Table 1
Details of implantation and function/programming during Holter monitoring

Implantation	
Fluoroscopy time	9.2 ± 14.6 min
Position, n	
High IVS	5
Mid IVS	3
RVOT	2
R wave	13 ± 4.4 mV
Impedance	1004 ± 273.7 Ω
Threshold (at 0.24 ms)	0.66 ± 0.43 V
Holter	
R wave	16.1 ± 5.5 mV
Impedance	690 ± 214.9 Ω
Threshold (at 0.24 ms)	0.55 ± 0.51 V
AV conduction, n	
Intact	1
Paroxysmal AV block	3
Second-degree AV block	5
Complete AV block	1
Programming, n	
VDD 40/105	7
VDD 50/105	3
Vector, n	
1 + 2	3
1 + 3	1
2 + 3	5
1 + 2 + 3	1
A3[a] threshold	8.0 ± 3.1 m/s^2
VE[b] window	620 ± 25.8 ms
A4[a] threshold	2.9 ± 1.3 m/s^2
A4 signal	4.4 ± 1.4 m/s^2

AV, atrioventricular; IVS, intraventricular septum; RVOT, right ventricular outflow tract.
Values are expressed as No. (%) or mean ± standard deviation.
[a] Automatic.
[b] Fixed.

In this pilot study, after manual adjustment of the atrial parameters, the percentage of AV synchrony in the short-term was high. The data on AV synchrony provided by the device appear to be reliable, when compared with the electrocardiographic recording. Nonetheless, larger analyses are needed to corroborate these findings.

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AUTHORS' CONTRIBUTIONS

S. Briongos Figuero: study design, data collection and analysis, writing of article. Á. Estévez Paniagua: study design, data collection and analysis, writing of article. A. Sánchez Hernández: data collection and critical review. A. Abad-Motos: data collection and critical review. A. Ruiz: data collection and critical review. R. Muñoz-Aguilera: data analysis, writing and critical review of the article.

CONFLICTS OF INTEREST

None of the authors declare conflicts of interest in relation to this study.

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REFERENCES

1. Cano Pérez Ó, Pombo Jiménez M, Lorente Carreño D, Chimeno García J; Spanish Pacemaker Registry. 16th Official Report of the Spanish Society of Cardiology Working Group on Cardiac Pacing (2018). *Rev Esp Cardiol.* 2019;72:944–953.
2. Steinwender C, Khelae SK, Garweg C, et al. Atrioventricular synchronous pacing using a leadless ventricular pacemaker: results from the MARVEL 2 Study. *JACC Clin Electrophysiol.* 2020;6:94–106.
3. Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P. A wavelet-based ECG delineator: evaluation on standard databases. *IEEE Trans Biomed Eng.* 2004;51:570–581.

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Temporal trends in hospitalization and in-hospital mortality rates due to heart failure by age and sex in Spain (2003-2018)

Tendencias temporales de las tasas de frecuentación y mortalidad hospitalaria de la insuficiencia cardiaca en España por edad y sexo (2003-2018)

To the Editor,

Heart failure (HF) has become a true cardiovascular "epidemic" with a declining mortality from acute heart disease and a prevalence that rises with age and is as high as 6.8% of the Spanish population older than 45 years, according to some studies.[1] In the PRICE trial conducted from 2004 to 2005, this prevalence increased exponentially with age and did not differ between men and women.[1] Other studies in various regions of Spain have reported an increased incidence of HF-related hospitalization in the past few decades,[2–4] but there are no recent data on hospitalization and mortality trends by age and sex for Spain as a whole.

Table 1
Hospitalization rate (admissions/100 000 inhabitants) by age group, for the total population and for men and women between 2003 and 2018 in Spain

	Age							
	35-44 y	45-64 y	65-74 y	75-79 y	80-84 y	85-89 y	90-94 y	> 94 y
Total								
2003	8.5	79.6	459.1	996.5	1559.7	2217.8	2410.4	2241.3
2004	9.4	81.0	482.2	1037.6	1656.2	2323.2	2747.6	2651.9
2005	8.8	79.9	482.9	1077.8	1757.2	2484.1	2889.5	2676.1
2006	9.6	78.5	467.6	1033.7	1709.2	2506.9	2943.9	2782.6
2007	9.2	82.3	491.5	1113.8	1876.0	2700.7	3178.5	3274.5
2008	8.6	75.8	478.6	1136.6	1911.1	2839.4	3568.5	3669.9
2009	7.9	73.8	457.6	1107.7	1856.3	2711.9	3350.0	3126.5
2010	8.1	74.8	451.2	1116.5	1891.1	2892.1	3397.4	3329.0
2011	7.6	73.1	430.4	1115.5	1899.2	2886.4	3461.5	3296.3
2012	8.0	73.6	420.0	1134.4	1943.2	2996.4	3587.6	3453.1
2013	7.4	72.8	407.2	1125.4	1931.4	2908.5	3485.7	3176.1
2014	7.1	71.9	411.0	1122.7	1879.1	2913.5	3484.7	3053.6
2015	7.7	73.4	420.6	1121.1	1979.0	3073.8	3801.0	3309.9
2016*	7.8	65.1	362.3	963.8	1769.6	2815.6	3539.5	3309.8
2017	8.1	67.1	378.1	938.8	1877.1	3051.6	3864.7	3644.7
2018	7.8	65.0	365.6	902.3	1821.5	3015.1	3818.4	3724.4
IRR	0.987	0.986	0.981	0.996	1.008	1.018	1.024	1.021
P	< .001	< .001	< .001	.356	.016	< .001	< .001	< .001
Men								
2003	12.1	104.3	528.3	1100.6	1577.8	2142.4	2309.6	2225.0
2004	13.5	109.5	554.5	1156.5	1744.2	2297.0	2728.3	2732.1
2005	12.0	107.0	550.8	1206.8	1867.3	2481.1	2790.3	2808.5
2006	13.0	106.7	547.1	1151.0	1835.8	2503.9	2919.9	2862.5
2007	13.1	113.1	580.3	1216.6	1993.5	2696.6	3255.8	3377.8
2008	11.9	103.5	560.2	1227.0	1959.8	2801.8	3261.6	3653.7
2009	10.8	100.3	540.6	1234.5	2011.4	2742.7	3368.3	3110.5
2010	11.3	103.9	543.8	1242.9	2051.0	2993.4	3499.0	3261.5
2011	10.0	102.4	525.8	1253.1	2055.9	2966.5	3523.7	3527.8
2012	10.9	102.2	515.9	1277.0	2078.6	3086.7	3775.5	3754.2
2013	10.2	102.7	511.7	1281.3	2110.0	3139.7	3773.2	3385.5
2014	9.6	101.4	515.1	1259.7	1971.2	2947.1	3356.2	2574.1
2015	11.3	104.3	540.1	1284.6	2138.8	3309.8	4004.5	3717.8
2016*	11.1	93.0	472.8	1106.2	1927.1	2944.6	3830.9	3274.7
2017	11.0	96.8	487.4	1122.1	2053.5	3288.0	4082.3	3948.0
2018	11.0	94.9	482.3	1063.6	1994.4	3251.1	4044.9	4037.7
IRR	0.986	0.992	0.991	1	1.011	1.024	1.03	1.023
P	< .001	< .001	< .001	.952	.003	< .001	< .001	< .001
Women								
2003	4.8	55.7	400.4	921.1	1548.7	2251.2	2447.9	2246.5
2004	5.3	53.2	421.0	951.8	1602.7	2334.1	2755.0	2624.1
2005	5.5	53.6	425.2	984.0	1689.9	2485.5	2927.0	2634.8
2006	6.2	51.0	399.7	947.7	1630.8	2508.3	2952.9	2757.7
2007	5.1	52.2	415.3	1037.9	1803.1	2702.5	3149.6	3242.9
2008	5.2	48.6	406.7	1066.2	1878.4	2860.0	3696.5	3675.5
2009	4.9	47.9	385.6	1012.4	1758.1	2696.0	3343.3	3131.3
2010	4.7	46.2	370.3	1020.9	1788.6	2839.9	3359.1	3347.3
2011	5.1	44.4	346.7	1010.9	1797.4	2844.8	3437.3	3227.9
2012	5.0	45.5	335.5	1025.9	1854.5	2948.7	3512.5	3363.7
2013	4.5	43.5	314.7	1006.3	1813.0	2785.3	3367.6	3113.9
2014	4.5	42.9	317.5	1015.0	1814.6	2893.7	3545.1	3224.6
2015	4.1	43.0	314.8	995.2	1871.0	2944.5	3714.7	3183.5
2016*	4.4	37.5	264.4	852.9	1662.7	2743.8	3414.1	3321.3
2017	5.2	37.9	281.3	794.7	1757.2	2918.1	3769.7	3548.1

Table 1 *(Continued)*
Hospitalization rate (admissions/100 000 inhabitants) by age group, for the total population and for men and women between 2003 and 2018 in Spain

	Age							
	35-44 y	45-64 y	65-74 y	75-79 y	80-84 y	85-89 y	90-94 y	> 94 y
2018	4.6	35.6	262.1	774.5	1703.6	2880.5	3718.5	3622.3
IRR	0.988	0.973	0.968	0.991	1.005	1.014	1.021	1.02
P	.016	< .001	< .001	.103	.094	< .001	< .001	< .001

ICD-10-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision; IRR, incidence rate ratio.
* In 2016, the Minimum Data Set coding system was updated from ICD-9-CM to ICD-10.

The aim of our study was to determine the influence of age and sex on HF-related hospitalization and in-hospital mortality trends in Spain by analyzing all hospital discharge reports listing HF as the principal diagnosis in Spanish public hospitals between 2003 and 2018. The data were obtained from hospital encounters recorded in the minimum data set (MDS) for hospitals between 1 January 2003 and 31 December 2018 with HF as the principal diagnosis. The hospitalization rate (hospital admissions due to HF/100 000 inhabitants) was analyzed. In 2016, the MDS coding system was updated in 2016 from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to the International Classification of Diseases, Tenth Revision (ICD-10). Consequently, the 2003 to 2015 and 2016 to 2018 series are not entirely homogeneous. However, not all hospital discharges were recorded in 2016, the first year that this change was made.

The risk-adjusted standardized mortality ratio (RA-SMR) for inpatients was calculated as described in recent articles.[5] The analysis was done according to the age groups listed in table 1 for the total population and for men and women. Temporal trends for hospitalization and in-hospital mortality rates during the study period were evaluated by a Poisson regression model, with year being the only independent variable. In all models, the incidence rate ratio (IRR) was calculated with 95% confidence intervals (95%CI).

A total of 6 308 178 hospitalizations due to cardiovascular disease were recorded from 2003 to 2018, with 1 720 458 (27.3%) specifically due to HF. Table 1 lists hospitalization rates for 2003 to 2018 by age group for the total population and for men and women. The total age- and sex-weighted HF-related hospitalization rate rose between 2003 and 2018 (from 326.5 to 352.4/100 000 inhabitants), but the difference was not significant (IRR = 1.003; $P < .001$). The rise in hospital admissions was due to an increase in the population aged 80 years or older, whereas rates remained stable or dropped significantly in the subgroup aged 35 to 74 years (table 1, total population; $P < .001$). The HF-related hospitalization rate was very significantly correlated with age (table 1, total population; $P < .001$). For instance, in 2018 it was 19.4 times higher in the group aged 75 years or older than in the group younger than 75 years. The same temporal trends were seen in men and women (table 1, men and women), with very significant increases seen between 2003 and 2018 in people aged 80 years or older. For patients younger than 75 years, the hospitalization rate for men was slightly (IRR = 1.008) but significantly ($P < .001$) higher whereas the hospitalization rate for women was lower (IRR = 0.982; $P < .001$). Overall, men were hospitalized more often across all age groups, and the increase between 2003 and 2018 was significantly higher in men in the age groups of 80 to 84, 85 to 89, and 90 to 94 years (men vs women, IRR = 1.011 vs 1.005; IRR = 1.024 vs 1.014 and IRR = 1.03 vs 1.021; $P < .001$ for all groups). Regarding in-hospital mortality, both crude and risk-adjusted (RA-SMR) rates were very significantly correlated with age in Spain as a whole ($P < .001$), with similar figures observed in both men and women over the entire period (RA-SMR, 10.59 vs 10.57). Crude and adjusted in-hospital mortality rates were unchanged during this period (table 2).

Table 2
Risk-adjusted standardized mortality ratio (RA-SMR, %) for men and women with heart failure between 2003 and 2018 in Spain

	CMR			RA-SMR		
Year	Men	Women	Total	Men	Women	Total
2003	10.97	10.24	11.55	10.84	10.9	10.78
2004	10.39	9.67	10.97	10.31	10.29	10.32
2005	10.89	10.31	11.35	10.89	10.99	10.81
2006	10.16	9.59	10.63	9.9	9.96	9.84
2007	10.50	10.10	10.83	10.28	10.41	10.17
2008	10.51	10.01	10.91	10.19	10.28	10.12
2009	10.40	9.98	10.74	10.15	10.19	10.12
2010	10.38	9.89	10.78	10.17	10.14	10.2
2011	10.52	10.17	10.81	10.38	10.42	10.34
2012	10.68	9.95	11.28	10.55	10.6	10.51
2013	10.24	9.79	10.63	10.18	10.19	10.17
2014	10.22	9.56	10.77	10.06	10.05	10.06
2015	10.95	9.99	11.78	10.8	10.78	10.82
2016*	10.74	10.12	11.27	10.21	10.25	10.2
2017	10.96	10.16	11.65	10.19	10.2	10.22
2018	11.44	10.48	12.27	10.23	10.27	10.01
IRR	1.002	1.001	1.004	0.999	0.998	0.999
P	.240	.538	.135	.349	.252	.375
Total	10.35	10.39	10.32	10.59	10.59	10.57

CMR, crude mortality rate; ICD-10-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision; IRR, incidence rate ratio; RA-SMR, risk-adjusted standardized mortality ratio.
* In 2016, the coding system was updated from ICD-9-CM to ICD-10.

In conclusion, in Spain, HF-related hospitalizations (hospitalizations/100 000 inhabitants) between 2003 and 2018 were higher in men but lower in women. However, this increase in hospital admissions was not uniform across all age groups, but seemed to be limited to the population aged 80 years or older, as both groups showed a significant decrease in people younger than 75 years between 2003 and 2018. In-hospital mortality was similarly high in men and women, around 10%, and has not declined. These data reveal the challenges of designing measures to reduce HF-related hospitalization and in-hospital mortality rates in the older population in Spain.

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AUTHORS' CONTRIBUTIONS

M. Anguita Sánchez, J.L. Bonilla Palomas, and F.J. Elola Somoza were responsible for the idea and conception of the study and for writing the article. M. García Márquez and J.L. Bernal Sobrino performed the design and statistical analysis and prepared the tables. F. Marín Ortuño was project coordinator and reviewed the document.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest with regard to this project.

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REFERENCES

1. Anguita M, Crespo-Leiro MG, de Teresa E, et al. Prevalencia de la insuficiencia cardíaca en la población general española mayor de 345 años Estudio PRICE. *Rev Esp Cardiol.* 2008;61:1041–1049.
2. Brotons C, Moral I, Ribera A, et al. Tendencias de la morbimortalidad por insuficiencia cardíaca en Cataluña. *Rev Esp Cardiol.* 1998;51:972–976.
3. López-Mesa JB, Andrés de Llano JM, López-Fernández L, et al. Evolución de las tasas de hospitalización y mortalidad hospitalaria por enfermedades cardiovasculares agudas en Castilla y León, 2001-2015. *Rev Esp Cardiol.* 2018;71:95–104.
4. Anguita Sánchez M, Bonilla Palomas JL, García Márquez M, Bernal Sobrino JL, Fernández Pérez C, Elola Somoza FJ. Tendencias temporales en ingresos y mortalidad hospitalaria por insuficiencia cardiaca en España, 2003-2015: diferencias por comunidades autónomas. *Rev Esp Cardiol.* 2020;73:1075–1077.
5. Martínez-Santos P, Bover R, Esteban A, et al. Mortalidad hospitalaria y reingresos por insuficiencia cardiaca en España Un estudio de los episodios índice y los reingresos por causas cardiacas a los 30 días y al año. *Rev Esp Cardiol.* 2019;72:988–1004.

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Prevalence and characteristics of clonal hematopoiesis in heart failure

Prevalencia y características de la hematopoyesis clonal en insuficiencia cardiaca

To the Editor,

Somatic mutations causing clonal expansion of hematopoietic cells (clonal hematopoiesis of indeterminate potential [CHIP]) increase with age and are associated with a higher risk of developing a hematological malignancy.[1] In the cardiovascular field, they have been found to be associated with atherosclerosis and inflammation.[2] Limited information is available in chronic heart failure (HF).

We studied a consecutive cohort of 60 patients with chronic HF without a previous history of cancer. Baseline characteristics are detailed in table 1. The study was performed in accordance with the ethics committee of Germans Trias and Pujol Hospital and all patients signed an informed consent form. Targeted deep sequencing was performed on a custom panel including 43 myeloid- and CHIP-related genes, using deoxyribonucleic acid extracted from peripheral blood samples. Libraries were prepared using the SureSelect QXT capture chemistry (Agilent Technologies, United States) and sequenced on a HiSeq2500 following a 2 x 75 bp paired-end reads standard protocol (Illumina, United States) at a mean depth of coverage of 2905-fold. Reads were aligned using BWA 0.7.12. Packages SAMtools 1.2 and VarScan 2.4.0 were used for variant calling without variant allele frequency (VAF) threshold. Sequencing and mapping errors were removed by discarding variants with a low mapping quality (< 20), variants located at highly variable regions, and variants occurring in $\geq 5\%$ of the cohort. Synonymous variants and variants with a minor allele frequency $> .01$, according to available population databases, were also excluded. Statistical analysis was performed using the statistical package SPSS, version 23.0 (SPSS Inc, United States). We reviewed the largest reported CHIP cohorts to determine the prevalence of CHIP.

CHIP was found in 28% of patients with a total of 30 variants detected. Overall, 9 (15%) patients carried 1 mutation, 4 (7%) had 2 concurrent mutations, 3 (5%) had 3 mutations, and 1 (2%) patient had 4. Consistent with previous studies, the prevalence of CHIP increased with age: 67% in patients ≥ 80 years (n = 8), 36% between 70 and 79 years (n = 15), 25% between 60 and 69 years (n = 16) and 17% between 50 and 59 years (n = 12) ($P = .01$; figure 1A). Of note, no CHIP carriers were detected in patients < 50 years (n = 9). The mean number of mutations detected per patient also increased with age: 2.3 (≥ 80 years), 1.7 (70-79 years), 1.4 (60-69 years), and 1 (< 60 years). The frequency of CHIP in HF was considerably higher in all age groups than in previously published cohorts, including unselected populations as well as patients with coronary heart disease.[2] However, this observation needs to be interpreted cautiously given that the prevalence of CHIP in the reported cohorts may have been influenced by the variety of sequencing technologies used in these studies, some of which did not reach the sensitivity reported for some of the variants detected in the current study. According to previous studies, the most frequently affected gene was *DNMT3A* (17%), followed by *TET2* (8%). Experimental studies have reported that mutations in these 2 genes promote cardiac dysfunction in murine models of HF.[3,4] Recurrent mutations were also detected in 2 patients (3%) in *JAK2* and *PPM1D*,