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Ethnic differences in atrial fibrillation in patients with heart failure from Asia-Pacific

Eugene J S Tan,1 Wan Ting Tay,2 Tiew-Hwa Katherine Teng,2 David Sim,2,3 Kui Toh Gerard Leong,4 Poh Shuan Daniel Yeo,5 Hean Yee Ong,6 Fazlur Jaueferally,3,7 Tze Pin Ng,8 Katrina Poppe,9 Mayanna Lund,10 Gerard Devlin,11 Richard W Troughton,12 Lieng Hsi Ling,1 Arthur Mark Richards,1,12,13 Robert N Doughty,9 Carolyn S P Lam2,3,14

ABSTRACT

Objective Ethnic differences in the prevalence of atrial fibrillation (AF) in heart failure (HF) remain unclear. We compared the prevalence and clinical correlates of AF among different ethnicities in an Asian-Pacific population with HF. Patients with validated HF were prospectively studied across Singapore and New Zealand (NZ).

Results Among 1746 patients with HF (62% Asian, 26% women, mean age 66 (SD 13) years, mean ejection fraction (EF) 37 (SD 16%), 39% had AF. The prevalence of AF was markedly lower in Singapore-Asians than NZ-Europeans (24% vs 63%; p<0.001), even after adjusting for age, clinical and echocardiographic covariates, regardless of EF group (pinteraction for EF=0.39). Patients with AF were older, had higher body mass index and were more likely to have a history of hypertension, stroke, peripheral vascular disease, renal disease, chronic respiratory disease and increased alcohol intake, but less likely to have diabetes. Clinical correlates were similar for Asians and NZ-Europeans, except diabetes: Asian diabetic patients with HF had less AF compared with Asian patients without diabetes (OR 0.66, 95% CI 0.50 to 0.88), whereas among NZ-Europeans there was no significant association between diabetes and AF (OR 1.22, 95% CI 0.85 to 1.75) (pinteraction for ethnicity=0.01). AF was associated with a higher crude composite outcome of mortality and HF hospitalisations at 2 years (HR 1.19, 95% CI 1.02 to 1.38).

Conclusion There is a strikingly lower prevalence of AF among Asian compared with NZ-European patients with HF. The underlying mechanisms for the lower prevalence of AF among Asians, particularly in the presence of diabetes, deserve further study.

Trial registration number ACTRN12610000374066.

We compared the prevalence of AF between Asian and New Zealand (NZ)-European ethnics in an Asian-Pacific HF population, and assessed whether ethnic interactions exist with clinical correlates of AF. We also examined the association of AF with outcomes and their interactions with ethnicity and ejection fraction (EF).

METHODS

Study population Participants from this study were from a prospectively designed dual-nation, parallel, contemporary, observational HF study conducted according to identical protocols—The Singapore Heart Failure Outcomes and Phenotypes (SHOP) study in Singapore and the Prospective Evaluation of Outcome in Patients with Preserved Left Ventricular Ejection Fraction (PEOPLE) in NZ. The SHOP-PEOPLE study design and outcomes have been reported previously.9 In brief, the same protocol was deployed across six centres in Singapore and four centres in NZ. Patients enrolled were those presenting to hospital with a primary diagnosis of HF or attending a hospital-clinic for management of HF within 6 months of decompensated HF. Diabetes was defined as the presence of a prior diagnosis (fasting plasma glucose ≥7 mmol/L or random plasma glucose ≥11.1 mmol/L or HbA1c ≥6.5%) and/or treatment with antidiabetic medications. All patients were above 21 years of age and provided informed consent. The studies comply with the Declaration of Helsinki. Missing data in our study were minimised by the prospective recruitment using standardised protocols.

Patients were assessed at recruitment (baseline visit), clinic visits at 6 weeks and 6 months, and with phone calls at 1 and 2 years. At time of recruitment, patient demographics, clinical risk factors, quality of life, standard 12-lead ECG and serum biomarkers were obtained. Only Asian patients (Chinese, Malay, Indian) from Singapore and Caucasian patients (NZ-Europeans) from NZ were included in this study. Other ethnic races from the original SHOP-PEOPLE study were excluded to limit comparisons between Asian and Caucasian patients with HF. Comprehensive transthoracic echocardiography was performed according to standard protocols, and interpreted in accordance with American Society...
of Echocardiography guidelines. Echocardiographic parameters obtained included EF, left atrial volume index (LAVI), left ventricular mass index (LVMI) and mitral E/e’ ratio.

Definition of AF
AF was defined as either a self-reported history of AF or presence of AF on 12-lead ECG at time of recruitment. Patients with a history of AF and AF on baseline ECG at recruitment were classified as persistent/permanent AF. Patients with a history of AF but no AF on baseline ECG were classified as paroxysmal AF. Those with no known history of AF but had AF on baseline ECG were classified as newly diagnosed AF.

Outcome
The primary outcome was the combined end point of all-cause mortality or HF hospitalisation over 2 years. Clinical outcomes and mortality status were ascertained through in-person clinic visits at 6 weeks and 6 months, phone calls at 1 year and 2 years as well as national death registries and linked hospital databases.

Statistical analysis
Baseline characteristics of patients with and without AF were reported as percentages (%) for categorical variables, and mean (SD) or median (lower quartile, upper quartile) for continuous variables. Differences in baseline characteristics were then assessed with independent t-test or Mann-Whitney U test for continuous variables or X² test (categorical). Univariable and multivariable analyses were performed for each clinical correlate on its association with AF, and tested for interaction by ethnicity. If there was an interaction with ethnicity, the association with AF was then stratified and compared separately according to ethnicity. The association of AF with outcomes was performed by univariable then multivariable Cox regression analysis, and testing for interaction by ethnicity, diabetes, EF and ischaemic heart disease (IHD). Time-to-event analyses were examined using multivariable Cox proportional hazards models in the absence of violation of the proportion hazard assumption.

RESULTS
Among 2039 patients from the SHOP-PEOPLE study, 1746 patients with HF (1086 Asian patients from Singapore and 660 European patients from NZ) met the inclusion criteria and were classified as newly diagnosed AF.

Baseline characteristics
Compared with those without AF, patients with AF were older, had higher body mass index (BMI), worse NYHA functional status, quality of life (based on the Minnesota Living with Heart Failure questionnaire) and were more likely to have a history of hypertension, non-ischaemic HF, stroke, peripheral vascular disease, renal disease, chronic respiratory disease and increased alcohol intake, but less likely to have diabetes (table 1). Patients with AF were also more likely to have larger LAVI, reduced EF, LVMI and mitral E/e’. Median heart rate measured at baseline visit in patients with and without AF were identical, likely a reflection of high beta-blocker usage in patients with and without AF (83% vs 86%, respectively).

Association of ethnicity with AF
The prevalence of AF was markedly lower in Asians than NZ-Europeans (24% vs 63%, p<0.001), irrespective of EF (pinteraction for EF=0.39). Asians were less likely to have AF compared with NZ-Europeans, even after adjusting for age, clinical and echocardiographic variables and medications (table 2). Comparison of baseline characteristics between patients with and without AF by ethnicity are shown in online supplementary table 1A.

Table 1 Baseline characteristics of patients with HF with AF (n=678) and without AF (n=1068)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>No AF</th>
<th>AF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63±13</td>
<td>72±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (females), (%)</td>
<td>273 (26)</td>
<td>189 (28)</td>
<td>0.29</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian, (%)</td>
<td>827 (76)</td>
<td>259 (24)</td>
<td></td>
</tr>
<tr>
<td>NZ-European, (%)</td>
<td>241 (37)</td>
<td>419 (63)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8±5.8</td>
<td>27.8±5.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate*, bpm</td>
<td>74 (65, 84)</td>
<td>73 (63, 84)</td>
<td>0.846</td>
</tr>
<tr>
<td>NYHA functional status</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA I+II, (%)</td>
<td>857 (82)</td>
<td>443 (66)</td>
<td></td>
</tr>
<tr>
<td>NYHA III+IV, (%)</td>
<td>194 (18)</td>
<td>227 (34)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>194 (19)</td>
<td>227 (34)</td>
<td>0.047</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>550 (52)</td>
<td>244 (36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>705 (68)</td>
<td>368 (56)</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>68 (7)</td>
<td>65 (10)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>109 (10)</td>
<td>127 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>125 (12)</td>
<td>132 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD</td>
<td>488 (47)</td>
<td>360 (54)</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking</td>
<td>596 (56)</td>
<td>367 (54)</td>
<td>0.49</td>
</tr>
<tr>
<td>Alcohol</td>
<td>454 (43)</td>
<td>436 (65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP*, pg/mL</td>
<td>1805 (687, 4097)</td>
<td>2315 (1209, 4559)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>914 (86)</td>
<td>564 (83)</td>
<td>0.18</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>909 (85)</td>
<td>540 (80)</td>
<td>0.003</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>464 (43)</td>
<td>183 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>839 (79)</td>
<td>439 (65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAVI, mL/m²</td>
<td>41.1±16.7</td>
<td>57.3±21.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>141.7±44.2</td>
<td>137.0±43.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>227 (22)</td>
<td>228 (37)</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>97 (10)</td>
<td>95 (15)</td>
<td></td>
</tr>
<tr>
<td>Average mitral E/e’</td>
<td>17.3±8.0</td>
<td>15.2±7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life (MLwHF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>34.5±23.4</td>
<td>40.3±24.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical score</td>
<td>15.9±11.2</td>
<td>18.9±10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emotional score</td>
<td>6.5±6.2</td>
<td>7.6±6.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. P values were obtained by independent t-test or Mann-Whitney U test for continuous variables or X² test for categorical variables.

*Values are expressed as median (lower quartile, upper quartile).

ACE-I, ACE inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m²); HF, heart failure; LAVI, left atrial volume index; LVMI, left ventricular mass index; MLwHF, Minnesota Living with HF; NYHA, New York Heart Association; NT-proBNP, NT-pro brain natriuretic peptide.
Association of clinical correlates with AF

Clinical correlates of AF were similar for Asians and NZ-Europeans except diabetes (pinteraction for diabetes=0.01): Asian diabetic patients with HF had less AF compared with Asian patients without diabetes (OR 0.66, 95% CI 0.50 to 0.88), whereas among NZ-Europeans there was no significant association between diabetes and AF (OR 1.22, 95% CI 0.85 to 1.75). Among 794 patients (175 NZ-European, 619 Asian) with diabetes, 718 patients (90% NZ-European vs 97% Asian, p=0.70) had type II diabetes. Duration of diabetes was reported in 129 (74%) NZ-European and 536 (87%) Asian patients, and were not different (median (lower quartile, upper quartile) 10 (2.5, 17) vs 10 (4.0, 17) years, respectively, p=0.65). Treatment for diabetes included oral hypoglycaemic agents in 575 (72%) patients (96 NZ-European, 479 Asian), and insulin therapy in 212 (27%) patients (57 NZ-European, 155 Asian). In the Singapore-Asian cohort, 338 (51%), 90 (75%) and 191 (66%) Chinese, Indian and Malay patients had diabetes, respectively (p<0.001). The association of diabetes with lower prevalence of AF was similar among the three major ethnic races in Singapore, with no significant interaction between the Asian ethnicities and diabetes on odds of AF (pinteraction=0.23).

Baseline comparisons between patients with and without diabetes by ethnicity are shown in online supplementary table 1B. Diabetic patients with HF had smaller LAVI, regardless of AF status, EF or ethnicity (on online supplementary table 2).

In multivariable analyses, older age, higher BMI, worse NYHA functional class, non-ischaemic HF, larger LAVI, higher NT-proBNP and LVEF were independently associated with higher likelihood of AF, while female sex, Asian ethnicity and statin usage conferred lower likelihood of AF (figure 1).

A significantly higher proportion of Asian patients had a history of hypertension (NZ-European (35%) vs Asian (63%), p<0.001). Asian patients had higher mean systolic blood pressure (SBP) (125 (SD 23) Asian vs 121 (SD 22) mm Hg NZ-European, p<0.001), but similar mean diastolic blood pressure compared with NZ-Europeans (71 (SD 13) Asian vs 71 (SD 12) mm Hg NZ-European, p=0.24). Conversely, NZ-Europeans had higher alcohol consumption than Asians (61% vs 39%, p<0.001). Among NZ-Europeans with alcohol use, 66% were current and 17% were ex-drinkers, while only 12% of Asians were current and 20% ex-drinkers. The variability in SBP and alcohol use between the two ethnicities did not however account for the differences in AF prevalence.

Outcomes

During 2 years of follow-up, 716 patients (41%) either died from any cause or were hospitalised for HF (44% AF vs 36% without AF, p=0.02). By univariate analysis, AF was significantly associated with higher composite event rates for all-cause mortality and HF hospitalisations at 2 years, irrespective of ethnicity (pinteraction for ethnicity=0.68), diabetes (pinteraction for diabetes=0.06), EF (pinteraction for EF=0.53) and IHD (pinteraction for IHD=0.94). This association was however no longer significant after adjusting for age, clinical covariates, echocardiographic parameters, serum biomarker and medications (table 3).
Sensitivity analyses
We repeated the analyses restricting the AF group strictly to those with persistent/permanent AF (n=435). Asian ethnicity continued to be associated with a lower prevalence of persistent/permanent AF than in NZ-Europeans after adjusting for clinical factors (online supplementary table 3). After further adjustment for echocardiographic correlates, the difference was attenuated, suggesting that echocardiographic left atrial (LA) remodelling may mediate, at least in part, the difference in AF prevalence between ethnicities (online supplementary table 3). The association of AF with mortality was however not seen in permanent/permanent AF (online supplementary table 4). Interestingly, paroxysmal AF showed an approximately 30% increase in hazard for the composite outcome at 2 years with the association attenuated on adjustment for (log)NT-proBNP.

DISCUSSION
This multinational study provides for the first time, evidence of a strikingly lower prevalence of AF among Asians compared with NZ-European patients with HF, even after adjusting for age and clinical covariates in both HFpEF and HFrEF. Importantly, patients were recruited in Singapore and NZ according to identical protocols and in the same time period. The majority of independent clinical correlates of AF were similarly associated with AF in both countries, including older age, male sex, higher BMI, more advanced HF, non-ischaemic aetiology of HF and lack of statin use. However, the relationship of diabetes to AF differed by ethnicity: AF was less frequent in patients with diabetes, specifically in Asians. Those with AF had higher death and HF hospitalisation rates in both ethnic groups; an effect largely accounted for by age.

Lower prevalence of AF in Asians
Population-based studies previously reported a lower prevalence of AF among Asians compared with NZ-European patients with HF, even after adjusting for age and clinical covariates in both HFpEF and HFrEF. Importantly, patients were recruited in Singapore and NZ according to identical protocols and in the same time period. The majority of independent clinical correlates of AF were similarly associated with AF in both countries, including older age, male sex, higher BMI, more advanced HF, non-ischaemic aetiology of HF and lack of statin use. However, the relationship of diabetes to AF differed by ethnicity: AF was less frequent in patients with diabetes, specifically in Asians. Those with AF had higher death and HF hospitalisation rates in both ethnic groups; an effect largely accounted for by age.

We present data showing a lower prevalence of AF in Asian patients with HF than in white patients with HF from the Swedish HF Registry, and we have previously compared Singapore patients with HF with white patients with HF in the GWTG-HF Registry, patients with HF and diabetes had a lower prevalence of chronic or recurrent AF than those without diabetes (32% vs 38%, p<0.001), although patients from this registry were predominantly white (69% vs 2% Asian) and separate analyses between different ethnicities were not performed.20 We have previously compared Singapore patients with HF with white patients with HF from the Swedish HF Registry, and found that although Asian patients with HF were threefold more likely to have diabetes, there was a lower prevalence of AF in Asian patients with HF than in white diabetic patients with HF (20.7% vs 51.8%, p<0.001) and lower prevalence of AF in Asian diabetic patients with HF than Asian non-diabetic patients with HF (20.7% vs 28.8%).21 Our current findings are consistent, showing that Asian diabetic patients with HF were 33% less likely to have AF than those without.

The association of diabetes with AF has been attributed to chronic systemic inflammation, enhanced adrenergic activation and increased LA volumes.22 23 We found that diabetic patients had smaller LA size than non-diabetic patients regardless of AF status, EF and ethnicity, suggesting that differences in cardiac remodelling may play a role in the relative protection of diabetic patients with HF against AF. Further work is needed to compare underlying cellular and molecular mechanisms of atrial remodelling in diabetic HF in Asian and Caucasian ethnicities.

**Table 3** Association of AF with composite outcome of HF hospitalisation and death at 2 years

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1.19</td>
<td>1.02 to 1.38</td>
<td>0.024</td>
</tr>
<tr>
<td>Model A</td>
<td>1.06</td>
<td>0.90 to 1.26</td>
<td>0.479</td>
</tr>
<tr>
<td>Model B</td>
<td>1.16</td>
<td>0.97 to 1.39</td>
<td>0.096</td>
</tr>
<tr>
<td>Model C</td>
<td>1.18</td>
<td>0.98 to 1.41</td>
<td>0.075</td>
</tr>
<tr>
<td>Model D</td>
<td>1.15</td>
<td>0.92 to 1.43</td>
<td>0.229</td>
</tr>
<tr>
<td>Model E</td>
<td>1.05</td>
<td>0.84 to 1.32</td>
<td>0.660</td>
</tr>
</tbody>
</table>

Model A: adjusted for age, sex, ethnicity, body mass index, NYHA class.
Model B: adjusted for variables from model A and hypertension, diabetes, ischaemic heart disease, stroke, chronic respiratory disease and renal disease.
Model C: adjusted for variables from model B and beta-blocker, ACE-I/ARB, spironolactone, statin.
Model D: adjusted for variables from model C and EF≥50%, LAVI, LVMi, mitral E/e'.
Model E: adjusted for variables from model D and logNT-proBNP.

ACE-I, ACE inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; EF, ejection fraction; LAVI, left atrial volume index; NYHA, New York Heart Association.

Heart failure and cardiomyopathies

Reasons for the lower prevalence of AF among Asian patients with HF remain unclear. Although Asian patients were younger, the association of ethnicity with AF prevalence remained significant after adjusting for age. Another potential explanation includes the smaller atrial size and consequent electrophysiological differences in the Asian atrium.13 Indeed, Asian patients in our cohort had smaller LA size compared with NZ-Europeans, in both HFpEF (39.9 vs 52.2 mL/m², p<0.001) and HFrEF (44.0 vs 56.7 mL/m², p<0.001). Nonetheless, LA size alone did not explain the ethnic difference in prevalence of AF, which remained highly statistically significant following adjustment for LAVI. The reduced association of Asian ethnicity with AF was also seen in our sensitivity analysis, although attenuated after adjusting for echocardiographic parameters.

Additionally, Bathia et al had previously described a higher proportion of whites in patients with HF and AF when compared with blacks, Asians and Hispanics, but had the lowest rate of diabetes, hypertension, cardiomyopathy, hyperthyroidism and second lowest rate of obesity, all of which are well-recognised risk factors of AF.7 Findings from our study are in agreement, suggesting that the higher prevalence of AF among white patients may be due to an inherent ethnicity-specific characteristic.

Lower prevalence of AF in diabetic patients with HF
Although diabetes has been recognised as a risk factor of AF, studies have shown conflicting associations between the two. Reports from the Framingham Heart Study differ with respect to the presence or absence of an independent association of diabetes with AF.16 17 To date, there have been few reports on the relationship between diabetes and AF in HF within Asia, with a Japanese community-based study and a large Chinese population-based study also showing conflicting results.18 19

In the context of HF, diabetes appears to be paradoxically protective against AF. In the National Inpatient Sample registry, an inverse correlation of AF with diabetes in Asian patients with HF was seen; among whom those with AF had less diabetes compared with those without (41% vs 52%, p<0.001).7 In the GWTG-HF Registry, patients with HF and diabetes had a lower prevalence of chronic or recurrent AF than those without diabetes (32% vs 38%, p<0.001), although patients from this registry were predominantly white (69% vs 2% Asian) and separate analyses between different ethnicities were not performed.20

We have previously compared Singapore patients with HF with white patients with HF from the Swedish HF Registry, and found that although Asian patients with HF were threefold more likely to have diabetes, there was a lower prevalence of AF in Asian patients with HF than in white diabetic patients with HF (20.7% vs 51.8%, p<0.001) and lower prevalence of AF in Asian diabetic patients with HF than Asian non-diabetic patients with HF (20.7% vs 28.8%).21 Our current findings are consistent, showing that Asian diabetic patients with HF were 33% less likely to have AF than those without.

The association of diabetes with AF has been attributed to chronic systemic inflammation, enhanced adrenergic activation and increased LA volumes.22 23 We found that diabetic patients had smaller LA size than non-diabetic patients regardless of AF status, EF and ethnicity, suggesting that differences in cardiac remodelling may play a role in the relative protection of diabetic patients with HF against AF. Further work is needed to compare underlying cellular and molecular mechanisms of atrial remodelling in diabetic HF in Asian and Caucasian ethnicities.
Furthermore, patients with and without diabetes were of similar age and received similar guideline-directed HF medical therapy among both Asians and NZ-Europeans, suggesting that neither age nor HF care differences explained the association of diabetes with lower prevalence of AF. Even though previous studies have suggested an association between some oral antihyperglycaemic agents and reduction in AF,24–26 the prevalence of HF in these studies was low. We did not find a similar association to account for the lower prevalence of AF in diabetic patients with HF.

Association of AF with mortality

Previous studies on the prognostic significance of AF in HF have yielded inconsistent results. Although AF was associated with an increase in the composite end point of mortality and HF hospitalisation in the Studies of Left Ventricular Dysfunction (SOLVD) trial,2 it conferred no significant increase in mortality or HF hospitalisations in mild-to-moderate HF in the Veterans Affairs Vasodilator-Heart Failure Trial (V-HeFT) I and II trials,27 or moderate-to-severe chronic HF in the Prospective Randomized study of Ibopamine on Mortality and Efficacy (PRIME) II study.28

We found that AF was associated with 19% higher likelihood of all-cause mortality or HF hospitalisation, but was no longer significant after adjusting for other prognostic variables and did not show any interactions with ethnicity, diabetes, EF or IHD. While AF confers a higher mortality risk in the general population,29 the inconsistent results noted from previous studies in patients with HF may be accounted for by the presence of risk factors and clinical status that may outweigh the influence of AF on outcomes.

The attenuated effect of AF on composite outcomes observed in our study may be explained by the dominant effect of age. AF was not associated with poorer outcomes after adjusting for age, suggesting that the prognostic effect of AF was not independent of, but tied to, the effects of age. The significant effect of age was also seen in the Swedish HF registry, where a reduction in risk of all-cause mortality and HF hospitalisation or death after adjusting for age was seen across all EF subgroups.30 In our sensitivity analysis, only patients with paroxysmal AF had an increase in mortality and HF hospitalisations but not patients with persistent/permanent AF. The prognostic importance of paroxysmal AF in HF remains uncertain but our study suggests poorer outcomes in this subset of patients.

Limitations

Patients from this study were recruited from Singapore and NZ, and may not be universally representative of all Asian and white patients with HF. Comparisons between the same ethnic groups in Singapore and NZ were not performed due to the small numbers of Chinese and Indian patients in NZ.

Analyses in our study were largely cross-sectional and do not allow ascertainment of causality or temporal relationships between the onset of AF and that of other abnormalities including diabetes. Data on the development of AF during follow-up was unavailable, with the possibility of patients developing asymptomatic paroxysmal AF. However, given the strong association between paroxysmal AF and poorer outcomes even after multiple models of multivariable adjustment, we do not expect this association to be attenuated. The inclusion of these patients with newly diagnosed paroxysmal AF will be helpful in validating our observations.

We acknowledge that healthcare systems in NZ and Singapore are different. NZ has a universal healthcare system, where healthcare services are provided free to citizens/permanent residents, while Singapore’s healthcare system entails a mixed financing system. However, our study was restricted to public healthcare institutions in Singapore (vs private), which provide inpatient care for 80% of the Singapore population, and where government subsidies of up to 80% of the total bill plus multiple layers of healthcare financing aid are in place to ensure that citizens are not denied access to healthcare. Hence, access to healthcare would be more similar than different in the populations we studied. Furthermore, the use of identical parallel protocols, broad inclusion criteria, nationwide approach and contemporaneous enrolment would all have minimised differences in selection/participation between the two countries. The prospective design with identical parallel protocols in NZ and Singapore and the nationwide mortality/hospital admission registers for complete follow-up and low rate of missing data are strengths of this study.

CONCLUSION

These are the first contemporaneous multinational data showing a strikingly lower prevalence of AF among Asian compared with NZ-European patients with HF. The underlying mechanisms for the lower prevalence of AF among Asians, particularly in the presence of diabetes, warrant further study.

Key messages

What is already known on this subject?

► Atrial fibrillation (AF) and heart failure (HF) frequently coexist and share many risk factors, including age, hypertension, diabetes and ischaemic heart disease.

► The impact of ethnicity on the prevalence of AF in HF remains unclear, with previous studies suggesting a higher prevalence of AF in white patients with HF.

► Although diabetes has been recognised as a risk factor of AF, studies have shown conflicting associations between the two, with few reports to date on the relationship between diabetes and AF in HF within Asia.

What might this study add?

► There is a strikingly lower prevalence of AF among Singapore Asian compared with New Zealand (NZ)-European patients with HF.

► Interestingly, the presence of diabetes was independently related to lower odds of AF.

► Ethnic interactions exist in the relationship between diabetes and AF, where AF was less frequent in diabetes specifically in Asian patients.

How might this impact on clinical practice?

► These novel data provide definitive epidemiological evidence confirming the common perception of lower prevalence of AF among Asian patients, and suggest an important role for diabetes in influencing the risk of AF in HF.

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Correction notice Since this paper was first published online, a change has been made to the text in the section Lower prevalence of AF in diabetic patients with HF:

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