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REVIEW ARTICLE

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Electrocardiographic characteristics in patients with heart failure and normal ejection fraction: A systematic review and meta-analysis

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Abstract

Background: Little is known about ECG abnormalities in patients with heart failure and normal ejection fraction (HeFNEF) and how they relate to different etiologies or outcomes.

Methods and Results: We searched the literature for peer-reviewed studies describing ECG abnormalities in HeFNEF other than heart rhythm alone. Thirty five studies were identified and 32,006 participants. ECG abnormalities reported in patients with HeFNEF include atrial fibrillation (prevalence 12%–46%), long PR interval (11%–20%), left ventricular hypertrophy (LVH, 10%–30%), pathological Q waves (11%–18%), RBBB (6%–16%), LBBB (0%–8%), and long JTc (3%–4%). Atrial fibrillation is more common in patients with HeFNEF compared to those with heart failure and reduced ejection fraction (HeFREF). In contrast, long PR interval, LVH, Q waves, LBBB, and long JTc are more common in patients with HeFREF. A pooled effect estimate analysis showed that QRS duration ≥120 ms, although uncommon (13%–19%), is associated with worse outcomes in patients with HeFNEF.

Conclusions: There is high variability in the prevalence of ECG abnormalities in patients with HeFNEF. Atrial fibrillation is more common in patients with HeFNEF compared to those with HeFREF. QRS duration ≥120 ms is associated with worse outcomes in patients with HeFNEF. Further studies are needed to address whether ECG abnormalities correlate with different phenotypes in HeFNEF.

KEYWORDS

atrial fibrillation, ECG, heart failure with normal ejection fraction, heart rhythm

1 | INTRODUCTION

Compared with patients with heart failure and reduced ejection fraction (HeFREF), patients with heart failure and normal ejection fraction (HeFNEF) are older, more likely to be female, have a higher prevalence of hypertension and anemia, and a lower prevalence of coronary artery disease (Olsson et al., 2006; Senni et al., 1998; Yap et al., 2015).

ECG abnormalities in HeFREF are widely described and guide medical and device therapy. However, many studies in HeFNEF do not report ECG characteristics other than heart rhythm. Hence, other than a high prevalence of atrial fibrillation, little is known about ECG features associated with HeFNEF. In recent years, attempts have been made to identify different phenotypic groups among patients with HeFNEF based on comorbidities, such as hypertension, obesity, or lung disease, in order to target therapeutic interventions and predict outcomes (Gorter et al., 2018; Shah et al., 2015). ECG variables may provide an additional noninvasive tool to help identify distinct phenotypes with different trajectories.

2 | METHODS

2.1 | Search strategy and selection criteria

We identified peer-reviewed studies published in English in patients with HeFNEF describing ECG variables other than heart rhythm alone. Participants included were men and women with a diagnosis of HeFNEF. We included the following types of studies performed in any healthcare setting:

1. Randomized controlled trials (RCTs)
2. Controlled trials
3. Observational studies with the following designs:
   a. Single-gate design (all participants had HeFNEF)
   b. Two-gate design (the same study includes participants with and without HeFNEF)

We excluded the following:

1. Studies without information on recruitment methods or study population
2. Case reports or case series
3. Studies reported only in abstract form or in conference proceedings where the full text was not available.

We searched the following databases to identify the published studies that reported ECG variables in patients with HeFNEF (inception to January 2019): CENTRAL, MEDLINE, EMBASE, CINAHL, Web of Science, LILACS, and TRIP. We also searched databases of trial registries and hand-searched the reference list of all relevant publications.

2.2 | Data collection and analysis

We examined abstracts and excluded duplicates, review articles, and articles reporting imaging and ECG variables alone without baseline clinical characteristics of heart failure (Figure 1). We also excluded studies of nonrepresentative cohorts, such as those with high prevalence of valvular heart disease, in order to minimize the risk of bias (Appendix I). Two review authors (TN and NS) independently assessed the full-text publication of the remaining articles. Disagreements were resolved by a third reviewer (ALC). The process of study selection was documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Figure 1).

2.3 | Statistical analysis

A pooled prevalence of right bundle branch block in HeFNEF and confidence intervals for individual studies were estimated using the Metaprop function (STATA-SE 14) using a random effects model and the Clopper–Pearson exact confidence intervals method (Nyaga, Arbyn, & Aerts, 2014). Between-study heterogeneity was statistically assessed by calculating an I^2 and chi-square.

Where studies compared adverse outcomes between patients with and without prolonged QRS/bundle branch block, a pooled effect estimate of abnormal QRS was estimated. Analysis was completed using Review Manager 5.3, and a random effects model was used due to between-study heterogeneity (Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre).

3 | RESULTS

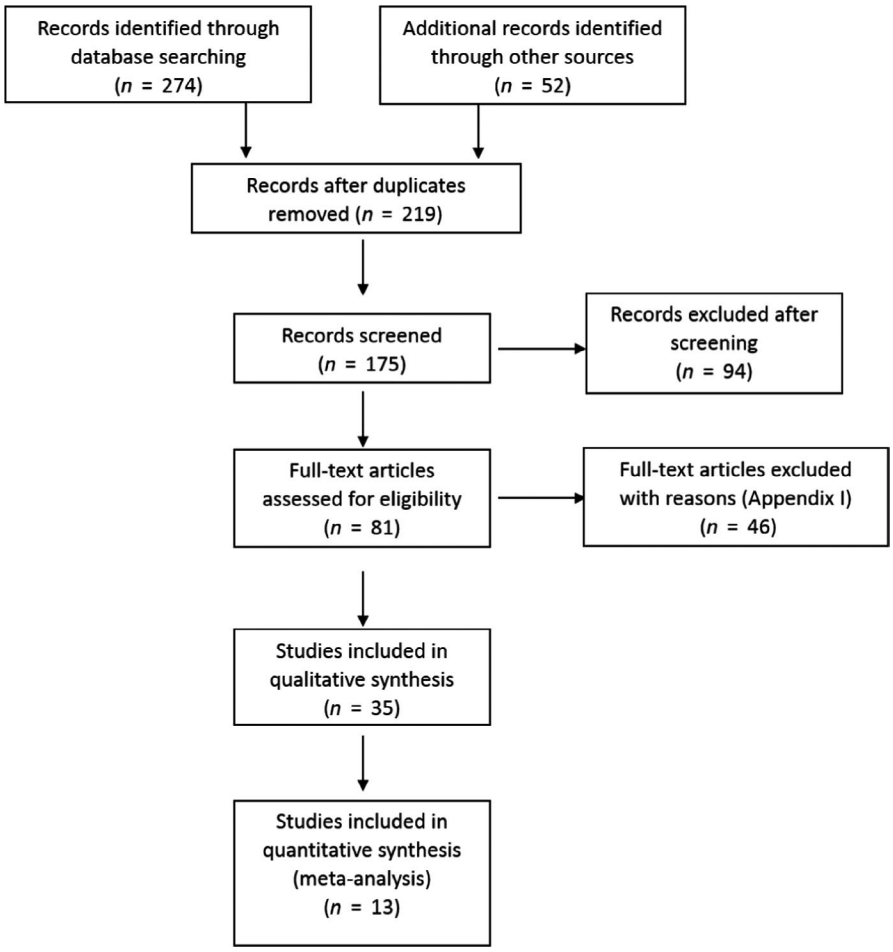
3.1 | Studies

The literature review identified 219 studies. After reviewing the abstracts, 94 studies were excluded and a further 46 were excluded after reviewing full-text articles (Figure 1; Appendix I); 35 studies were included in the final review (Table 1). When multiple reports from the same cohort were published the report, most representative of ECG variables was included (Table 2).

The definition of HeFNEF varied among studies (Appendix II). In addition, different cutoffs for left ventricular ejection fraction (LVEF) were used to define HeFNEF: ≥40% (Cenkerova, Dubrava, Pokorna, Kaluzay, & Jurkovicova, 2016; Danciu et al., 2006; Hendry, Krisdinarti, & Erika, 2016), >40% (Hawkins et al., 2007; Olsson et al., 2006), ≥45% (Adabag et al., 2014; Donal et al., 2014; Joseph et al., 2016; Komajda et al., 2011; Nikolaidou et al., 2017; Shah et al., 2013), >45% (Ho et al., 2013; Lee et al., 2009; Park et al., 2013; Zile et al., 2011), ≥50% (Gigliotti et al., 2017; Gijsberts et al., 2016; Hummel, Skorcz, & Koelling, 2009; Khan et al., 2007; Lund et al., 2013; Martinez Santos et al., 2016; Masoudi et al., 2003; Menet et al., 2014; O'Neal et al., 2017; Pascual-Figal et al., 2017; Peyster, Norman, & Domanski, 2004; Senni et al., 1998; Shenkman et al., 2002; Yap et al., 2015), >50% (Eicher et al., 2012; Oskouie, Prenner, Shah, & Sauer, 2017; Sanchis et al., 2015; Selvaraj et al., 2014; Shah et al., 2015), and ≥55% (Varadarajan & Pai, 2003). The following methods were used to measure ejection fraction: echocardiography, nuclear scintigraphy, and contrast ventriculography. Six studies included patients with heart failure and valvular heart disease (3%–20% of patients with HeFNEF) (Donal et al., 2014; Ho et al., 2013; Lee et al., 2009; Lund et al., 2013; Park et al., 2013; Peyster et al., 2004).

Three studies assessed the risk of future heart failure associated with baseline ECG characteristics in populations without heart failure at baseline (suspected coronary ischemia (O'Neal et

FIGURE 1 PRISMA flowchart



al., 2017) and the general population (Ho et al., 2013; Lee et al., 2009)).

Two studies provided ECG characteristics specifically in patients with heart failure and mid-range ejection fraction 40%–49% (HeFmrEF) (Lund et al., 2013; Pascual-Figal et al., 2017).

3.2 | Participants

A total of 32,006 participants with HeFNEF were included. The mean age was 74 years, and 56% were women. Participant comorbidities are summarized in Appendix II.

3.3 | Atrial fibrillation

In the studies we identified, the prevalence of atrial fibrillation or atrial flutter on ECG was 12%–46% (Adabag et al., 2014; Cenkerova et al., 2016; Donal et al., 2014; Ho et al., 2013; Khan et al., 2007; Lee et al., 2009; Masoudi et al., 2003; Nikolaidou et al., 2017; Olsson et al., 2006; Oskouie et al., 2017; Pascual-Figal et al., 2017; Peyster et al., 2004; Sanchis et al., 2015; Selvaraj et al., 2014; Senni et al., 1998; Shah et al., 2013; Yap et al., 2015). The percentage of patients with a history of atrial fibrillation (where reported) was greater (Lee et al., 2009; Shah et al., 2013). In the studies including patients with HeFREF, the prevalence of atrial fibrillation was lower (15%–36%) in HeFREF than in HeFNEF (16%–46%) (Cenkerova et al., 2016; Hawkins et al., 2007; Nikolaidou et al., 2017; Park et al., 2013; Pascual-Figal et al., 2017; Peyster et al., 2004; Senni et al., 1998; Yap et al., 2015). Only one study (of 2,258 patients admitted with heart failure) found a higher prevalence of atrial fibrillation in patients with reduced ejection fraction (26% vs. 20%) (Varadarajan & Pai, 2003).

In the CHARM program, 7,599 patients with heart failure and NYHA class symptoms II-IV were randomized to candesartan or placebo and followed up for 38 months. 3,023 patients had HeFNEF (ejection fraction > 40%) and 478 (16%) of these had atrial fibrillation at baseline. The presence of atrial fibrillation at baseline was an independent risk factor for cardiovascular death or hospitalization for heart failure and all-cause mortality after adjusting for 32 covariates (Olsson et al., 2006).

3.4 | P/PR duration

First-degree AV block (PR ≥ 200 ms) was present in 11%–21% of patients with HeFNEF (Donal et al., 2014; Khan et al., 2007; Nikolaidou et al., 2017) but was more common in patients with HeFREF (21%–26%) (Khan et al., 2007; Nikolaidou et al., 2017). In a prospective observational study of 539 patients admitted to hospital with clinical signs of heart failure and LVEF > 45%, 11% had 1st-degree heart block (Donal et al., 2014). Higher degree

TABLE 1 Details of included studies

	Study type Population F/U (years)	Type of HF	*N*	Age (mean, years)	Men (%)	EF (%)	LA diameter (mm)	AF/flutter on ECG *N* (%)	P wave (ms)	PR (ms)	QRS (ms)	LBBB *N* (%)	RBBB *N* (%)	QT (ms)	LVH *N* (%)	ST/T changes *N* (%)	Other
HFpEF and HFrEF																	
Nikolaidou et al (2018)[†]	Prospective study							Excluded		PRc[*]				QTc[*]			
	Consecutive patients referred to a community HF clinic with suspected HF 2001–14	No HF HeFNEF HeFREF	1,155 1,107 1,434	68[*] 76[*] 71[*]	51 47 71	59 54 33		6/1193 (0.1) 707/1950 (36) 553/2333 (24)		163 168 174	90[*] 92[*] 112[*]			418 429 453			
Pascual-Figal et al. (2017)	Prospective study						Index (mm/m^2)										
	Ambulatory patients with chronic HF from 2 national registries 2003–04, 2007–11 F/U: 41 months	HeFNEF HeFmrEF HeFREF	635 460 2,351	72 67 64	43 73 77		25 24 25	221 (35) 94 (20) 442 (19)			108 117 130	47 (7) 777 (17) 733 (32)	55 (9) 35 (8) 106 (5)				
Hendry et al. (2016)	Cross-sectional study													QTc			Q wave
	In- and outpatients with chronic HF at one centre 2015	HeFNEF HeFREF	50 60	60 58	56 82	59 29	34 42	N/A			97 124	0 12 (20)	7 (14) 3 (5)	453 499	15 (30) 33 (55)	19 (38) 42 (70)	9 (18) 17 (28)
Gijsberts et al. (2016)[†**]	Observational study										Adjusted QRS						
	Patients with HF (in- or outpatient). 839 SHOP cohort and 11,221 SwedeHF 2010–14 F/U: 445 days	All HF HeFNEF HeFREF	12,060 2,913 9,147	73	63			5,807 (48)			103 95 106	1834 (15)					
Sanchis et al (2016)	Prospective study						Volume (ml)										
	Consecutive patients with new-onset HF, referred to a clinic 2009–12	No HF HeFNEF	32 34	73 75	23 28	61 60	17 21	Excluded 29/138 (21)	74 81	158 173	97 95						
Cenkerova et al. (2016)	Prospective study									PQ				QTc			
	Consecutive patients with HF admitted to one centre 2010–11 F/U: 24 months	HeFNEF HeFREF	63 46	74 67	54 76	59 27	50 53	29 (46) 12 (27)		160 170	80 100			435 452			
Yap et al. (2015)[†]	Prospective study																
	Consecutive patients admitted with HF to any public hospital in Singapore 2008–09	HeFNEF HeFREF	751 1,209	73 67	35 64			255 (34) 254 (21)			94 106						
Menet et al. (2014)	Cohort study						Vol index (ml/m^2)	Excluded									
	Patients hospitalized for HF	No HF-HT HeFNEF HeFREF CRT HeFREF (QRS < 120)	40 40 40 40	68 70 70 62	23 23 70 80	69 63 25 30	23 33 41 33				91 92 157 97	2 (5) 2 (5) 38 (95) 0 (0)					

(Continues)

TABLE 1 (Continued)

	Study type Population F/U (years)	Type of HF	*N*	Age (mean, years)	Men (%)	EF (%)	LA diameter (mm)	AF/flutter on ECG *N* (%)	P wave (ms)	PR (ms)	QRS (ms)	LBBB *N* (%)	RBBB *N* (%)	QT (ms)	LVH *N* (%)	ST/T changes *N* (%)	Other
Lund et al. (2013)[†**]	Prospective study										QRS ≥ 120						
	SwedeHF registry (online registry of in- and outpatients with HF) F/U: 2 years	All HF HeFNEF HeFmrEF HeFREF	25,171 6,193 5,601 13,377	75	60			11,452 (46)			7,803 (31) 1,115 (18) 1,400 (25) 5,217 (39)	4,028 (16)					
Park et al. (2013)[†]	Prospective registry										QRS ≥ 120						
	Korean Acute Heart Failure Registry 2004–09 (patients admitted to 24 hospitals with HF) F/U: 656 days	HeFNEF HeFREF	523 966	70 66	39 56	58 30		180 (34) 213 (22)			67 (13) 232 (24)						
Eicher et al. (2012)	Cross-sectional study							History of AF									
	Consecutive patients admitted for HF (3 months). Controls: CAD or mild valve disease	No HF HeFNEF	27 29	80 81	52 38	69 66	37 45	5 (19) 20 (69)	118 126								
Khan et al. (2007)	Retrospective study									PR > 250	QRS ≥ 120			JTc > 400		Abnormal T wave	Q wave
	EuroHeart Failure Survey of inpatients with HF in 24 European countries over a period of 6 weeks 2001–02	No echo abnormality LVDD Mild LVSD Mod/sev LVSD	523 109 667 735					103 (20) 21 (19) 152 (23) 143 (20)		10/408 3/86 15/490 21/572	70 (13) 21 (19) 151 (23) 227 (31)	18 (3) 5 (5) 66 (9) 137 (19)	40 (8) 10 (9) 50 (8) 39 (5)	16 (3) 3 (3) 18 (3) 31 (4)	40 (8) 11 (10) 82 (12) 92 (13)	33 (6) 6 (1) 56 (8) 77 (11)	52 (10) 12 (11) 107 (16) 154 (21)
Hawkins et al. (2007)[†] and Olsson et al. (2006)[†]	RCT																BBB
	Patients with HF from the CHARM program F/U: 38 months	HeFNEF HeFREF	3,023 4,576	67 65	60 73	55 29		478 (16) 670 (15)							444 (15) 696 (15)		434 (14) 1,377 (30)
Danciu et al. (2006)[†]	Retrospective study							History of AF									IVCD
	Patients hospitalized with decompensated HF	HeFNEF HeFREF	108 109	72 70	39 67	60 22		30 (28) 30 (28)				13 (12) 25 (23)	17 (16) 8 (7)				13 (12) 25 (23)
Peyster et al. (2004)	Retrospective study											LBBB/ IVCD			ECG/ echo		
	Consecutive patients aged ≥ 65 with discharge diagnosis of HF	HeFNEF HeFREF	97 150	78 76	25 49			22 (23) 38 (25)				3 (3) 39 (26)			59 (61) 52 (35)		
Varadarajan and Pai (2003)[†]	Retrospective study																MI
	Patients with HF discharge diagnosis and echo 1990–99 F/U: 786 days	HeFNEF HeFREF	963 1,295	70 71		62 31		193 (20) 337 (26)				19 (2) 155 (12)	87 (9) 143 (11)				366 (38) 777 (60)
Masoudi et al. (2003)	Retrospective study							History of AF									
	Medicaid beneficiaries aged ≥ 65 hospitalized for HF 1998–99	HeFNEF HeFREF	6,754 12,956	80 78	29 51			2,431 (36) 3,887 (30)				540 (8) 3,109 (24)					

(Continues)

TABLE 1 (Continued)

	Study type Population F/U (years)	Type of HF	*N*	Age (mean, years)	Men (%)	EF (%)	LA diameter (mm)	AF/flutter on ECG *N* (%)	P wave (ms)	PR (ms)	QRS (ms)	LBBB *N* (%)	RBBB *N* (%)	QT (ms)	LVH *N* (%)	ST/T changes *N* (%)	Other
Shenkman et al. (2002)†	Retrospective study										QRS ≥ 120						
	Patients from the REACH study 1989–99 F/U 32 months	All HF HeFNEF HeFREF	3,471 1811 1,660	66	50						721 (21) 230 (13) 491 (30)						
Senni et al. (1998)	Retrospective study											LBBB/IVCD					
	Patients receiving a first diagnosis of HF and echo in 1991 in Olmsted County	HeFNEF HeFREF	59 78	78 74	31 59	≥50 <50		17 (29) 19 (24)				0 9 (12)			10 (17) 15 (19)		
HeFNEF only																	
Gigliotti et al. (2017)†	Retrospective study						Area (cm^2)							QTc			
	Patients discharged with a HF diagnosis from one centre and echo 2006–09	HeFNEF + SR HeFNEF + AF	57 25	69 79	42 44		21 30				99 103			443 447			
Oskouie et al. (2017)	Prospective study						Vol index (ml/m^2)	Excluded						QTc			
	Consecutive patients following hospitalization with HeFNEF in a centre 2008–11	HeFNEF	201	64	23	62	31	48/397 (12)		173	96			454			
Martinez Santos et al. (2016)	Prospective study																
	Consecutive patients admitted with HeFNEF in a centre 2011–12	HeFNEF	123	81	37								20 (16)				
Shah et al. (2015)†	Prospective study						Vol index (ml/m^2)	History of AF						QTc			QRS-T angle
	Consecutive patients from outpatient clinic following hospitalization for HF 2008–11	Phenotypic Group 1 Group 2 Group 3	128 120 149	61 66 67	33 32 45	62 61 60	29 32 41	17 (13) 26 (22) 64 (43)		167 174 183	94 91 113			451 450 464			43 53 87
Donal et al. (2014)	Prospective study									PR > 200	QRS > 120						
	Consecutive patients with HF in the ED in 10 French and 3 Swedish centres 2007–11	HeFNEF at admission HeFNEF after 4–8 weeks treatment	539 438	77 77	44 44	56 62	45	218 (44) 171 (39)		26 (11) 25 (14)	69 (15) 57 (16)	16 (3.5) 14 (3.8)	35 (7.6) 24 (6.6)				
Adabag et al. (2014)† and Komajda et al. (2011)† and Zile et al. (2011)†	RCT																2°or 3° HB
	I-PRESERVE study on the effect of Irbesartan in patients with HeFNEF F/U: 4.1 years	HeFNEF (alive at follow-up) HeFNEF (non-SCD) HeFNEF(SCD)	3,247 650 231	71 75 74	37 47 55	60 58 57		844 (26) 273 (42) 85 (37)				260 (8) 59 (9) 32 (14)			974 (30) 189 (29) 83 (36)		65 (2) 26 (4) 14 (6)

(Continues)

TABLE 1 (Continued)

	Study type Population F/U (years)	Type of HF	*N*	Age (mean, years)	Men (%)	EF (%)	LA diameter (mm)	AF/flutter on ECG *N* (%)	P wave (ms)	PR (ms)	QRS (ms)	LBBB *N* (%)	RBBB *N* (%)	QT (ms)	LVH *N* (%)	ST/T changes *N* (%)	Other
Selvaraj et al. (2014)†	Prospective study						Vol index (ml/m^2)							QTc		T wave inversion	IVCD
	Patients with HF identified from inpatient records, reviewed in the outpatient clinic 2008–11 F/U: 12 months	HeFNEF QRS-T angle 0–26° 27–75° 76–179°	124 125 127	62 66 64	31 37 39	62 61 61	31 33 37	18 (15) 30 (24) 40 (32)		167 174 183	86 94 109	0 (0) 2 (2) 11 (9)	1 (1) 6 (5) 17 (13)	447 450 462		18 (15) 31 (26) 81 (68)	1 (1) 8 (6) 12 (9)
Shah et al. (2013) and Joseph et al. (2016)†	RCT							History of AF			QRS ≥ 120						Q wave
	Patients with HeFNEF enrolled in the TOPCAT trial in six countries 2006–12	HeFNEF	3,445	69	48	57		28% ECG 35%			100 18%	204 (8)	287 (11)		742 (29)		399 (16)
Hummel et al. (2009)†	Retrospective study																
	Patients admitted to eight Michigan hospitals in two 6-month periods 2002–04 F/U: 660 days	HeFNEF all) HeFNEF (QRS < 120 ms) HeFNEF (QRS ≥ 120 ms)	872 679 193	74 72 78	33 31 40	60 60 59		235 (27) 224 (33) 91 (47)			89 148						
No symptoms of heart failure at baseline																	
O'Neal et al. (2017)	Cohort study								p > 120	PR > 200	QRS > 100			Long QT			Abnormal P axis
	MESA population, no cardiovascular disease at baseline from six field centres 2000–02 F/U: 12.1 years	No HF Developed HeFREF Developed HeFNEF	6,420 127 117	62 67 70	47 72 50				699 (11) 27 (21) 21 (18)	492 (8) 19 (15) 15 (13)	1,239 (19) 56 (44) 34 (29)	16 (<1) 5 (3.9) 1 (<1)	145 (2.3) 6 (4.7) 7 (5.9)	481 (7.5) 28 (22) 6 (5.1)	236 (3.7) 12 (9.5) 8 (6.8)	852 (13) 44 (35) 25 (21)	548 (8.5) 11 (8.7) 18 (15)
Ho et al. (2013)**	Cohort study																
	Characteristics at baseline FHS participants with HF hospitalization 1980–2008 F/U 15 years	No HF HeFNEF HeFREF	5,828 196 261	60 74 72	45 39 64			22 (11) 26 (10)				9 (5) 10 (4)	14 (7) 15 (5)		35 (18) 69 (26)		
Lee et al. (2009)**	Cohort study																
	Characteristics at HF onset FHS participants with HF occurring 1981–2004 F/U: 3.2 years	HeFNEF HeFREF	178 270	79 77	36 60			61 (34) 53 (2)			103 112	13 (7) 54 (20)	22 (12) 24 (9)				

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; echo, echocardiogram; ED, emergency department; EF, ejection fraction; F/U, follow-up; F/U, follow-up; FHS, Framingham heart study; HB, heart block; HF, heart failure; HT, hypertension; IVCD, interventricular conduction delay; LA, left atrium; LVSF, left ventricular systolic function; MI, myocardial infarction; PAF, paroxysmal atrial fibrillation; RCT, randomized controlled trial; RV, right ventricular; SCD, sudden cardiac death.

*Median

**Overlapping cohorts

†Outcome or mortality data available

TABLE 2 Relative prevalence of ECG abnormalities in HeFNEF and HeFREF

	HeFNEF	HeFREF
AF	+++	++
Long PR	+	++
LVH	++	+++
Q wave	+	++
LBBB	Rare	+++
RBBB	+(+)	+
Long JTc	Rare	+

atrioventricular block (second or third) was present in 2%–6% of patients with HeFNEF in the I-PRESERVE trial (Adabag et al., 2014).

In a population of 3,664 referred to a community clinic with suspected heart failure, 20% of 1,094 patients with HeFNEF and 21% of 1,420 with HeFREF had first-degree heart block (as did 9% of those without heart failure) (Nikolaidou et al., 2017). Among patients with HeFNEF and QRS ≥ 130 ms, the prevalence of first-degree heart block was even higher (40%).

Twenty-seven patients with HeFNEF requiring hospitalization and 27 controls (outpatients referred for echocardiography or with stable coronary disease or mild valve disease but no HeFNEF) underwent ECG and echocardiographic assessment. Patients with HeFNEF had longer P waves and shorter echocardiographic A waves (Eicher et al., 2012).

3.5 | QRS

Left bundle branch block (LBBB) is present in up to 50% of patients with HeFREF(Danciu et al., 2006; Khan et al., 2007; Lund et al., 2013; Senni et al., 1998; Varadarajan & Pai, 2003) but only 0%–8% of patients with HeFNEF (Donal et al., 2014; Khan et al., 2007; Komajda et al., 2011; Lee et al., 2009; Masoudi et al., 2003; Menet et al., 2014; Peyster et al., 2004; Shah et al., 2013; Varadarajan & Pai, 2003). Right bundle branch block (RBBB) is present in 5%–11% of patients with HeFREF (weighted average 7%) (Donal et al., 2014; Khan et al., 2007; Lee et al., 2009; Shah et al., 2013; Varadarajan & Pai, 2003) and in 6%–16% (weighted average 9%) of patients with HeFNEF (Figure 2a) (Danciu et al., 2006; Donal et al., 2014; Hendry et al., 2016; Khan et al., 2007; Lee et al., 2009; Martinez Santos et al., 2016; Pascual-Figal et al., 2017; Selvaraj et al., 2014; Varadarajan & Pai, 2003). RBBB is more common in patients with HeFNEF compared to HeFREF but without reaching statistical significance due to limited data available.

In an analysis of the CHARM trials, which included 3,023 patients with normal LVEF, any bundle branch block was present in 14% of patients with HeFNEF (and 30% of those with HeFREF) (Hawkins et al., 2007). Data from the TOPCAT trial reported QRS duration ≥ 120 ms in 18% of 3,426 patients with HeFNEF (Joseph et al., 2016). Similarly, Donal et al reported a prevalence of QRS > 120 ms of 15% among 539 patients admitted to hospital with HeFNEF (3.5% had LBBB and 7.6% had RBBB) (Donal et al., 2014). A study of 3,696 ambulatory patients referred with suspected heart failure reported that 5% of 1,107 patients with HeFNEF had QRS ≥ 150 ms versus 18% of those with HeFREF (Nikolaidou et al., 2017).

Increasing QRS duration (especially with LBBB morphology) is associated with increased mortality in HeFREF (Shamim et al., 1999). Conflicting results have been reported in patients with HeFNEF. In a study of 25,171 patients from the SwedeHF registry, increasing QRS duration was an independent risk factor for increasing all-cause mortality regardless of ejection fraction (Lund et al., 2013). An analysis of the TOPCAT trial showed that the risk of heart failure hospitalization was significantly higher in patients with HeFNEF and QRS ≥ 120 ms (Joseph et al., 2016). Another study of 872 patients admitted to Michigan community hospitals with HeFNEF reported that QRS duration >120 ms on a predischarge ECG was an independent predictor of postdischarge death (Hummel et al., 2009).

Increasing QRS duration was an independent predictor of increasing 2-year cardiovascular mortality but not all-cause mortality in an Asian population with heart failure and ejection fraction >50% (Yap et al., 2015). In a retrospective study of 108 patients admitted with HeFNEF, the presence of intraventricular conduction defects with QRS > 120 ms was associated with higher 180-day readmission and mortality rates (adjusted for age) compared to patients with narrower QRS (Danciu et al., 2006).

In contrast, in the CHARM trials, the presence of bundle branch block increased the risk of the primary outcome of cardiovascular death or unplanned hospital admission for heart failure only in patients with HeFREF and not those with HeFNEF (Hawkins et al., 2007). Similarly, in the REACH (Resource Utilization Among Congestive Heart Failure) study of 3,471 patients with heart failure, 1,811 of whom had normal ejection fraction (LVEF > 45%), longer QRS duration was again only associated with worse survival in patients with HeFREF (Shenkman et al., 2002).

In an observational study of 2,913 inpatients and outpatients with heart failure (Singaporean Asian patients from the SHOP cohort and Swedish patients in the SwedeHF Registry), longer QRS increased the composite risk of heart failure hospitalization or death in patients with HeFREF but not HeFNEF (Gijsberts et al., 2016). The difference between this report and the main SwedeHF registry (Lund et al., 2013) may reflect the fact that this study was designed to assess differences between Singaporean and Swedish cohorts. Only the subset of patients from SwedeHF enrolled after 2009 was included (fewer than half of the total cohort), limiting statistical power, and the patients were followed for a much shorter period of time than in the main study.

In another observational study of 1,107 outpatients with HeFNEF followed up in the heart failure clinic for 3.7 years, QRS duration was associated with worse survival in univariable analysis but not when corrected for other variables (increasing log[NT-ProBNP], male sex, higher New York Heart Association class, age and a faster baseline heart rate) (Nikolaidou et al., 2017). A report from the prospective Korean Acute Heart Failure Registry of patient admitted with heart failure showed that increasing QRS duration was not associated with

all-cause mortality and heart failure hospitalization in patients with HeFNEF (Park et al., 2013).

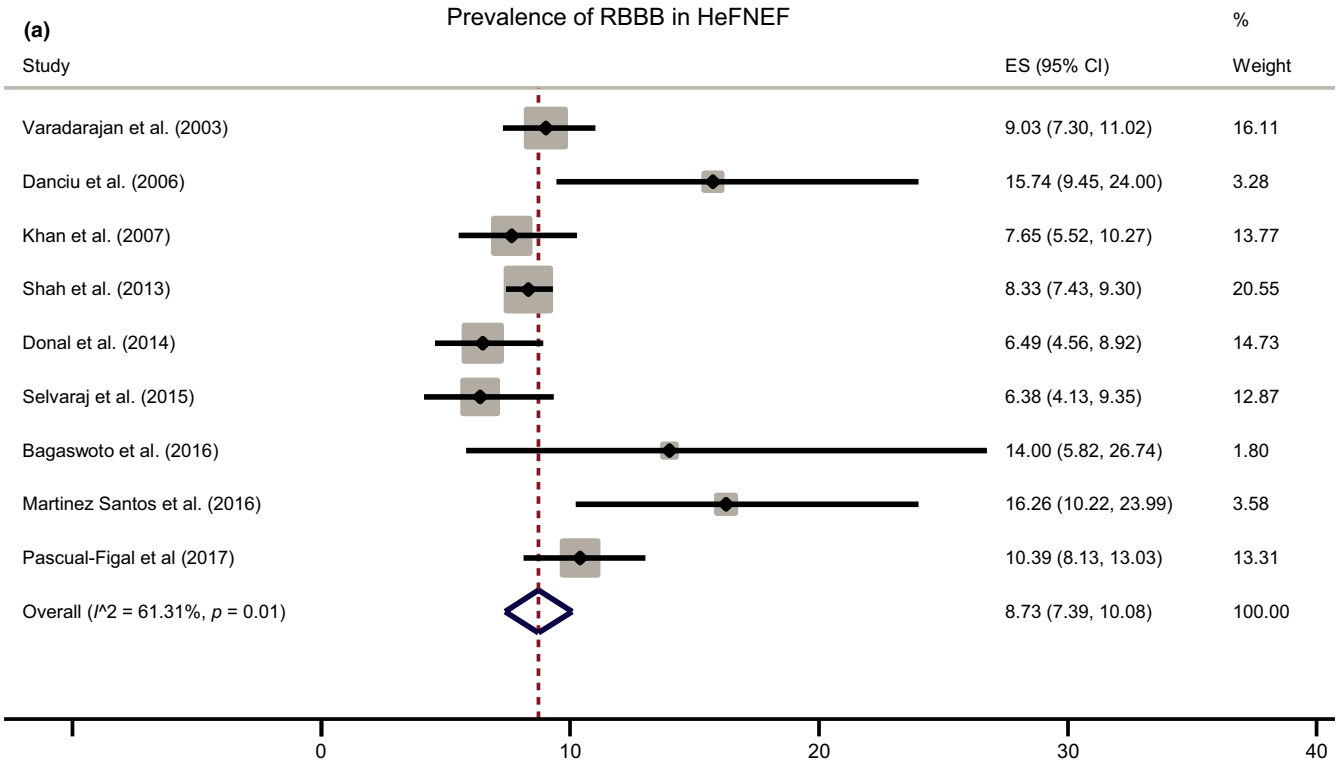
We were able to pool outcome data associated with QRS duration in patients with HeFNEF from five studies (Figure 2b), showing increased risk of death and heart failure admission when QRS ≥ 120 ms.

3.6 | Pathological Q waves

The prevalence of pathological Q waves in patients with HeFNEF was 11%–18% (Hendry et al., 2016; Khan et al., 2007; Shah et al., 2013). In a study of 137 patients with a new diagnosis of heart failure, 15% of those with HeFNEF and 42% of those with HeFREF had evidence of previous myocardial infarction on ECG (history of coronary artery disease was present in 31% and 53%, respectively) (Senni et al., 1998). In a study of 963 patients admitted to hospital with heart failure with LVEF ≥ 55%, 35% had evidence of acute myocardial infarction on ECG (compared with 60% of those with reduced ejection fraction) (Varadarajan & Pai, 2003).

3.7 | Ventricular repolarization

Prolonged ventricular repolarization is associated with ventricular arrhythmias and increased risk of death (Moss, 1986). Ventricular repolarization is measured on ECG by the QT interval (or the JT interval which is independent of QRS duration). Measurement of the QT interval is usually corrected for heart rate (QTc) because faster heart rates shorten the QT interval. The corrected JT interval (JTc) is calculated by subtracting QRS duration from the QTc: a JTc of over 350 ms is pathological.



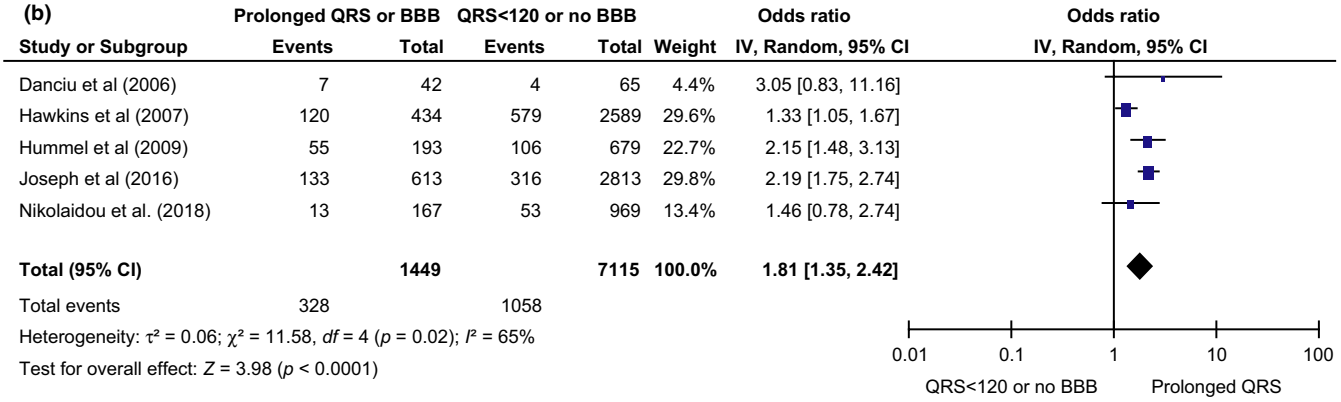


FIGURE 2 A. Prevalence of RBBB in HeFNEF B. The effect of QRS duration ≥120 ms or BBB (whether left or right) on the risk of death or hospitalization for heart failure in patients with HeFNEF

The JTc interval was longer in 1,107 patients with HeFNEF in an outpatients clinic compared to 1,155 patients in the same clinic found not to have heart failure (p = .01). However, abnormal duration of repolarization is uncommon in HeFNEF with 4.3% of patients with HeFNEF having severe JTc interval prolongation (>400 ms) compared to 4.7% of those without heart failure (Nikolaidou et al., 2017). Similarly, the prevalence of JTc > 400 ms among 5,934 patients hospitalized with a suspected diagnosis of heart failure (excluding patients with ventricular pacing) was 3.1% in patients with no echocardiographic abnormality and 2.8% in those with echocardiographic evidence to support a diagnosis of HeFNEF (Khan et al., 2007) In these studies, the prevalence of JTc > 400 ms in patients with HeFREF was 4%–8% (Khan et al., 2007; Nikolaidou et al., 2017).

In an observational study of 376 outpatients with HeFNEF, increasing frontal QRS-T angle was independently associated with higher B-type natriuretic peptide (BNP) level, worse left ventricular diastolic function and worse right ventricular systolic function. Increasing QRS-T angle was also independently associated with an increase in the composite outcome of cardiovascular hospitalization even after adjusting for BNP (Selvaraj et al., 2014).

3.8 | Left ventricular hypertrophy (LVH)

The prevalence of electrocardiographic evidence of LVH in studies of patients with HeFNEF ranges between 10% and 30% (Hendry et al., 2016; Khan et al., 2007; Komajda et al., 2011; Senni et al., 1998; Shah et al., 2013). LVH may be more common in patients with HeFREF (Hendry et al., 2016; Senni et al., 1998). In six studies where information was available (Adabag et al., 2014; Hawkins et al., 2007; Komajda et al., 2011; Olsson et al., 2006; Shah et al., 2013), criteria used to define LVH included the Sokolow-Lyon (Antikainen et al., 2003), Cornell (Casale, Devereux, Alonso, Campo, & Kligfield, 1987), and Estes criteria (Romhilt & Estes, 1968).

3.9 | Multivariable models

A cross-sectional ECG study of 110 inpatients and outpatients with chronic heart failure in sinus rhythm at a single centre (50 with HeFNEF and EF > 40%) identified ECG variables that helped distinguish patients with HeFREF from those with HeFNEF. Those with HeFREF were more likely to have left atrial hypertrophy, QRS duration >100 ms, LBBB, absence of RBBB, ST-T segment changes, and QT interval prolongation. A model including all these variables separated the two conditions with 96% specificity and 76% sensitivity (Hendry et al., 2016).

In 534 participants with new-onset heart failure from the Framingham heart study, those with HeFREF (LVEF ≤ 45%) were less likely to have atrial fibrillation and more likely to have LBBB and a faster heart rate at heart failure onset compared to patients with HeFNEF in multivariable analysis (Lee et al., 2009).

In an analysis of the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE), four ECG variables (heart rate, LVH, LBBB, and atrial fibrillation/flutter) were included among 58 variables in a multivariable model for predicting morbidity and mortality. Only a faster heart rate was an independent predictor of all-cause mortality (Komajda et al., 2011).

A study of 397 patients with HeFNEF previously hospitalized for heart failure used 67 variables (including six ECG variables) and model-based clustering to describe distinct phenotypes among patients with HeFNEF (Shah et al., 2015). Phenogroup 1 included younger patients with fewer symptoms and lower BNP, as well as fewer ECG and echocardiographic abnormalities. Phenogroup 2 had the highest prevalence of obesity, diabetes, and COPD. Phenogroup 3 patients were older with higher BNP and higher prevalence of CKD and with the longest PR, QRS and QTc duration as well as greatest QRS-T angle compared to other groups. Phenogroup classification 1–3 was associated with a step-wise increase in the risk of heart failure hospitalization, cardiovascular hospitalization, or death even after adjusting for BNP.

3.10 | Risk of developing future heart failure

In a study of 6,340 participants from the Framingham Heart Study followed for 10 years, 196 developed HeFNEF and 261 HeFREF. There were 14 predictors of incident heart failure. Higher body mass index, smoking, and atrial fibrillation predicted HeFNEF only, while male sex, higher cholesterol, higher heart rate, hypertension, cardiovascular disease, LVH, and LBBB predicted HeFREF (Ho et al., 2013). The MESA (Multi-Ethnic Study of Atherosclerosis) study followed 6,664 participants free from cardiovascular disease at baseline for a median of 12 years. Higher resting heart rate, abnormal P-wave axis, and abnormal QRS-T axis were independent predictors of future HeFNEF (O'Neal et al., 2017).

4 | DISCUSSION

We have found that atrial fibrillation is more common in patients with HeFNEF compared to those with HeFREF. RBBB is also more common in patients with HeFNEF. In contrast, long PR interval, LVH, Q waves, LBBB, and long JTc are more common in patients with HeFREF. Therefore, a combination of variables, such as the presence of atrial fibrillation and the absence of LBBB, may help differentiate patients with HeFNEF compared to those with HeFREF, when echocardiography is not immediately available or in patients with mid-range left ventricular function.

There is high variability in the prevalence of ECG abnormalities among the included studies. This is likely to reflect different populations with different characteristics. There may well be substantial differences between, for example, inpatient and outpatient cohorts, and differences depending upon disease etiology and severity, and differences depending upon the variable prevalence of comorbidities such as COPD and hypertension. Different diagnostic criteria and analysis methods used for interpretation of ECG variables may be a further source of variability. In addition, electrocardiographic intervals can change over time and with treatment and few studies have reported serial measurements.

Only two studies specifically discussed patients with HeFmrEF (LVEF 40%–49%). The data we have found cannot fully address the subject of ECG changes in HeFmrEF, particularly given the different boundary definitions of LVEF in the studies we found. In one study comparing patients across the three ejection fraction groups, QRS duration as well as the prevalence of atrial fibrillation, and LBBB and RBBB were intermediate between those of patients with HeFNEF and HeFREF in patients with HeFmrEF.

Hypertension is the commonest cause of HeFNEF. LVH is one of the diagnostic criteria for HeFNEF (Ponikowski et al., 2016a) and is associated with worse outcomes (Zile et al., 2011). Electrocardiographic LVH is a strong predictor of diastolic dysfunction and treatment of hypertension results in regression of electrocardiographic LVH (Krepp, Lin, Min, Devereux, & Okin, 2014). In an analysis of the I-PRESERVE trial, LVH was present in 59% of patients with HeFNEF using echocardiographic criteria and 28% using ECG criteria (Zile et al., 2011). The overall prevalence of electrocardiographic LVH in patients with HeFNEF included in this review was 10%–30%.

Right ventricular systolic dysfunction as a consequence of increased pulmonary artery pressure is common in HeFNEF. It is present in at least one-fifth of patients with HeFNEF and is associated with worse prognosis (Gorter et al., 2018; Martinez Santos et al., 2016). Right heart failure is a common mode of death in patients with HeFNEF (Aschauer et al., 2017). 9% of patients with HeFNEF have RBBB and a proportion of these patients may have lung disease and/or right heart failure contributing to their symptoms, consistent with phenogroup 2 features (Shah et al., 2015). The prevalence of COPD/lung disease in the studies included in this review was 12%–40%.

Left atrial enlargement is one of the hallmarks of HeFNEF (Ponikowski et al., 2016a) and is associated with atrial fibrillation and worse outcomes (Zile et al., 2011). Only two studies have reported electrocardiographic P-wave duration in patients with HeFNEF. PR interval duration is prolonged in patients with HeFNEF compared to patients without heart failure, which may at least partly reflect atrial enlargement. In the absence of symptoms, an abnormal P-wave axis is independently associated with future HeFNEF (O'Neal et al., 2017).

Clinical variables known to be associated with worse all-cause mortality in HeFNEF include older age and the presence of renal impairment, lower blood pressure, anemia, history of stroke, or dementia (Nikolaidou et al., 2017; Yap et al., 2015). Our analysis shows that QRS duration ≥ 120 ms is a risk factor associated with worse outcomes in patients with HeFNEF.

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APPENDIX I

Studies excluded	Reason for exclusion
(Tanoue, Kjeldsen, Devereux, & Okin, 2017)	No heart failure symptoms
(van Boven et al., 1998)	No heart failure symptoms
(Ofman et al., 2012)	No heart failure symptoms
((Murkofsky et al., 1998)	No heart failure symptoms
(Okin, Wachtell, Gerdts, Dahlof, & Devereux, 2014)	No heart failure symptoms
(Triola et al., 2005)	No heart failure symptoms
(Onoue et al., 2016)	No heart failure symptoms
(Sauer et al., 2012)	No heart failure symptoms
(Namdar et al., 2013)	No heart failure symptoms
(Basnet, Manandhar, Shrestha, Shrestha, & Thapa, 2009)	No heart failure symptoms
(Nielsen, Hansen, Hilden, Larsen, & Svanegaard, 2000)	No heart failure symptoms
(Okin et al., 2001)	No heart failure symptoms
(Mewton et al., 2016)	No heart failure symptoms, nonrepresentative population
(Wachtell et al., 2007)	No heart failure symptoms
(Wilcox, Rosenberg, Vallakati, Gheorghiade, & Shah, 2011)	No heart failure symptoms
(Sartipy, Dahlstrom, Fu, & Lund, 2017)	No ECG data other than heart rhythm
(West et al., 2011)	No ECG data other than heart rhythm
(Zakeri, Chamberlain, Roger, & Redfield, 2013)	No ECG data other than heart rhythm
(Eapen et al., 2014)	No ECG data other than heart rhythm
(Brouwers et al., 2013)	No ECG data other than heart rhythm
(Perez de Isla et al., 2008)	No ECG data other than heart rhythm
(Martin, 2007)	No ECG data other than heart rhythm
(Gotsman et al., 2008)	No ECG data other than heart rhythm
(Goda et al., 2010)	No ECG data other than heart rhythm
(Zhang, Liebelt, Madan, Shan, & Taub, 2017)	No ECG data other than heart rhythm
(Cleland et al., 2006)	No ECG data other than heart rhythm
(Ahmed et al., 2006)	No ECG data other than heart rhythm
(Yusuf et al., 2003)	No ECG data other than heart rhythm
(Quiroz et al., 2014)	No ECG data other than heart rhythm
(Phan et al., 2010)	No ECG data other than chronotropic incompetence
(Arora et al., 2004)	No ECG data other than chronotropic incompetence
(De Sutter et al., 2005)	Echocardiographic study of ventricular dyssynchrony
(Wang, Kurrelmeyer, Torre-Amione, & Nagueh, 2007)	Echocardiographic study of ventricular dyssynchrony
(Oluleye et al., 2014)	Overlapping analyses of same data
(McMurray et al., 2008)	Overlapping analyses of same data
(Selvaraj et al., 2018)	Overlapping analyses of same data
(Santhanakrishnan et al., 2016)	Overlapping analyses of same data
(Silverman et al., 2016)	Overlapping analyses of same data
(Okin et al., 2007)	No distinction of heart failure subtype
(Mureddu et al., 2012)	No distinction of heart failure subtype
(McCullough et al., 2005)	HeFREF only
(Shamim et al., 1999)	HeFREF only
(Karaye & Sani, 2008)	Nonrepresentative population
(Park et al., 2012)	Nonrepresentative population
(Beladan et al., 2014)	Nonrepresentative population
(Bauer et al., 2009)	Nonrepresentative population

APPENDIX II

	Definition of HF	*N*	Definition of HeFNEF	Exclusion criteria	Kidney disease N (%)	HT N (%)	COPD N (%)	IHD N (%)	Pacemaker/defibrillator N (%)	Diabetes N (%)	BNP median ng/L
Nikolaidou et al (2018)									Excluded		NT-proBNP
	No HF HeFNEF HeFREF	1,155 1,107 1,434	HeFNEF definition: ESC 2016 (Ponikowski et al., 2016) -Symptoms compatible with HF -NT-pro-B ≥ 220 ng/ml for patients in sinus rhythm -LVEF ≥ 45%	-Inability to provide consent -Pregnancy -Atrial fibrillation/flutter -Pacemaker even if not pacing at the time of the ECG recording				246 (22) 479 (44) 944 (66)	5/1193 (0.4) 99/1950 (5) 234/2333 (10)	260 (23) 291 (26) 360 (25)	86 548 1,291
Pascual-Figal et al. (2017)											NT-proBNP
	HeFNEF HeFMEF HeFREF	635 460 2,351	HF diagnosis: -Prior hospitalization for HF -Objective signs of HF confirmed by symptoms, chest X-ray, and/or echocardiography HeFMEF: LVEF 40%–49% HeFNEF: LVEF ≥ 50%	-Acute coronary syndrome -Severe valvular disease -Life-limiting comorbidity		511 (81) 305 (66) 1,414 (60)		165 (26) 256 (56) 1,203 (51)		258 (41) 211 (46) 930 (40)	1,023 936 1557
Hendry et al. (2016)									Excluded		
	HeFNEF HeFREF	50 60	HF diagnosis: ESC 2012 or AHA 2013 (McMurray et al., 2012; Yancy et al., 2013) HeFNEF: LVEF > 40%	-Congenital Heart Disease -Primary valve disease -Acute coronary syndrome -Massive pericardial effusion -Severe pulmonary disease		46 (92) 36 (65)				19 (38) 13 (22)	
Gijsberts et al. (2016)	All HF HeFNEF HeFREF	12,060 2,913 9,147	SHOP cohort Clinical diagnosis of HF based on ESC 2012 guidelines (McMurray et al., 2012) SwedeHF registry HF diagnosis: Clinician-judged HF HeFNEF: LVEF ≥ 50%	SHOP cohort: -Severe valve disease -ACS -End-stage renal failure -Specific subgroups of HF (e.g., constrictive pericarditis, ACHD) -Isolated right HF -Life-limiting comorbidity -Concurrent participation in a clinical trial of new medication			2,157 (18)			3,126 (26)	

(Continues)

APPENDIX II (Continued)

	Definition of HF	*N*	Definition of HeFNEF	Exclusion criteria	Kidney disease N (%)	HT N (%)	COPD N (%)	IHD N (%)	Pacemaker/defibrillator N (%)	Diabetes N (%)	BNP median ng/L
Sanchis et al. (2016)	No HF HeFNEF	32 34	HeFNEF definition: ESC 2007 (Paulus et al., 2007) LVEF > 50%	-Age < 18 years -Life expectancy < 1 year -AF or atrial flutter -Significant valvular disease	8 (24) 13 (41)	21 (62) 30 (94)				6 (18) 7 (22)	37† 120†
Cenkerova et al. (2016)											NT-proBNP
	HeFNEF HeFREF	63 46	HF diagnosis: ESC 2012 (McMurray et al., 2012) HeFNEF: LVEF > 40%	Known advanced malignancy with expected survival < 1 year		57 (91) 34 (74)		43 (68) 32 (70)		26 (41) 16 (35)	3,006 5,467
Yap et al. (2015)											NT-proBNP
	HeFNEF HeFREF	751 1,209	HeFNEF definition: HF with LVEF ≥ 50% and ≥ grade 1 diastolic dysfunction on echo or NT-proBNP > 220 ng/L			603 (80) 838 (69)	107 (14) 139 (12)	308 (41) 588 (49)		354 (47) 666 (55)	5,814 12,323
Menet et al. (2014)									Excluded		
	No HF (HTN) HeFNEF HeFREF (CRT+) HeFREF (QRS < 120)	40 40 40 40	HF definition: Framingham (McKee, Castelli, McNamara, & Kannel, 1971) and physical and radiographic evidence of pulmonary congestion HeFNEF: LVEF ≥ 50%	-History of MI -Atrioventricular or sinoatrial conduction defects -Atrial fibrillation or flutter -Primary valvular disease -Prosthetic heart valve -Restrictive or hypertrophic cardiomyopathy -Constrictive pericarditis -End-stage kidney disease -Nephrotic syndrome -Isolated right HF -Liver cirrhosis -Congenital heart disease -High-output HF		40 (100) 37 (93) 13 (33) 21 (54)	1 (3) 7 (18) 5 (13) 5 (13)	2 (5) 9 (23) 13 (33) 20 (50)		15 (38) 24 (60) 11 (28) 14 (36)	54 471 959 722
Lund et al. (2013)							Lung disease		Excluded		
	All HF HeFNEF HeFMEF HeFREF	25,171 6,193 5,601 13,377	Clinician judged HF HeFMEF: LVEF 40%–49% HeFNEF: LVEF ≥ 50%		16,017 (64)	11,595 (46)	4,568 (18)	11,891 (47)	5,150/37,974	6,070 (24)	

(Continues)

APPENDIX II (Continued)

	Definition of HF	*N*	Definition of HeFNEF	Exclusion criteria	Kidney disease N (%)	HT N (%)	COPD N (%)	IHD N (%)	Pacemaker/defibrillator N (%)	Diabetes N (%)	BNP median ng/L
Park et al. (2013)									Excluded		
	HeFNEF	523	Framingham (McKee et al., 1971)	-Paced rhythm		272 (52)		78 (15)		155 (30)	
	HeFREF	966		-Patients lost to follow-up		425 (44)		223 (23)		334 (35)	
				-Unavailable data							
Eicher et al. (2012)											NT-proBNP
	No HF	27	HF diagnosis:	-Significant valve disease		20 (74)				5 (19)	523
	HeFNEF	29	ESC guidelines 2007 (Paulus et al., 2007)	-Hypertrophic/restrictive cardiomyopathy		24 (83)				9 (31)	4,653
			HeFNEF: LVEF > 50%	-Not in sinus rhythm							
Khan et al. (2007)							Lung disease				
	All	5,935	Included in the study:		1,069 (18)	3,211 (54)	1731 (29)	3,821 (64)	636 (11)	1601 (27)	
	No echo abnormality	523	-A clinical diagnosis of heart failure recorded during admission								
	LVDD	109									
	Mild LVSD	667	-A diagnosis of HF at any time in the last 3 years								
	Mod/severe LVSD	735									
			-Loop diuretic for any reason other than renal failure during the 24 hr prior to death or discharge								
			-Treatment for HF within 24 hr of death or discharge								
			HeFNEF: LVEF ≥ 50%								
Hawkins et al. (2007) and Olsson et al. (2006)								Angina			
	HeFNEF	3,023	Symptomatic HF NYHA II-IV for at least 4 weeks	-Serum creatinine ≥ 3 mg/dl	52 (2)	1943 (64)		1817 (60)	244 (8)	857 (28)	
	HeFREF	4,576		-Serum potassium ≥ 5.5 mmol/l	101 (2)	2,243 (49)		2,535 (55)	584 (13)	1,306 (29)	
			HeFNEF: LVEF > 40%	-Symptomatic hypotension							
				-Bilateral renal artery stenosis							
				-Critical aortic or mitral stenosis, MI, stroke, or open-heart surgery in the previous 4 weeks							
				-Use of an ARB in last 2 weeks							
				-Life-limiting comorbidity							

(Continues)

APPENDIX II (Continued)

	Definition of HF	*N*	Definition of HeFNEF	Exclusion criteria	Kidney disease N (%)	HT N (%)	COPD N (%)	IHD N (%)	Pacemaker/defibrillator N (%)	Diabetes N (%)	BNP median ng/L
Danciu et al. (2006)†	HeFNEF HeFREF	108 109	HF definition: ICD−9 discharge diagnosis of HF HeFNEF: LVEF ≥ 40%	-Implantable devices	69 (64) 64 (59)	90 (83) 87 (80)		63 (58) 83 (76)		59 (55) 52 (48)	
Peyster et al. (2004)							Restrictive/ COPD				
	HeFNEF HeFREF	59 78	Framingham (McKee et al., 1971) HeFNEF: LVEF ≥ 50%		32 (33) 71 (47)	95 (98) 120 (80)	COPD 30 (31) 35 (23)	36 (37) 122 (81)	9 (9) 27 (18)	54 (56) 80 (53)	
Varadarajan and Pai (2003)								MI			
	HeFNEF HeFREF	963 1,295	Framingham (McKee et al., 1971) HeFNEF: LVEF ≥ 55%		10 (1) 13 (1)	260 (27) 350 (27)	39 (4) 117 (9)	10 (1) 39 (3)		39 (4) 155 (12)	
Masoudi et al. (2003)	HeFNEF HeFREF	6,754 12,956	HF definition: Patients hospitalized with a diagnosis of HF and prior history of HF or evidence of HF on admission chest X-ray HeFNEF: LVEF ≥ 50%	-Chronic renal failure on hemodialysis -Patient transferred to another facility or self-discharged	2,431 (36) 6,089 (47)	4,660 (69) 7,903 (61)	2,296 (34) 4,016 (31)	3,107 (46) 8,421 (65)		2,499 (37) 5,182 (40)	
Shenkman et al. (2002)	All HF HeFNEF HeFREF	3,471 1811 1,660	HF definition: A minimum of two outpatient ICD−9-CM codes for HF or one inpatient hospitalization under diagnosis-related group 127 or 124 and one of the above codes HeFNEF: LVEF ≥ 50%								
Senni et al. (1998)	HeFNEF HeFREF	59 78	HF definition: Modified Framingham criteria (McKee et al., 1971) HeFNEF: LVEF ≥ 50%		22 (37) 40 (51)	34 (58) 39 (50)	9 (15) 11 (14)	18 (31) 41 (53)			
Gigliotti et al. (2017)											NT-proBNP
	HeFNEF SR AF	57 25	HF definition: Framingham (McKee et al., 1971) HeFNEF: LVEF ≥ 50%	-Paced rhythm -Atrial flutter -Severe valvular disease		46 (81) 18 (72)		31 (54) 16 (64)		32 (56) 11(44)	4,951* 6,019*

(Continues)

APPENDIX II (Continued)

	Definition of HF	*N*	Definition of HeFNEF	Exclusion criteria	Kidney disease N (%)	HT N (%)	COPD N (%)	IHD N (%)	Pacemaker/defibrillator N (%)	Diabetes N (%)	BNP median ng/L
Oskouie et al. (2017)									Paced ventricular rhythm		
	HeFNEF	201	HeFNEF definition: All patients met the Framingham (McKee et al., 1971) and ESC (McMurray et al., 2012) criteria for HF LVEF > 50%	-Atrial fibrillation/flutter -Ventricular pacing -T-wave abnormality -TpTe amplitude < 1.5 mV -Heart block -ECGs not accessible	66/201 (33)	155/201 (77)		89/201 (44)	21/397 (5)	65/201 (32)	192
Martinez Santos et al. (2016)	HeFNEF	123	HF definition: Framingham (McKee et al., 1971) All patients also met the ESC HeFNEF criteria.(McMurray et al., 2012; Paulus et al., 2007) HeFNEF: LVEF ≥ 50%	-Advanced renal disease -High-output failure -Congenital heart disease -Mitral or aortic prosthesis -Severe left valvular disease -RBBB			46 (37)				
Shah et al. (2015)	Group 1 Group 2 Group 3		HF definition: Framingham (McKee et al., 1971) HeFNEF: LVEF > 50% -BNP > 100 ng/L -Evidence of diastolic dysfunction on echocardiography or -Raised LV filling pressures		8 (6) 41 (34) 79 (53)	84 (66) 108 (90) 112 (75)	43 (34) 46 (38) 56 (38)	54 (42) 58 (48) 75 (50)		12 (9) 63 (52) 50 (34)	72 188 607
Donal et al. (2014)									Paced ventricular rhythm		
	HeFNEF at admission HeFNEF after 4–8 weeks treatment	539 438	HeFNEF definition: Framingham (McKee et al., 1971) -Signs and symptoms of HF -BNP > 100 ng/L or NT-proBNP > 300 ng/L -LVEF ≥ 45% Verified within 72 hr of presentation	-Evidence of primary hypertrophic or restrictive cardiomyopathy -Systemic illness known to be associated with infiltrative heart disease -Known cause of right heart failure not related to LVSD -Pericardial constriction	146 (27)	419 (78)	73 (14)	158 (29)	35 (7)	161 (30)	BNP 429 NT-proBNP 2,448 BNP 277 NT-proBNP 1,409

(Continues)

APPENDIX II (Continued)

	Definition of HF	*N*	Definition of HeFNEF	Exclusion criteria	Kidney disease N (%)	HT N (%)	COPD N (%)	IHD N (%)	Pacemaker/defibrillator N (%)	Diabetes N (%)	BNP median ng/L
Adabag et al. (2014) and Komajda et al. (2011) and Zile et al. (2011)	HeFNEF (alive at follow-up) HeFNEF (non-SCD) HeFNEF (SCD)	3,247 650 231	HF definition: -HF symptoms -Hospitalization for HF during the previous 6 months and NYHA class II, III, or IV symptoms with corroborative evidence If not hospitalized, ongoing class III or IV symptoms with corroborative evidence HeFNEF: LVEF ≥ 45%	-≤60 years of age -Intolerance to ARB -Previous LVEF < 40% -ACS, coronary revascularization, or stroke within the previous 3 months -Significant valvular disease -Hypertrophic or restrictive cardiomyopathy -Pericardial disease - Isolated right HF -Systolic BP < 100 mm Hg or > 160 mm Hg or a diastolic BP > 95 mm Hg despite HT therapy -Life-limiting comorbidity -Laboratory abnormalities	877 (27) 306 (47) 81 (35)	2,889 (89) 553 (85) 201 (87)	260 (8) 85 (13) 37 (16)	1624 (50) 358 (55) 146 (63)		NT-ProBNP 812 (25) 228 (35) 88 (38)	647 1733 1722
Selvaraj et al. (2014)	HeFNEF (QRS-T 0–26°) HeFNEF (QRS-T 27–75°) HeFNEF (QRS-T 76–179°)	124 125 127	HF definition: Framingham (McKee et al., 1971) Identified from inpatient records: -Diagnosis of HF or the term HF in the hospital notes - BNP > 100 pg/ml or -Two or more doses of intravenous diuretic administered HeFNEF definition: LVEF > 50% and LV end-diastolic volume index <97 ml/m^2 (Paulus et al., 2007)	-Significant valvular disease -Prior cardiac transplantation, -History of overt LV systolic dysfunction (LVEF < 40%) -Constrictive pericarditis. -Ventricular paced rhythm	47 (38) 74 (59) 73 (57)	COPD/asthma 92 (74) 100 (80) 99 (78)	50 (40) 47 (38) 46 (36)	40 (32) 37 (30) 54 (43)		32 (26) 46 (37) 51 (40)	123 222 379

(Continues)

APPENDIX II (Continued)

	Definition of HF	*N*	Definition of HeFNEF	Exclusion criteria	Kidney disease N (%)	HT N (%)	COPD N (%)	IHD N (%)	Pacemaker/defibrillator N (%)	Diabetes N (%)	BNP median ng/L
Shah et al. (2013)	HeFNEF	3,445	HeFNEF definition: -At least one HF symptom at the time of study screening and at least one HF sign within the 12 months prior to screening. -At least 1 HF hospitalization in the 12 months prior to study screening or BNP > 100 pg/ml or NT-proBNP > 360 pg/ml within the 60 days prior to screening -Controlled systolic BP -Serum potassium < 5.0 mmol/L -LVEF ≥ 45%	-Life-limiting comorbidity -Chronic pulmonary disease -Infiltrative or hypertrophic cardiomyopathy -Constrictive pericarditis -Cardiac transplant or LVAD -Chronic hepatic disease -CKD -Significant hyperkalemia -Intolerance to aldosterone antagonist -Recent MI, CABG, or PCI	1,332 (39)	3,147 (91)	403 (12)	2023 (59)	269 (8)	1,114 (32)	BNP 234 NT-proBNP 950
Hummel et al. (2009)	HeFNEF (overall) HeFNEF (QRS < 120) HeFNEF (QRS ≥ 120)	872 679 193	No definition of HF. HeFNEF: LVEF ≥ 50%	-Patients without numerical assessment of LVEF -Pacemaker or defibrillator -Moderate/severe valve disease -Documented ventricular tachycardia, cardiac arrest, or death during hospitalization		733 (84) 570 (84) 158 (82)		497 (57) 367 (54) 124 (64)	Excluded 17/963		
O'Neal et al. (2017)						On HT medication					
	No HF Developed HeFREF Developed HeFNEF	6,420 127 117	HF definition: Composite of probable and definite HF events Probable: -Symptoms of HF -Previous physician diagnosis Definite: -Evidence of structural defect HeFNEF: LVEF ≥ 50%	-Prevalent cardiovascular disease -Missing ECG data or baseline characteristics -Missing HF follow-up data		2,329 (36) 76 (60) 65 (56)				866 (13) 39 (31) 36 (31)	

(Continues)

APPENDIX II (Continued)

	Definition of HF	*N*	Definition of HeFNEF	Exclusion criteria	Kidney disease N (%)	HT N (%)	COPD N (%)	IHD N (%)	Pacemaker/defibrillator N (%)	Diabetes N (%)	BNP median ng/L
Ho et al. (2013)	No HF HeFNEF HeFREF	5,828 196 261	Framingham (McKee et al., 1971) Inclusion criteria: HF hospitalization with an evaluation of LVEF HeFNEF: LVEF > 45%			152 (78) 209 (80)		44 (22) 88 (34)		47 (24) 77 (30)	
Lee et al. (2009)						On HT medication					
	HeFNEF HeFREF	220 314	Framingham (McKee et al., 1971) Inclusion criteria: HF hospitalization with an evaluation of LVEF near the time of hospitalization HeFNEF: LVEF > 45%			130 (59) 177(56)				49 (22) 86 (27)	

Abbreviations: ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; CHD, congenital heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HeFNEF, heart failure with normal ejection fraction; HF, heart failure; HT, hypertension; HT, hypertension; ICD-9, international classification of diseases, ninth revision; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RV, right ventricular; SR, sinus rhythm.