ORIGINAL RESEARCH

Association of Atrial Fibrillation and/or Flutter With Adverse Cardiac Outcomes and Mortality in Patients With Wolff-Parkinson-White Syndrome

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Background: Wolff-Parkinson-White (WPW) syndrome is characterized by the presence of accessory pathways and development of potentially malignant arrhythmias that can lead to sudden cardiac death. We aimed to determine the impact of atrial fibrillation and/or flutter (AF/AFL) on adverse cardiac outcomes and mortality in patients with WPW syndrome.

Methods: This study identified a cohort of Military Health System patients with WPW syndrome from January 1, 2014, to December 31, 2019. The cohort was divided into 2 subgroups by the presence or absence of AF/AFL. Cardiac composite outcome and mortality were assessed. Kaplan-Meier curves were constructed to assess the bivariate association between exposure and these 2 study outcomes. Cox proportional models were used to estimate the hazard ratios and 95% CIs associated with the cardiac composite outcome and mortality.

Results: Of 35,539 patients included in the study, 19,961 were female (56.2%), the mean (SD) age was 62.9 (18.0) years, and 5291 patients (14.9%) had AF/AFL. The cardiac composite outcome and mortality incidence rates per 100 person-years in the AF/AFL vs non-AF/AFL subgroups were 8.18 vs 4.90, and 4.09 vs 2.13, respectively (P < .001). There were 3130 (8.8%) deaths. After adjusting for confounding variables, the AF/AFL subgroup maintained a 12% and 16% higher association with the composite outcome and mortality, respectively.

Conclusions: Patients with WPW syndrome and AF/AFL have a higher association with adverse cardiac outcomes and death. Consideration for more aggressive electrophysiology screening and ablation strategies may be warranted in this population.

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Wolff-Parkinson-White (WPW) syndrome is characterized by the presence of ≥ 1 accessory pathways and the development of both recurrent paroxysmal atrial fibrillation (AF) and supraventricular tachycardia that can lead to further malignant arrhythmias resulting in sudden cardiac death (SCD).[1-7] Historically, incidental, ventricular pre-excitation on electrocardiogram has conferred a relatively low SCD risk in adults; however, newer WPW syndrome data suggest the endpoint may not be as benign as previously thought.[7] The current literature has defined atrioventricular reentrant tachycardia triggering AF, rather than symptoms, as an independent risk factor for malignant arrhythmias. Still, long-term data detailing the association of AF with serious cardiac events and death in patients with WPW syndrome are still limited.[1-7]

While previous guidelines for the treatment of WPW syndrome only recommended routine electrophysiology testing (EPT) with liberal catheter ablation for symptomatic individuals, the 2015 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines now suggest its potential benefit for risk stratification in the asymptomatic population.[8-12] Given the limited existing data, more long-term studies are needed to corroborate the latest EPT recommendations before routinely applying them in practice. Furthermore, since concomitant AF can lead to adverse cardiac outcomes in patients with WPW syndrome, additional data evaluating this association are also necessary. In this study, we aimed to determine the impact of atrial fibrillation and/or flutter (AF/AFL) on adverse cardiac outcomes and mortality in patients with WPW syndrome.

METHODS

This study used data from the Military Health System (MHS) Database Repository. The MHS is one of the largest health care systems in the country and includes information on about 10 million active duty and retired military service members and their families (51% male; 49% female).[13,14] Data were fully anonymized and complied in accordance with federal and state laws, including the Health Insurance Portability and

FIGURE 1 Baseline Comorbid Profile of Patients With Wolff-Parkinson-White Syndrome by Atrial Fibrillation and/or Flutter Status
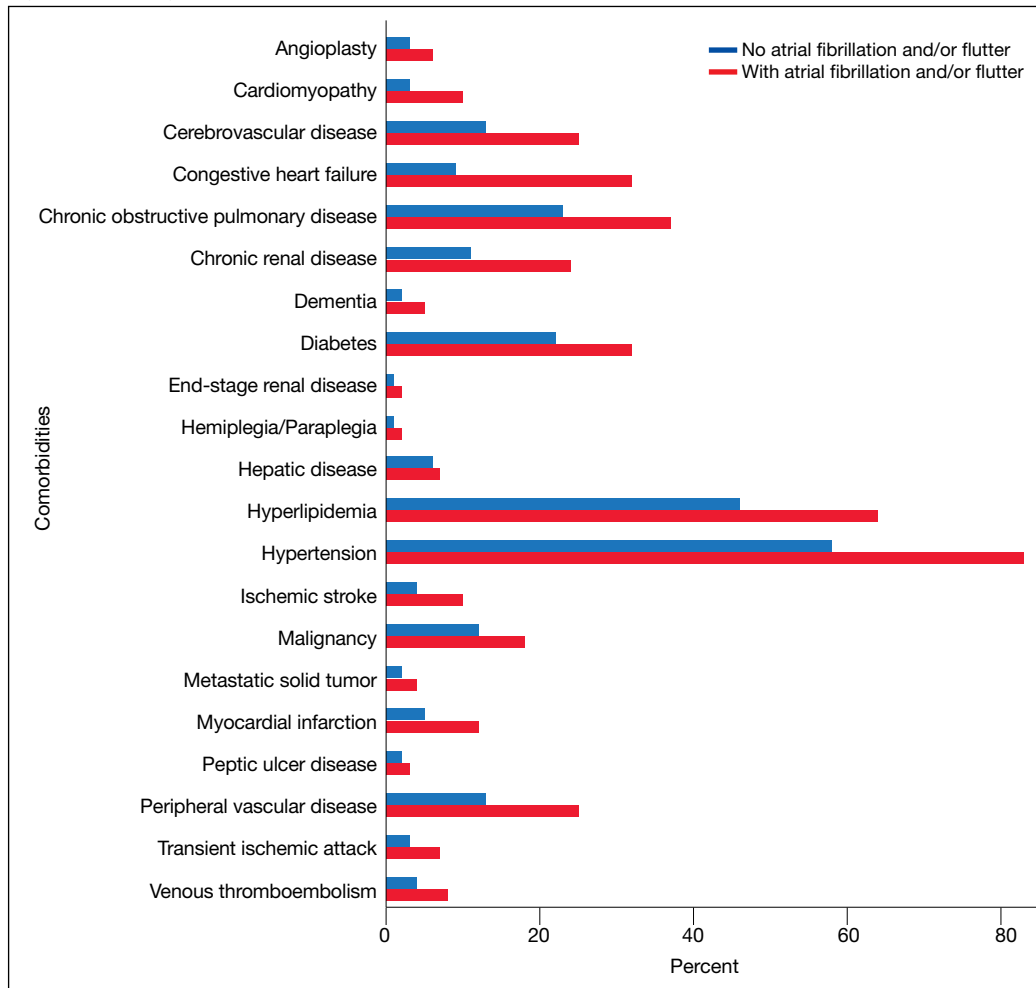
Accountability Act of 1996. The Naval Medical Center Portsmouth Institutional Review Board approved this study.

Study Design

This retrospective, observational cohort study identified MHS patients with WPW syndrome from January 1, 2014, to December 31, 2019. Patients were included if they had ≥ 2 *International Classification of Diseases, Ninth Revision* (ICD-9) or *International Classification of Diseases, Tenth Revision* (ICD-10) diagnosis codes for WPW syndrome (ICD-9, 426.7; ICD-10, I45.6) on separate dates; were aged ≥ 18 years at index date; and had ≥ 1 year of continuous eligibility prior to the index date (enrollment gaps ≤ 30 days were considered continuous). Patients were then divided into 2 subgroups by the presence or absence of AF/AFL using diagnostic codes. Patients were excluded if they had evidence of an implantable cardioverter-defibrillator, permanent pacemaker or were missing age or sex data. Patients were followed from index date until the first occurrence of the outcome of interest, MHS disenrollment, or the end of the study period.

Cardiac composite outcomes comprised of sudden cardiac arrest (SCA), ventricular fibrillation (VF), ventricular tachycardia and death, as well as death specifically, were the outcomes of interest and assessed after index date using ICD-9 and ICD-10 codes. Death was defined as all-cause mortality. Time to event was calculated based on the date of the initial component from the composite outcome and date of death

TABLE 1 Baseline Patient Characteristics

Characteristics	Total	No AF/AFL	AF/AFL	P value
Patients, No. (%)	35,539	30,248 (85.1)	5291 (14.9)	< .001
Sex, No. (%)				
Female	19,961 (56.2)	17,342 (57.3)	2619 (49.5)	
Male	15,578 (43.8)	12,906 (42.7)	2672 (50.5)	
Age, y				< .001
Mean (SD)	62.9 (18.0)	61.3 (18.4)	72.1 (13.0)	
Median (min, max)	67 (18,89)	65 (18,89)	74 (18,89)	
Cohorts, No. (%)				< .001
18-34 y	3607 (10.1)	3517 (11.6)	90 (1.7)	
35-44 y	2206 (6.2)	2134 (7.1)	72 (1.4)	
45-54 y	3252 (9.2)	3022 (10.0)	230 (4.3)	
55-64 y	6169 (17.4)	5473 (18.1)	696 (13.2)	
65-74 y	8563 (24.1)	7151 (23.6)	1412 (26.7)	
≥ 75 y	11,742 (33.0)	8951 (29.6)	2791 (52.7)	
Atrial conditions, No. (%)				< .001
Atrial fibrillation only	4121 (11.6)	–	4121 (77.9)	
Atrial flutter only	322 (0.9)	–	322 (6.1)	
Both	848 (2.4)	–	848 (16.0)	
None	30,248 (85.1)	30,248 (100)	–	
WPW visits				
Mean (SD)	6.7 (6.0)	6.8 (6.0)	6.3 (6.1)	
Median (IQR) [Range]	5 (3-8) [2-122]	5 (3-8) [2-122]	4 (3-8) [2-111]	
Cardiology visits				
Mean (SD)	3.9 (3.0)	3.9 (3.0)	3.8 (3.0)	
Median (IQR) [Range]	3 (2-5) [2-122]	3 (2-5) [2-122]	3 (2-4) [2-29]	
Baseline CCI score				< .001
Mean (SD)	4 (3.3)	3.7 (3.2)	5.9 (3.5)	
Median (IQR) [Range]	3 (1-6) [0-24]	3 (1-5) [0-24]	5 (3-8) [9-24]	
Pre-index time, y				
Mean (SD)	6.7 (2.1)	6.7 (2.2)	6.7 (1.8)	
Median (IQR) [Range]	6.3 (5.5-8.2) [1.0-11.1]	6.4 (5.5-8.3) [1.0-11.1]	6.2 (5.5-7.7) [1.0-11.1]	
Index year, No. (%)				< .001
2014	11,909 (33.5)	9713 (32.1)	2196 (41.5)	
2015	8206 (23.1)	6857 (22.7)	1349 (25.5)	
2016	4022 (11.3)	3566 (11.8)	456 (8.6)	
2017	4029 (11.3)	3580 (11.8)	449 (8.5)	
2018	4060 (11.4)	3607 (11.9)	453 (8.6)	
2019	3313 (9.3)	2925 (9.7)	388 (7.3)	
Duty status, No. (%)				< .001
Active duty/Guard	2289 (6.4)	2209 (7.3)	80 (1.5)	
Dependents	14,584 (41.0)	12,988 (42.9)	1596 (30.2)	
Retirees	13,482 (37.9)	10,875 (36.0)	2607 (49.3)	
Other	5184 (14.6)	4176 (13.8)	1008 (19.1)	
Rank group				< .001
Enlisted, junior	2079 (5.8)	1922 (6.4)	157 (3.0)	
Enlisted, senior	23,063 (64.9)	19,763 (65.3)	3300 (62.4)	
Officer, junior	1196 (3.4)	1044 (3.5)	152 (2.9)	
Officer, senior	8078 (22.7)	6661 (22.0)	1467 (27.7)	
Warrant officer	1123 (3.2)	908 (3.0)	215 (4.1)	

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; CCI, Charlson Comorbidity Index; WPW, Wolff-Parkinson-White syndrome.

specifically for mortality. Those not experiencing an outcome were followed until MHS disenrollment or the end of the study period.

Various patient characteristics were assessed at index including age, sex, military sponsor (the patient's active or retired duty member through which their dependent receives TRICARE benefits) rank and branch, geographic region, type of US Department of Defense beneficiary, and index year. Clinical characteristics were assessed over a 1-year baseline period prior to index date and included the number of cardiologist and clinical visits for WPW syndrome, Charlson Comorbidity Index (CCI) scores calculated from diagnostic codes outlined in the Quan coding method, and preindex time.[15] Comorbidities were assessed at baseline and defined as having ≥ 1 ICD-9 or ICD-10 code for a corresponding condition within 1 year prior to index.

Statistical Analysis

Baseline characteristics were assessed and descriptive statistics for categorical and continuous variables were presented accordingly. To assess bivariate association with exposure, χ^2 tests were used to compare categorical variables, while t tests were used to compare continuous variables by exposure status. Incidence proportions and rates were reported for each outcome of interest. Kaplan-Meier curves were constructed to assess the bivariate association between exposure and study outcomes. Cox proportional hazard modeling was performed to estimate the association between AF/AFL and time to each of the outcomes. Multiple models were designed to assess cardiac and metabolic covariates, in addition to baseline characteristics. This included a base model adjusted for age, sex, military sponsor rank and branch, geographic region, and duty status.

Additional models adjusted for cardiac and metabolic confounders and CCI score. A comprehensive model included the base, cardiac, and metabolic covariates. Multicollinearity between covariates was assessed. Variables with a variance inflation factor > 4 or a tolerance level < 0.1 were added to the models. Cox proportional hazard models were used to estimate the unadjusted and adjusted hazard ratios (HRs) and 95% CIs

FIGURE 2 Kaplan-Meier Curve of Cardiac Composite Outcome by Atrial Fibrillation and/or Flutter Status
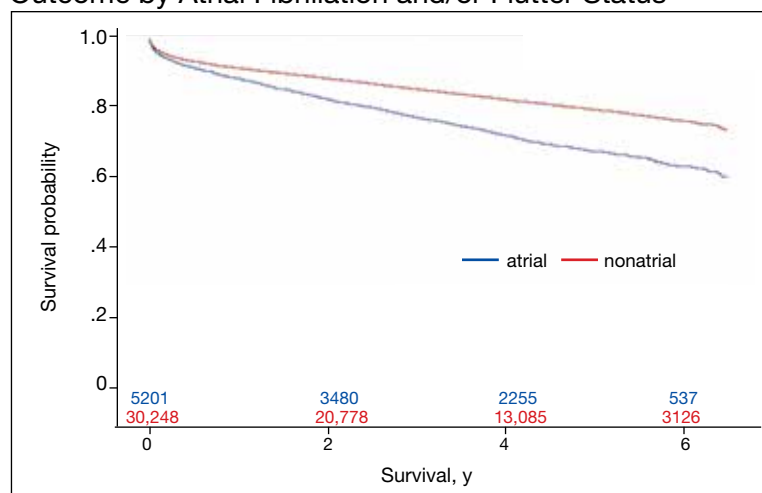
of the association between AF/AFL and the study outcomes. Data were analyzed using SAS, version 9.4 for Windows.

RESULTS

From 2014 through 2019, 35,539 patients with WPW syndrome were identified in the MHS, 5291 had AF/AFL (14.9%); 19,961 were female (56.2%), the mean (SD) age was 62.9 (18.0) years, and 11,742 were aged ≥ 75 years (33.0%) (Table 1).

There were 4121 (11.6%), 322 (0.9%), and 848 (2.4%) patients with AF, AFL, and both arrhythmias, respectively. The mean (SD) number of cardiology visits was 3.9 (3.0). The mean (SD) baseline CCI score for the AF/AFL subgroup was 5.9 (3.5) vs 3.7 (2.2) for the non-AF/AFL subgroup ($P < .001$). The most prevalent comorbid conditions were hypertension, hyperlipidemia, chronic obstructive pulmonary disease, and diabetes ($P < .001$) (Figure 1).

Composite Outcomes

In the overall cohort, during a mean (SD) follow-up time of 3.4 (2.0) years comprising 119,682 total person-years, the components of the composite outcome occurred 6506 times with an incidence rate of 5.44 per 100 person-years. Ventricular tachycardia was the most common event, occurring 3281 times with an incidence rate of 2.74 per 100 person-years. SCA and VF occurred 841 and 135 times with

TABLE 2 Incidence Rates of All-Cause Mortality and Cardiac Composite Outcomes in Patients With WPW Syndrome in the Military Health System

| Outcomes | Overall (N = 35,539) | Atrial fibrillation and/or flutter | | P value |
		No (n = 30,248)	Yes (n = 5291)	
Mortality, No.	3130	2344	786	
Total person years	129,391	110,151	19,240	
Follow-up, mean (SD), y	3.7 (1.9)	3.7 (1.9)	3.6 (2.0)	
Incidence proportion, %	8.81	7.75	14.86	< .001
Incidence rate, PY	2.42	2.13	4.09	< .001
Cardiac composite, No.	6506	5082	1424	
Total person years	119,682	102,270	17,412	
Follow-up, mean (SD), y	3.4 (2.0)	3.4 (2.0)	3.3 (2.1)	
Incidence proportion, %	18.31	16.80	26.91	< .001
Incidence rate, PY	5.44	4.97	8.18	< .001
Sudden cardiac arrest, No.	841	608	233	
Incidence proportion, %	2.37	2.01	4.40	< .001
Incidence rate, PY	0.70	0.59	1.34	< .001
Ventricular fibrillation, No.	135	97	38	
Incidence proportion, %	0.38	0.32	0.72	< .001
Incidence rate, PY	0.11	0.09	0.22	< .001
Ventricular tachycardia, No.	3281	2677	604	
Incidence proportion, %	9.23	8.85	11.42	< .001
Incidence rate, PY	2.74	2.62	3.47	< .001
Mortality, No.	2249	1700	549	
Incidence proportion, %	6.33	5.62	10.38	< .001
Incidence rate, PY	1.88	1.66	3.15	< .001

Abbreviations: PY, per 100 person-years; WPW, Wolff-Parkinson-White syndrome.

incidence rates of 0.70 and 0.11 per 100 person-years, respectively. Death was the initial event 2249 times with an incidence rate of 1.88 per 100 person-years. Figure 2 shows the Kaplan-Meier curve of cardiac composite outcome by AF/AFL status.

The subgroup with AF/AFL comprised 17,412 total person-years and 1424 cardiac composite incidences compared with 102,270 person years and 5082 incidences in the no AF/AFL group (Table 2). Comparing AF/AFL vs no AF/AFL incidence rates were 8.18 vs 4.97 per 100 person-years, respectively (*P* < .001). SCA and VF occurred 233 and 38 times and respectively had incidence rates of 1.34 and 0.22 per 100 person-years in the AF/AFL group vs 0.59 and 0.09 per 100 person-years in the no AF/AFL group (*P* < .001). There were 549 deaths and a 3.15 per 100 person-years incidence rate in the AF/AFL group vs 1700 deaths and a 1.66 incidence rate in the no AF/AFL group (*P* < .001).

The HR for the composite outcome in the base model was 1.33 (95% CI, 1.26-1.42,

P < .001) (Table 3). The association between AF/AFL and the composite outcome remained significant after adjusting for additional metabolic and cardiac covariates. The HRs for the metabolic and cardiac models were 1.30 (95% CI, 1.23-1.38, *P* < .001) and 1.11 (95% CI, 1.05-1.18, *P* < .001), respectively. After adjusting for the full model, the HR was 1.12 (95% CI, 1.05-1.19, *P* < .001).

Mortality

Over the 6-year study period, there was a lower survival probability for patients with AF/AFL. In the overall cohort, during a mean (SD) follow-up time of 3.7 (1.9) years comprising 129,391 total person-years, there were 3130 (8.8%) deaths and an incidence rate of 2.42 per 100 person-years. Death occurred 786 times with a 4.09 incidence rate per 100 person-years in the AF/AFL vs 2344 deaths and a 2.13 incidence rate per 100 person-years in the no AF/AFL group (*P* < .001). In the non-AF/AFL subgroup, death occurred 2344 times during a mean (SD) follow-up of

3.7 (1.9) years comprising 110,151 total person-years. Figure 3 shows the Kaplan-Meier curve of mortality by AF/AFL status.

After adjusting for the base, metabolic and cardiac covariates, the HRs for mortality were 1.45 (95% CI, 1.33-1.57, $P < .001$), 1.40 (95% CI, 1.29-1.51, $P < .001$) and 1.15 (95% CI, 1.06-1.25, $P = .001$), respectively (Table 4). The HR after adjusting for the full model was 1.16 (95% CI, 1.07-1.26, $P < .001$).

DISCUSSION

In this large retrospective cohort study, patients with WPW syndrome and comorbid AF/AFL had a significantly higher association with the cardiac composite outcome and death during a 3-year follow-up period when compared with patients without AF/AFL. After adjusting for confounding variables, the AF/AFL subgroup maintained a 12% and 16% higher association with the composite outcome and mortality, respectively. There was minimal difference in confounding effects between demographic data and metabolic profiles, suggesting one may serve as a proxy for the other.

To our knowledge, this is the largest WPW syndrome cohort study evaluating cardiac outcomes and mortality to date. Although previous research has shown the relatively low and mostly anecdotal SCD incidence within this population, our results demonstrate a higher association of adverse cardiac outcomes and death in an AF/AFL subgroup.[16-18] Notably, in this study the AF/AFL cohort was older and had higher CCI scores than their counterparts ($P < .001$), thus inferring an inherently greater degree of morbidity and 10-year mortality risk. Our study is also unique in that the mean patient age was significantly older than previously reported (63 vs 27 years), which may suggest a longer living history of both ventricular pre-excitation and the comorbidities outlined in Figure 1.[19] Given these age discrepancies, it is possible that our overall study population was still relatively low risk and that not all reported deaths were necessarily related to WPW syndrome. Despite these assumptions, when comparing the WPW syndrome subgroups, we still found the AF/AFL cohort maintained a statistically significant higher association with the 2 study outcomes, even after adjusting for the greater presence of comorbidities. This suggests that the presence of AF/AFL may still portend a worse prognosis in patients with WPW syndrome.

Although the association of AF and development of VF in patients with WPW syndrome—due to rapid conduction over the accessory pathway(s)—was first reported > 40 years ago, there has

TABLE 3 Association of AF/AFL with Cardiac Composite Outcome in MHS Patients With WPW Syndrome (N = 35,539)

Models	Hazard ratio (95% CI)	*P* value
Unadjusted	1.64 (1.55-1.74)	< .001
Base[a]	1.33 (1.26-1.42)	< .001
Base + Carlson Comorbidity Score	1.16 (1.09-1.23)	< .001
Cardiac[b]	1.11 (1.05-1.18)	< .001
Metabolic[c]	1.30 (1.23-1.38)	< .001
Full[d]	1.12 (1.05-1.19)	< .001

[a]Adjusted for age, sex, military sponsor rank and branch, geographic region, and duty status.
[b]Adjusted for base model + hypertension, cardiovascular disease, peripheral vascular disease, congestive heart failure, and angioplasty.
[c]Adjusted for base model + diabetes, chronic kidney disease, and hyperlipidemia.
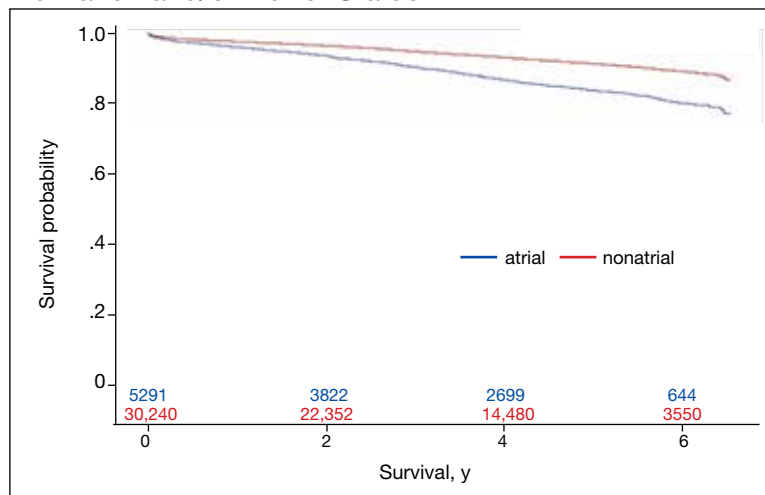[d]Adjusted for base model + cardiac model + metabolic models.
Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; MHS, Military Health System; WPW, Wolff-Parkinson-White syndrome.

TABLE 4 Association of AF/AFL with Mortality in MHS Patients With WPW Syndrome (N = 35,539)

Model	Hazard ratio (95% CI)	*P* value
Unadjusted	1.91 (1.76-2.07)	< .001
Base[a]	1.45 (1.33-1.57)	< .001
Base + Carlson Comorbidity Score	1.17 (1.07-1.27)	< .001
Cardiac[b]	1.15 (1.06-1.25)	.001
Metabolic[c]	1.40 (1.29-1.51)	< .001
Full[d]	1.16 (1.07-1.26)	< .001

[a]Adjusted for age, sex, military sponsor rank and branch, geographic region, and duty status.
[b]Adjusted for base model + hypertension, cardiovascular disease, peripheral vascular disease, congestive heart failure, and angioplasty.
[c]Adjusted for base model + diabetes, chronic kidney disease, and hyperlipidemia.
[d]Adjusted for base model + cardiac model + metabolic models.
Abbreviations: AF/AFL, atrial fibrillation and/or flutter; MHS, Military Health System; WPW, Wolff-Parkinson-White syndrome.

FIGURE 3 Kaplan-Meier Curve of Mortality by Atrial Fibrillation and/or Flutter Status

Given these conflicting recommendations, we hope our data elucidates the higher association of adverse outcomes and support considerations for more intensive EPT indications in patients with WPW syndrome.

While our study does not report SCD incidence, it does provide robust and reliable mortality data that suggests a greater association of death within an AF/AFL subgroup. Our findings would support more liberal EPT recommendations in patients with WPW syndrome.[1-5,8,9] In this study, the SCA incidence rate was more than double the rate in the AF/AFL cohort ($P < .001$) and is commonly the initial presenting event in WPW syndrome.[9] Even though the reported SCD incidence rate is low in WPW syndrome, our data demonstrated an increased association of death within the AF/AFL cohort. Physicians should consider early risk stratification and ablation to prevent potential recurrent malignant arrhythmia leading to death.[1-5,8,9,12,19,20]

Limitations

As a retrospective study and without access to the National Death Index, we were unable to determine the exact cause or events leading to death and instead utilized all-cause mortality data. Subsequently, our observations may only demonstrate association, rather than causality, between AF/AFL and death in patients with WPW syndrome. Additionally, we could not distinguish between AF and AFL as the arrhythmia leading to death. However, since overall survivability was the outcome of interest, our adjusted HR models were still able to demonstrate the increased association of the composite outcome and death within an AF/AFL cohort.

Although a large cohort was analyzed, due to the constraints of utilizing diagnostic codes to determine study outcomes, we could not distinguish between symptomatic and asymptomatic patients, nor how they were managed prior to the outcome event. However, as recent literature demonstrates, updated predictors of malignant arrhythmia and decisions for early EPT are similar for both symptomatic and asymptomatic patients and should be driven by the intrinsic electrophysiologic properties of the accessory pathway, rather than symptomatology;

still been few large, long-term data studies exploring mortality in this cohort.[19-25] Furthermore, even though the current literature attributes the development of AF with the electrophysiologic properties of the accessory pathway, as well as intrinsic atrial architecture and muscle vulnerability, there is still equivocal consensus regarding EPT screening and ablation indications for asymptomatic patients with WPW syndrome.[26-28] Notably, Pappone and colleagues demonstrated the potential benefit of liberal ablation indications for asymptomatic patients, arguing that the intrinsic electrophysiologic properties of the accessory pathway—ie, short accessory-pathway antegrade effective refractory period, inducibility of atrioventricular reentrant tachycardia triggering AF, and multiple accessory pathway—rather than symptoms, are independent predictors of developing malignant arrhythmia.[1-5]

These findings contradict those reported by Obeyesekere and colleagues, who concluded that the low SCD incidence rates in patients with WPW syndrome precluded routine invasive screening.[19,28] They argued that Pappone and colleagues used malignant arrhythmia as a surrogate marker for death, and that the positive predictive value of a short accessory-pathway antegrade effective refractory period for developing malignant arrhythmia was lower than reported (15% vs 82%, respectively) and that its negative predictive value was 100%.[1,19,28]

thus, our inability to discern this should have negligible consequence in determining when to perform risk stratification and ablation.[1]

MHS eligible patients have direct access to care; the generalizability of our data may not necessarily correspond to a community population with lower socioeconomic status (we did adjust for military sponsor rank which has been used as a proxy), reduced access to care, or uninsured individuals. However, the prevalence of WPW syndrome within our cohort was comparable to the general population, 0.4% vs 0.1%-0.3%, respectively.[13,14,19] Similarly, the incidence of AF within our population was comparable to the general population, 15% vs 16%-26%, respectively.[23] These similar data points suggest our results may apply beyond MHS patients.

CONCLUSIONS
Patients with WPW syndrome and AF/AFL have a higher association with adverse cardiac outcomes and death. Despite previously reported low SCD incidence rates in this population, our study demonstrates the increased association of mortality in an AF/AFL cohort. The limitations of utilizing all-cause mortality data necessitate further investigation into the etiology behind the deaths in our study population. Since ventricular pre-excitation can predispose patients to AF and potentially lead to malignant arrhythmia and SCD, understanding the cause of mortality will allow physicians to determine the appropriate monitoring and intervention strategies to improve outcomes in this population. Our results suggest consideration for more aggressive EPT screening and ablation recommendations in patients with WPW syndrome may be warranted.

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Disclaimer
The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner,* Frontline Medical Communications Inc., the US Government, or any of its agencies.

Ethics and consent
Research and data from this study were reviewed and approved by the Naval Medical Center Portsmouth Institutional Review Board.

References
1. Pappone C, Vicedomini G, Manguso F, et al. The natural history of WPW syndrome. *Eur Heart J Suppl*. 2015; 17 (Supplement A):A8-A11.doi:10.1093/eurheartj/suv004
2. Pappone C, Vicedomini G, Manguso F, et al. Risk of malignant arrhythmias in initially symptomatic patients with Wolff-Parkinson-White syndrome: results of a prospective long-term electrophysiological follow-up study. *Circulation*. 2012;125(5):661-668. doi:10.1161/CIRCULATIONAHA.111.065722
3. Pappone C, Santinelli V, Rosanio S, et al. Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern: results from a large prospective long-term follow-up study. *J Am Coll Cardiol*. 2003;41(2):239-244. doi:10.1016/s0735-1097(02)02706-7
4. Pappone C, Vicedomini G, Manguso F, et al. Wolff-Parkinson-White syndrome in the era of catheter ablation: insights from a registry study of 2169 patients. *Circulation*. 2014;130(10):811-819. doi:10.1161/CIRCULATIONAHA.114.011154
5. Pappone C, Santinelli V, Manguso F, et al. A randomized study of prophylactic catheter ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. *N Engl J Med*. 2003;349(19):1803-1811. doi:10.1056/NEJMoa035345
6. Santinelli V, Radinovic A, Manguso F, et al. Asymptomatic ventricular preexcitation: a long-term prospective follow-up study of 293 adult patients. *Circ Arrhythm Electrophysiol*. 2009;2(2):102-107. doi:10.1161/CIRCEP.108.827550
7. Santinelli V, Radinovic A, Manguso F, et al. The natural history of asymptomatic ventricular pre-excitation a long-term prospective follow-up study of 184 asymptomatic children. *J Am Coll Cardiol*. 2009;53(3):275-280. doi:10.1016/j.jacc.2008.09.037
8. Al-Khatib SM, Arshad A, Balk EM, et al. Risk Stratification for Arrhythmic Events in Patients With Asymptomatic Pre-Excitation: A Systematic Review for the 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2016;67(13):1624-1638. doi:10.1016/j.jacc.2015.09.018
9. Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation*. 2003;108(15):1871-1909. doi:10.1161/01.CIR.0000091380.04100.84
10. Pediatric and Congenital Electrophysiology Society (PACES); Heart Rhythm Society (HRS); American College of Cardiology Foundation (ACCF); PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). *Heart Rhythm*. 2012;9(6):1006-1024. doi:10.1016/j.hrthm.2012.03.050
11. Cohen M, Triedman J. Guidelines for management of

asymptomatic ventricular pre-excitation: brave new world or Pandora's box?. *Circ Arrhythm Electrophysiol*. 2014;7(2):187-189. doi:10.1161/CIRCEP.114.001528

12. Svendsen JH, Dagres N, Dobreanu D, et al. Current strategy for treatment of patients with Wolff-Parkinson-White syndrome and asymptomatic preexcitation in Europe: European Heart Rhythm Association survey. *Europace*. 2013;15(5):750-753. doi:10.1093/europace/eut094

13. Gimbel RW, Pangaro L, Barbour G. America's "undiscovered" laboratory for health services research. *Med Care*. 2010;48(8):751-756. doi:10.1097/MLR.0b013e3181e35be8

14. Dorrance KA, Ramchandani S, Neil N, Fisher H. Leveraging the military health system as a laboratory for health care reform. *Mil Med*. 2013;178(2):142-145. doi:10.7205/milmed-d-12-00168

15. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83

16. Finocchiaro G, Papadakis M, Behr ER, Sharma S, Sheppard M. Sudden Cardiac Death in Pre-Excitation and Wolff-Parkinson-White: Demographic and Clinical Features. *J Am Coll Cardiol*. 2017;69(12):1644-1645. doi:10.1016/j.jacc.2017.01.023

17. Munger TM, Packer DL, Hammill SC, et al. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953-1989. *Circulation*. 1993;87(3):866-873. doi:10.1161/01.cir.87.3.866

18. Fitzsimmons PJ, McWhirter PD, Peterson DW, Kruyer WB. The natural history of Wolff-Parkinson-White syndrome in 228 military aviators: a long-term follow-up of 22 years. *Am Heart J*. 2001;142(3):530-536. doi:10.1067/mhj.2001.117779

19. Obeyesekere MN, Leong-Sit P, Massel D, et al. Risk of arrhythmia and sudden death in patients with asymptomatic preexcitation: a meta-analysis. *Circulation*. 2012;125(19):2308-2315. doi:10.1161/CIRCULATIONAHA.111.055350

20. Waspe LE, Brodman R, Kim SG, Fisher JD. Susceptibility to atrial fibrillation and ventricular tachyarrhythmia in the Wolff-Parkinson-White syndrome: role of the accessory pathway. *Am Heart J*. 1986;112(6):1141-1152. doi:10.1016/0002-8703(86)90342-x

21. Pietersen AH, Andersen ED, Sandøe E. Atrial fibrillation in the Wolff-Parkinson-White syndrome. *Am J Cardiol*. 1992;70(5):38A-43A. doi:10.1016/0002-9149(92)91076-g

22. Della Bella P, Brugada P, Talajic M, et al. Atrial fibrillation in patients with an accessory pathway: importance of the conduction properties of the accessory pathway. *J Am Coll Cardiol*. 1991;17(6):1352-1356. doi:10.1016/s0735-1097(10)80146-9

23. Fujimura O, Klein GJ, Yee R, Sharma AD. Mode of onset of atrial fibrillation in the Wolff-Parkinson-White syndrome: how important is the accessory pathway?. *J Am Coll Cardiol*. 1990;15(5):1082-1086. doi:10.1016/0735-1097(90)90244-j

24. Montoya PT, Brugada P, Smeets J, et al. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *Eur Heart J*. 1991;12(2):144-150. doi:10.1093/oxfordjournals.eurheartj.a059860

25. Klein GJ, Bashore TM, Sellers TD, Pritchett EL, Smith WM, Gallagher JJ. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *N Engl J Med*. 1979;301(20):1080-1085. doi:10.1056/NEJM197911153012003

26. Centurion OA. Atrial Fibrillation in the Wolff-Parkinson-White Syndrome. *J Atr Fibrillation*. 2011;4(1):287. Published 2011 May 4. doi:10.4022/jafib.287

27. Song C, Guo Y, Zheng X, et al. Prognostic Significance and Risk of Atrial Fibrillation of Wolff-Parkinson-White Syndrome in Patients With Hypertrophic Cardiomyopathy. *Am J Cardiol*. 2018;122(9):1546-1550. doi:10.1016/j.amjcard.2018.07.021

28. Obeyesekere M, Gula LJ, Skanes AC, Leong-Sit P, Klein GJ. Risk of sudden death in Wolff-Parkinson-White syndrome: how high is the risk?. *Circulation*. 2012;125(5):659-660. doi:10.1161/CIRCULATIONAHA.111.085159