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Methods to identify heart failure patients in general practice and their impact on patient characteristics: A systematic review ☆

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ABSTRACT

Background: Identifying patients with heart failure (HF) in general practice is challenging. Our aim was to provide an overview of methods used to identify patients with HF in general practice and to assess their impact on patient characteristics.

Methods and results: A systematic review was conducted using MEDLINE, EMBASE and CENTRAL. Taken together, 105 studies on HF in general practice were included, totalling 196,105 patients. Five main identification methods for HF were distinguished, including 1) echocardiographic assessments, 2) results of echocardiography in general practitioner (GP) charts, 3) GP judgment after chart review, 4) GP judgment of consecutive patients and 5) only chart review. Only 30% of studies used the results of echocardiography. Despite a large heterogeneity between studies the pooled data revealed a predominant phenotype of older women with hypertension rather than ischaemic heart disease. Linear regression analysis showed that the impact of the identification method on patient characteristics was limited. However, study design had a greater impact, with randomized-controlled trials (RCTs) including younger, male patients with ischaemic heart disease and higher HF drug prescription rates at baseline.

Conclusion: Pooled data of 196,105 patients with HF confirmed a phenotype of older women with hypertension rather than ischaemic heart disease as the predominant HF population in general practice. The lack of a gold standard definition of HF introduced a large heterogeneity in identification methods with remarkably limited impact on patient characteristics. However, RCTs did include patients with a different phenotype, emphasizing the need to promote inclusion of real-world HF patients.

1. Introduction

Heart failure (HF) is a prevalent disease associated with high morbidity and mortality and has a strong impact on quality of life [1,2]. Evidence-based data on HF in general practice is needed since the characteristics of these patients differ from those in hospitals and clinical trials. Patients with HF in general practice are generally older, more often female and have hypertensive rather than ischaemic HF [3,4]. The latter are typical characteristics of patients with HF with preserved ejection fraction (HFpEF), who are more prevalent in the community than in the hospital (55% vs 45%) [5].

Unfortunately, the identification of patients with HF in general practice is difficult. First, the symptoms and signs are non-discriminating and therefore of minimal diagnostic value [1,6,7]. This is particularly relevant for older people, who often have multiple comorbidities and may present with many other possible causes of dyspnea, fatigue or peripheral edema. Additionally, natriuretic peptide biomarkers and echocardiography are underused, leading to under- and over-diagnosis of HF [3,4,8–10].

Consequently, studying HF in general practice is challenging. A primary discharge diagnosis of HF after hospitalization is a validated method of identifying patients with HF, but it is not a sensitive one in general practice [11]. Searching for coded diagnoses in electronic medical records is a potential strategy [12], but studies have failed to confirm HF in 50%–75% of patients with a coded diagnosis of HF, and many HF cases remain undetected with this methodology [9,13]. However, a robust method of identifying patients with HF is the initial requirement for studying and improving care for this important patient population.

Therefore, the aim of this systematic review was to provide an overview of the methods used to identify patients with HF in general practice and to assess the impact of these different identification methods on the characteristics of the included patients.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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0167-52730167-5273/

2. Methods

2.1. Design

A systematic review of the literature was performed to provide an overview of all studies that identified patients with HF in general practice. PRISMA statement recommendations and the Cochrane handbook for systematic reviews of interventions were followed to conduct and report the review [14,15].

2.2. Information sources and eligibility criteria

MEDLINE (via PubMed), EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 01/01/2001 to 31/12/2015 for all articles studying patients with HF in general practice. This time period was selected because some major changes in HF diagnostics and treatment were adopted by international guidelines in 2001. Additional articles were obtained by snowball technique, e.g., from reference lists of pertinent studies.

2.3. Search

The search strategy included the following search terms: "heart failure", "general practice", "primary care", "family practice", "general practitioner", "family physician", "physicians, primary care"; both MESH terms and free text terms were searched. The full electronic search strategy used in each database can be found in Appendix A.1.

2.4. Study selection

A set of in- and exclusion criteria was predefined. First, both interventional and observational studies were included, with the exception of case series and case descriptions. Reviews, guidelines, letters to the editor and study protocols were excluded, as were qualitative studies. Simple diagnostic studies with the aim of screening a population were only included if they used a prospective design. Second, HF had to be one of the main topics of the article. Consequently, articles that described HF as a comorbidity were excluded, together with articles that did not separately report the characteristics of patients with HF. No articles were excluded based on the type of HF described. Third, the identification of patients with HF had to occur in general practice. If this identification occurred in different settings and was not reported separately for general practice, the study was excluded from the systematic review. General practice was chosen as the setting instead of primary care because primary care also includes specialized HF nurses and office-based cardiologists. Access to echocardiography is a determining factor in the identification of patients with HF and differs too much between different actors in primary care. Fourth, only articles in English were extracted. Fifth, articles only published as supplements, not as full text articles, were excluded.

A pilot search was performed to test and determine the selection criteria. The first reviewer (M.S.) divided the selected articles into three categories (definitely excluded, included, and in doubt) based on title and abstract. The second reviewer (B.V.) checked all

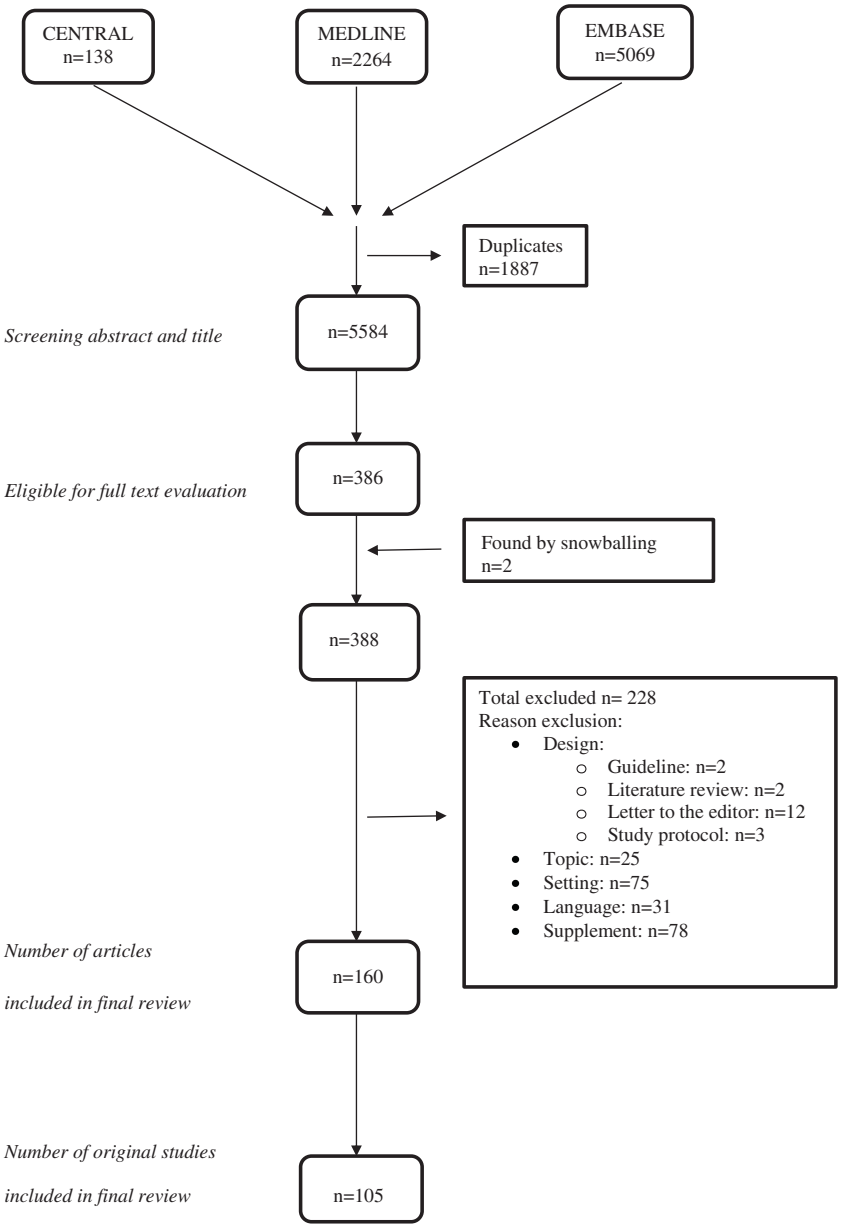

Fig. 1. PRISMA flow diagram of study selection.

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studies in the last two categories, plus a random selection of the excluded articles. Disagreements were resolved by consensus or by a third reviewer (B.A.). A log of the excluded articles, with the reasons for exclusion, was maintained.

2.5. Data collection process

A predefined data extraction form was used to collect the data. The second reviewer studied uncertainties in the data collection process and a random sample of the whole process. Discrepancies were discussed to reach consensus. All authors were contacted by email up to three times to provide additional data when data were missing or to clarify uncertainties.

2.6. Data items

For each article, the authors, year of publication and data collection, country, design, number of general practitioners (GPs) or general practices involved, number of patients with HF, use of diagnostic criteria, use of identification method and differentiation between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) were obtained.

For patient characteristics, the mean age; number of women included; number of patients treated with diuretics; use of renin-angiotensin-aldosterone system blockers (RAAS-blockade), B-blockers, mineralocorticoid receptor antagonists (MRA) or cardiac glycosides; the number of patients with ischaemic heart disease (IHD), diabetes, hypertension, lung disease, chronic kidney disease, cerebrovascular disease, depression, atrial fibrillation or valvular heart disease as comorbidities; NYHA class and the number of patients with HFrEF/HFpEF were extracted.

2.7. Quality assessment

The aim of the review was to assess the methods used to identify patients with HF in general practice and the patients' characteristics independent of the overall quality of the article. Therefore, a quality assessment of the studies did not provide added value to this review.

2.8. Data analysis

Continuous variables were presented as the medians and inter-quartile ranges (IQRs), and the weighted mean was calculated. Baseline categorical variables were compared with Pearson's Chi-squared test, Pearson's Chi-squared test with Yates continuity correction, or Fisher-Freeman-Halton exact test, as appropriate. Continuous variables were compared with the Kruskal-Wallis test. Study characteristics and patient characteristics were described according to each identification method. A linear regression analysis was performed with all relevant study characteristics as the independent variables and patient characteristics as the dependent variables. All variables with a p-value <0.20 in the univariate model were candidates for the multivariable model. Adjusted R^2 and p-values for each multivariable model were calculated. Imputation for missing values was not performed. All analyses were conducted using SPSS 23.0 for Windows (SPSS Inc. Chicago, Illinois, USA) and R Software version 3.0.3 (Free Software Inc. Boston, MA, USA).

3. Results

The search strategy and results are presented in Fig. 1. One hundred and sixty articles met the inclusion criteria, corresponding with 105 original studies. A list of all included studies with their corresponding characteristics can be found in Appendix A.2.

3.1. Identification methods

Five main identification methods were distinguished (Fig. 2). Distinction was made between studies that included patients with HF based on echocardiography results (n = 31, 30%) and studies that did not (n = 74, 70%). Within the studies using echocardiography results as an inclusion criterion, we distinguished between studies performing standardized echocardiography as part of the study assessment (Method 1, n = 18, 17%) and studies that used echocardiography results in GP charts to confirm the HF diagnosis (Method 2, n = 13, 12%). Of the studies that did not account for echocardiography results, those using GP judgment to identify patients with HF were recognized (n = 35, 33%). Within these studies, GPs were asked to either confirm the HF diagnosis in patients identified through GP chart review (Method 3, n = 14, 13%) or to include patients with HF consecutively during consultation (Method 4, n = 21 studies, 20%; n = 28,536 patients, 15%). The final identification method did not use echocardiography nor GP judgment, it only used GP chart review (Method 5, n = 39 studies, 37%; 127,267 patients, 65%). GP chart review meant that GP patients' charts were reviewed electronically or manually for a coded or free-text diagnosis of HF, and/or HF medication, and/or HF comorbidities. Patients included by Method 1 accounted for only 1.2% of the total study population, Methods 2,3,4 and 5 for 12%, 6.9%, 15% and 65% respectively (Table 3) (Appendix A.3: Methods used to identify patients with HF through chart review).

3.2. Study characteristics

Data collection began before 2001 in 38 studies (36%), more frequently in studies that only used GP chart review (Method 5) as the identification method (n = 18/34, 53%) (Table 1). In general, the included studies were predominantly implemented in Europe (n = 88, 84%). Studies using consecutive inclusion of patients by the GP

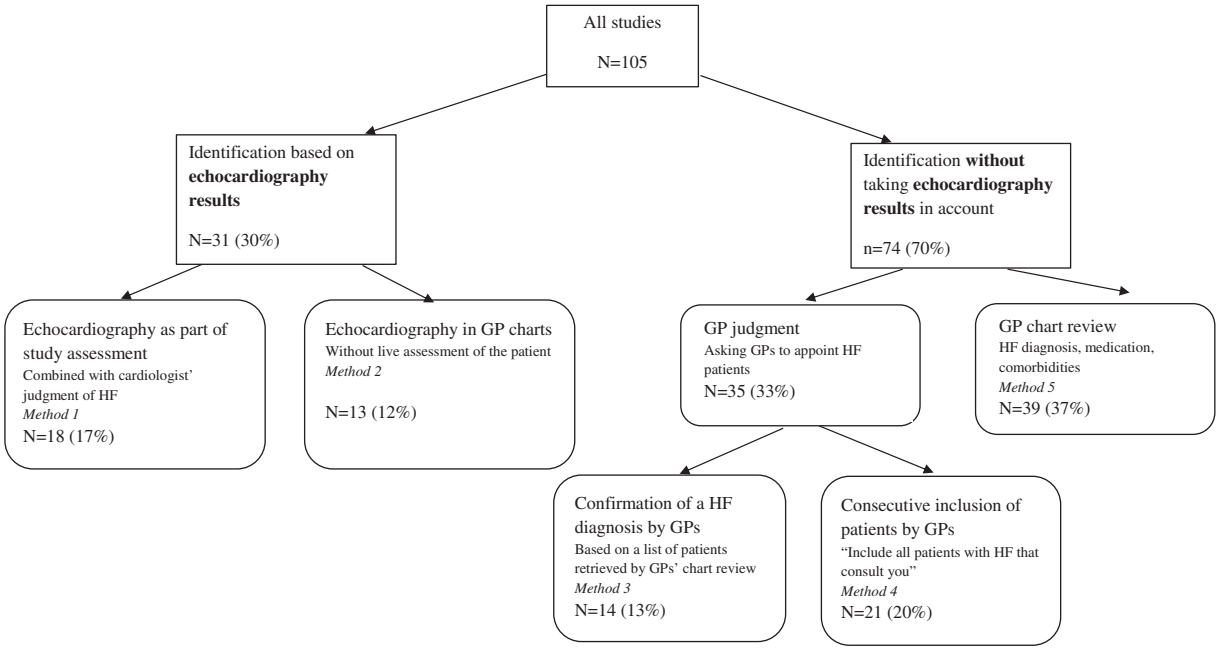

Fig. 2. Overview of methods used to identify patients with heart failure in general practice.

Table 1
Study characteristics according to identification method.

Total: N = 105	Echocardiography results used to identify patients with HF N = 31 (30%)		No echocardiography results used to identify patients with HF N = 74, 70%			
	US: part of study assessment Method 1 N = 18	US in GP charts Method 2 N = 13	GP judgment, N = 35		Only GP chart review Method 5 N = 39	*p*-Value
			After chart review Method 3 N = 14	Consecutive inclusion by GP Method 4 N = 21		
Time						
Publication year						0.87[a]
2001–2005, n (%)	6 (33)	5 (39)	4 (29)	8 (38)	12 (31)	
2006–2011, n (%)	9 (50)	4 (31)	7 (50)	9 (43)	12 (31)	
2012–2015, n (%)	3 (17)	4 (31)	3 (21)	4 (19)	15 (39)	
Start data collection						0.079[b]
<2001, n (%)	6/15 (40)	5/12 (42)	3/11 (27)	6/19 (32)	18/34 (53)	
2001–2005, n (%)	2/15 (13)	5/12 (42)	7/11 (64)	9/19 (47)	9/34 (27)	
2006–2011, n (%)	7/15 (47)	1/12 (8.3)	1/11 (9.1)	3/19 (16)	7/34 (21)	
2012–2015, n (%)	0/15 (0)	1/12 (8.3)	0/11 (0)	1/19 (5.3)	0/34 (0)	
Geography						0.19[b]
Europe, n (%)	16 (89)	11 (85)	13 (93)	15 (71)	33 (85)	
US/Canada, n (%)	0 (0)	2 (15)	0 (0)	1 (4.8)	5 (13)	
South-America, n (%)	1 (5.6)	0 (0)	0 (0)	1 (4.8)	0 (0)	
Asia/Russia, n (%)	1 (5.6)	0 (0)	0 (0)	1 (4.8)	0 (0)	
Australia/New Zealand, n (%)	0 (0)	0 (0)	1 (7)	3 (14)	1 (2.6)	
Subject						
Studies including palliative patients, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	3 (7.7)	0.49[b]
Design						<0.001[b]
Retrospective observational, n (%)	1 (5.6)	7 (54)	4 (29)	1 (4.8)	22 (56)	
Cross-sectional observational, n (%)	7 (39)	1 (7.7)	3 (21)	9 (43)	10 (26)	
Prospective observational, n (%)	6 (33)	2 (15)	5 (36)	8 (38)	6 (15)	
Prospective, randomized-controlled, n (%)	4 (22)	3 (23)	2 (14)	3 (14)	1 (2.6)	
Participants						
Number of participating GPs (median, IQR)	30 (16–209) (missing n = 13)	25 (5–46) (missing n = 11)	34 (16–72) (missing n = 6)	143 (27–341) (missing n = 10)	43 (15–114) (missing n = 28)	0.28[c]
Number of participating General practices (median, IQR)	3 (1−20) (missing n = 6)	29 (16–42) (missing n = 7)	29 (16–42) (missing n = 7)	127 (30–178) (missing n = 14)	22 (4–55) (missing n = 13)	0.005[c]
Number of patients (median, IQR)	84 (48–168)	191 (99–1418)	342 (194–786)	557 (251–1706)	548 (170–2771)	<0.001[c]
Number of studies with >1000 participants (n,%)	0 (0)	3 (23)	2 (14)	8 (38)	14 (36)	0.012[b]
Quality in reporting on Heart Failure diagnosis						
Definition Heart Failure						
Diagnostic criteria used to define HF, n (%)	12 (67)	6 (46)	5 (36)	10 (48)	11 (28)	0.087[a]
Type of diagnostic criteria used to define HF						
ESC, n (%)	9 (50)	1 (7.7)	0 (0)	1 (7.7)	3 (7.7)	
Boston, n (%)	1 (5.6)	0 (0)	0 (0)	0 (0)	1 (2.6)	
Framingham, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	3 (7.7)	
Modified WHO, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
ICPC-2 criteria, n (%)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	
National heart failure guidelines, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.6)	
Own study criteria, n (%)	2 (11)	5 (39)	4 (29)	5 (39)	3 (7.7)	
Not mentioned, n (%)	6 (33)	7 (54)	9 (64)	7 (54)	28 (72)	
Distinction made between HFrEF/HFpEF, n (%)	14 (78)	6 (46)	4 (28)	11 (52)	7 (18)	<0.001[b]
HFrEF only, n (%)	4 (22)	5 (24)	2 (14)	2 (14)	0 (0)	0.002[b]
HFpEF only, n (%)	1 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)	0.17[b]

HF, heart failure; GPs, general practitioners; US, echocardiography; IQR, interquartile range; US, United States of America; NA, not applicable; ESC, European Society of Cardiology; WHO, World Health Organization; ICPC-2, International classification of Primary Care second edition; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

[a] Pearson's Chi-squared test with Yates continuity correction.
[b] Fisher-Freeman-Halton Exact test.
[c] Kruskal-Wallis test.

(Method 4) were more diverse geographically than studies using other identification methods (71% vs 85–93% in Europe). Studies using GP chart review as the identification method (without GP judgment) (Methods 2 and 5) used a retrospective design more frequently (n = 29, 56%). Studies identifying patients with HF by performing an echocardiographic assessment (Method 1) were smaller, as this method requires more resources. Even in these studies, the diagnostic criteria used to define HF were not reported in a third (n = 12, 67%). Out of 105 studies, 42 (40%) distinguished between HFrEF and HFpEF (Table 1). The definitions used for both HFrEF and HFpEF were diverse (Appendix A.4: Used definitions of HFrEF/HFpEF).

3.3. Patient characteristics

In total, 196,105 patients were studied; however, not all patient characteristics were described in every study (Table 2). The mean age of patients with HF identified in general practice was 75 (SD 5.2) years, and the mean percentage of women was 51%. Out of 196,105 patients, 16,689 were categorized as HFrEF patients (8.5%) and 3546 as HFpEF patients (1.5%). The remaining 175,870 patients (90%) were not categorized as either HFrEF or HFpEF. Patients categorized with HFrEF were more frequently treated with RAAS-blockade or B-blockers than uncategorized patients (mean 69% vs 57% and

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Table 2
Patient characteristics in the total study population.

Total number of studies N = 105 Total number of patients N = 196,105	Number of studies reporting this data n (%)	Number of patients with data n (%)	Weighted mean (%)	Median (IQR)
Demographics				
Age (±SD)	88 (86)	106,379 (54)	75 ± 5.2	76 (73–78)
Women	95 (90)	188,511 (96)	51	48 (42–56)
Heart failure medication				
Diuretics[a]	73 (70)	149,275 (76)	75	78 (66–88)
RAAS-blockade[b]	74 (70)	166,110 (85)	57	66 (49–82)
ACE-I	56 (53)	119,950 (61)	43	54 (38–73)
ARB	34 (32)	114,119 (58)	8.6	10 (4.9–17)
B-blocker	69 (66)	165,050 (84)	31	37 (20–64)
MRA	39 (37)	120,830 (62)	11	14 (5.7–25)
Cardiac glycosides	53 (50)	74,227 (38)	24	25 (16–34)
Heart failure medication HFrEF (N = 16,689)				
RAAS-blockade HFrEF	13 (12)	10,202 (61)	69	82 (48–92)
B-blocker HFrEF	13 (12)	10,202 (61)	46	62 (8–78)
Comorbidities				
Hypertension	67 (64)	158,158 (81)	54	55 (44–71)
Ischaemic heart disease[c]	71 (68)	159,275 (81)	35	37 (28–52)
Atrial fibrillation	43 (41)	112,609 (57)	24	30 (20–38)
Diabetes	69 (66)	153,341 (78)	20	23 (18–30)
COPD[d]	56 (53)	150,109 (77)	18	20 (13–27)
Chronic kidney disease[e]	33 (31)	112,848 (58)	15	13 (5–32)
Cerebrovascular disease	29 (28)	123,766 (63)	13	13 (8–17)
Valvular heart disease	20 (19)	38,397 (20)	12	17 (6.6–23)
Depression[f]	11 (10)	5463 (2.8)	19	20 (8.6–24)
NYHA stages				
NYHA stage I	29 (28)	15,992 (8.2)	14	12 (4–22)
NYHA stage II	38 (36)	17,953 (9.2)	45	45 (35–55)
NYHA stage III	38 (36)	17,953 (9.2)	31	31 (24–38)
NYHA stage IV	28 (27)	16,287 (8.3)	6.1	3.9 (1.2–7.4)

RAAS blockade, renin-angiotensin-aldosterone system blockade; ACE-I, angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor antagonist; MRA, mineralocorticoid receptor antagonist; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; NYHA, New York Heart Association; HFrEF, heart failure with reduced ejection fraction.
[a] Loop diuretics or thiazide diuretics or any diuretics.
[b] ACE-I and ARB or ACE-I alone.
[c] Ischaemic heart disease or angina pectoris or coronary heart disease or myocardial infarction.
[d] COPD or COPD/asthma or treated lung disease or respiratory disease.
[e] As defined in original study: ranging from eGFR <30 to 60, creatinine >1.2 to 1.8 mg/dL.
[f] Depression (mild, major, not defined) or anxiety/depression or severe psychiatric disease.

46% vs 31%, respectively) (Table 2). Hypertension was the leading comorbidity, with a prevalence of 54% (weighted mean). The prevalence of depression was high (weighted mean 19%) but it was rarely reported compared to CV comorbidities (5463 patients, 2.8% of the total population) (Table 2).

3.4. Associations between study characteristics and patient characteristics

All study characteristics described in Table 1 were potential candidates for the multivariate linear regression analysis. Use of diagnostic criteria (yes/no) was included in the univariate analysis but was not withheld as an influencing factor in any of the multivariate models. As dependent variables, mean age, % of women, % of patients treated with diuretics, RAAS-blockade, B-blockers and % of patients with hypertension, diabetes or ischaemic heart disease as comorbidities were selected, as these variables were reported in most of the studies.

Although variation was shown in patient characteristics according to the method used to identify patients with HF (Table 3, Fig. 3), the multivariate linear regression analysis showed that identification method was not the only influencing factor (Fig. 3).

3.4.1. Demographic variables

An independent, but weak association was found between younger patients and studies identifying patients by GP judgment (Methods 3 and 4) and randomized-prospective studies. In contrast, elderly patients were associated with European studies. Additionally, lower percentage of women was associated with studies that collected their data more recently, randomized-prospective studies and studies distinguishing between HFrEF and HFpEF (Fig. 3).

3.4.2. Heart failure medication

Having a lower percentage of patients treated with diuretics was associated with HF identification by echocardiographic assessment (Method 1), while no other significant associations between prescriptions of diuretics and study characteristics were found. A very strong association was found between higher proportions of patients treated with RAAS-blockade and B-blockers and more recent data collection. Additionally, having higher percentages of patients treated with RAAS-blockade and B-blockers was associated with randomized-controlled designs and studies distinguishing between HFrEF and HFpEF. A greater use of B-blockers was observed in European studies (Fig. 3).

3.4.3. Comorbidities

A higher prevalence of ischaemic heart disease was associated with identifying HF by GP judgment (Methods 3 and 4) and randomized-prospective studies. A higher prevalence of both ischaemic heart disease and hypertension was found to be associated with studies distinguishing between HFrEF and HFpEF. In addition, an association was found between a higher prevalence of hypertension and diabetes and more recent data collection (Fig. 3).

4. Discussion

This systematic review with pooled data of 196,105 patients with HF provides an overview of all studies reported since January 1st, 2001 that identified patients with HF in general practice. Despite a large heterogeneity between studies in terms of methods to identify patients with HF and used definitions of HF, the pooled data revealed a

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Table 3
Patient characteristics according to identification method.

	Echocardiography results used to identify patients with HF (N = 31, 30%)		No echocardiography results used to identify patients with HF (N = 74, 70%)		
	US as part of study assessment Method 1 N = 18 studies N = 2422 pts	US in GP chart Method 2 N = 13 studies N = 24,407 pts	GP judgment		Only GP chart review Method 5 N = 39 studies N = 127,267 pts
			After chart review Method 3 N = 14 studies N = 13,473 pts	Consecutive inclusion Method 4 N = 21 studies N = 28,536 pts	
Demographics					
Age, median (IQR)	75 (73–77)	77 (73–79)	75 (72–76)	74 (69–77)	78 (75–79)
Women, median (IQR)	46 (37–61)	48 (41–53)	48 (43–53)	47 (42–57)	52 (45–55)
Heart failure medication					
Diuretics[a], median (IQR)	71 (61–78)	86 (65–93)	76 (67–96)	82 (69–89)	82 (54–89)
RAAS-blockade[b], median (IQR)	72 (51–90)	71 (51–76)	57 (42–84)	75 (54–89)	55 (44–73)
ACE-I, median (IQR)	64 (50–79)	56 (31–75)	47 (36–68)	58 (47–87)	44 (34–62)
ARB, median (IQR)	11 (0.6–32)	13 (9.7–15)	13 (9–19)	21 (4.6–27)	6 (2.2–9.3)
B-blocker, median (IQR)	53 (26–71)	53 (30–64)	39 (23–76)	34 (13–75)	22 (18–38)
MRA, median (IQR)	16 (6.0–21)	6.3 (2.5–12)	17 (4–29)	20 (12 − 31)	10 (5.6–20)
Cardiac glycosides, median (IQR)	20 (11–26)	20 (14–37)	24 (13–28)	33 (23–41)	28 (17–35)
Comorbidities					
Hypertension, median (IQR)	53 (44–77)	45 (36–57)	58 (46–78)	62 (46–75)	53 (46–67)
Ischaemic heart disease[c], median (IQR)	34 (29–49)	53 (39–65)	46 (31–52)	47 (32–58)	31 (23–43)
Atrial fibrillation, median (IQR)	20 (18–30)	33 (25–39)	26 (16–33)	37 (22–41)	30 (20–43)
Diabetes, median (IQR)	22 (14–27)	22 (20–25)	29 (17–35)	24 (17–34)	25 (18–30)
COPD[d], median (IQR)	15 (10–19)	28 (11–29)	26 (22 − 32)	21 (15–27)	19 (13–26)
CKD[e], median (IQR)	18 (0.8–42)	25 (4.5–40)	9.5 (4.6–27)	7.2 (5.0–13)	15 (11 − 31)

GP, general practitioner; US, echocardiography; pts., patients; IQR, interquartile range; RAAS blockade, renin-angiotensin-aldosterone system blockade; ACE-I, angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor antagonist; MRA, mineralocorticoid receptor antagonist; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.

[a] Loop diuretics or thiazide diuretics or any diuretics.

[b] ACE-I and ARB or ACE-I alone.

[c] Ischaemic heart disease or angina pectoris or coronary heart disease or myocardial infarction.

[d] COPD or COPD/asthma or treated lung disease or respiratory disease.

[e] As defined in original study: ranging from eGFR <30 to 60, creatinine >1.2 to 1.8 mg/dL.

predominant phenotype of older women with hypertension rather than ischaemic heart disease. Although an association between identification methods and certain patient characteristics was shown, other study characteristics, especially study design, had a greater impact. RCTs tended to include younger, male patients with ischaemic heart disease and higher HF drug prescription rates at baseline. Our findings have started a discussion about the definition of HF and the preferred methods to identify real-world patients with HF.

Five main approaches to identify patients with HF in general practice were found. The majority of studies (70%) did not incorporate echocardiography and included patients with HF based on GP judgment or GP chart review; however, several studies have shown a poor validity of GP's HF diagnoses [7,9,13]. Nevertheless, the only associations found between patient characteristics and identification methods were a shift towards a younger age and a higher prevalence of ischaemic heart disease in studies where general practitioners' decided on the presence of HF and a lower prevalence of diuretics in studies using echocardiographic assessments. It is possible that GPs tend to categorize younger patients with HF more easily as attributable to ischaemic heart disease, although this contradicts the characteristics of actual GP patients with HF. Also, diuretic prescriptions could be interpreted as a surrogate marker of persistent symptoms and it is possible that studies using echocardiographic assessments could have included fewer symptomatic patients. In contrast, a much stronger association between study design and patient characteristics was found. Randomized controlled trials in general practice were associated with younger, male patients with ischaemic heart disease who had higher rates of B-blocker and RAAS-blockade prescription at baseline. This is in line with the findings of a recent systematic review that provided an overview of HFpEF patient characteristics stratified by study design. Vaduganathan et al. also noted heterogeneity in the definition of HFpEF across studies, although no association was found between the cut-off values of EF used and the prevalence of HFpEF. However, they did find an association between outcomes and study design: RCTs tended to exclude high-risk patients with multiple comorbidities, leading to more favourable patient outcomes than those of registries [16]. Another recent review confirmed that although 97% of patients with HF had a concomitant chronic condition, 81% of RCTs targeting patients with HF excluded patients with concomitant chronic conditions [17]. Consequently, patients with HF who are included in RCTs differ from the typical phenotype in general practice. By comparing the characteristics of the 196,105 patients with HF studied in this review with the characteristics of patients with HF treated by cardiologists, the typical phenotype in general practice of an older (mean age 75 vs 64 years) [3], predominantly female (51% women vs 35%) [18] population with hypertension (54% vs 41%) [3] rather than ischaemic heart disease (35% vs 56%) [3] was confirmed. Additionally, the progressive implementation of HF guidelines into practice was clearly shown by the association between more recent years of data collection and the number of patients prescribed RAAS-blockade (β 43 (95% CI −8.8; 78)) and B-blockers (β 51 (95% CI 13; 88)). Undertreatment of patients with HF is an important problem in general practice [8]; however, the sub-selection of studies that started collecting data after 2005 showed substantial progress in the prescription of RAAS-blockade (83%) and B-blocker (66%) therapy, with the aside that dosage was not taken into account [19,20]. Additionally, it is important to point out that 90% of HF patients studied in this review were not categorized as either HFrEF or HFpEF, precluding robust conclusions about undertreatment. Furthermore, a high prevalence (19%) of comorbid depression in patients with HF was found, in line with previous research [21]. However, despite its importance, depression was only reported by 11 out of 105 studies (10%).

Our findings open a discussion about the definition of HF, as the heterogeneity in results can be explained by the lack of a clear gold standard definition of HF. In the timeframe studied in this review, the definition and classification of HF constantly evolved [1,22]. To date, there is no agreement regarding a universal definition of HFpEF patients

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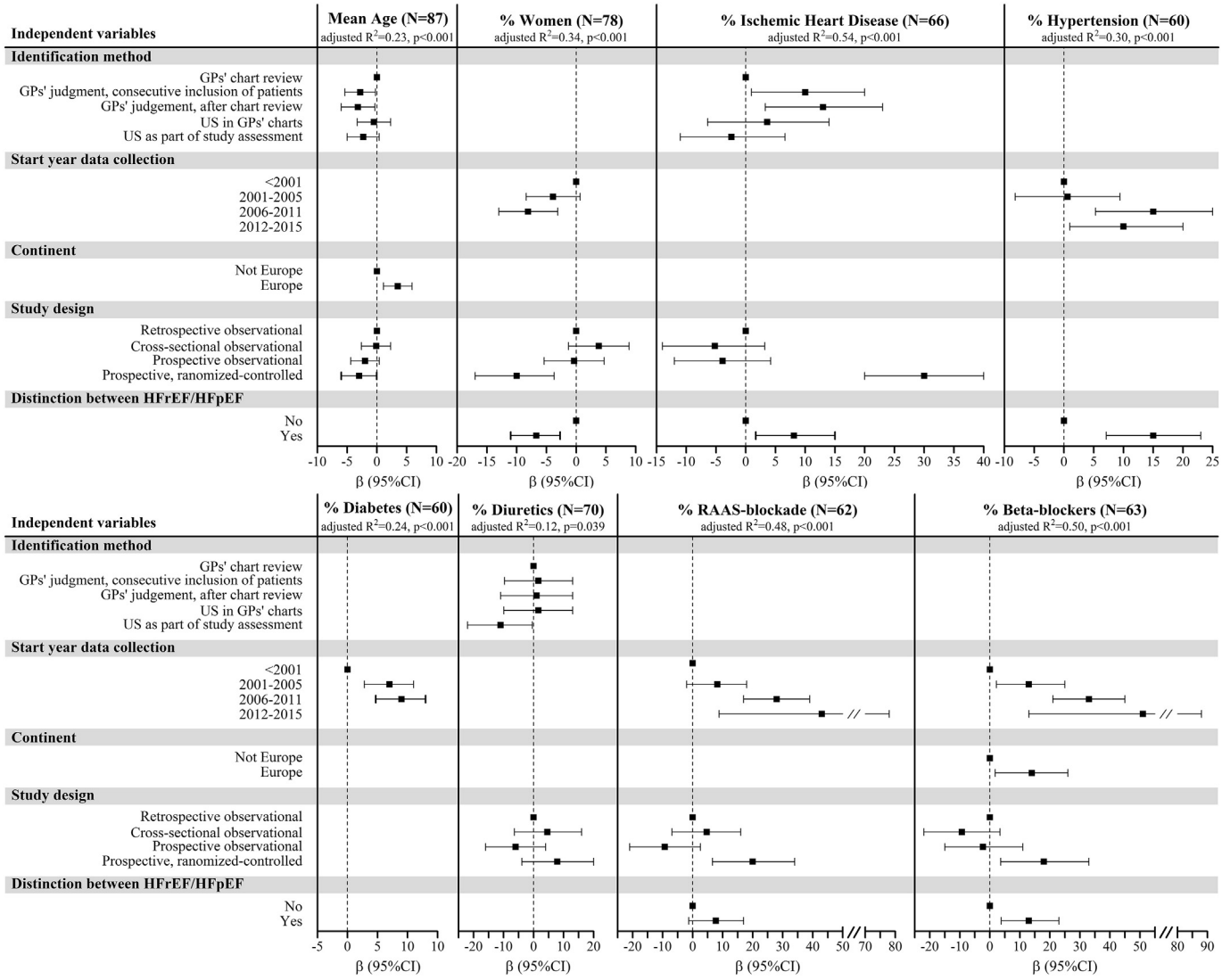

Fig. 3. Association between study characteristics and patient characteristics: results of the linear regression analysis.

[16,23,24]. HFpEF patients form a heterogeneous group in which a common pathophysiology cannot be found [23,24]. They typically have multiple comorbidities that drive their prognosis and are likely causally interrelated [23,25]. Defining HFpEF patients solely based on ejection fraction has several limitations [1,16,23,25]. However, the exact role of additional diagnostic criteria (echocardiographic diastolic dysfunction, other echocardiographic abnormalities, markers of inflammation, comorbidities, etc.) is the subject of an ongoing debate [1,16,23–25]. Currently, natriuretic peptides have potentially the largest added diagnostic value to exclude HF in suspected HFpEF patients in general practice [1,26]. However, their use is not yet widespread [27]. Nonetheless, although the prevalence of HFrEF patients is declining, the prevalence of HFpEF has increased and is higher in the community than in the hospital [5,23,28].

The classic definition of HF as a clinical syndrome is of limited use in the elderly, in whom HF symptoms and signs are common in both patients with or without objective cardiac abnormalities [7]. Moreover, HF symptoms and signs and measures of cardiac dysfunction can evolve over time in response to treatment and contextual factors. Accordingly, the poor validity of GPs' diagnoses can be questioned because the confirmation of their diagnoses depends on the reference standard used at one moment in time [6,9]. Furthermore, it has been shown that patients with HF according to GPs had similar mortality rates as "objectified" patients with HF [7,29]. Moreover, this systematic review did not show large differences in patient characteristics between studies using echocardiography as an inclusion criterion and studies that did not. Therefore, covering real-world community-based patients with HF seems more important than the identification method or definition of HF used.

However, the lack of a clear gold standard definition of HF demands high quality reporting of the identification method and definition of HF used, which often is not the case in HF studies in general practice, as shown in our review. From a research perspective, a more uniform use of diagnostic HF criteria and a stricter definition of those criteria would increase the generalizability and transparency of research findings [16]. However, on the other hand, applying strict diagnostic criteria conflicts with the clinical reality of complex elderly patients. A shift towards more comprehensive and less disease-oriented or vertical care of complex elderly patients is needed [30]. HF could be evaluated using a horizontal approach through the manifestation of clinically relevant cardiac abnormalities, taking full account of the interactions with concomitant chronic conditions. Moreover, the clinical impact could be evaluated by objectively measuring the physical performance of the patient in addition to self-reported non-specific symptoms [7]. The latter

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could meet the needs of both research and clinical practice if a good balance between objectively measured parameters and a comprehensive holistic assessment can be maintained.

Patients with HF in general practice are an important patient population that has not been extensively studied. A critical assessment of the influence of study characteristics on patient characteristics is important for evaluating the generalizability of the studies performed. However, a few limitations should be noted. Since the majority of studies was performed in Western countries, the findings may apply only to developed countries. Additionally, the authors were contacted up to three times to collect additional data or to clarify uncertainties. However, since data collection occurred before 2001 in 53% of the studies, additional data often could not be retrieved.

In conclusion, the phenotype of patients with HF in general practice, specifically of older, female patients with hypertension rather than ischaemic heart disease, was confirmed. However, a large heterogeneity in the methods used to identify patients with HF in general practice was found. This heterogeneity could be explained by the lack of a clear gold standard definition of HF. To address this limitation, a balance should be found between the need for clarity and uniformity in research and the need to cover real-life clinical complexity. Although the influence of these different identification methods on patient characteristics was limited, RCTs did tend to include patients with a different phenotype. Therefore, covering real-world community-based patients with HF may be equally or even more important than the identification method or definition of HF used.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.06.108.

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