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 a 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 I² 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, Kristinart, & 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
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
| Study type | Population | Type of HF | N   | Age (mean, years) | Men (%) | EF (%) | LA diameter (mm) | AF/flutter on ECG (%) | P wave (ms) | PR (ms) | QRS (ms) | LBBB N (%) | RBBB N (%) | QT (ms) | LVH N (%) | ST/T changes | Other |
|------------|------------|------------|-----|------------------|---------|--------|------------------|-----------------------|-------------|---------|---------|------------|------------|---------|-----------|---------------|-------|
| **HFrEF and HFrEF** | | | | | | | | | | | | | | | |
| Nikolaidou et al (2018)† | Prospective study | Consecutive patients referred to a community HF clinic with suspected HF 2001-14 | No HF | 1,155 | 68' | 51 | 59 | Excluded | PRc | QTc | 6/1193 (0.1) | 163 | 90 | 112 | 418 |
| | | | | | | | | | | | | | | | | |
| Pascual-Figal et al. (2017) | Prospective study | Ambulatory patients with chronic HF from 2 national registries 2003-04, 2007-11 | HeFNEF | 635 | 72 | 43 | 25 | 221 (35) | 108 | 47 (7) | 55 (9) |
| | | | | | | | | | | | | | | | | |
| Hendry et al. (2016) | Cross-sectional study | In- and outpatients with chronic HF at one centre 2015 | HeFNEF | 50 | 60 | 56 | 59 | 34 | N/A | 97 | 124 | 3 (5) | 45 (3) | 33 (55) | 17 (28) |
| | | | | | | | | | | | | | | | | |
| Gijsberts et al. (2016)** | Observational study | Patients with HF (in- or outpatient), 839 SHOP cohort and 11,221 SweDEHF 2010-14 | All HF | 12,060 | 73 | 63 | 5,807 (48) | 103 | 95 | 1834 (15) |
| | | | | | | | | | | | | | | | | |
| Sanchis et al (2016) | Prospective study | Consecutive patients with new-onset HF, referred to a clinic 2009-12 | No HF | 32 | 73 | 23 | 61 | 17 | Excluded | 74 | 158 | 97 |
| | | | | | | | | | | | | | | | | |
| Cenkerova et al. (2014) | Prospective study | Consecutive patients with HF admitted to one centre 2010-11 | HeFNEF | 63 | 74 | 54 | 59 | 50 | 29 (46) | 160 | 80 | 435 |
| | | | | | | | | | | | | | | | | |
| Yap et al. (2015)† | Prospective study | Consecutive patients admitted with HF to any public hospital in Singapore 2008-09 | HeFNEF | 751 | 73 | 35 | 255 (34) | 94 |
| | | | | | | | | | | | | | | | | |
| Menet et al. (2014) | Cohort study | Patients hospitalized for HF | No HF-HT | 40 | 68 | 23 | 23 | 23 | 91 | 2 (5) |
| | | | | | | | | | | | | | | | | |

(Continues)
| Study type | Population | Type of HF | N | Age (mean, years) | Men (%) | EF (%) | LA diameter (mm) | AF/flutter on ECG (%) | P wave (ms) | PR (ms) | QRS (ms) | QT (ms) | LVH N (%) | ST/T changes N (%) | Other |
|------------|------------|------------|---|------------------|--------|--------|------------------|------------------------|-------------|---------|----------|---------|-----------|---------------------|-------|
| Lund et al. (2013)† | Prospective study | SwedeHF registry (online registry of in- and outpatients with HF) | 25,171 | 75 | 60 | 1,452 (46) | 11,452 | 4,028 (16) | 7,803 (31) | 2,145 (25) | 1,151 (18) | 5,217 (39) |
| Park et al. (2013)† | Prospective registry | Korean Acute Heart Failure Registry 2004-09 (patients admitted to 24 hospitals with HF) | 523 | 70 | 39 | 180 (34) | 213 (22) | 67 (13) | 232 (24) |
| Eicher et al. (2012) | Cross-sectional study | Consecutive patients admitted for HF (3 months). Controls: CAD or mild valve disease | 27 | 80 | 52 | 37 | 5 (19) | 20 (69) | 126 |
| Khan et al. (2007) | Retrospective study | EuroHeart Failure Survey of inpatients with HF in 24 European countries over a period of 6 weeks 2001-02 | 523 | 109 | 66 | 143 (20) | 103 (20) | 3,016 (15) | 6,70 (13) |
| Hawkins et al. (2007)† and Olsson et al. (2006)† | Retrospective study | Patients with HF from the CHARM program F/U: 38 months | 108 | 72 | 39 | 30 (28) | 13 (12) | 13 (12) | 25 (23) | 1 (1) | 44 (1) | 1,777 (30) |
| Danciu et al. (2006)† | Retrospective study | Patients hospitalized with decompensated HF | 97 | 78 | 25 | 22 (23) | 39 (26) | 59 (61) | 52 (35) |
| Peyster et al. (2004) | Retrospective study | Consecutive patients aged ≥ 65 with discharge diagnosis of HF | 150 | 76 | 49 | 38 (25) | 59 (61) | 52 (35) |
| Varadarajan and Pai (2003)† | Retrospective study | Patients with HF discharge diagnosis and echo 1990-99 F/U: 786 days | 963 | 70 | 62 | 193 (20) | 19 (2) | 366 (38) | 777 (60) |
| Masoudi et al. (2003) | Retrospective study | Medicaid beneficiaries aged ≥ 65 hospitalized for HF 1998-99 | 6,754 | 80 | 29 | 2,431 (36) | 540 (8) | 3,109 (24) | (Continues) |
| Study type                        | Population | Study type | Type of HF | N   | Age (mean, years) | Men (%) | EF (%) | LA diameter (mm) | AF/flutter on ECG N (%) | P wave (ms) | PR (ms) | QRS (ms) | QT (ms) | LVH N (%) | ST/T changes N (%) | Other |
|----------------------------------|------------|------------|------------|-----|------------------|---------|--------|------------------|------------------------|-------------|---------|----------|---------|------------|---------------------|-------|
| Sherkman et al. (2002)†          | Patients from the REACH study 1989–99 F/U 32 months | Retrospective study | All HF     | 3,471 | 66                | 50      |         | 1.660            |                         |             |         | 120       |         |           |                      |       |
|                                   | HeFNEF     |            | HeFREF    | 1,811 |                   |         |         |                  | 721 (21)                |             |         | 230 (13) |         |           |                      |       |
| Sullivan et al. (1993)           | HeFNEF     |            | HeFREF    | 354   | 55                | 20      |         | 36.5 (7.4)        | 16 (18)                |             |         | 3 (1.5)  |         |           |                      |       |
|                                   | HeFNEF     |            | HeFREF    | 354   | 55                | 20      |         | 36.5 (7.4)        | 16 (18)                |             |         | 3 (1.5)  |         |           |                      |       |
| Senni et al. (1998)              | Patients receiving a first diagnosis of HF and echo in 1991 in Olmsted County | Retrospective study | HeFNEF | 3,471 | 66                | 50      |         | 1.660            |                         |             |         | 120       |         |           |                      |       |
|                                   | HeFREF     |            |          | 1,660 |                   |         |         |                  |                         |             |         | 230 (13) |         |           |                      |       |
| HeFNEF only                       |            |            |          |       |                   |         |         |                  |                         |             |         | 230 (13) |         |           |                      |       |
| Gigliotti et al. (2017)†         | Patients discharged with a HF diagnosis from one centre and echo 2006–09 | Retrospective study | HeFNEF | 3,471 | 66                | 50      |         | 1.660            |                         |             |         | 120       |         |           |                      |       |
|                                   | HeFREF     |            |          | 1,660 |                   |         |         |                  |                         |             |         | 230 (13) |         |           |                      |       |
| Oskouie et al. (2017)            | Consecutive patients following hospitalization with HeFNEF in a centre 2008–11 | Prospective study | HeFNEF | 201   | 64                | 23      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
|                                   |            |            |          |       |                   |         |         |                  |                         |             |         | 120       |         |           |                      |       |
| Martinez Santos et al. (2016)    | Consecutive patients admitted with HeFNEF in a centre 2011–12 | Prospective study | HeFNEF | 123   | 81                | 37      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
|                                   |            |            |          |       |                   |         |         |                  |                         |             |         | 120       |         |           |                      |       |
| Shah et al. (2015)†              | Consecutive patients from outpatient clinic following hospitalization for HF 2008–11 | Prospective study | Phenotypic Group 1 | 128   | 61                | 33      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
|                                   | Group 2     |            |          | 120   | 66                | 32      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
|                                   | Group 3     |            |          | 149   | 67                | 45      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
| Donal et al. (2014)              | Consecutive patients with HF in the ED in 10 French and 3 Swedish centres 2007–11 | Prospective study | HeFNEF | 539   | 77                | 44      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
|                                   | HeFNEF at admission |            |          | 438   | 77                | 44      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
|                                   | HeFNEF after 4–8 weeks treatment |            |          |       |                   |         |         |                  |                         |             |         | 120       |         |           |                      |       |
| Adabag et al. (2016) and Komádka et al. (2011) and Zile et al. (2011)† | I-PRESENTE study on the effect of Telrapirin in patients with HeFNEF F/U: 4.1 years | RCT      | HeFNEF (alive at follow-up) | 3,247 | 71                | 37      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
|                                   | HeFNEF (non-SCD) |            |          | 650   | 75                | 47      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |
|                                   | HeFNEF (SCD) |            |          | 231   | 74                | 55      |         | 120 (4)          |                         |             |         | 120       |         |           |                      |       |

TABLE 1 (Continued)
| Study type | Population | F/U (years) | Type of HF | 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 | Patients with HF identified from inpatient records, reviewed in the outpatient clinic 2008–11 | HeFNEF QRST 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) 450 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 | Patients with HeFNEF enrolled in the TOPCAT trial in six countries 2006–12 | HeFNEF | 3,445 | 69 48 57 | 28% ECG | 100 204 (8) 287 | 18% 11% 29% | QTc 35% | QTc 120 | Q wave | 399 |
| Hummel et al. (2009)‡ | Retrospective study | Patients admitted to eight Michigan hospitals in two 6-month periods 2002–04 | HeFNEF all (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 |
| O’Neal et al. (2017) | Cohort study | MESA population, no cardiovascular disease at baseline from six field centres 2000–02 | No HF Developed HeFNEF | 6,420 127 117 | 62 67 70 | 47 72 50 | No HF Developed HeFNEF | 699 (11) 27 (21) 21 (18) | 419 (8) 56 (44) 34 (29) | 12.39 (19) 19 (15) 15 (13) | 16 (1) 5 (3.9) 1 (1) | 145 6 (4.7) 7 (5.9) 35 (18) | 481 (7.5) 28 (22) 6 (5.1) | 236 12 9 (1.5) | 852 (13) 8 (5.1) 18 (15) |
| Ho et al. (2013)† | Cohort study | Characteristics at baseline FHS participants with HF hospitalization 1980–2008 | No HF HeFNEF | 5,828 196 261 | 60 74 72 | 45 39 64 | No HF HeFNEF | 22 (11) 24 (10) | 9 (5) 10 (4) | 14 (7) 15 (5) 15 (5) | 35 (18) 69 (26) | 14 (7) 69 (26) | 35 (18) 69 (26) | 35 (18) 69 (26) |
| Lee et al. (2009)‡ | Cohort study | Characteristics at HF onset FHS participants with HF occurring 1981–2004 | HeFNEF HeFREF | 178 270 | 79 77 | 36 60 | HeFNEF HeFREF | 61 (34) 53 (2) | 103 112 | 13 (7) 54 (20) | 22 (12) 24 (9) | 22 (12) 24 (9) | 22 (12) 24 (9) | 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
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 HeFREF (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 (Shenkan 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 (Gijbbers 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](image-url) 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 greater 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 (Nikolaaidou 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, non-representative 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 |

(Continues)
## 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) | | | | | | | | | | |
| No HF | 1,155 | HeFNEF definition: ESC 2016 (Ponikowski et al., 2016) | -Inability to provide consent | 246 (22) | 5/1193 (0.4) | Excluded | 260 (23) | 548 |
| HeFNEF | 1,107 | -Symptoms compatible with HF | -Pregnancy | 479 (44) | 99/1950 (5) | | 291 (26) | |
| HeFREF | 1,434 | -NT-pro-B ≥ 220 ng/ml for patients in sinus rhythm | -Atrial fibrillation/flutter | 944 (66) | 234/2333 (10) | | 360 (25) | |
| | | -LVEF ≥ 45% | -Pacemaker even if not pacing at the time of the ECG recording | | | | | |
| Pascual-Figal et al. (2017) | | | | | | | | | |
| HeFNEF | 635 | HF diagnosis: | -Acute coronary syndrome | 511 (81) | 165 (26) | NT-proBNP | 258 (41) | 1,023 |
| HeFMEF | 460 | -Prior hospitalization for HF | -Severe valvular disease | 305 (66) | 256 (56) | | 211 (46) | 936 |
| HeFREF | 2,351 | -Objective signs of HF confirmed by symptoms, chest X-ray, and/or echocardiography | -Life-limiting comorbidity | 1,414 (60) | 1,203 (51) | | 930 (40) | 1557 |
| Hendry et al. (2016) | | | | | | | | | |
| HeFNEF | 50 | HF diagnosis: ESC 2012 or AHA 2013 (McMurray et al., 2012; Yancy et al., 2013) | -Congenital Heart Disease | 46 (92) | Excluded | | 19 (38) | |
| HeFREF | 60 | HeFNEF: LVEF > 40% | -Primary valve disease | 36 (65) | | | 13 (22) | |
| Gijsberts et al. (2016) | | | | | | | | | |
| All HF | 12,060 | SHOP cohort Clinical diagnosis of HF based on ESC 2012 guidelines (McMurray et al., 2012) | SHOP cohort: | 2,157 (18) | 3,126 (26) | |
| HeFNEF | 2,913 | SwedeHF registry HF diagnosis: Clinician-judged HF | -Severe valve disease | | | | |
| HeFREF | 9,147 | HeFNEF: LVEF ≥ 50% | -ACS | | | | |

(Continues)
## APPENDIX II (Continued)

| Study                        | Type of HF | N   | Definition of HF | Definition of HeFNEF | Exclusion criteria | Kidney disease | COPD N (%) | IHD N (%) | Pacemaker/defibrillator N (%) | Diabetes N (%) | BNP median ng/L |
|------------------------------|------------|-----|-----------------|----------------------|--------------------|----------------|-------------|-----------|-------------------------------|----------------|-----------------|
| Sanchis et al. (2016)        | No HF      | 32  |                 | HeFNEF definition: ESC 2007 (Paulus et al., 2007) LVEF > 50% | - Age < 18 years | 8 (24) | 21 (62) | 30 (94) | 6 (18) | 7 (22) | 120† |
|                              | HeFNEF     | 34  |                 |                      | - Life expectancy < 1 year |                 |             |           |                               |                |                 |
|                              |            |     |                 |                      | - AF or atrial flutter  |                 |             |           |                               |                |                 |
|                              |            |     |                 |                      | - Significant valvular disease |                 |             |           |                               |                |                 |
| Cenkerova et al. (2016)      | HeFNEF     | 63  | HeFNEF definition: ESC 2012 |                      | Known advanced malignancy with expected survival < 1 year | 57 (91) | 43 (68) | 32 (70) | 26 (41) | 16 (35) | 5,467 |
|                              | HeFREF     | 46  |                 |                      | NT-proBNP          |                |             |           |                               |                |                 |
| Yap et al. (2015)            | HeFNEF     | 751 | HeFNEF definition: |                      |                      | 603 (80) | 107 (14) | 308 (41) | 354 (47) | 5,814 |
|                              | HeFREF     | 1,209 |                   |                      |                      | 838 (69) | 139 (12) | 588 (49) | 666 (55) | 12,323 |
| Menet et al. (2014)          | No HF (HTN)| 40  | HF definition:  | Framingham (McKee, Castelli, McNamara, & Kannel, 1971) and physical and radiographic evidence of pulmonary congestion | - History of MI | 40 (100) | 1 (3) | 2 (5) | 15 (38) | 54 |
|                              | HeFNEF     | 40  |                 |                      | - Atrioventricular |                |             |           |                               |                |                 |
|                              | HeFREF     | 40  |                 |                      | or sinoatrial conduction defects |                |             |           |                               |                |                 |
|                              | HeFREF (CRT+) | 40 |                 |                      | - Atrial fibrillation or flutter |                |             |           |                               |                |                 |
|                              | HeFREF (QRS < 120) | 40 |                 |                      | - Primary valvular disease |                |             |           |                               |                |                 |
|                              |            |     |                 |                      | - Prosthetic heart valve |                |             |           |                               |                |                 |
|                              |            |     |                 |                      | - Restrictive or hypertrophic cardiomyopathy |                |             |           |                               |                |                 |
|                              |            |     |                 |                      | - Constrictive pericarditis |                |             |           |                               |                |                 |
|                              |            |     |                 |                      | - Heart failure secondary to chronic kidney disease |                |             |           |                               |                |                 |
|                              |            |     |                 |                      | - High-output HF |                |             |           |                               |                |                 |
| Lund et al. (2013)           | All HF     | 25,171 | Clinician judged HF |                      | Excluded | 16.017 (64) | 11,595 (46) | 4,568 (18) | 11,891 (47) | 5,150/37,974 | 6,070 (24) |
|                              | HeFNEF     | 6,193 | HeFNEF: LVEF 40%–49% |                      |                      |                |             |           |                               |                |                 |
|                              | HeFREF     | 13,377 | HeFNEF: LVEF ≥ 50% |                      |                      |                |             |           |                               |                |                 |
|                              | HeFMEF     | 5,601 |                      |                      |                      |                |             |           |                               |                |                 |

(Continues)
### APPENDIX II (Continued)

| Study                          | 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)**        |       | Framingham (McKee et al., 1971)                                                   | - Paced rhythm                                                                   | 272 (52)             | 78 (15)  | 223 (23)  |           |                               | 155 (30)       |                 |
| HeFNEF                        | 523   |                                                                                    |                                                                                    |                      |          |            |           |                               |                 |                 |
| HeFREF                        | 966   |                                                                                    |                                                                                    |                      |          |            |           |                               |                 |                 |
| **Eicher et al. (2012)**      |       | HF diagnosis: ESC guidelines 2007 (Paulus et al., 2007)                              | - Significant valve disease                                                      | 20 (74)              |          |            |           |                               | 5 (19)         |                 |
| No HF                         | 27    |                                                                                    |                                                                                    |                      |          |            |           |                               |                 |                 |
| HeFNEF                        | 29    |                                                                                    |                                                                                    | 24 (83)              |          |            |           |                               | 9 (31)         |                 |
| **Khan et al. (2007)**        |       | Included in the study:                                                             | A clinical diagnosis of heart failure recorded during admission                  | 1,069 (18)           | 3,211 (54)| 1,731 (29) | 3,821 (64) | 636 (11)                      | 1,601 (27)     |                 |
| All                           | 5,935 | - A diagnosis of HF at any time in the last 3 years                                 | - Loop diuretic for any reason other than renal failure during the 24 hr prior to death or discharge |                      |          |            |           |                               |                 |                 |
| No echo abnormality           | 523   | - Treatment for HF within 24 hr of death or discharge                               |                                                                                    |                      |          |            |           |                               |                 |                 |
| LVDD                          | 109   |                                                                                    |                                                                                    |                      |          |            |           |                               |                 |                 |
| Mild LVSD                     | 667   |                                                                                    |                                                                                    |                      |          |            |           |                               |                 |                 |
| Mod/severe LVSD               | 735   |                                                                                    |                                                                                    |                      |          |            |           |                               |                 |                 |
| **Hawkins et al. (2007) and Olsson et al. (2006)** |       | Symptomatic HF NYHA II-IV for at least 4 weeks                                    | - Serum creatinine ≥ 3 mg/dl                                                     | 52 (2)              | 1,943 (64)|           |           |                               | 1817 (60)   |                 |
| HeFNEF                        | 3,023 |                                                                                    | - Serum potassium ≥ 5.5 mmol/l                                                   | 101 (2)             | 2,243 (49)|           |           |                               | 244 (8)      |                 |
| HeFREF                        | 4,576 |                                                                                    | - Symptomatic hypotension                                                        |                      |          |            |           |                               | 584 (13)     |                 |
|                               |       |                                                                                    | - Bilateral renal artery stenosis                                                |                      |          |            |           |                               | 2,535 (55)   |                 |
|                               |       |                                                                                    | - 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                                                       |                      |          |            |           |                               |                 |                 |
## 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 108 | HF definition: ICD-9 discharge diagnosis of HF HeFNEF: LVEF ≥ 40% | -Implantable devices | 69 (64) | 90 (83) | | 63 (58) | 59 (55) | 52 (48) |
|                  | HeFREF 109 |                    |                    | 64 (59) | 87 (80) | | 83 (76) | | |
| Peyster et al. (2004) | HeFNEF 59 | | Framingham (McKee et al., 1971) HeFNEF: LVEF ≥ 50% | 32 (33) | 95 (98) | COPD | 36 (37) | 54 (56) | 80 (53) |
|                  | HeFREF 78 | | | 71 (47) | 120 (80) | 30 (31) | 35 (23) | | |
| Varadarajan and Pai (2003) | HeFNEF 963 | | Framingham (McKee et al., 1971) HeFNEF: LVEF ≥ 55% | | | | | | |
|                  | HeFREF 1,295 | | | 10 (1) | 260 (27) | 39 (4) | 10 (1) | 39 (3) | 155 (12) |
| Masoudi et al. (2003) | HeFNEF 6,754 | | Patients hospitalized with a diagnosis of HF and prior history of HF or evidence of HF on admission chest X-ray HeFNEF: LVEF ≥ 50% | 2,431 (36) | 4,660 (69) | 2,296 (34) | 3,107 (46) | 2,499 (37) | 5,182 (40) |
|                  | HeFREF 12,956 | | -Chronic renal failure on hemodialysis -Patient transferred to another facility or self-discharged | 6,089 (47) | 7,903 (61) | 4,016 (31) | 8,421 (65) | | |
| Shenkman et al. (2002) | All HF 3,471 | | 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% | 22 (37) | 34 (58) | 9 (15) | 18 (31) | | |
|                  | HeFNEF 1,811 | | | 40 (51) | 39 (50) | 11 (14) | 41 (53) | | |
|                  | HeFREF 1,660 | | | | | | | | |
| Senni et al. (1998) | HeFNEF 59 | | Modified Framingham criteria (McKee et al., 1971) HeFNEF: LVEF ≥ 50% | 22 (37) | 34 (58) | 9 (15) | 18 (31) | | |
|                  | HeFREF 78 | | | 40 (51) | 39 (50) | 11 (14) | 41 (53) | | |
| Gigliotti et al. (2017) | HeFNEF SR AF 57 | | Framingham (McKee et al., 1971) HeFNEF: LVEF ≥ 50% | -Paced rhythm | 46 (81) | | 31 (54) | 32 (56) | 4,951* |
|                  |                  | | -Atrial flutter | 18 (72) | | | 16 (64) | 11(44) | 6,019* |

(Continues)
| 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) | 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 | 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) | 84 (66) | 43 (34) | 54 (42) | 12 (9) | 72 |
| | Group 2 |  |  | 41 (34) | 108 (90) | 46 (38) | 58 (48) | 63 (52) | 188 |
| | Group 3 |  |  | 79 (53) | 112 (75) | 56 (38) | 75 (50) | 50 (34) | 607 |
| Donal et al. (2014) | HeFNEF at admission 539 | 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) |
| | HeFNEF after 4–8 weeks treatment 438 |  |  |  |  |  |  | BNP 429 NT-proBNP 2,448 | BNP 277 NT-proBNP 1,409 |  |
| 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) 3,247 | -HF definition: | -<60 years of age | 877 (27) | 2,889 (89) | 260 (8) | 1624 (50) | NT-ProBNP 812 (25) | 647 |
| | HeFNEF (non-SCD) 650 | -HF symptoms | -Intolerance to ARB | 553 (85) | 201 (87) | 81 (35) | 358 (55) | 146 (63) | 228 (35) | 1733 |
| | HeFNEF (SCD) 231 | -Hospitalization for HF during the previous 6 months and NYHA class II, III, or IV symptoms with corroborative evidence | -Previous LVEF < 40% | 306 (47) | 85 (13) | 37 (16) | 358 (55) | 146 (63) | 88 (38) | 1722 |
| | If not hospitalized, ongoing class III or IV symptoms with corroborative evidence | -ACS, coronary revascularization, or stroke within the previous 3 months | -Significant valvular disease | 87 (40) | 47 (38) | 46 (36) | 54 (43) | 37 (30) | 46 (37) | 222 |
| | HeFNEF: LVEF ≥ 45% | -Hypertrophic or restrictive cardiomyopathy | -Pericardial disease | 51 (40) | 379 |
| | | -Isolated right HF | -Systolic BP < 100 mm Hg or > 160 mm Hg or a diastolic BP > 95 mm Hg despite HF therapy | | | | | |
| | | -Life-limiting comorbidity | -Laboratory abnormalities | | | | | |
| | | | | | | | | |
| Selvaraj et al. (2014) | HeFNEF (QRS-T 0–26°) 124 | HF definition: | -Significant valvular disease | 47 (38) | 92 (74) | 50 (40) | 40 (32) | 32 (26) | 123 |
| | | Framingham (McKee et al., 1971) | -Prior cardiac transplantation | 74 (59) | 100 (80) | 47 (38) | 37 (30) | 46 (37) | 222 |
| | | Identified from inpatient records: | -History of overt LV systolic dysfunction (LVEF < 40%) | 73 (57) | 99 (78) | 46 (36) | 54 (43) | 51 (40) | 379 |
| | | -Diagnosis of HF or the term HF in the hospital notes | -Constrictive pericarditis. | | | | | |
| | | -BNP > 100 pg/ml or | -Ventricular paced rhythm | | | | | |
| | | -Two or more doses of intravenous diuretic administered | | | | | | |
| | | HeFNEF definition: | | | | | | |
| | | LVEF > 50% and LV end-diastolic volume index <97 ml/m² (Paulus et al., 2007) | | | | | | |
### NIKOLAIDOU et al. (2013)

**HeFNEF**

**Definition of HF**

- 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

**Exclusion criteria**

| Kidney disease N (%) | HT N (%) | COPD N (%) | IHD N (%) | Pacemaker/defibrillator N (%) | Diabetes N (%) | BNP median ng/L |
|----------------------|----------|------------|-----------|------------------------------|----------------|----------------|
| 1,332 (39)           | 3,147 (91) | 403 (12)  | 2023      | 269 (8)                      | 1,114 (32)     | BNP 234 NT-proBNP 950 |

### Shah et al. (2013)

**HeFNEF**

**Definition of HF**

- 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

**Exclusion criteria**

| Kidney disease N (%) | HT N (%) | COPD N (%) | IHD N (%) | Pacemaker/defibrillator N (%) | Diabetes N (%) | BNP median ng/L |
|----------------------|----------|------------|-----------|------------------------------|----------------|----------------|
| 1,332 (39)           | 3,147 (91) | 403 (12)  | 2023      | 269 (8)                      | 1,114 (32)     | BNP 234 NT-proBNP 950 |

### Hummel et al. (2009)

**HeFNEF**

**Definition of HF**

- No definition of HF.
- HeFNEF: LVEF ≥ 50%

**Exclusion criteria**

| Kidney disease N (%) | HT N (%) | COPD N (%) | IHD N (%) | Pacemaker/defibrillator N (%) | Diabetes N (%) | BNP median ng/L |
|----------------------|----------|------------|-----------|------------------------------|----------------|----------------|
| 733 (84)             | 570 (84) | 158 (82)   | 124 (64)  |                             |                |                |

### O’Neal et al. (2017)

**HeFNEF**

**Definition of HF**

- Composite of probable and definite HF events
  - Probable:
    - Symptoms of HF
    - Previous physician diagnosis
  - Definite:
    - Evidence of structural defect
- LVEF ≥ 50%
- Prevalent cardiovascular disease
- Missing ECG data or baseline characteristics
- Missing HF follow-up data

**Exclusion criteria**

| Kidney disease N (%) | HT N (%) | COPD N (%) | IHD N (%) | Pacemaker/defibrillator N (%) | Diabetes N (%) | BNP median ng/L |
|----------------------|----------|------------|-----------|------------------------------|----------------|----------------|
| 2,329 (36)           | 76 (60)  | 65 (56)    | 39 (31)   |                             |                |                |
### 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           | 5,828 | 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) |
| HeFNEF         | 196  |                      |                    |                      |          |            |           |                               |                |                 |
| HeFREF         | 261  |                      |                    |                      |          |            |           |                               |                |                 |
| Lee et al. (2009) |    |                      |                    |                      |          |            |           |                               |                |                 |
| HeFNEF         | 220  | Framingham (McKee et al., 1971) | On HT medication HeFNEF: LVEF > 45% | 130 (59) | 177 (56) | 49 (22) | 86 (27) |                |                 |
| HeFREF         | 314  |                      |                    |                      |          |            |           |                               |                |                 |

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; 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.