts, dan aanwezig waren. Het was erg inspirerend om in een prettige sfeer gezamenlijk, maar ieder vanuit zijn eigen optiek, naar patiënten te kijken. René van Brugge, klinisch geriater, hartelijk dank voor je enthousiasme om continu patiënten te includeren. Daarnaast wil ik alle andere geriaters die daar werken of gewerkt hebben ook bedanken voor hun bijdrage aan mijn onderzoek. Atie Meurs, secretaresse van het eerste uur van mijn onderzoek, wat heb ik altijd lekker met je samengewerkt. En ook in de jaren dat ik af en toe langskwam voor mijn onderzoek was het heerlijk om door jou ontvangen te worden en weer bij te praten. Hartelijk dank voor alles wat je voor me geregeld en uitgezocht hebt.

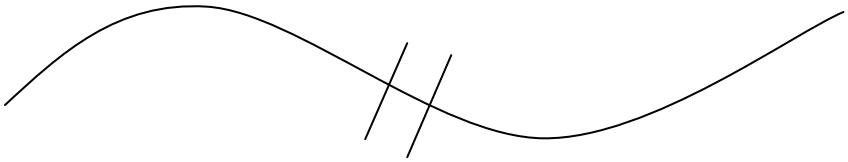
In het Elkerliek ziekenhuis Helmond, is het gelukt te starten met mijn onderzoek nog voordat ik er als klinisch geriater werkte. Hanny Bloemen, zeer gewaardeerde collega van me, je nuchtere kijk op al mijn ‘beren op de weg’ helpt me regelmatig verder. Dank voor je steun en voor je bijdrage aan patiëntenbesprekingen, beoordelingen van artikelen en andere hand- en spandiensten. Fijn dat je één van mijn paranimfen bent. Mijn andere collega’s, Benoit de Leest, Brigide van den Bliek, Loes van Nuland-van Wolferen en Sonja Coppens-Maessen, wil ik ook graag bedanken voor de mogelijkheden die er geweest zijn om aan mijn onderzoek te werken en voor het includeren van patiënten. Natuurlijk heb ik ook veel steun gekregen van iedereen van de afdeling geriatrie. Dan bedoel ik: Jan, Annie, Kees, Esther, Esther, Wim, Hans, Annet, Lodewijk, Marieke, Ria, Carla T, en eigenlijk iedereen: hartelijk dank voor jullie interesse. In het bijzonder wil ik Ingrid H (dank voor je steun, wanneer gaan we weer uit eten?), Lieke (je bent top), Loes, Tineke en Yvonne bedanken. En natuurlijk Marije, lieve meid, heerlijk om altijd bij je terecht te kunnen voor cola, een knuffel of een bemoedigend woord. Dat blijven we wat mij betreft nog jaren doen.

Verder wil ik nog de volgende mensen van het Elkerliek ziekenhuis bedanken. Cardioloog Frans van Asperdt en hartfunctielaborant Berrie Kweens, dank jullie wel voor het verrichten en verzamelen van echocardiogrammen. Klinisch chemicus dr. C.H.H. Schoenmakers, beste Christian, en destijds Unithoofd Logistiek van het Algemeen Klinisch Laboratorium Jacques Leenders, dank voor jullie medewerking om bij alle patiënten het NT-proBNP te bepalen en spijtserum op te slaan.

Beste Kees de Kock, huisarts, leuk is het geweest om samen met jou over hartfalen en geriatrische en huisartspatiënten na te denken. Ik heb ook genoten van de presentaties die we samen hebben gedaan. Natuurlijk wil ik jullie, de geriaters Carolien van der Linden en Ralf Vingerhoets, en de huisartsen Anke Pril, Edith Plum en Rutger Verouden ook bedanken voor jullie medewerking aan patiëntbesprekingen. Het waren leerzame avonden waarin we hard werken en plezier combineerden.

Beste Maurice, Marietje, Johan, Joanneke en Rina, wat zijn onze intervisiebijeenkomsten van essentieel belang geweest om de goede keuzes te maken in mijn leven. Veilig en met warmte kan ik met jullie moeilijkheden en mogelijkheden bespreken, waarbij vanuit vriendelijkheid oplossingen aangedragen worden. Hartelijk dank daarvoor. Jeanette, het is geruststellend te weten dat je altijd in mijn leven bent, ook als dat op de achtergrond is. Er gaat een bepaalde kracht uit van onze vriendschap die me veel sterkte geeft. Ik ben er trots op dat je één van mijn paranimfen bent. Mary, er is zoveel meer te doen voor patiënten dan de individuele patiëntenzorg. En wat is het prettig om in jou een gesprekspartner daarover te hebben. Ik wil je graag bedanken voor je interesse in mij en mijn onderzoek en hoop dat we nog heel lang ons warme contact blijven houden. Corné, hartelijk dank voor je interesse en het samen nadenken over moeilijk te vertalen woorden. Gezellig dat je regelmatig komt eten. Sandra, Pieter en Eva, heel erg bedankt voor alle gezelligheid en warmte. Laten we daar nog lang van genieten.
Als laatste kom ik dan toe aan mijn familie. Allereerst mijn vader en zijn vrouw. Hans, in de periode dat ik twijfelde of ik promotieonderzoek wilde gaan doen vroeg je mij: ’Stel dat je over tien jaar terug zou kijken, zou je dan vinden dat je een kans gemist hebt als je nu niet verder gaat met je onderzoek?’ Dit was de doorslaggevende vraag. Gezellig ook, dat je wel eens mee gaat naar buitenlandse congressen. Annemarie, wat is het heerlijk om samen in de sauna goede gesprekken te hebben over de dagelijkse beslommeringen en de richting in ons leven. Laten we dat nog jaren zo doen.

Beste Wil, jij zag veel eerder dan ik dat ik een ‘mensenmens’ ben, iemand die floreert zolang ze maar kan werken met mensen. Inderdaad is dat zo, waarbij onderzoek doen me onverwacht veel voldoening heeft gegeven. De combinatie onderzoek en klinisch werk is dan ook voor mij ideaal. Dank voor dit inzicht. Judith, lieve zus, maar ook lieve Alwin, Kayleigh, Yasmin en Beer, wat jammer dat we zo ver bij elkaar vandaan wonen. Ik hoop dat we elkaar nu vaker gaan zien.
Lieve meiden, Dieuwertje en Sien, er is in de wereld geen groter geluk dan jullie (ik hoor jullie denken: ’Saai, saai, dat weten we wel’). En ja, Sien, nu kan ik veel vaker mee naar paardrijden.
Als allerlaatste, Luuk, wil ik jou bedanken. Met al mijn liefde draag ik mijn proefschrift aan je op. Hoewel je geen medeauteur bent, ben je de belangrijkste in mijn leven die dit allemaal mogelijk heeft gemaakt. Je bent mijn basis van waaruit ik kan groeien en bloeien. Ik geniet er erg van dat je je nooit aflatende enthousiasme om mij in de maling te nemen, hebt doorgegeven aan onze meiden en kijk er naar uit dat we met zijn viertjes weer meer tijd hebben voor elkaar.



Curriculum Vitae

Curriculum Vitae

Irène Oudejans-Mooijaart was born on July 5, 1969 in Zaandam, The Netherlands. In 1988, she graduated from the Hermann Wesselink College (secondary school, Gymnasium) in Amstelveen. She did her medical studies at the Free University of Amsterdam and obtained her medical degree in 1999. Her specialty training in geriatric medicine was conducted at the Geriatric Department of Utrecht University Medical Center (P.A.F. Jansen, MD, PhD), at the Department of Internal Medicine of the St. Antonius Hospital, Nieuwegein (H.C.M. Haanen, MD, PhD), and completed at the Elderly Department Den Eik of Psychiatric Hospital Altrecht, Zeist (professor W.A. Nolen, MD, PhD) in 2004. In 2003 she worked at the Geriatric Department of Meander Medical Center, Amersfoort (R. van Brugge, MD) where the initial steps for the work described in this thesis were taken. In 2006 she started her PhD work at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, supervised by professor A.W. Hoes, MD, PhD and A. Mosterd, MD, PhD.

Since 2004 she is settled as a geriatrician at the Geriatric Department, Elkerliek Hospital, Helmond. She is married to Luuk Oudejans and they have two daughters, Dieuwertje (1997) and Sien (2000).