Valvular heart disease among non-valvular atrial fibrillation: a misnomer, in search of a new term

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This editorial refers to ‘Prognostic value of CHA2DS2-VASc score in patients with ‘non-valvular atrial fibrillation’ and valvular heart disease: the Loire Valley Atrial Fibrillation Project’1, by R. Philippart et al., on page 1822.

A 76-year-old male patient with arterial hypertension and moderate aortic stenosis presents with the first episode of atrial fibrillation (AF). His CHA2DS2-VASc score is 3. Can we use the CHA2DS2-VASc score that has been developed in patients with non-valvular AF for assessment of his need for long-term oral anticoagulation? Also, since the underlying trials were done in patients with non-valvular AF, is this patient eligible for a non-vitamin K antagonist (NOAC) or does he have valvular disease and, thus, would need a vitamin K antagonist?

These are frequently raised questions among cardiologists. Based on registry data, patients with AF and valve disease are common in clinical practice,1−6 with a higher proportion of these patients among those with permanent than those with paroxysmal or persistent AF.1,2 (Table 1). While the prevalence was reported as 21% in the Euro Heart Survey (defined as ‘any type of valve disease’)1 and 24.6% in AFNET (‘non-rheumatic valve disease’),2 it was only 4.2% in the AFNET registry.2 However, differences in patient cohorts may also reflect different interpretation of the definition of non-valvular AF when recruiting patients. The ACC/AHA/ESC Guidelines 2006 defined non-valvular AF as AF in the absence of rheumatic mitral valve disease, prosthetic heart valves, or valve repair.6 The 2012 focused update of the ESC Guidelines9 states that it is conventional to divide AF into cases which are described as ‘valvular’ or ‘non-valvular’. Valvular AF was defined as rheumatic valve disease (predominantly mitral stenosis) or prosthetic heart valves. Similarly, the 2014 AHA/ACC/HRS Guideline for the management of patients with AF defined non-valvular AF as AF in the absence of rheumatic mitral stenosis, or a mechanical heart valve, but explicitly added bioprosthetic heart valves or mitral valve repair (Figure 1).10

In clinical practice, the term non-valvular AF has created considerable confusion among physicians who use it to ask which patients fall into which category and may be treated by novel anticoagulants. This has been confirmed in a recent prospectively conducted web-based survey of cardiologists and internists.11 Co-existence of both medical history of rheumatic disease and clinical signs of valvular involvement were considered as essential prerequisites for the diagnosis of rheumatic AF by half of the respondents, and one-third assumed that lone aortic valve disease was sufficient for AF to be defined as valvular. A similar proportion of respondents considered that in the presence of mitral regurgitation, AF had to be defined as valvular. The majority of responding physicians considered the degree of valvular disease of lesser importance for the definition of valvular or non-valvular origin of AF.

Proper understanding of which type of valve disease belongs to non-valvular AF is critical when considering the use of an NOAC in patients with AF. The importance of restricting the indications to available trial data has been shown by the RE-ALIGN study which advises against the use of the NOAC dabigatran in patients with mechanical heart valve prostheses.12 Recent trials on NOACs and the labelling of their respective compounds by the European Medicines Agency refer to non-valvular AF as an indication for dabigatran, rivaroxaban, and apixaban to prevent ischaemic stroke and systemic embolism. Despite apparent
similarities, the inclusion criteria have varied in these trials. For instance, RE-LY13 used criteria that were narrower than those in the guidelines mentioned above by excluding any type of heart valve disorder (i.e. prosthetic valve or haemodynamically relevant valve disease). In contrast, in ROCKET AF, the exclusion criteria were haemodynamically significant mitral valve stenosis, prosthetic heart valves, and a planned invasive procedure with potential for uncontrolled bleeding, including major surgery, whereas annuloplasty with or without a prosthetic ring, commissurotomy, and/or valvuloplasty were permitted. This also allowed the inclusion of a variety of valvular lesions such as aortic stenosis and aortic or mitral regurgitation (which was the case in 2003 of 14 171 patients; 14.1%).14

In this respect, the current report from the Loire Valley Atrial Fibrillation Project adds to our knowledge of patients with valve disease who, nevertheless, meet the criteria of non-valvular AF.15 Among 8962 patients (Table 1) from a large cardiology department, there were 909 (10.1%) with valvular AF in the strict sense, whereas the remaining 8053 patients had non-valvular AF (as defined in the ESC guidelines). These patients were categorized into those without any valve disease (n = 6851; 85%) and those with valve disease but neither rheumatic mitral stenosis nor valve prosthesis (n = 1202; 15%). The latter figure corresponds to the 14.1% of patients with valve disease in the ROCKET AF trial.14 The main objective of this study from the Loire Valley Project was to assess whether the CHA2DS2-VASc score allows stratification even in patients with valvular AF. Patients with valve disease were older, had a higher CHA2DS2-VASc score, and had a higher risk of thrombo-embolic events than patients without valve disease. The main finding was that the predictive value of the CHA2DS2-VASc score was similar in both groups. While this is important information that corroborates the strength of this score, the data of this registry are also of great interest with regard to the more general issue of non-valvular AF.

The majority of these registry patients had mitral regurgitation (61%), aortic regurgitation (24%), and aortic stenosis (32%), which reflects the results of the ROCKET AF trial.14 By univariate analysis, patients with non-valvular AF and valve disease had a significantly higher risk of stroke or systemic embolism [hazard ratio (HR) 1.39, 95% confidence interval (CI) 1.14–1.69, P = 0.001] than patients with non-valvular AF and no valve disease, but this lost significance after multivariable adjustment (HR 1.24, 95% CI 0.84–1.83, P = 0.28) which is similar to our findings in ROCKET AF in patients all allocated to oral anticoagulation (HR 1.07, 95% CI 0.85–1.35, P = 0.59).14 However, their conclusion that left-sided valvular heart disease (excluding mitral stenosis and prostheses) was associated with an increased risk of stroke and thrombo-embolic events is only based on univariate analysis but does not stand the test of multivariate adjustment. Interestingly, the severity of valve disease in this registry was not independently associated with a higher risk of stroke or systemic embolism.

Their rate of stroke and thrombo-embolism of 2.94 events/100 patient-years (our own calculation) in the combined groups of patients with non-valvular AF with or without valve disease is somewhat higher than what we found in similar patients with non-valvular AF and valve disease (HR 2.23 events/100 patient-years) and no valve disease (HR 2.09 events/100 patient-years); HR 1.07, 95% CI 0.85–1.35, P = 0.58. This higher event rate may be due to the fact that only ~50–60% of their patients were on oral anticoagulation. This comparison suggests that the patient selection and the outcomes in a trial such as ROCKET AF reflect real-world data as found in the Loire Valley registry.

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### Table 1  Composition of patient cohorts in some recent registries and trials of patients with atrial fibrillation showing the large variability in these registries and compared with a clinical trial

<table>
<thead>
<tr>
<th>Registry (reference)</th>
<th>No. of patients</th>
<th>Type of patients</th>
<th>Category of valve disease</th>
<th>All (%)</th>
<th>Paroxysmal (%)</th>
<th>Persistent (%)</th>
<th>Permanent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euro Heart Survey1</td>
<td>5333</td>
<td>A + H</td>
<td>Valv HD</td>
<td>21</td>
<td>19</td>
<td>24</td>
<td>40</td>
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<tr>
<td>German AFNET Registry2</td>
<td>9582</td>
<td>A + H</td>
<td>Non-rheumatic valvular disease</td>
<td>24.6</td>
<td>22.6</td>
<td>33.7</td>
<td>42.7</td>
</tr>
<tr>
<td>Realise-AF5</td>
<td>9816</td>
<td></td>
<td>Rheumatic valvular disease</td>
<td>3.1</td>
<td>2.5</td>
<td>3.3</td>
<td>5.3</td>
</tr>
<tr>
<td>MOVE4</td>
<td>2753</td>
<td>A + H</td>
<td>Valv HD (undefined)</td>
<td>16.7</td>
<td>21.2</td>
<td>35.8</td>
<td></td>
</tr>
<tr>
<td>PREFER-AF6</td>
<td>7243</td>
<td>A + H</td>
<td>Mitral stenosis</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loire Valley AF Cardiology Project15</td>
<td>8962</td>
<td>A + H</td>
<td>Valve disease (exclusion of valvular AF)</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>ROCKET AF Trial14</td>
<td>14 171</td>
<td>A + H</td>
<td>Left-sided valve disease (exclusion of valvular AF)</td>
<td>13.4</td>
<td>13.4</td>
<td>13.4</td>
<td>13.4</td>
</tr>
</tbody>
</table>

A, ambulatory patients; H, hospitalized patients; MR, mitral regurgitation; Valv HD, valvular heart disease.

1 Patients from cardiological units.

2 Patients from cardiological and non-cardiological units.

3 83.1% cardiologists, 7.8% internists, and 9.1% who defined themselves as both internists and cardiologists.

4 98% cardiologists.

5 Valvular AF as defined by guidelines (exclusion of mitral stenosis and prostheses).
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In conclusion, the generally accepted term of non-valvular AF is definitely misleading. The fact that ROCKET AF as well as registries (Table 1) have included patients who, although not having mitral stenosis or artificial heart valves, nevertheless had other types of valvular heart disease is widely not acknowledged. Risk assessment as well as treatment decisions—including the use of NOACs—that have been established for so-called ‘non-valvular’ AF appear to be adequate for patients with valvular disease as long as mitral stenosis and mechanical heart valves are excluded. These two entities, however, are very different and there is no justification to merge them into a single group called ‘valvular’ AF. As recently demonstrated, mechanical valves require anticoagulation with vitamin K antagonists irrespective of the presence of AF in order to avoid thrombus formation on the prosthesis. Patients with mitral stenosis and AF have been accepted to be high risk patients for thrombo-embolic events and have been excluded from any further trials studying anticoagulation regimens for AF. Therefore, it would be better if the terms valvular and non-valvular AF were abandoned. Instead, AF in the presence of a mechanical valve and AF in association with mitral stenosis should be highlighted as conditions with special needs for anticoagulation.

Conflict of interest: G.B. is a Consultant to Bayer Health Care, J & J, Boehringer Ingelheim, Sanofi-Aventis, MSD, 3M, BMS/Pfizer, and Portola. H.B. has no conflicts with regard to this work.

References


Figure 1 Subtypes of atrial fibrillation (AF) based on ESC Guidelines. The 2014 ACC/AHA/HRS Guidelines add bioprosthetic heart valves and mitral repair to the valve diseases that constitute valvular AF.


