Estimated Population Prevalence of Heart Failure with Reduced Ejection Fraction in Spain, According to DAPA-HF Study Criteria

Anna Camps-Vilaró 1,2*, Juan F. Delgado-Jiménez 2,3,4*, Núria Farré 5,6,7, Helena Tizón-Marcos 5,6, Jesús Álvarez-García 2,7,8*, Juan Cinca 2,7,8, Irene R. Dégano 1,2,9,*,† and Jaume Marrugat 1,2,*,†

1 REGICOR Study Group, IMIM (Hospital del Mar Medical Research Institute), 08003 Barcelona, Spain; acamps@imim.es
2 CIBER of Cardiovascular Diseases (CIBERCV), Instituto de Salud Carlos III (ISCIII), 28029 Madrid, Spain; juan.delgado@salud.madrid.org (J.F.D.-J.); jalvarezg@santpau.cat (J.A.-G.); JCinca@santpau.cat (J.C.)
3 Department of Cardiology, Hospital Universitario 12 de Octubre, 28041 Madrid, Spain
4 Faculty of Medicine, Complutense University of Madrid (UCM), 28040 Madrid, Spain
5 Department of Cardiology, Hospital del Mar, 08003 Barcelona, Spain; NFarreLopez@parcedesalmar.cat (N.F.); hitzon@psmar.cat (H.T.-M.)
6 Heart Diseases Biomedical Research Group (GREC), IMIM (Hospital del Mar Medical Research Institute), 08003 Barcelona, Spain
7 Faculty of Medicine, Universitat Autònoma de Barcelona (UAB), 08193 Barcelona, Spain
8 Department of Cardiology, Hospital de la Santa Creu i Sant Pau, 08041 Barcelona, Spain
9 Faculty of Medicine, University of Vic-Central University of Catalonia (UVic-UCC), 08500 Vic, Spain
* Correspondence: ironman@imim.es (I.R.D.); jmarrugat@imim.es (J.M.); Tel.: +349-3316-0714 (I.R.D.);
† These authors contributed equally to this work.

Received: 9 June 2020; Accepted: 30 June 2020; Published: 3 July 2020

Abstract: Heart failure (HF) is one of the main causes of morbidity, mortality, and high healthcare costs. Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, reduced cardiovascular mortality and hospitalization for HF compared to placebo in patients with chronic HF, and reduced ejection fraction (EF) in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study. Our aim was to estimate the number of patients with DAPA-HF characteristics in Spain. Our literature review identified epidemiological studies whose objective was to quantify the prevalence of HF and its comorbidities in Spain. We estimated the prevalence of HF with reduced EF, of New York Heart Association (NYHA) functional class II–IV, and with a glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m². In this population, we analysed the prevalence of diabetes using data from the REDINSCOR (Spanish Network for Heart Failure) registry. Our estimations indicate there are 594,684 patients ≥45 years old with HF in Spain (2.6% of this population age group), of which 52.4%, 84.0%, and 93.9% have reduced EF, are NYHA II–IV, and have a GFR ≥ 30 mL/min/1.73 m², respectively. By our calculations, approximately 245,789 Spanish patients would meet the DAPA-HF patient profile, and therefore could benefit from the protective cardiovascular effects of dapagliflozin.

Keywords: heart failure; reduced ejection fraction; cardiovascular disease; cardiovascular therapy; dapagliflozin; sodium-glucose cotransporter-2 inhibitor; epidemiology; prevalence

1. Introduction

Heart failure (HF) is a clinical syndrome caused by a structural or functional heart abnormality leading to a reduction of cardiac output or an increase in intracardiac pressure. Characterization of
HF is usually based on the ejection fraction (EF): preserved (≥50%), mid-range (40–49%), or reduced (<40%) [1].

Although HF is increasingly treatable and preventable, it remains one of the main causes of morbidity, mortality, and high healthcare costs. Incidence and prevalence of HF increase with population aging. Greater prevalence is related to increased survival, due to successful HF treatment, and higher incidence is related to the increasing population prevalence of atrial fibrillation, hypertension, obesity, and diabetes [1–3]. In 2018, HF caused 19,142 deaths in Spain [4]. While the morbidity and mortality of patients with reduced EF (40–60% of HF patients) [5–7] have decreased, thanks to improved clinical management in recent decades [8], the average total cost per patient with HF in Spain was €12,995–18,220 in 2010, with the largest cost item (59.1–69.8%) being non-professional care [9]. The total HF-patient healthcare expenditure as a percentage of the annual healthcare budget is 1.5% in all of Spain and 7.1% in Catalonia, with the highest cost in both cases related to hospitalizations [10,11].

Prevalence, clinical characteristics, and prognosis of HF differ according to EF category. Time series based on data from hospitalized patients suggest a more pronounced decrease in HF incidence and show higher all-cause mortality but fewer comorbidities in patients with reduced EF, compared to preserved EF [1].

Comorbidities are a key component in the management of patients with HF, as treatments for accompanying pathologies can worsen HF prognosis [1]. Two of the most common comorbidities are diabetes (20–40%) and chronic kidney disease (10–30%) [12,13]. Both are associated with more hospitalizations and higher mortality in HF patients [14].

The good quality of HF mortality data in Spain contrasts with the lesser-known prevalence of the disease. Several studies have analysed the population prevalence of HF in Spain, providing estimations that vary considerably (2.7–6.8%) for the population older than 44 years [14–16]. Most of these figures exceed the estimations in adult populations of Europe (1–2%) [1,17,18] and North America (2.2–2.4%) [2,19]. Moreover, no data are available on the prevalence of HF with reduced EF and comorbidities, the patient profile associated with the highest HF mortality.

Although advances in HF treatment have significantly reduced mortality risk in clinical trials, particularly in patients with reduced EF, the real-life impact of improved treatment has been more modest [20]. One new option is dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor with solid clinical evidence in patients with type 2 diabetes mellitus (T2D) that also markedly reduces hospitalization for HF [21]. Dapagliflozin has reduced cardiovascular mortality and hospitalization for HF, compared to a placebo, as an additional treatment in patients with chronic HF and reduced EF, with and without T2D [22]. In view of these promising results, it would be useful to determine the target population for this new treatment indication, based on the criteria used in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study [22]. Spain did not participate in the DAPA-HF study; therefore, there is a great interest to know the impact of the DAPA-HF study criteria in the Spanish population.

The aim of this study was to estimate the population in Spain, stratified by its autonomous communities, that meets the DAPA-HF criteria for dapagliflozin indication: HF and reduced EF (≤40%), functional class II–IV of the New York Heart Association (NYHA), and glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2, all with and without T2D.

2. Materials and Methods

2.1. Study Design and Population

To determine the number of patients with HF with reduced EF, in NYHA functional class II–IV, and with normal or moderate kidney function (≥30 mL/min/1.73 m^2), we carried out a systematic literature search in PubMed of English or Spanish cross-sectional, cohort, population-based, or other epidemiological studies. To this end, we selected articles that contained the terms “heart failure” in the title; “prevalence” or “burden” in the title or abstract; “ejection fraction”, “systole”, or “systolic” in the
Patients’ eligibility criteria for the population candidates for dapagliflozin treatment are summarized in Table 1. Full details are provided in the design paper [25].

Table 1. Summary of inclusion and exclusion criteria of the DAPA-HF study [25].

| Inclusion Criteria |
|-------------------|
| (1) Provision of signed informed consent prior to any study specific procedures |
| (2) Men or women, aged ≥18 years at the time of consent |
| (3) Diagnosis of HF with left ventricular EF ≤40%, which has been present for at least 12 months prior to enrolment |
| (4) Diagnosis of symptomatic HF (NYHA functional class II–IV), within the previous 2 months |
| (5) Optimally treated with pharmacological and/or device therapy for HF |
| (6) NT-proBNP ≥600 pg/mL (or if hospitalised for HF within the previous 12 months, NT-proBNP ≥400 pg/mL) at enrolment. Patients with atrial fibrillation or atrial flutter must have a level ≥900 pg/mL, irrespective of history of HF hospitalization |

| Exclusion Criteria |
|--------------------|
| (1) Treatment with SGLT2 inhibitors within 8 weeks prior to enrolment, or previous intolerance of an SGLT2 inhibitor |
| (2) Diagnosis of type 1 diabetes mellitus |
| (3) Symptomatic hypotension or systolic blood pressure <95 mmHg |
| (4) Recent worsening HF or other cardiovascular events or procedures |
| (5) Severe (GFR <30 mL/min/1.73 m² by CKD-EPI equation), unstable, or rapidly progressing renal disease at the time of randomization |
| (6) Other conditions likely to prevent patient participation in the trial or greatly limit life expectancy |

DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; HF: heart failure; EF: ejection fraction; NYHA: New York Heart Association; NT-proBNP: N-terminal proB-type natriuretic peptide; GFR: glomerular filtration rate; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; SGLT2: sodium-glucose cotransporter-2.

2.2. Estimation of Population Prevalence and Number of Patients with Heart Failure in Spain

Our analysis applied the prevalence of HF reported for individuals older than 44 years in the largest and most recent representative population study [14] to the entire Spanish population and to each autonomous community’s population, according to the 2019 Spanish National Statistics Institute data [26].

2.3. Estimation of Ejection Fraction ≤40% and New York Heart Association Functional Class II–IV Prevalence in the Heart Failure Population in Spain

The proportion of HF patients with EF ≤40% and NYHA functional class II–IV was determined according to the average percentages observed in the most recent Spanish registries of patients with chronic HF [6,7,27–29]. The study designs, in reverse chronological order, are summarized as follows: Prospective cohort studies:

- RICA (National Registry for Heart Failure), carried out in internal medicine units in 52 public and private hospitals [27];
- REDINSCOR (Spanish Network for Heart Failure), carried out in HF units in 18 hospitals [27];
- BADAPIC (Database of Patients with Heart Failure), involving 62 centres with specific HF units or clinics [6];

Cross-sectional studies:

- INCA (Heart Failure Study), involving 415 primary care physicians and 93 cardiologists [7];
• EPISERVE (Heart Failure in Outpatients), carried out by 181 primary care physicians, 172 cardiologists, and 154 internal medicine physicians [28];
• GALICAP (Galician Study of Heart Failure in Primary Care), involving 149 primary care physicians distributed in eight areas of Galicia [29].

2.4. Estimation of Glomerular Filtration Rate \( \geq 30 \text{ mL/min/1.73 m}^2 \) Prevalence in the Heart Failure Population in Spain

The proportion of patients with GFR \( \geq 30 \text{ mL/min/1.73 m}^2 \) was estimated from the most generalizable data, obtained from patients with chronic HF in 28 Spanish hospitals included in the European Society of Cardiology (ESC) Heart Failure Long-Term Registry [23]. The prevalence of GFR \( \geq 30 \text{ mL/min/1.73 m}^2 \) was applied to the estimated HF population with EF \( \leq 40\% \) and with NYHA functional class II–IV (obtained in Section 2.3).

A sensitivity analysis with the total REDINSCOR prevalence of EF, NYHA functional class II–IV, and GFR \( \geq 30 \text{ mL/min/1.73 m}^2 \) was done to determine the reliability of our estimates (Tables S1–S3).

2.5. Estimation of Type 2 Diabetes Mellitus Prevalence in the Heart Failure Population in Spain

Finally, the prevalence of patients with and without T2D was obtained from a specific analysis of a chronic HF cohort provided by REDINSCOR investigators. The cohort characteristics have been described previously [27,30]. We calculated the prevalence of patients with and without diabetes who met the criteria for HF with EF \( \leq 40\% \), NYHA functional class II–IV, and GFR \( \geq 30 \text{ mL/min/1.73 m}^2 \) (Tables S1 and S2).

2.6. Statistical Analysis

The arithmetic means of reduced EF and NYHA functional class II–IV estimations were obtained. The 95% confidence interval (CI) for the described estimations were obtained by assuming a Poisson distribution of patient counts. Analysis was carried out using R software, version 4.0.0.

3. Results

3.1. Estimation of Population Prevalence and Number of Patients with Heart Failure in Spain

Table 2 describes the prevalence of HF in Spain and in Europe, as reported in the largest, most recent, and most representative population-based candidate studies. The 2012 study by Farré et al. [14] was considered the most appropriate for estimating prevalence in Spain, since it included a representative population of more than 88,000 people and the results closely resembled those of similar studies in Europe. Applying the prevalence of specific ages used by Farré et al. [14] to current Spanish population in the same age groups yielded a prevalence of approximately 2.6% in the group older than 44 years, or 594,684 (95% CI: 593,175–596,196) patients with HF.

### Table 2. Summary of the heart failure prevalence by age group in population studies in Spain and Europe.

| Year of Publication | Country/Region     | Study Population | Age, Years (SD) | Women,% | Age Group Prevalence, By Years |
|---------------------|--------------------|------------------|----------------|---------|-------------------------------|
| Farre et al. [14]   | Catalonia          | 88,195           | 77 (12)        | 55.0%   | 2.70% 0.30% 0.90% 2.50% 8.80% |
| Anguita et al. [15] | Spain              | 1776             | 64 (12)        | 55.9%   | 6.80% 1.30% 5.00% 8.00% 16.1% |
| Cortina et al. [16] | Asturias           | 391              | 60 (13)        | 53.6%   | <1.00% 2.00% 5.00% 13.0% 18.0% |
| Cortina et al. [16] | Asturias           | 391              | 60 (13)        | 53.6%   | 5.00% 1.00% 2.00% 5.00% 13.0% 18.0% |
**Table 2. Cont.**

| Study | Year of Publication | Country/Region | Study Population | Age, Years (SD) | Women, % | Age Group Prevalence, By Years | Total | 45–54 | 55–64 | 65–74 | ≥75 |
|-------|---------------------|----------------|------------------|-----------------|----------|--------------------------------|-------|-------|-------|-------|-----|
| Ohlmeier et al. [17] | 2015 | Germany | 6,284,194 | 39 (21) | 48.2% | 1.70% | 0.10% | 1.28% | 3.88% | 10.8% | 25.9% | 45.7% |
| Paré et al. [18] | 2014 | Sweden | 144,925 | - | 48.9% | 1.99% | 0.13% | 1.06% | 3.20% | 9.23% | 20.4% |
| Murphy et al. [31] | 2004 | Scotland | 307,741 | - | 50.6% | 0.71% | 0.38% | 2.30% | 6.53% |
| Bleumink et al. [32] | 2004 | Rotterdam | 7983 | 70 (10) | 61.0% | 6.70% | - | 0.90% | 4.00% | 9.70% | 17.4% |
| Ceia et al. [33] | 2002 | Portugal | 5434 | 68 (15) | 62.7% | 4.36% | 1.36% | 2.93% | 7.63% | 12.7% | 16.1% |

SD: standard deviation.

### 3.2. Estimation of Ejection Fraction ≤ 40% and New York Heart Association Functional Class II–IV Prevalence in the Heart Failure Population in Spain

Characteristics of patients with HF included in the selected Spanish studies are shown in Table 3. The average proportion of HF patients with EF ≤ 40% was 52.4%, of which 84.0% had NYHA functional class II–IV. Applying these percentages to the estimated number of patients with HF in Spain, 311,614 (95% CI: 310,522–312,709) patients would have EF ≤ 40%, and 261,756 (95% CI: 260,755–262,760) patients would also have NYHA functional class II–IV.

**Table 3. Studies of patients with heart failure in Spain.**

| Study | Year of Publication | Study Population | Age, Years (SD) | Women, % | Type of Heart Failure | Geographical Area | Specialty | Reduced EF | NYHA Class II–IV |
|-------|---------------------|------------------|-----------------|----------|----------------------|------------------|-----------|------------|----------------|
| RICA [27] | 2017 | 1396 | 79 (8) | 54.0% | chronic | Spain | Internal medicine | 39.5% | 80.2% |
| REDINSCOR [27] | 2017 | 2150 | 70 (10) | 31.0% | chronic | Spain | Cardiology | 79.6% | 100% |
| BADAPIC [6] | 2010 | 4720 | 65 (12) | 29.0% | chronic | Spain | Cardiology | 63.4% | 100% |
| INCA [7] | 2009 | 2161 | 71 (11) | 44.4% | chronic | Spain | Primary care and cardiology | 58.3% | 84.0% |
| EPISERVE [28] | 2008 | 2249 | 72 (10) | 45.0% | - | Spain, except La Rioja | Cardiology | 55.0% | 90.4% |
| GALICAP [29] | 2007 | 1195 | 76 (10) | 52.1% | - | Galicia | Primary care | 38.6% | 81.5% |

Mean 52.4% 84.0%

1 Data not included in the calculation of NYHA functional class II–IV average. RICA: National Registry for Heart Failure; REDINSCOR: Spanish Network for Heart Failure; BADAPIC: Database of Patients with Heart Failure; INCA: Heart Failure Study; EPISERVE: Heart Failure in Outpatients; GALICAP: Galician Study of Heart Failure in Primary Care; SD: standard deviation; Reduced EF: ejection fraction less than 40–50%; NYHA: New York Heart Association.

The Spanish population and the number of patients with HF, by age group and by autonomous community, are shown in Table 4. In Table 5, these data are disaggregated by EF ≤ 40%, and by the combination of EF ≤ 40% and NYHA functional class II–IV.
Table 4. Total population in Spain according to 2019 data from the National Statistics Institute [26], and the number of patients with heart failure in Spain and its autonomous communities, according to prevalence data published by Farré et al. [14].

| General Population (by Age Group) | Heart Failure Prevalence (by Age Group) |
|-----------------------------------|----------------------------------------|
| Total 45–54 | 55–64 | 65–74 | Total 45–54 | 55–64 | 65–74 | 75+ |
| **Autonomous Communities** | | | | | | | |
| Andalucía | 3,895,025 | 1,341,487 | 1,093,149 | 770,187 | 690,202 | 93,855 | 4024 | 9838 | 19,255 | 60,738 |
| Aragón | 674,882 | 207,355 | 180,224 | 136,385 | 151,318 | 18,947 | 622 | 1622 | 3405 | 13,298 |
| Principado de Asturias | 589,263 | 164,027 | 161,384 | 131,949 | 131,983 | 16,851 | 492 | 1452 | 3299 | 11,607 |
| Illes Balears | 529,589 | 194,110 | 145,007 | 103,545 | 86,927 | 12,126 | 582 | 1305 | 2589 | 7650 |
| Canarias | 1,048,012 | 390,823 | 293,621 | 199,438 | 164,130 | 23,244 | 1172 | 2643 | 4986 | 14,443 |
| Cantabria | 307,255 | 93,358 | 85,403 | 65,351 | 63,143 | 8239 | 280 | 769 | 1634 | 5357 |
| Castilla y León | 1,347,618 | 376,632 | 361,698 | 275,863 | 333,425 | 40,623 | 1130 | 3255 | 6897 | 29,341 |
| Castilla-La Mancha | 974,147 | 320,338 | 265,833 | 180,457 | 207,519 | 26,127 | 961 | 2392 | 4511 | 18,262 |
| Catalunya | 3,593,391 | 1,184,206 | 946,935 | 738,057 | 720,393 | 93,853 | 3565 | 8522 | 18,451 | 63,395 |
| Comunitat Valenciana | 2,437,743 | 799,940 | 658,274 | 508,440 | 471,089 | 62,491 | 2400 | 5924 | 12,711 | 41,456 |
| Extremadura | 537,686 | 166,131 | 151,011 | 104,505 | 116,039 | 14,682 | 498 | 1359 | 2613 | 10,211 |
| Galicia | 1,484,698 | 424,418 | 377,370 | 322,257 | 360,653 | 44,463 | 1273 | 3396 | 8056 | 31,737 |
| Comunidad de Madrid | 3,099,482 | 1,074,013 | 826,152 | 609,975 | 589,342 | 77,769 | 3222 | 7435 | 15,249 | 51,862 |
| Región de Murcia | 648,115 | 234,820 | 176,760 | 123,046 | 113,489 | 15,358 | 704 | 1591 | 3076 | 9987 |
| Comunidad Foral de Navarra | 317,203 | 102,519 | 84,911 | 64,649 | 65,124 | 8419 | 308 | 764 | 1616 | 5731 |
| País Vasco | 1,156,253 | 347,445 | 312,977 | 247,796 | 248,125 | 31,887 | 1042 | 2817 | 6193 | 21,835 |
| La Rioja | 158,846 | 49,143 | 43,080 | 32,058 | 34,565 | 4378 | 147 | 388 | 801 | 3042 |
| Ciudad Autónoma de Ceuta | 32,632 | 10,209 | 10,246 | 8,076 | 8,461 | 680 | 36 | 92 | 142 | 409 |
| Ciudad Autónoma de Melilla | 30,008 | 9,057 | 9,977 | 7,077 | 7,077 | 437 | 16 | 33 | 88 | 127 |
| All Communities | 22,862,048 | 7,497,881 | 6,183,772 | 4,624,421 | 4,555,974 | 594,684 | 22,494 | 55,654 | 115,611 | 400,926 |
| 95% CI | 22,852,679–22,871,420 | 7,492,516–7,503,249 | 6,178,900–6,188,647 | 4,620,208–4,628,637 | 4,551,792–4,560,158 | 593,175–596,196 | 22,202–22,789 | 55,194–56,117 | 114,947–116,278 | 399,687–402,168 |

CI: Confidence interval.
Table 5. Total number of patients in Spain and its autonomous communities with heart failure and ejection fraction ≤ 40%, as well as the number of heart failure patients with average ejection fraction ≤ 40% and in New York Heart Association functional class II–IV (based on data summarized in Table 3).

| Heart Failure + Ejection Fraction ≤ 40% (by Age Group) | Heart Failure + Ejection Fraction ≤ 40% + NYHA Class II–IV (by Age Group) |
|--------------------------------------------------------|-------------------------------------------------------------|
| Total | 45–54 | 55–64 | 65–74 | 75+ | Total | 45–54 | 55–64 | 65–74 | 75+ |
| Autonomous Communities | | | | | | | | | |
| Andalucía | 49,180 | 2109 | 5155 | 10,089 | 31,827 | 41,311 | 1771 | 4330 | 8475 | 26,734 |
| Aragón | 9928 | 326 | 850 | 1784 | 6968 | 8540 | 274 | 714 | 1499 | 5853 |
| Principado de Asturias | 8530 | 258 | 761 | 1729 | 6082 | 7417 | 217 | 639 | 1452 | 5109 |
| Illes Balears | 6354 | 305 | 684 | 1356 | 4008 | 5337 | 256 | 574 | 1139 | 3627 |
| Canarias | 12,180 | 614 | 1385 | 2613 | 7568 | 10,231 | 516 | 1163 | 2195 | 6357 |
| Cantabria | 4317 | 147 | 403 | 856 | 2912 | 3627 | 123 | 338 | 719 | 2446 |
| Castilla y León | 21,287 | 592 | 1706 | 3614 | 15,375 | 17,881 | 497 | 1433 | 3036 | 12,915 |
| Castilla-La Mancha | 13,690 | 504 | 1254 | 2364 | 9569 | 11,500 | 423 | 1053 | 1986 | 8038 |
| Cataluña | 49,221 | 1868 | 4466 | 9669 | 33,219 | 41,346 | 1569 | 3751 | 8122 | 27,904 |
| Comunitat Valenciana | 32,745 | 1258 | 3104 | 6661 | 21,723 | 27,506 | 1056 | 2608 | 5595 | 18,247 |
| Extremadura | 7693 | 261 | 712 | 1369 | 5351 | 6462 | 219 | 598 | 1150 | 4495 |
| Galicia | 25,299 | 667 | 1790 | 4222 | 16,630 | 19,571 | 560 | 1495 | 3546 | 13,970 |
| Comunidad de Madrid | 40,751 | 1688 | 3896 | 7991 | 27,176 | 34,213 | 1418 | 3273 | 6712 | 22,828 |
| Región de Murcia | 8048 | 369 | 834 | 1612 | 5233 | 6760 | 310 | 700 | 1354 | 4396 |
| Comunidad Foral de Navarra | 4411 | 161 | 480 | 847 | 3803 | 3760 | 135 | 336 | 711 | 2523 |
| País Vasco | 16,709 | 546 | 1476 | 3245 | 11,442 | 14,033 | 459 | 1240 | 2726 | 9611 |
| La Rioja | 2294 | 77 | 203 | 420 | 1594 | 1927 | 65 | 171 | 353 | 1339 |
| Ciudad Autónoma de Ceuta | 356 | 19 | 48 | 74 | 214 | 299 | 16 | 41 | 62 | 180 |
| Ciudad Autónoma de Melilla | 321 | 17 | 46 | 67 | 191 | 269 | 15 | 39 | 56 | 160 |
| All Communities | 311,614 | 11,787 | 29,163 | 60,580 | 210,085 | 261,756 | 9901 | 24,497 | 50,887 | 176,471 |
| 95% CI | 310,522–312,709 | 11,576–12,001 | 28,830–29,499 | 60,100–61,063 | 209,189–210,984 | 260,755–262,760 | 9708–10,097 | 24,192–24,805 | 50,447–51,330 | 175,650–177,295 |

NYHA: New York Heart Association; CI: Confidence interval.
3.3. Estimation of Glomerular Filtration Rate ≥ 30 mL/min/1.73 m² Prevalence in the Heart Failure Population in Spain

According to the prevalence of chronic HF patients with GFR ≥ 30 mL/min/1.73 m² described by Crespo-Lerio [23], we estimated the number of HF patients with the combination of EF ≤ 40%, NYHA functional class II–IV, and GFR ≥ 30 mL/min/1.73 m² (Table 6). In Spain, an estimated 245,789 (95% CI: 244,819–246,762) patients would have these characteristics.

Table 6. Total number of patients with heart failure ejection fraction ≤ 40%, New York Heart Association functional class II–IV, and glomerular filtration rate ≥ 30 mL/min/1.73 m² in Spain and its autonomous communities [23].

| Autonomous Communities | Total 45–54 | 55–64 | 65–74 | 75+ |
|------------------------|-------------|-------|-------|-----|
| Andalucía              | 38,791      | 1663  | 4066  | 7958 |
| Aragón                 | 7831        | 257   | 670   | 1407 |
| Principado de Asturias | 6965        | 203   | 600   | 1363 |
| Illes Balears          | 5012        | 241   | 539   | 1070 |
| Canarias               | 9607        | 485   | 1092  | 2061 |
| Cantabria              | 3405        | 116   | 318   | 675  |
| Castilla y León        | 16,790      | 467   | 1345  | 2850 |
| Castilla-La Mancha     | 10,798      | 397   | 989   | 1865 |
| Cataluña               | 38,823      | 1473  | 3522  | 7626 |
| Comunitat Valenciana   | 25,828      | 992   | 2449  | 5254 |
| Extremadura            | 6068        | 206   | 562   | 1080 |
| Galicia                | 18,377      | 526   | 1404  | 3330 |
| Comunidad de Madrid    | 32,143      | 1332  | 3073  | 6303 |
| Región de Murcia       | 6348        | 291   | 658   | 1271 |
| Comunidad Foral de Navarra | 3480    | 127   | 316   | 668  |
| País Vasco             | 13,179      | 431   | 1164  | 2559 |
| La Rioja               | 1810        | 61    | 160   | 331  |
| Ciudad Autónoma de Ceuta | 281      | 15    | 38    | 59   |
| Ciudad Autónoma de Melilla | 253   | 14    | 36    | 52   |
| All Communities        | 245,789     | 9297  | 23,002| 47,783|

95% CI: 244,819–246,762, 9,110–9,487, 22,707–23,300, 47,357–48,212, 164,911–166,506.

HF: heart failure; EF: ejection fraction; NYHA: New York Heart Association; GFR: glomerular filtration rate. (mL/min/1.73 m²); CI: Confidence interval.

A sensitivity analysis with REDINSCOR estimates (Table S3), however, showed that the estimated number of patients who met the clinical characteristics of participants in the DAPA-HF trial were 353,658 (95% CI: 352,494–354,825).

3.4. Estimation of Type 2 Diabetes Mellitus Prevalence in the Heart Failure Population in Spain

The number of HF patients with EF ≤ 40%, NYHA functional class II–IV, and GFR ≥ 30 mL/min/1.73 m², with and without T2D, are shown in Table 7 by age group and autonomous community. With these prevalence data, Spain would have 115,473 (95% CI: 114,809–116,140) patients with T2D and 130,316 (95% CI: 129,610–131,025) without T2D who would meet the diagnostic criteria of HF with EF ≤ 40%, NYHA functional class II–IV, and GFR ≥ 30 mL/min/1.73 m².

Figure 1 summarizes the sequence of patient selection by the prevalence of patient characteristics or comorbidities analysed, as well as the estimated number of patients with and without each characteristic in Spain.
Table 7. Total number of patients with heart failure, ejection fraction ≤ 40%, New York Heart Association functional class II–IV, and glomerular filtration rate ≥ 30 mL/min/1.73 m², with or without type 2 diabetes mellitus, in Spain and its autonomous communities, according to prevalence data from the REDINSCOR registry (Tables S1 and S2).

| HF + EF ≤ 40% + NYHA Class II–IV + GFR ≥ 30 + Diabetes (by Age Group) | HF + EF ≤ 40% + NYHA Class II–IV + GFR ≥ 30 (No Diabetes) (by Age Group) |
|-------------------------------------------------|-------------------------------------------------|
| Total 45–54 | 55–64 | 65–74 | 75+  | Total 45–54 | 55–64 | 65–74 | 75+  |
| Autonomous Communities | | | | | | | |
| Andalucía | 18,157 | 478 | 1654 | 3914 | 12,111 | 20,634 | 1185 | 2412 | 4044 | 12,993 |
| Aragón | 3690 | 74 | 273 | 692 | 2652 | 4141 | 183 | 398 | 715 | 2845 |
| Principado de Asturias Illes Balears | 3288 | 58 | 244 | 671 | 2314 | 3677 | 145 | 356 | 693 | 2493 |
| Castilla – La Mancha | 4477 | 139 | 444 | 1014 | 2880 | 5310 | 345 | 648 | 1047 | 3090 |
| Cataluña | 1603 | 33 | 129 | 332 | 1106 | 1803 | 82 | 188 | 342 | 1189 |
| Castilla y León | 7934 | 134 | 547 | 1402 | 5853 | 8856 | 333 | 798 | 1448 | 6277 |
| Canarias | 5075 | 114 | 402 | 917 | 3641 | 5724 | 283 | 587 | 947 | 3906 |
| Cantabria | 18,248 | 423 | 1433 | 3751 | 12,641 | 20,576 | 1050 | 2090 | 3875 | 15,361 |
| Comunitat Valenciana Extremadura | 12,131 | 285 | 996 | 2584 | 8266 | 13,697 | 707 | 1453 | 2670 | 8868 |
| Cádiz | 2855 | 59 | 228 | 531 | 2036 | 3213 | 147 | 333 | 549 | 2184 |
| Cantabria | 8688 | 151 | 571 | 1638 | 6328 | 9669 | 375 | 633 | 1462 | 6789 |
| Comunidad de Madrid | 15,074 | 383 | 1250 | 3100 | 10,341 | 17,869 | 949 | 1823 | 3215 | 11,094 |
| Región de Murcia | 2968 | 84 | 267 | 625 | 1991 | 3380 | 207 | 390 | 646 | 2136 |
| Comunidad Foral de Navarra | 1636 | 37 | 128 | 329 | 1143 | 1843 | 91 | 187 | 339 | 1226 |
| País Vasco | 6210 | 124 | 473 | 1299 | 4354 | 6969 | 307 | 691 | 1330 | 4671 |
| La Rioja | 852 | 18 | 65 | 163 | 607 | 957 | 43 | 95 | 168 | 651 |
| Ciudad Autónoma de Ceuta | 130 | 4 | 16 | 29 | 82 | 151 | 11 | 23 | 30 | 88 |
| Ciudad Autónoma de Melilla | 117 | 4 | 15 | 26 | 73 | 136 | 10 | 21 | 27 | 78 |
| All Communities | 115,473 | 2672 | 9355 | 23,503 | 79,943 | 130,316 | 6625 | 13,647 | 24,280 | 85,764 |

95% CI: 114,809–116,140 2573–2774 9167–9546 23,205–23,804 79,391–80,498 129,610–131,025 6467–6786 13,420–13,877 23,977–24,586 85,192–86,339

HF: heart failure; EF: ejection fraction; NYHA: New York Heart Association; GFR: glomerular filtration rate (mL/min/1.73 m²); CI: Confidence interval.
Figure 1. Flow chart of the Spanish population older than 44 years with heart failure (HF), ejection fraction (EF) ≤ 40%, New York Heart Association (NYHA) functional class II–IV, glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m², and type 2 diabetes mellitus (T2D), according to the estimation specified in the Methods section.

4. Discussion

4.1. Main Findings

Among all Spanish patients with HF, the estimated prevalence of patients older than 44 years with reduced EF, NYHA functional class II–IV, and with normal or moderate kidney function (≥ 30 mL/min/1.73 m²) was about 41.3%. Since the population was selected to meet the clinical characteristics of participants in the DAPA-HF trial, it is conceivable that these patients might also benefit from the positive cardiovascular effects attributed to dapagliflozin, in addition to its glucose-lowering benefits. This new therapeutic indication would benefit the defined HF patient population, with and without T2D, as shown in the DAPA-HF clinical trial [22]. Regardless of the presence of T2D and the risk of worsening HF, death from cardiovascular causes and hospitalizations for HF were significantly less
frequent among DAPA-HF participants who received dapagliflozin, compared to those who received a placebo. In the DAPA-HF study, dapagliflozin represents the first in a new class of drug for HF with reduced EF. The DAPA-HF study results introduce the opportunity to further study the potential cardiovascular benefits of SGLT2 inhibitors. Prior studies with empagliflozin [34] and canagliflozin [35] showed a reduction in the relative risk of HF hospitalization in T2D patients, suggesting that the observed benefit is not restricted to a particular drug, but is rather a class effect. The Canagliflozin Cardiovascular Assessment Study (CANVAS) showed that canagliflozin reduced the overall risk of HF events in patients with T2D and high cardiovascular risk. No clear difference in effects on HF with reduced versus preserved events was noted [36]. In addition, the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) study with dapagliflozin included a reanalysis of retrospectively-obtained EF. The clinical benefit of dapagliflozin was found to be strong in reduced EF in the subset of patient with available EF. In patients with HF without reduced EF, there was only a reduction of hospitalizations, but not in total or cardiovascular mortality [37]. The former was confirmed in the DAPA-HF study. The dapagliflozin effect on mortality in HF-preserved EF patients remains to be conclusively answered.

4.2. Reliability of Prevalence Estimates

Based on updated demographic information and a comprehensive literature review to obtain reliable prevalence data, we selected the most recent population-based cross-sectional study, in which Farré et al. analysed data from 88,000 individuals representative of the population of Catalonia, with an estimated a 2.7% HF prevalence in people older than 44 years [14]. Due to slight regional differences in age group population distribution, our estimations yielded 2.6% prevalence when applied to all of Spain. The estimations obtained by Farré et al. are also close to European and North American figures, and are more recent than the larger prevalence estimates reported in the meta-analysis by Hernández et al. [24] and the 2008 Heart Failure Prevalence Study in Spain (PRICE) by Anguita et al. [15].

Given the diversity of hospital departments and primary care settings participating in the published studies, our estimated prevalence of HF patients with reduced EF and NYHA functional class II–IV (52.4% and 84.0%, respectively) reflects the mean values of the main published Spanish registries [6,7,27–29]. The obtained prevalence values are in good agreement with the most recent European publications [5,38] in the Southern Europe population. Spanish cardiology departments were well-represented in these European studies, carried out in the context of the ESC Heart Failure Long-Term Registry, which had indicated that the prevalence of reduced EF in patients with chronic HF predominantly admitted to cardiology departments would be around 60%. This is slightly higher than our study’s estimate, which was based on HF data from cardiology units, internal medicine, and primary care settings. The Linx Registry, one of the most recent HF studies in Spain, also had a large sample of patients and was carried out in cardiology departments in Catalonia. In that registry, de Frutos et al. [39] estimated that the prevalence of NYHA functional class II–IV in patients with HF and EF ≤ 40% was 85.5%, remarkably close to the estimate obtained in the present study.

We used the 6.1% prevalence of GFR < 30 mL/min/1.73 m² among chronic HF patients, reported by Crespo-Leiro et al. [23], based on data from 28 Spanish hospitals included in the ESC Heart Failure Long-Term Registry. This is the most recent publication with HF data from Spain, includes the largest series of Spanish patients, and is the only study to provide GFR data generalizable to the HF population. The 6.1% prevalence is among the lowest published in recent decades in Spain, although it is close to the REDINSCOR registry prevalence of 5.5% in HF units within cardiology departments (Tables S1 and S2).

4.3. Potential Translational Perspective

The results of the DAPA-HF study demonstrated that the primary composite outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio = 0.74; 95% CI: 0.65–0.85; p < 0.001). The largest number of events
of worsening HF was hospitalizations. Of the patients receiving dapagliflozin, 231 (9.7%) were hospitalized for HF, compared with 318 patients (13.4%) receiving the placebo (hazard ratio = 0.70; 95% CI: 0.59–0.83). Death from cardiovascular causes occurred in 227 patients (9.6%) who received dapagliflozin, and in 273 (11.5%) who received the placebo (hazard ratio = 0.82; 95% CI: 0.69 to 0.98) [22]. Under the placebo group incidence assumptions, among all 245,789 patients of the estimated Spanish target population, the primary outcome would occur in 52,107 patients, 32,936 patients would be hospitalized for HF, and 28,266 patients would die from cardiovascular causes. With dapagliflozin therapy, the expected annual reduction would consist of 5996 hospitalized patients for HF and 3079 deaths from cardiovascular causes.

4.4. Strengths and Limitations

The main strength of this study is that it combines the estimates from recently published HF prevalence data, enriched by a specific analysis of the REDINSCOR registry database to estimate HF with reduced EF, NYHA functional class II–IV, and GFR \( \geq 30 \text{ mL/min/1.73 m}^2 \), with and without T2D prevalence in the Spanish population. However, we decided not to use the estimates based on REDINSCOR database, because the REDINSCOR registry could be biased toward the profile of patients admitted to HF units in cardiology departments, which could depart from the general HF patient population characteristics. All patients included in the REDINSCOR registry had a NYHA class > I, and the mean estimate of patients with reduced EF was 73%, considerably different from the average of the main Spanish registries that we summarize in Table 3. A sensitivity analysis with REDINSCOR patient characteristics is presented in Table S3, showing rather higher figures than its corresponding Table 6 results.

The study also has several limitations. First, we did not take into account the N-terminal pro B-type natriuretic peptide (NT-proBNP) eligibility criteria prevalence in our estimates, due to the absence of prevalence information in the literature and to the probably small reduction in the number of eligibility patients. Second, among the Spanish studies summarized in Table 3, the definition of reduced EF varied from EF \( \leq 40\% \) to EF \( \leq 50\% \). Furthermore, the GALICAP and EPISERVE studies did not differentiate between chronic and acute HF. Third, we had to assume that the prevalence of NYHA functional class II–IV was the same for reduced, mid-range, and preserved EF, owing to the absence of stratified information in the literature. Likewise, we had to assume that the prevalence of GFR \( \geq 30 \text{ mL/min/1.73 m}^2 \) was the same for each type of EF and NYHA functional class, and for all age groups considered in our study. Fourth, the prevalence of diabetic and non-diabetic patients in the REDINSCOR registry could be biased toward the profile of patients admitted to HF units in cardiology departments. Finally, our study does not report prevalence by sex, as the published studies did not provide this stratified information. We firmly support stratification by sex in all future studies, in order to identify the best treatment guidelines to apply in the whole population.

5. Conclusions

In this population analysis, we estimated that approximately 245,789 Spanish patients would meet the inclusion criteria of the DAPA-HF: EF \( \leq 40\% \), NYHA functional class II–IV, and GFR \( \geq 30 \text{ mL/min/1.73 m}^2 \), as well as 115,473 with T2D. The magnitude of this population highlights the need to introduce effective and safe new drugs to reduce morbidity and mortality in these patients.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/7/2089/s1, Table S1: Number of patients with the four selection criteria of the DAPA-HF study in the REDINSCOR cohort in Spain. Table S2: Average prevalence of the four main selection criteria of the DAPA-HF study in the REDINSCOR cohort in Spain. Table S3: Total number of patients with heart failure, ejection fraction \( \leq 40\% \), New York Heart Association functional class II–IV, and glomerular filtration rate \( \geq 30 \text{ mL/min/1.73 m}^2 \) in Spain and its autonomous communities, according to prevalence data from the REDINSCOR registry (Tables S1 and S2).
Author Contributions: Conceptualization, J.F.D.-J., J.M.; methodology, J.F.D.-J., I.R.D., and J.M.; validation, all authors; formal analysis, A.C.-V. and I.R.D.; investigation, A.C.-V., I.R.D., J.F.D.-J., and J.M.; resources, N.F., H.T.-M., J.C., J.A.-G., and J.M.; data curation, A.C.-V., I.R.D., and J.M.; writing—original draft preparation, A.C.-V., I.R.D., J.F.D.-J. and J.M.; writing—review and editing, all authors; visualization, A.C.-V., I.R.D., and J.M.; supervision, J.M.; project administration, J.M.; funding acquisition, J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by Spain’s Ministry of Science and Innovation (Madrid, Spain), co-financed with European Union European Regional Development Funds (ERDF) (CIBERCV CB16/11/00229), as well as the Health Department of the Generalitat de Catalunya (Barcelona, Spain) through the Agència de Gestió d’Ajuts Universitaris de Recerca de Catalunya (AGAUR) (Barcelona, Spain) (2017SGR222), the Strategic Plan for Research and Health Innovation (PERIS) (Barcelona, Spain) (SLT06/17/00029 to I.R.D.), and the Private Foundation Daniel Bravo Andreu (Barcelona, Spain) (J.A.-G.). CIBER of Cardiovascular Diseases (CIBERCV) is an initiative of the Instituto de Salud Carlos III (Madrid, Spain).

Acknowledgments: We appreciate the English language editing done by Elaine Lilly, PhD, of Writer’s First Aid.

Conflicts of Interest: J.F.D.-J. reports consultancy fees from AstraZeneca; N.F. reports grants and consultancy fees from Novartis, Bayer, Rovi, and AstraZeneca; J.A.-G. reports consultancy fees from AstraZeneca, Boehringer Ingelheim, and Lilly; J.M. reports grants and consultancy fees from AstraZeneca, Sanofi, Shire, Gilead, Daichii-Sankyo, Genincode, and Ferrer. The other authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, and interpretation of data; in the writing of the manuscript; and in the decision to publish the results.

References
1. Ponikowski, P.; Voors, A.A.; Anker, S.D.; Bueno, H.; Cleland, J.; Coats, A.; Falk, V.; González-Juanatey, J.R.; Harjola, V.P.; Jankowska, E.A.; et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur. Heart J. 2016, 37, 2129–2200. [CrossRef] [PubMed]
2. Heidenreich, P.A.; Albert, N.M.; Allen, L.A.; Bluemke, D.A.; Butler, J.; Fonarow, G.C.; Ikonomidis, J.S.; Khavjou, O.; Konstam, M.A.; Maddox, T.M.; et al. Forecasting the impact of heart failure in the United States: A policy statement from the American Heart Association. Circ. Heart Fail. 2013, 6, 606–619. [CrossRef]
3. Carlisle, M.A.; Fudim, M.; Devore, A.D.; Piccini, J.P. Heart Failure and Atrial Fibrillation, Like Fire and Fury. JACC: Heart Fail. 2019, 7, 447–456. [CrossRef] [PubMed]
4. National Statistics Institute. INEBase. Deaths according to Causes by Sex and Age Group. Available online: https://www.ine.es/jaxiT3/Datos.htm?t=7947#tabs-tabla (accessed on 18 March 2020).
5. Chioncel, O.; Lainscak, M.; Seferovic, P.M.; Anker, S.; Crespo-Leiro, M.G.; Harjola, V.-P.; Parissis, J.; Laroche, C.; Piepoli, M.; Fonseca, C.; et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC Heart Failure Long-Term Registry. Eur. J. Heart Fail. 2017, 19, 1574–1585. [CrossRef] [PubMed]
6. Jiménez-Navarro, M.; Castillo, J.; Marrero, M.A.R.; Anguita-Sánchez, M. Influence of Gender on Long-term Prognosis of Patients With Chronic Heart Failure Seen in Heart Failure Clinics. Clin. Cardiol. 2010, 33, E13–E18. [CrossRef] [PubMed]
7. Otero, B.; Pernamany-Miralda, G.; Cuixart, C.B.; Costa, J.A.; Blázquez, E.S.; INCA investigators. Clinical profile and management patterns in outpatients with heart failure in Spain: INCA study. Aten. Primaria 2009, 41, 394–401. [CrossRef]
8. Lupón, J.; Díez-López, C.; De Antonio, M.; Domingo, M.; Zamora, E.; Moliner, P.; González, B.; Santesmases, J.; Troya, M.I.; Bayés-Genis, A. Recovered heart failure with reduced ejection fraction and outcomes: A prospective study. Eur. J. Heart Fail. 2017, 19, 1615–1623. [CrossRef] [PubMed]
9. Delgado, J.F.; Oliva, J.; Llano, M.; Pascual-Figal, D.A.; Grillo, J.J.; Comín-Colet, J.; Díaz, B.; De La Concha, L.M.; Martí, B.; Peña, L.M.; et al. Health Care and Nonhealth Care Costs in the Treatment of Patients with Symptomatic Chronic Heart Failure in Spain. Rev. Esp. Cardiol. (Eng. Ed.) 2014, 67, 643–650. [CrossRef]
10. Oliva, J.; Jorgensen, N.; Barrios, J.M.R. Carga socioeconómica de la insuficiencia cardíaca: Revisión de los estudios de coste de la enfermedad. Pharm. Span. Res. Artic. 2010, 7, 68–79. [CrossRef]
21. Baglioni, P.; Wiviott, S.D.; Raz, I.; Sabatine, M.S.; Akinci, B. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N. Engl. J. Med. 2019, 380, 1880–1881. [CrossRef]

22. McMurray, J.J.; Solomon, S.D.; Inzucchi, S.E.; Köber, L.; Kosiborod, M.N.; Martínez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Bélohlávěk, J.; et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N. Engl. J. Med. 2019, 381, 1995–2008. [CrossRef]

23. Crespo-Leiro, M.G.; Barge-Caballero, E.; Segovia-Cubero, J.; González-Costello, J.; López-Fernández, S.; García-Pinilla, J.M.; Almenar-Bonet, L.; De Juan-Bagué, J.; Roig-Minguell, E.; Bayés-Genís, A.; et al. Hyperkalemia in heart failure patients in Spain and its impact on guidelines and recommendations: ESC-EORP-HFA Heart Failure Long-Term Registry. Rev. Esp. Cardiol. (Eng. Ed.) 2020, 73, 313–323. [CrossRef]

24. Hernández, Á.; Delgado, J.F.; Cinca, J.; Fernández-Avilés, F.; Marrugat, J. Prevalence and incidence of hyperkalaemia in the Spanish population with heart failure with reduced ejection fraction: A systematic review and populational relevance. Rev. Clin. Esp. 2018, 218, 253–260. [CrossRef]

25. McMurray, J.J.; DeMets, D.L.; Inzucchi, S.E.; Köber, L.; Kosiborod, M.N.; Langkilde, A.M.; Martínez, F.A.; Bengtsson, O.; Ponikowski, P.; Sabatine, M.S.; et al. A trial to evaluate the effect of the sodium–glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur. J. Heart. Fail. 2019, 21, 665–675. [CrossRef]

26. National Statistics Institute. INEbase. Resident Population by Date, Sex, Age Group and Nationality. Available online: https://www.ine.es/jaxiT3/Tabla.htm?+t=9683&L=0 (accessed on 5 February 2020).

27. Álvarez-García, J.; Salamanca-Bautista, P.; Ferrero-Gregori, A.; Montero-Pérez-Barquero, M.; Puig, T.; Aramburu-Bodas, Ó.; Vázquez, R.; Formiga, F.; Delgado, J.; Delgado, J.F.; et al. Prognostic Impact of Physician Specialty on the Prognosis of Outpatients With Heart Failure: Propensity Matched Analysis of the REDINSCOR and RICA Registries. Rev. Esp. Cardiol. (Eng. Ed.) 2017, 70, 347–354. [CrossRef]
28. González-Juanatey, J.R.; Ezquerra, E.A.; Martínez-Sellés, M.; Gutiérrez, P.C.; Nocito, A.D.S.; Fradera, I.Z. Heart failure in outpatients: Comorbidities and management by different specialists. The EPISERVE Study. Rev. Esp. Cardiol. 2008, 61, 611–619. [CrossRef]

29. Otero-Raviña, F.; Grigorian-Shamagian, L.; Fransi-Galiana, L.; Názara-Otero, C.; Fernández-Villaverde, J.M.; Del Alamo-Alonso, A.; Nieto-Pol, E.; De Santiago-Boullón, M.; López-Rodríguez, I.; Cardona-Vidal, J.M.; et al. Galician study of heart failure in primary care (GALICAP Study). Rev. Esp. Cardiol. 2007, 60, 373–383. [CrossRef] [PubMed]

30. Pascual-Figal, D.A.; Ferrero-Gregori, A.; Otero, I.G.; Vazquez-Garcia, R.; Delgado, J.F.; Álvarez-García, J.; Gimeno, J.R.; Wörner-Diz, E.; Bardájí, A.; Alonso-Pulpon, L.; et al. Mid-range left ventricular ejection fraction: Clinical profile and cause of death in ambulatory patients with chronic heart failure. Int. J. Cardiol. 2017, 240, 265–270. [CrossRef] [PubMed]

31. Murphy, N.F.; Simpson, C.R.; McAlister, F.A.; Stewart, S.; MacIntyre, K.; Kirkpatrick, M.; Chalmers, J.; Redpath, A.; Capewell, S.; McMurray, J.J. National survey of the prevalence, incidence, primary care burden, and treatment of heart failure in Scotland. Heart 2004, 90, 1129–1136. [CrossRef] [PubMed]

32. Bleumink, G.S.; Knetsch, A.M.; Sturkenboom, M.C.J.M.; Straus, S.; Hofman, A.; Deckers, J.W.; Witteman, J.C.; Stricker, B.H. Quantifying the heart failure epidemic: Prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur. Heart J. 2004, 25, 1614–1619. [CrossRef] [PubMed]

33. Ceia, F.; Fonseca, C.; Mota, T.; Morais, H.; Matias, F.; De Sousa, A.; Oliveira, A.G.; on behalf of the EPICA Investigators. Prevalence of chronic heart failure in Southwestern Europe: The EPICA study. Eur. J. Heart Fail. 2002, 4, 531–539. [CrossRef]

34. Zinman, B.; Wanner, C.; Lachin, J.M.; Fitchett, D.; Bluhmki, E.; Hantel, S.; Matthies, M.; Devins, T.; Johansen, O.E.; Woeber, H.J.; et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N. Engl. J. Med. 2015, 373, 2117–2128. [CrossRef] [PubMed]

35. Neal, B.; Perkovic, V.; Mahaffey, K.W.; De Zeeuw, D.; Fulcher, G.; Erondo, N.; Shaw, W.; Law, G.; Desai, M.; Matthews, D.R.; et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N. Engl. J. Med. 2017, 377, 644–657. [CrossRef] [PubMed]

36. Figtree, G.A.; Rådholm, K.; Barrett, T.D.; Perkovic, V.; Mahaffey, K.W.; De Zeeuw, D.; Fulcher, G.; Matthews, D.R.; Shaw, W.; Neal, B. Effects of Canagliflozin on Heart Failure Outcomes Associated With Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus. Circulation 2019, 139, 2591–2593. [CrossRef]

37. Kato, E.T.; Silverman, M.G.; Mosenzon, O.; Zelniker, T.A.; Cahn, A.; Furtado, R.H.M.; Kuder, J.; Murphy, S.A.; Bhatt, D.L.; Leiter, L.A.; et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. Circulation 2019, 139, 2528–2536. [CrossRef]

38. Crespo-Leiro, M.G.; Anker, S.; Maggioni, A.P.; Coats, A.J.; Filippatos, G.; Ruschitzka, F.; Ferrari, R.; Piepoli, M.; Delgado, J.F.; Metra, M.; et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur. J. Heart Fail. 2016, 18, 613–625. [CrossRef] [PubMed]

39. De Frutos, F.; Mirabet, S.; Ortega-Paz, L.; Buera, I.; Darnés, S.; Farré, N.; Perez, B.; Adelino, R.; Bascompte, R.; Pérez-Rodón, J.; et al. Management of Heart Failure with Reduced Ejection Fraction after ESC 2016 Heart Failure Guidelines: The Linx Registry. ESC Heart Fail. 2020, 7, 26–36. [CrossRef]