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ORIGINAL RESEARCH

Heart Failure–Related Death in Subjects With Atrial Fibrillation in the United States, 1999 to 2020

Marco Zuin, MD, MS*; Matteo Bertini, MD, PhD*; Francesco Vitali, MD, PhD; Mintu Turakhia, MD, MAS; Giuseppe Boriani, MD, PhD

BACKGROUND: Population-based data on heart failure (HF)-related death in patients with atrial fibrillation (AF) are lacking. We assessed HF-related death in people with AF in the United States over the past 21 years and examined differences by age, sex, race, ethnicity, urbanization, and census region.

METHODS AND RESULTS: Data were extracted from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research to determine trends in age-adjusted mortality rates per 100 000 people, due to HF-related death among subjects with AF aged ≥15 years. To calculate nationwide annual trends, we assessed the average annual percent change (AAPC) and annual percent change with relative 95% CIs using joinpoint regression. Between 1999 and 2020, 916 685 HF-related deaths (396 205 men and 520 480 women) occurred among US adults having a concomitant AF. The overall age-adjusted mortality rates increased (AAPC: +4.1% [95% CI, 3.8–4.4]; $P<0.001$), especially after 2011 (annual percent change, +6.8% [95% CI, 6.2–7.4]; $P<0.001$) in men (AAPC, +4.8% [95% CI, 4.4–5.1]; $P<0.001$), in White subjects (AAPC: +4.2% [95% CI, 3.9 to 4.6]; $P<0.001$) and in subjects aged <65 years (AAPC: +7.5% [95% CI, 6.7–8.4]; $P<0.001$). The higher percentage of deaths were registered in the South (32.8%). During the first year of the COVID-19 pandemic, a significant excess in HF-related deaths among patients with AF aged >65 years was observed.

CONCLUSIONS: A worrying increase in the HF-related mortality rate among patients with AF has been observed in the United States over the past 2 decades.

Key Words: atrial fibrillation ■ heart failure ■ death ■ trends

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide.[1] According to recent epidemiological projections, the prevalence of AF will exceed 12 million people in the United States by 2030,[2,3] generating important repercussion on the associated cardiovascular morbidity and death.[4,5] Similarly, heart failure (HF) remains a major public health issue,[6] affecting more than 5 million Americans[7] and increasing both the cardiovascular-related death and morbidity rates, especially among older subjects.[8] AF is a common comorbidity in patients with HF with an estimated prevalence ranging from 25% to 39% in subjects with preserved ejection fraction.[9,10] Conversely, in patients with a reduced ejection fraction the prevalence of AF increases with worsening New York Heart Association class, ranging from 4.2% for class I to 49.8% for class IV.[9,10]

From a pathophysiological perspective, AF and HF share mutual bidirectional interactions and risk factors that lead to a vicious circle, with AF worsening HF

Correspondence to: Matteo Bertini, MD, PhD, FAIAC, Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, 44142 Cona, Ferrara, Italy.
Email: matteo.bertini@unife.it
*M. Zuin and M. Bertini contributed equally as co-first authors.

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CLINICAL PERSPECTIVE

What Is New?

- The heart failure–related mortality rate in patients with atrial fibrillation has increased in the United States, especially in men aged <65 years, with differences across different census regions, over the past 2 decades.
- This worrying increase was mainly driven by the increased of heart failure–related death in patients with atrial fibrillation having as underlying causes of death hypertensive heart disease and chronic obstructive pulmonary disease.

What Are the Clinical Implications?

- Preventive and treatment strategies for atrial fibrillation in patients with heart failure have not penetrated equally with ethnic and regional disparities.
- The observed increasing mortality trend warrants an intensification of public health efforts aimed to promptly identify and treat these patients, increasing the promotion of targeted health policy measures.

Nonstandard Abbreviations and Acronyms

AAMR	age-adjusted mortality rate
AAPC	average annual percent change
APC	annual percent change
CDC	Centers for Disease Control and Prevention's
WONDER	Wide-Ranging Online Data for Epidemiologic Research

and vice versa.[10–12] Recent analyses, performed in the United States, have showed that both cardiovascular deaths related to AF[13] and HF[14] are increasing at an alarming rate. However, the contemporary burden and trends regarding HF-related death in patients with AF have not yet been investigated. Epidemiological data assessing the demographic and regional distribution of HF-related deaths in AF remains crucial to identify patients at highest risk who may benefit from targeted interventions.[15] Therefore, the aim of the present study is to assess current trends in HF-related death among patients with AF over the past 2 decades and determine differences by sex, age, race, ethnicity, urbanization, and census region, using the data from US Centers for Disease Control and Prevention's (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER) data set.[16]

METHODS

Study Population

We performed a retrospective cohort study aimed to assess the HF-related mortality rate in patients with concomitant AF in the United States over the past 2 decades. Data were retrieved through the publicly available CDC's WONDER[16] data set, which provides information from death certificates of all US residents according to the *International Classification of Diseases*, *Tenth Revision* (*ICD-10*). Moreover, this data set provides mortality estimates by age, sex, race, ethnicity, urbanization category, and census region. In the analysis, we included deaths in adults (aged >15 years) occurring between 1999 and 2020. Specifically, decedents were ascertained when HF (*ICD-10* codes I11.0, I13.0, I13.2, and I50.x)[13] were listed as the primary cause of death and AF (*ICD-10* code I48)[14] was listed as a contributing cause of death. Although *ICD-10* codes were implemented in billing and care of patients at the end of 2015, the World Health Organization authorized the publication of *ICD-10* in 1999. This was implemented for mortality coding and classification for cause of death on death certificates in the United States beginning in 1999 and spanning the entire study period.[17] Additionally, to further characterize the trends in of HF-related death in subjects with AF we also analyzed the trends of the first 5 underlying causes of deaths over the entire study period.

For sex-, race-, and ethnicity-specific estimates, we used annual national population totals for sex, age group, race, and Latinx/Hispanic ethnicity obtained by the US Census Bureau.[18] The stratification between urban and rural counties was performed in accordance with the 2013 National Center for Health Statistics Urban–Rural Classification Scheme. Ethnicity was defined as Latinx/Hispanic and non-Latinx/Hispanic, while race was categorized as White, Black, American Indian or Alaska native, and Asian or Pacific Islander. Furthermore, mortality trends were also analyzed by the US census regions (Northeast, Midwest, South, and West). The study did not require institutional review board approval since the analysis was based on anonymized and publicly available data. All data are publicly available consulting the CDC WONDER data set and can be accessed at https://wonder.cdc.gov/mcd.html.

Data Extraction

Data extraction and validation were performed separately by 2 independent investigators (M.Z. and M.B.). Specifically, the population size, number of deaths for all causes as well as data on HF-related death in patients with AF, stratified by age class, sex, race, ethnicity, urbanization, and census region were abstracted for the entire study period.

Statistical Analysis

HF age-adjusted mortality rates (AAMRs) in subjects with AF, per 100 000 people, with the relative 95% CI, were calculated by standardizing the related deaths using the annual national population totals from the US Census Bureau and the 2000 US standard population.[18] Proportionate death was defined as the number of HF-related deaths in patients with AF per 1000 deaths due to all causes. To calculate nationwide annual trends in HF-related death in patients with AF, we assessed the annual percent change (APC) as well as average annual percent change (AAPC) and relative 95% CIs. Since the abstracted data contain 22 time points, we identified a maximum of 4 potential inflection points across the study period, as currently suggested by the current guidelines.[19] Statistical analyses were performed using joinpoint regression (Joinpoint, version 4.6.0.0; National Cancer Institute, Bethesda, MD). Specifically, joinpoint regression software determines the inflection points for each population of interest, and accordingly across the study period, time intervals of interest vary. A parallelism test was used to examine whether groups have a similar or different trends.[20] A significant *P* value on this interaction test indicated that the 2 trends, in terms of AAPC, were statistically significantly different from each other. The trends of the first 5 of the underlying causes of death were assessed using linear models in the SPSS package version 20.0 (SPSS, Chicago, IL). Statistical significance was prespecified at $P \leq 0.05$ for findings in the entire population.

RESULTS

Between 1999 and 2020, 916 685 HF-related deaths (396 205 men and 520 480 women) occurred among US adults aged ≥15 years having a concomitant AF. In particular, the absolute number of deaths increased from 22 075 subjects in 1999 (8190 men and 13 885 women) to 85 311 subjects (41 827 men and 43 484 women) in 2020 (Figure 1A). HF-related death in patients with AF increased with age, with a seemingly exponential distribution, especially in subjects aged >45 years (Figure 1B). Accordingly, the AAMR for HF-related death in patients with AF increased from 8.15 (95% CI, 8.05–8.26) per 100 000 in 1999 to 20.48 (95% CI, 20.34–20.62) per 100 000 in 2020 (AAPC, +4.1% [95% CI, 3.8–4.4]; *P*<0.001; Table 1 and Figure 2). Notably, the AAMR slightly increased from 1999 to 2011 (APC, +2.1% [95% CI, 1.8–2.5]; *P*<0.001) and then sharply increased from 2011 to 2020 (APC, +6.8% [95% CI, 6.2–7.4]; *P*<0.001).

Sex

US men with HF and concomitant AF (AAPC, +4.8% [95% CI, 4.4–5.1]), compared with women (AAPC, +3.6% [95% CI, 3.3–4.0]), experienced a greater AAMR increase over the entire study period (*P* for parallelism=0.002). Specifically, in men, a slight increase from 1999 to 2011 (APC, +2.6% [95% CI, 2.2–2.9]) was followed by a more pronounced slope from 2011 to 2020 (APC, +7.8% [95% CI, 7.1–8.4]). Similarly, in women, the AAMR increased from 1999 to 2012 (APC, +2.0% [95% CI, 1.7–2.4]) and then further increased between 2012 and 2020 (APC, +6.3% [95% CI, 5.5–7.1]; Table 1 and Figure 3).

Race and Ethnicity

In White individuals, the AAMR for HF-related death in patients with AF rose from 8.49 (95% CI, 8.37–8.60) per 100 000 in 1999 to 21.76 per 100 000 (95% CI, 21.61–21.92) in 2020 (AAPC, +4.2% [95% CI, 3.9–4.6]). The AAMR slightly increased from 1999 to 2011 (APC, +2.2 [95% CI, 1.9–2.6]; *P*<0.001) and then further increased from 2011 to 2020 (APC, +7.0% [95% CI, 6.4–7.6]). In non-Latinx/Hispanic Black individuals, the AAMR rose from 5.41 (95% CI, 5.10–5.72) per 100 000 in 1999 to 14.62 (95% CI, 14.24–15.01) per 100 000 in 2020 (AAPC, +4.2% [95% CI, 3.6–4.9]). A slightly increased from 1999 to 2011 (APC, +1.8% [95% CI, 1.0–2.5]; *P*<0.001) was followed by a more pronounced slope from 2011 to 2020 (APC, +7.6% [95% CI, +7.6% 6.4–8.9]). In Asian/Pacific Islanders, the AAMR rose from 4.05 (95% CI, 3.47–4.63) per 100 000 in 1999 to 8.18 (95% CI, 7.79–8.57) per 100 000 in 2020 (AAPC, +3.5% [95% CI, 2.4–4.6]). The relative AAMR increased between 1999 to 2015 (APC, +2.6% [95% CI, 1.8–3.4]) and then further increased from 2015 to 2020 (APC, +6.5% [95% CI, 1.9–11.2]). Similarly, in American Indians/Alaska natives, the AAMR rose from 5.22 (95% CI, 3.84–6.02) per 100 000 in 1999 to 12.56 (95% CI, 11.31–13.80) per 100 000 in 2020 (AAPC, +4.5% [95% CI, 3.4–5.7]). Also, in this demographic group, a slight increase from 1999 to 2010 (APC, +2.7% [95% CI, 1.0–4.3]) was followed by a more pronounced slope from 2010 to 2020 (APC, +6.7% [95% CI, +4.7–8.7]). Regarding the ethnicity, only data for Latinx/Hispanic individuals were available. In this group, the AAMR rose from 4.18 (95% CI, 3.78–4.57) per 100 000 in 1999 to 11.23 (95% CI, 10.88–11.58) per 100 000 in 2020 (AAPC, +4.5% [95% CI, 3.9–5.0]). Specifically, the relative AAMR increased from 1999 to 2011 (APC, +2.3% [95% CI, 1.6–3.0]) and then further increased from 2011 to 2020 (APC, +7.4% [95% CI, 6.3–8.6]; Table 1).

Age

Decedents aged <65 years accounted for 42 247 (27 595 men and 15 652 women; 4.5%) HF-related deaths in patients with AF. Although the AAMR was markedly lower than in patients aged ≥65 years (876 438 decedents: 368 610 men and 507 828

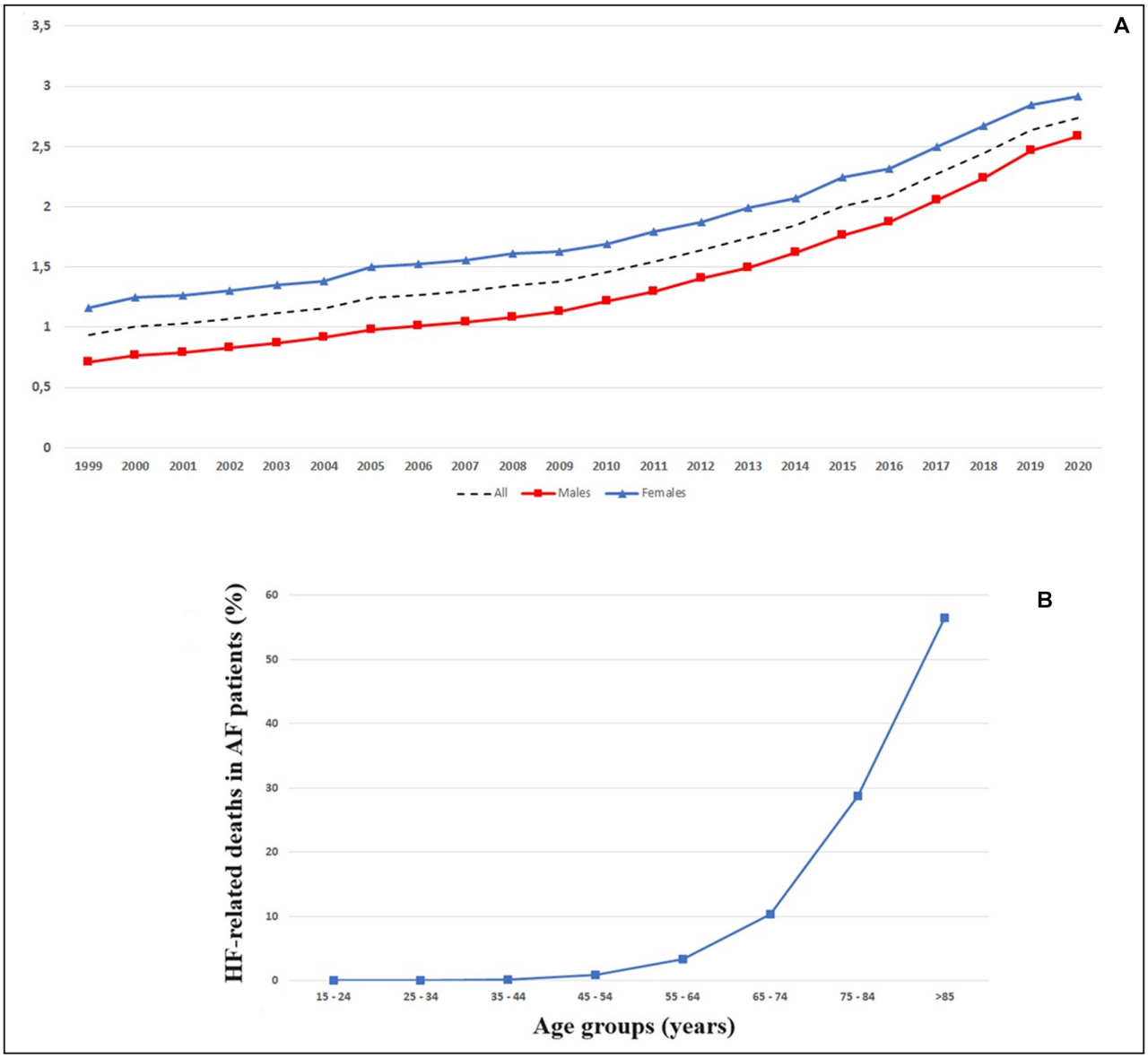

Figure 1. Proportional death and HF-related death in patients with AF according to age groups.
A, Proportional death over time. This is defined as the ratio between the number of HF-related deaths in subjects with AF per 1000 deaths due to all causes. **B**, Percentages of HF-related death in US subjects with AF by age groups, 1999 to 2020. AF indicates atrial fibrillation; and HF, heart failure.

women), the AAPC was twice as high in the younger group (AAPC: +7.5% [95% CI, 6.7–8.4]) compared with the older group (AAPC, +4.0% [95% CI, 3.7–4.3]); *P* for parallelism <0.001; Table 2).

Geographical Patterns

Over the study period, HF-related death in patients with AF similarly increased in both urban (AAPC, +4.0% [95% CI, 3.7–4.4]) and rural (AAPC: +4.6% [95% CI, 4.2–4.6]) areas, respectively (*P* for parallelism=0.12) (Table 3). The higher AAMRs were clustered in the West (14.1 per 100 000 [95% CI, 13.1–13.2]) and in the Midwest (13.2 per 100 000 [95% CI, 13.1–13.2]), despite the fact that a higher percentage of HF-related deaths in AF was registered in the South (32.8%; n=300 846). Full data regarding the HF-related death in patients with AF are presented in Tables S1 and S2.

Underlying Causes of Death

The first 5 underlying causes of death in patients with HF with AF were ischemic heart disease, hypertensive heart disease, cardiomyopathies, stroke, and chronic obstructive pulmonary disease, respectively. Specifically, from 1999 to 2020, the prevalence of HF decedents with AF having as underlying causes of death hypertensive heart disease (from 5.0% in 1999

Table 1. Age-Adjusted Mortality Rate Trend in US Subjects With Heart Failure and Atrial Fibrillation, 1999 to 2020, Stratified by Sex and Race or Ethnicity

	AAMR 1999 (95% CI)	AAMR 2020 (95% CI)	AAPC (95% CI), *P* value	Number of joinpoints	Period 1 [y]; APC (95% CI); *P* value	APC period 2 [y]; APC (95% CI); *P* value	*P* (for parallelism)
Overall	8.15 (8.05–8.26)	20.48 (20.34–20.62)	+4.1 (3.8–4.4); <0.001	1	[1999–2011]; +2.1 (1.8–2.5), <0.001	[2011–2020]; +6.8; (6.2–7.4), <0.001	…
Men	8.63 (8.44–8.82)	24.53 (24.30–24.77)	+4.8; (4.4–5.1); <0.001	1	[1999–2011]; +2.6 (2.2–2.9); <0.001	[2011–2020]; +7.8 (7.1–8.4); <0.001	0.002
Women	7.75 (7.62–7.88)	17.37 (17.21–17.54)	+3.6 (3.3–4.0); <0.001	1	[1999–2012]; +2.0 (1.7–2.4); <0.001	[2012–2020]; +6.3 (5.5–7.1); <0.001	
Race							
White	8.49 (8.37–8.60)	21.76 (21.61–21.92)	+4.2 (3.9–4.6); <0.001	1	[1999–2011]; +2.2 (1.9–2.6); <0.001	[2011–2020]; +7.0 (6.4–7.6); <0.001	White vs Black individuals, 0.48
Black	5.41 (5.10–5.72)	14.62 (14.24–15.01)	+4.2 (3.6–4.9); <0.001	1	[1999–2011]; +1.8 (1.0–2.5);<0.001	[2011–2020]; +7.6 (6.4–8.9);<0.001	White vs Asian/Pacific Islander individuals, *P*=0.003
Asian or Pacific Islander	4.05 (3.47–4.63)	8.18 (7.79–8.57)	+3.5 (2.4–4.6); <0.001	1	[1999–2015]; +2.6 (1.8–3.4); <0.001	[2015–2020]; +6.5 (1.9–11.2); <0.001	White vs Native Alaska/American Indian individuals, 0.33
Native Alaskan/ American Indian	5.22 (3.84–6.02)	12.56 (11.31–13.80)	+4.5 (3.4–5.7); <0.001	1	[1999–2010]; +2.7 (1.0–4.3); <0.001	[2010–2020]; +6.7 (4.7–8.7);<0.001	Black vs Asian/Pacific Islander individuals, 0.009 Black vs Native Alaskan/American Indian individuals, 0.10 Asian/Pacific Islander vs Native Alaskan/ American individuals, <0.001
Ethnicity							
Latinx/ Hispanic	4.18 (3.78–4.57)	11.23 (10.88–11.58)	+4.5 (3.9–5.0); <0.001	1	[1999–2011]; +2.3 (1.6–3.0); <0.001	[2011–2020]; +7.4 (6.3–8.6); <0.001	…

AAMR indicates age-adjusted mortality rate, expressed as deaths per 100 000 population; AAPC, average annual percent change; and APC, annual percent change.

to 8.2% in 2020; *P* for trend <0.001) or chronic obstructive pulmonary disease (from 4.2% to 4.8%; *P* for trend <0.001) increased. Conversely, subjects dying due to HF with AF presenting ischemic heart disease (from 38.3% in 1999 to 22.7% in 2020; *P* for trend <0.001) or stroke (from 3.1% in 1999 to 1.5% in 2020; *P* for trend <0.001) decreased. Finally, the trend of HF-related deaths in patients with AF having cardiomyopathies as underlying causes of death remained stable over the entire study period (from 2.0 in 1999 to 2.1 in 2020; *P*=0.86; Figure 4A through 4D).

Impact of COVID-19 Pandemic

During 2020, 85 311 deaths due to HF in patients with AF were registered in the United States. Of these, 57 373 and 27 938 were recorded in subjects with and without SARS-CoV-2 infection (Table S3). In that year, the overall HF-related AAMR in subjects with AF was 14.0 (95% CI, 13.9–14.1) per 100 000 and 20.6 (95% CI, 20.5–20.8) per 100 000 population in individuals with and without COVID-19 infection, respectively. The HF-related AAMR in COVID-19 patients with AF was higher in men than in women (17.6; 95% CI, 17.4–17.8 per 100 000 versus 10.8; 95% CI, 10.7–11.0 per 100 000), as well as in subjects aged >65 years (97.8 [95% CI, 96.9–98.6) per 100 000 compared with those aged <65 years (1.9% [95% CI, 1.8–2.0). HF-related deaths in subjects with COVID-19 were observed in 88.2% of patients aged >65 years.

DISCUSSION

In this 21-year retrospective analysis of mortality data from the CDC WONDER data set, the overall AAMR for HF-related deaths in patients with AF increased by ≈286.4%, especially in men. Furthermore, the

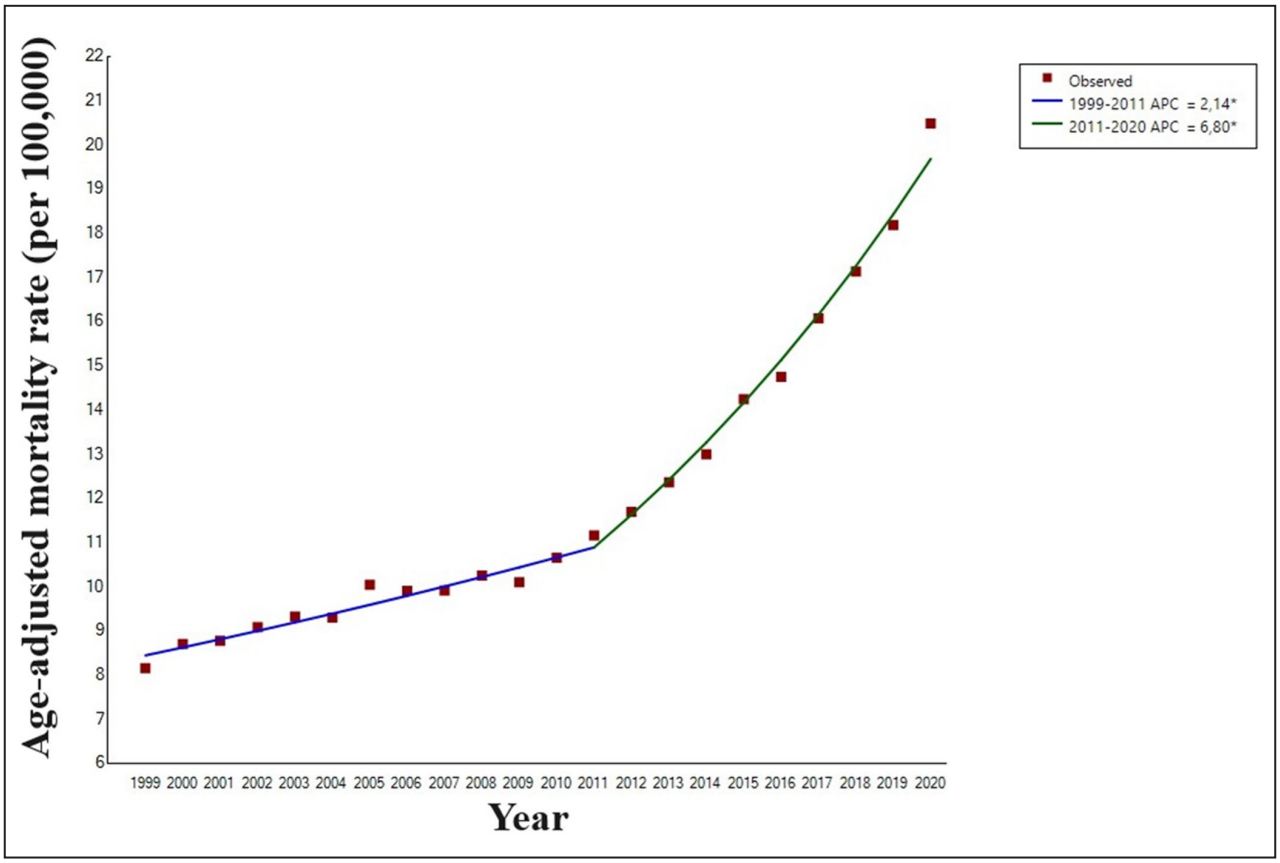

Figure 2. Trends in age-adjusted mortality rates related to heart failure in subjects with atrial fibrillation, in the United States, 1999 to 2020.
APC indicates annual percent change.

higher AAPC increase was observed in patients aged <65 years. Moreover, the COVID-19 pandemic, during its first year, determined a significant excess in HF-related deaths among patients with AF aged >65 years. As evidenced by the complementary analysis exploring the 5 most common underlying causes of death, the observed HF-related mortality trends in patients with AF may be explained by the increasing prevalence in subjects with hypertensive heart disease and chronic obstructive pulmonary disease. Traditionally, these conditions have been associated with a higher mortality risk either in patients with HF and patients with AF.[21–24]

Present findings are in accordance with previous investigations, always on the basis of the CDC WONDER data set, that separately assessed the HF-[13] and AF-[14] related mortality rates and their trends in the United States over the past 2 decades. Although our findings cannot confer causation, several previous analyses have shown a pathophysiological association between AF and HF and vice versa,[25–29] which increases the mortality risk across all HF subtypes.[30] A variety of explanations may support the observed trends. First, the prevalence of several cardiovascular risk factors and comorbidities for both HF and AF, such as obesity, arterial hypertension, and diabetes, especially among young adults, has risen, increasing the relative risk of death.[31–34] At the same time, the continuous improvement in the diagnosis of both HF and AF[35–37] may have facilitated the recognition of some previously "unexplained" deaths. Additionally, the aging of the population may have substantially contributed to the observed trends since a larger proportion of HF-related deaths in subjects with AF over time have been composed of older adults.[38]

However, the cardiovascular-related mortality rates may have been influenced by the presence of some competing risk factor events that could have precluded the occurrence of the cardiovascular outcome.[39] Indeed, in patients with HF, different concomitant conditions, such as diabetes, stroke, hemoglobin levels, and kidney function, may shift toward a higher rate of non–cardiovascular disease–related deaths, preventing the occurrence of cardiovascular events.[40]

Although the continuous improvement in the diagnostic and therapeutic approaches to HF and AF achieved over the past 2 decades, the rise in HF-related mortality rate among patients with AF aged <65 years is

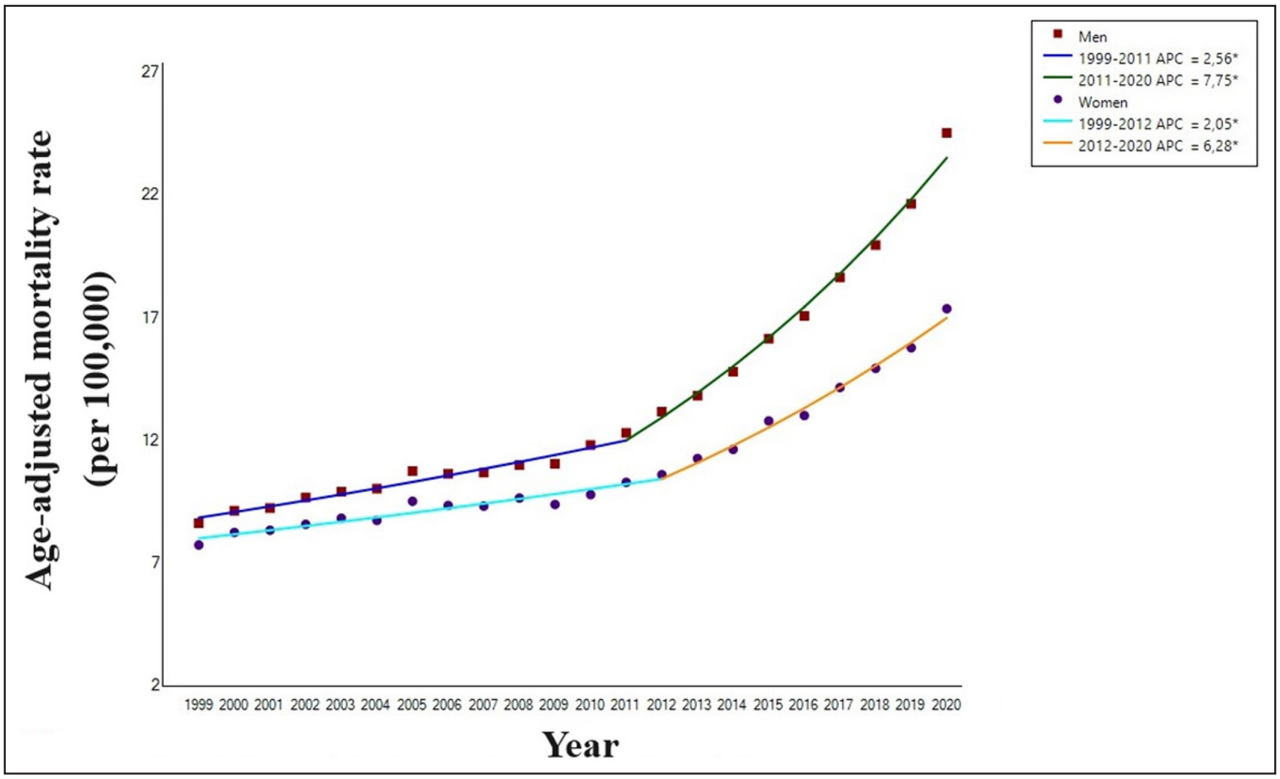

Figure 3. Trends in age-adjusted mortality rates related to heart failure in subjects with atrial fibrillation, stratified by sex, in the United States, 1999 to 2020.
APC indicates annual percent change.

particularly concerning because it may be interpreted as unexpected. Doubtless, the continuous increase in the prevalence of cardiovascular comorbidities in US young adults, including diabetes,[41] has significantly contributed to the increasing HF-related mortality trend in AF subjects. Furthermore, growing evidence has shown that psychosocial and lifestyle factors are important modulators of AF occurrence at a younger age.[1]

Our results also highlight important racial and ethnic disparities in patients. Although previous studies have demonstrated a higher prevalence of cardiovascular disease, comorbidities, and risk factors among Black, Asian, American Indian, Alaskan Native, and Hispanic individuals, their relative AAMR for HF-related death in subjects with AF was lower compared with White individuals. In this regard, disparities in diagnosis,

Table 2. Age-Adjusted Mortality Rate Trend in US Subjects With Heart Failure and Atrial Fibrillation, 1999 to 2020, Stratified by Age

	AAMR 1999 (95% CI)	AAMR 2020 (95% CI)	AAPC; (95% CI), *P*	Number of joinpoints	Period 1 [y]; APC (95% CI); *P* value	APC period 2 [y]; APC (95% CI); *P* value	*P* (for parallelism)
<65 y (all)	0.23 (0.21–0.25)	1.32 (1.28–1.36)	+7.5 (6.7–8.4); <0.001	1	[1999–2010]; +3.9 (2.8–5.1); <0.001	[2010–2020]; +11.6 (10.2–13.0); <0.001	…
Men	0.33 (0.11–0.15)	1.89 (1.83–1.96)	+8.1 (7.4–8.7); <0.001	1	[1999–2010]; +4.7 (3.8–5.6), *P*<0.001	[2010–2020]; +11.9 (10.7–13.1), *P*<0.001	0.46
Women	0.13 (0.11–0.15)	0.75 (0.71–0.79)	+7.5 (6.3–8.6);<0.001	1	[1999–2009]; +3.7 (1.9–5.6); <0.001	[2009–2020]; +11.0 (9.3–12.7); <0.001	
≥65 y (all)	62.93 (62.09–63.77)	152.90 (151.84–153.96)	+4.0 (3.7–4.3); <0.001	1	[1999–2011]; +2.1 (1.7–2.4); <0.001	[2011–2020]; +6.6 (6.0–7.2); <0.001	…
Men	66.03 (64.54–67.53)	181.05 (179.23–182.88)	+4.6 (4.2–4.9); <0.001	1	[1999–2011]; +2.5 (2.1–2.9); <0.001	[2011–2020]; +7.4 (6.8–8.1);<0.001	<0.001
Women	60.46 (59.45–61.48)	132.26 (130.98–133.54)	+3.5 (3.1–3.8); <0.001	1	[1999–2011]; +1.7 (1.3–2.2); <0.001	[2011–2020]; +5.8 (5.1–6.5); <0.001	

AAMR indicates age-adjusted mortality rate, expressed as deaths per 100 000 population; AAPC, average annual percent change; and APC, annual percent change.

Table 3. Age-Adjusted Mortality Rate Trend in US Subjects With Heart Failure and Atrial Fibrillation, 1999 to 2020, Stratified by Urbanization Level

	AAMR 1999 (95% CI)	AAMR 2020 (95% CI)	AAPC (95% CI); *P* value	Number of joinpoints	Period 1 [y]; APC (95% CI), *P* value	APC period 2 [y]; APC (95% CI), *P* value	*P* value
County-level urbanization							
Urban	7.95 (7.83–8.06)	19.58 (19.43–19.73)	+4.0 (3.7–4.4); <0.001	1	[1999–2011]; +2.2 (1.8–2.6); <0.001	[2011–2020]; +6 (6.0–7.2); <0.001	0.12
Rural	9.04 (8.78–9.29)	25.00 (24.63–25.38)	+4.6 (4.2–4.9); <0.001	1	[1999–2012]; +2.5 (2.1–2.9), <0.001	[2012–2020]; +8.1 (7.2–9.0); <0.001	

AAMR indicates age-adjusted mortality rate, expressed as deaths per 100 000 population; AAPC, average annual percent change; and APC, annual percent change.

awareness of the disease, access to advanced health care systems, or socioeconomic status may have influenced the observed trends. Additionally, we observed some geographic variations in HF-related death in individuals with AF, with the Midwestern regions having the highest burden compared with other census regions. These results are consistent with a previous analysis examining the HF-related mortality rates in the United States between 1999 and 2019 reporting a higher mortality rate in the same census regions.[14]

The major inflection point observed between 2011 and 2012 in HF-related mortality rates among patients with AF is probably due, at least in part, to the increased awareness on AF, and therefore to a greater diagnostic accuracy, as evidenced by the release of dedicated US guidelines in those years.[37] Moreover, also the publication of European guidelines on the management of patients with HF in 2012 have probably influenced the diagnostic management of these subjects in the United States.[42]

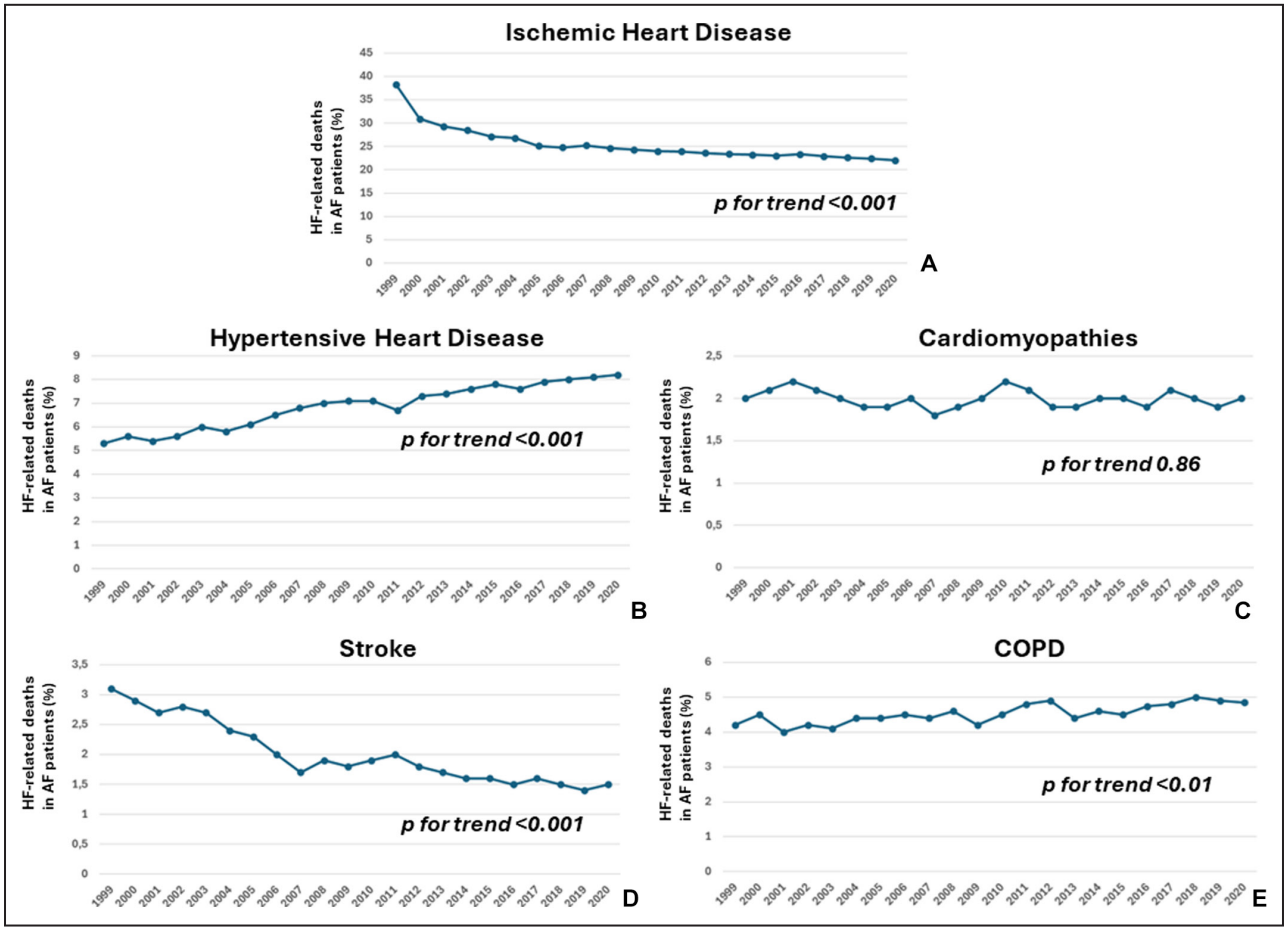

Figure 4. Changes in the first underlying causes of deaths among patients with HF having concomitant AF.
A, Ischemic heart disease; **B**, hypertensive heart disease; **C**, cardiomyopathy; **D**, stroke; and **E**, COPD. AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; and HF, heart failure.

As evidenced by our subanalysis, the first year of the COVID-19 pandemic significantly contributed to the observed trends.[43] Indeed, during 2020, an excess HF-related mortality rate in patients with AF was observed, especially in men aged >65 years. This phenomenon seems to be multifactorial. Indeed, new-onset AF was observed in about 6% of hospitalized patients with COVID-19, and almost half of them died during their index hospitalization.[44] Moreover, clinical evidence demonstrated that COVID-19, by a complex interaction between inflammation, prothrombotic state, and sympathetic–vagal imbalances increases the risk of AF.[45,46] Additionally, cardiac consultations, electrophysiology procedures,[47] and hospitalization for HF declined[48] during the pandemic, potentially influencing the outcome of these patients.[49,50] Furthermore, during the first year of the pandemic, US census regions were disproportionately affected by the COVID-19 pandemic, leading to a different mortality excess in the country.[51] Specifically, the higher COVID-19 related mortality rates were registered in the South due to a higher infection rate, limited access to health care resources, differences in the prevalence of underlying conditions associated with higher mortality rates, such as arterial hypertension, diabetes, and obesity as well as to different implementation of COVID-19 preventive strategies.[52]

The rising trend of HF-related death in patients with AF noted in the present analysis is concerning. This underscores the need for more robust cardiovascular surveillance in patients with HF through the implementation of opportunistic/systematic AF screening programs aimed to identify early the subjects at risk and to institute appropriate treatments.[53] Furthermore, the present data suggest that further research is warranted to understand which of the contributing factors is the primary driver of the trends and, if related to an increase in the disease burden, to reverse the observed increasing trend.[54] At the same time, the promotion of primordial, primary, and secondary prevention strategies remains fundamental to provide rapid and individualized expert-based care. Additionally, the present findings should be used as an impetus to redouble efforts to consider AF ablation as an early therapeutic option.[55,56] Indeed, the degree of atrial derangement, due to the underlying atrial fibrosis, remains a major determinant for AF outcomes[57] and for the maintenance of sinus rhythm in the long-term period.[58] In this regard, although AF ablation has been associated with a lower risk of HF hospitalization and all-cause death by several randomized controlled trials and small observational studies,[59] the beneficial effect of such electrophysiological procedure appears to be more modest analyzing large data set.[60] This phenomenon is likely to be multifactorial. Indeed, results derived from randomized controlled trials derived from a highly selected population, whereas such strict eligibility criteria are not used in daily clinical practice. Furthermore, the prevalence of comorbidities is frequently different comparing validating studies and population derived from a large database influencing the selection of patients for AF ablation; indeed, in daily practice, several patients are often considered poor candidates for the interventional procedure.[61] Finally, the timing of the procedure, which is currently very heterogeneous in clinical practice, may significantly impact patients' outcomes.[12]

Limitations

Our study has several limitations. As with any investigation relying on large nationwide administrative databases, we cannot exclude potential miscoding that may have impacted the accuracy of our results. However, death certificates remain a valuable health information source used worldwide for epidemiology, research, and public health policy. A previous analysis based on the Framingham Heart Study showed that death certificates were least accurate for individuals aged >85 years and that no change in coding accuracy was observed over time.[62] Furthermore, it has been reported that the amount of diagnostic information available to the certifying physician was associated with the reporting of chronic heart disease such as HF and AF.[63] Additionally, previous analyses, based on US subjects, although not representative for the entire country, showed an acceptable positive predictive value for both HF and AF of about 93%[64] and 88%,[65] respectively, using *ICD-10* codes for patients' identification. However, because up to one third of AF patients were asymptomatic, our findings may have conservatively underestimated the HF-related mortality rate over the study period. Moreover, no data regarding the patient's baseline cardiovascular condition, risk factors, and left ventricular ejection fraction at presentation were provided by the CDC WONDER data set, limiting our final conclusions. In the same manner, we cannot assess how many patients received any sort of treatment for HF and/or AF, making it impossible to explore procedure usage, including advanced AF therapies. We cannot exclude that education regarding the evaluation and management of acute HF and AF, as well as increased awareness on the diseases, may have ameliorated the diagnosis on death certificates.

CONCLUSIONS

In conclusion, the HF-related mortality rate in patients with AF has increased in the United States, especially in men with differences across different census regions. The observed mortality trend was coincident with the increase of HF-related death in patients with AF having as underlying causes of death hypertensive

heart disease and chronic obstructive pulmonary disease. This unexpected trend warrants an intensification of public health efforts aimed to promptly identify and treat AF in patients with HF, increasing promotion of targeted health policy measures.

ARTICLE INFORMATION

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Affiliations

Cardiology Unit, Department of Translational Medicine, Sant'Anna University Hospital, University of Ferrara, Ferrara, Italy (M.Z., M.B., F.V.); Division of Cardiovascular Medicine, The Center for Digital Health, Stanford University, Stanford, CA (M.T.); and Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, Italy University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy (G.B.).

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Supplemental Material

Tables S1–S3

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