Atrial fibrillation is independently associated with senile, vascular, and Alzheimer’s dementia

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BACKGROUND The aging population has resulted in more patients living with cardiovascular disease, such as atrial fibrillation (AF). Recent focus has been placed on understanding the long-term consequences of chronic cardiovascular disease, such as a potential increased risk of dementia.

OBJECTIVE This study sought to determine whether there is an association between AF and dementia and whether their coexistence is an independent marker of risk.

METHODS A total of 37,025 consecutive patients from the large ongoing prospective Intermountain Heart Collaborative Study database were evaluated and followed up for a mean of 5 years for the development of AF and dementia. Dementia was sub-typed into vascular (VD), senile (SD), Alzheimer’s (AD), and nonspecific (ND).

RESULTS Of the 37,025 patients with a mean age of 60.6 ± 17.9 years, 10,161 (27%) developed AF and 1,535 (4.1%) developed dementia (179 VD, 321 SD, 347 AD, 688 ND) during the 5-year follow-up. Patients with dementia were older and had higher rates of hypertension, coronary artery disease, renal failure, heart failure, and prior strokes. In age-based analysis, AF independently was significantly associated with all dementia types. The highest risk was in the younger group (<70). After dementia diagnosis, the presence of AF was associated with a marked increased risk of mortality (VD: hazard ratio [HR] = 1.38, P = <.01; SD: HR = 1.41, P = .001; AD: HR = 1.45; ND: HR = 1.38, P <.0001).

CONCLUSION AF was independently associated with all forms of dementia. Although dementia is strongly associated with aging, the highest risk of AD was in the younger group, in support of the observed association. The presence of AF also identified dementia patients at high risk of death.

KEYWORDS Atrial fibrillation; Dementia; Alzheimer’s; Hypertension; Aging; Stroke

ABBREVIATIONS AD = Alzheimer’s disease; AF = atrial fibrillation; HR = hazard ratio; ICD = International Classification of Diseases; ND = nonspecific dementia; SD = senile dementia; VD = vascular dementia

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Dementia is a disorder that is characterized by impairment of memory and at least one additional cognitive domain. The consequences of dementia must represent a decline from the previous level of function and impact quality of life and daily function. Because of an aging population, dementia is an increasing problem as it primarily affects elderly patients. Alzheimer’s disease (AD) is the most common form of dementia in the elderly, accounting for 60% to 80% of cases, followed by vascular dementia (VD), which accounts for 10% to 20%. 1,2 Dementia in general tends to increase with increasing age, 3–5 diabetes, 6–10 hypertension, and systemic inflammation, 5,10–13 smoking history, 14 and systemic inflammation. 15,16

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and similar to dementia, its prevalence increases with age. It is a significant risk factor for thromboembolic stroke, and affects up to 9% of the population by age 80. 17,18 It also independently increases total mortality in patients with and without cardiovascular disease. 19 Hypertensive heart disease and coronary heart disease are the most common underlying disorders in patients with AF in developed countries. 20,21 Similar to the association with dementia, the risk of AF increases with age, 21 diabetes, 22 hypertension, 21 and increases in systemic inflammation. 23,24

Recent data have emerged to show an association between AF and AD progression. 13 This observation is not surprising because the disease states of dementia and AF share similar background risk factors. Furthermore, AF has been independently linked to memory impairment, cognitive decline, and general dementia in patients without pre-
existing disease. Nonetheless, more studies are required to verify and confirm the independent risk of AD in AF patients. In addition, it is unclear whether those patients with AF and dementia represent a high-risk group for long-term adverse outcomes. To understand the independent risk of AF and dementia and their combined long-term outcomes, we studied the association in a large patient population with comparison of results across multiple age strata. The primary objective was to confirm the independent risk of AF and AD. The secondary objective was to determine the impact of AF in those subsequently diagnosed with AD and other dementia types on risk of mortality.

**Methods**

We examined the Intermountain Heart Collaborative Study database to examine an association of AF and dementia. This database includes all patients who receive care within the Intermountain Healthcare system and were seen by cardiologists with consent to participate in research. The population studied as noted in the prior publications is predominantly white (89%), with other races as follows: Hispanic 7%, Polynesian/Asian 1%, black 2%, and Native American 1%. We studied 37,026 consecutive patients who had a mean of 5 years of follow-up. Patients with pre-existing dementia or AF were excluded. Extracted clinical variables were based on inpatient and outpatient clinical visits and included age, hypertension, diabetes, hyperlipidemia, renal failure, smoking history, prior myocardial infarction or cerebral vascular accident, and heart failure. Included in the extracted data was use of medications (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors [statins], angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and diuretics). In 20,471 patients, an ejection fraction was available through search of the echocardiogram database.

Patients’ AF status was determined by searching the hospital discharge summary for diagnostic (International Classification of Diseases, Ninth Revision [ICD-9]) codes for AF at index and previous admissions to Intermountain Healthcare hospitals (Salt Lake City, Utah, and its surrounding areas) and by searching the electrocardiographic database of all Intermountain Healthcare hospitals, which was maintained on electronic records. The electrocardiogram database includes electrocardiograms, ambulatory monitors, and symptom- and auto-triggered event monitors from all Intermountain Healthcare facilities. These databases are updated daily with completion of the dictated medical reports and physician review of the ordered electrocardiograms.

Dementia was studied in general and as subtypes. Dementia was subtyped into AD, VD, senile dementia (SD), and nonspecified dementia (ND) based on diagnostic ICD code (ICD-9 codes 290 to 294, 331, or equivalent). The subtype ND comprised all dementia types searched. To assess the reliability of ICD-9 codes for end point analysis, we examined the study variable diabetes mellitus and found a 95% accuracy between the diagnosis from the ICD-9 codes and demographic data entered in the coronary angiogram database in those presenting for catheterization.

The other study end point considered was mortality (all-cause and coronary artery disease–related mortality [ICD-9 codes 410 to 414 or equivalent]). Deaths were determined by telephone survey, hospital records, and Utah State Health Department records (death certificates), and were verified through Social Security death records. Patients not listed as deceased in any registry were considered to be alive.

The Student t-test and the chi-square statistic were used to evaluate baseline and clinical characteristics among patients with and without AF. Multivariable Cox hazard regression analysis (SPSS version 15.0; SPSS Inc., Chicago, Illinois) was used to evaluate the association of AF with the incidence of the study end points. Final models entered the significant (P < .05) and confounding (10% change in hazard ratio [HR]) covariables. Two-tailed P values of <.05 were designated as nominally significant. To assess the reliability of ICD-9 codes for end point analysis, we examined the study variable diabetes and found a 95% accuracy in the information from the ICD-9 codes and demographic data entered in the coronary angiogram database in those presenting for catheterization.

**Results**

Of the 37,025 patients with a mean age of 60.6 ± 17.9 years studied, 10,161 (27%) developed AF and 1,535 developed (4.1%) dementia (179 VD, 321 SD, 347 AD, 688 ND) during the 5-year follow-up. The basic demographics of the patient population listed and compared by AF status are shown in Table 1. Patients with AF were older and had higher rates of hypertension, coronary artery disease, renal failure, heart failure, and prior strokes. Statin use was similar between the groups. On average, the ejection fraction was lower in the AF group. Patients with AF were more likely to be treated with an angiotensin-converting enzyme inhibitor or beta-blocker. Over the 5-year study period of follow-up, there was an increased incidence of dementia in general and all dementia subtypes in those patients with AF (ND: 1.3% (355) vs. 3.3% (333), P < .0001; AD: 0.7% (199) vs. 1.5% (148), P < .0001; SD: 0.6% (161) vs. 1.6% (160), P < .0001; VD: 0.3% (89) vs. 0.9% (90), P < .0001) (Figure 1). The average time to the development of dementia was modestly distinct between subtypes (AD: 1285.3 ± 1220.3 days; VD: 1280.5 ± 1258.8 days; SD: 1206.8 ± 1141.5 days). Across all dementia states, the cognitive decline occurred earlier in patients with AF versus no AF (AD: 1225.4 ± 1184.4 vs. 1340.0 ± 1253.7; VD: 1224.6 ± 1244.8 vs. 1336.4 ± 1278.2; SD: 1110.8 ± 1121.1 vs. 1300.7 ± 1158.7). In this population, all patients who developed both AF and dementia (n = 764), developed AF first, but the dementia diagnosis could have occurred simultaneously with AF or after AF diagnosis.

We examined the multivariable-adjusted age-based association of AF and dementia (Figure 2). For nonspecific dementia, the greatest risk with AF was in the younger cohort (≤70 years) and declined in a linear fashion in the
next 2 age strata. A similar association was found with AD, with the greatest risk in the young (odds ratio 2.30, \(P < .0001\)) with no apparent association in older patients. Both SD and VD were more likely to occur in AF patients in the younger groups (\(<70\) and \(70\) to \(79\) years).

There was also a significant association between dementia and total mortality (ND: \(HR = 1.61, P < .0001\); AD: \(HR = 1.46, P < .0001\); SD: \(HR = 1.51, P < .0001\); VD: \(HR = 2.14, P < .0001\)). The presence of AF further increased the risk of general mortality across all dementia subtypes (Figure 3). The increased risk of death with dementia was greatest in the younger groups (\(<70\) to \(89\), \(\geq 90\) years). Over the follow-up period, there was a total of 775 computed tomography scans and 343 magnetic resonance imaging studies. Of those, 106 patients received both. From these studies, 156 patients were identified as having a stroke. This accounts for 87% of those classified as having vascular dementia.

### Discussion

AF was independently associated with risk of all forms of dementia. Although dementia is strongly associated with aging, the highest risk of AD was in the younger AF group, in support of the observed association. The presence of AF in all dementia subtypes identified patients at higher risk of mortality. This mortality risk was most prominent in the youngest population studied.

Age remains the strongest risk factor for dementia, particularly for AD. In a community-based study, the estimated annual incidence of AD was 0.6% for patients ages 65 to 69 years, 1.0% for those 70 to 74 years, 2.0% for those 75 to 79 years, 3.3% for those 80 to 84 years, and 8.4% for

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**Table 1** Baseline patient characteristics in general and compared by the presence of atrial fibrillation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (37,025)</th>
<th>Non-AF (26,864)</th>
<th>AF (10,161)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.6 ± 17.9</td>
<td>57.8 ± 18.9</td>
<td>68.1 ± 12.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male</td>
<td>60.1%</td>
<td>59.5%</td>
<td>61.5%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44.0%</td>
<td>43.8%</td>
<td>44.3%</td>
<td>.40</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39.3%</td>
<td>41.3%</td>
<td>34.2%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15.7%</td>
<td>15.7%</td>
<td>15.6%</td>
<td>.82</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.3%</td>
<td>1.1%</td>
<td>1.8%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>14.7%</td>
<td>15.6%</td>
<td>12.3%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Family history</td>
<td>28.2%</td>
<td>30.0%</td>
<td>23.4%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6.0%</td>
<td>5.4%</td>
<td>7.6%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>3.6%</td>
<td>3.2%</td>
<td>4.7%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.1%</td>
<td>0.8%</td>
<td>1.8%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Statin</td>
<td>31.7%</td>
<td>31.7%</td>
<td>31.9%</td>
<td>.68</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>3.5%</td>
<td>3.6%</td>
<td>3.2%</td>
<td>.03</td>
</tr>
<tr>
<td>ARB</td>
<td>0.9%</td>
<td>0.8%</td>
<td>1.1%</td>
<td>.009</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>4.7%</td>
<td>5.0%</td>
<td>4.2%</td>
<td>.001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>3.8%</td>
<td>3.3%</td>
<td>5.2%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EF (n = 20,471)</td>
<td>58.7 ± 16.2</td>
<td>60.0 ± 15.9</td>
<td>55.5 ± 16.6</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; EF = ejection fraction; ARB = angiotensin receptor blocker.

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**Figure 1** The incidence of dementia by the patient’s AF status. There is a significant increase in dementia in general and in all subtypes in patients with AF.

**Figure 2** Multivariate-adjusted odds ratios based on dementia type and age subgroup. Younger patients who had AF were at higher risk for all types of dementia. The association diminished with advancing age and becomes nonsignificant.
In this study, the incidence of hyper-tension was similar in the AF and non-AF groups. In determining the independent risk of dementia in AF patients, adjustment for hypertension did not influence the significant association.

An interesting observation in these data was that hypertension was common, but often undertreated with pharmacologic agents. Outside of diuretics that were used slightly more often in the AF group, there were similar hypertension treatment trends in the AF and non-AF groups. Prior studies have sought to determine whether hypertension treatment can attenuate dementia risk. Although there are conflicting data, the majority of studies suggest a slight decreased risk of cognitive impairment in hypertensive patients who have controlled versus poorly controlled pressure. This undertreatment of hypertension is an important limitation to these data, and also represents an area for future study to determine whether treatment of hypertension in AF patients will alter the observed disease state association.

The role of inflammation in the pathogenesis of dementia remains an area of active investigation. Systemic markers of inflammation and hemostasis have been shown to be associated with cognitive decline. In an interesting study of more than 4,000 patients, the association between inflammatory markers (C-reactive protein and interleukin-6) and cognitive decline was modest, but was much stronger in those with inherited risk. Similarly, the role of AF and inflammation is an area of investigation. Recently, we found that AF increases highly sensitive C-reactive protein in a linear and independent manner in patients without and with coexistent cardiovascular diseases. Studies are required to investigate whether early targeted treatment of inflammation can influence the development of AF, dementia, or the combined disease state.

There are many potential intriguing mechanisms that may explain these observations. One is that AF and dementia both may be caused by early vascular disease from central hypertension or microvascular dysfunction. Those patients with AF with underlying comprised vascular/microvascular dysfunction may be more likely to have cerebral perfusion dysfunction and to manifest dementia earlier. Patients with AF are more likely to develop heart failure, both systolic and diastolic, which may serve as a distinct mechanism underlying reduced cerebral perfusion. AF is also associated with silent cerebral infarctions and transient ischemic attacks. The long-term impact of multiple small subclinical strokes underlies the early cognitive decline observed in this study. This possibility brings up the question of whether aggressive rhythm management or anticoagulation may improve outcomes. Finally, as discussed previously, dementia increases in those patients with elevated markers of systemic inflammation. AF independently increases systemic inflammation beyond other cardiac risk factors, and may thereby accelerate the inflammation-mediated progressive cognitive decline.

The long-term mortality rate of dementia patients with AF is increased. The higher mortality rates were seen in all forms of dementia. The highest hazard was primarily noted in the younger cohorts. Previous studies have shown that patients with dementia who develop AF have faster rates of cognitive decline. The increased mortality in patients with earlier presentations of dementia and more rapid progression of dementia has been previously reported. Our data are unique in that they show that AF identifies additional risk in these patients. It is unknown whether treatment of AF will decrease this additional risk.

Our study has several limitations. It is an epidemiologic study from a large health care database that we have used to identify associations but not to establish causality or mechanisms. The study relies on physicians to make and document the disease states. Furthermore, the treatment of patients is individualized, and this may directly influence risks of morbidity and mortality. However, the data were derived from a very large database of consecutive patients with an average of 5 years of follow-up, and insight is gleaned into the association of AF and dementia. Regarding arrhythmia diagnosis, by using ICD-9 codes, a comprehensive electro-
cardiogram database, and medical records to determine the presence of AF, the actual incidence of the arrhythmia in our study population may be higher than what we reported due to subclinical events. However, the size of the population studied should minimize the influence of this potential limitation. Similar to AF, dementia and dementia subtypes were determined by ICD-9 codes, and these were assigned by the caring physicians. Therefore, there may have been some mischaracterization of dementia subtype. Nonetheless, the association of AF with dementia was seen dramatically across all subtypes, supporting the findings in general.

Conclusion
AF was independently associated with all forms of dementia. Although dementia is strongly associated with aging, the highest risk of AD was in the younger group, in support of the observed association. The presence of AF also identified dementia patients at high risk of death. These findings require further investigation and confirmation in an effort to understand and prevent dementia as well as to optimally manage dementia patients at higher risk of adverse outcomes.

References