SCIENTIFIC EDITORIAL

PALLAS: Insights into permanent atrial fibrillation

L'étude PALLAS : à propos de la fibrillation atriale permanente

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In recent months, pharmaco-vigilance alerts have emerged for dronedarone, followed by discontinuation of the Permanent Atrial fibrillLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) study in July 2011. The recent publication of this study [1] undoubtedly leads us to question the current position of this antiarrhythmic drug, but also to analyse the currently available treatments for permanent atrial fibrillation (AF).

Permanent atrial fibrillation

Permanent AF -- the final stage within the AF continuum -- is not yet well understood. It is only recently, that data from some large registries [2,3] and a few randomized studies [4,5] have become available. However, of the three forms of AF -- paroxysmal, persistent, and permanent -- permanent AF is the most common, representing nearly 50% of cases, when excluding 'first access' AF. Compared with paroxysmal AF, permanent AF tends to occur in older patients (more than 70 years of age on average versus 65 years for the other forms of AF); as many as 30—40% of AF patients over 75 years of age can have permanent AF. When compared with paroxysmal AF, the prevalence of hypertension is similar, that of diabetes is twice as frequent (17—28% of patients), and that for structural heart diseases (ishaemic, non-ishaemic, valvular) is greater. Not surprisingly, the average CHADS2 score is higher in patients with permanent AF, calculated at between 1.8 and 2.2, against 0.9—1.7 for paroxysmal AF.

At first glance, the therapeutic approach in permanent AF may appear simple. By definition, there is no room for any "rhythm-control" strategy; antithrombotic guidelines are well established with regard to risk scores and they do not include AF forms. For a "rate-control" strategy, the medications are beta-blockers, calcium-channel blockers and digoxin, proposed in international guidelines as class I indications with a level

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of evidence A [6,7]. When adequate rate control is not obtained with such medications, the next step is atrioventricular node ablation, performed in 1–5% of patients, combined with permanent right ventricular pacing, upgraded to biventricular pacing in the presence of heart failure, ventricular dilatation and left bundle branch block. However, two questions remain about the rate-control strategy.

First, the drugs available are perhaps suboptimal, digoxin use remains controversial, and registries consistently report the use of antiarrhythmic drugs in 5–10% of patients with permanent AF. Indeed, in the 2010 guidelines [6], amiodarone use was considered possible (class IIb) while dronedarone even appeared as a class IIA recommendation.

Second, the "ideal" ventricular rate is not yet known. Indeed, the latest recommendations offer two rate-control strategies: a "lenient" rate control (less than 110 beats per minute) in asymptomatic patients and a "strict" rate control (less than 80 beats per minute) in symptomatic patients or in those with heart failure. However, Canadian and US guidelines, prudently, retain a maximum ventricular rate of 100 beats per minute in asymptomatic patients [7]. Indeed, sub analysis studies have shown that, paradoxically, the benefit of the rate-control strategy was independent of the ventricular rate obtained. As a result, a study comparing "lenient" with "strict" rate control was performed in 614 patients with permanent AF and rapid ventricular rates despite usual treatment (more than 80 beats per minute). No differences were found between the two strategies, but this small study, which used a composite endpoint, is not without any critic.

The Permanent Atrial fibrillAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) study

The specific objective of the PALLAS study [1] was to evaluate the impact of dronedarone on the hard endpoints of mortality and cardiovascular morbidity in a very large planned cohort of 10,800 patients.

The PALLAS study began in July 2010, and was stopped for safety reasons a year later. This study focused on patients who had had permanent AF for at least 6 months and were at high cardiovascular risk: more than 65 years of age with ischaemic heart disease, a history of stroke or peripheral artery disease, or more than 75 years of age with hypertension and diabetes. Patients were randomized to receive, in addition to their usual treatment, placebo or dronedarone 400 mg twice daily. The planned follow-up was 2–3 years, driven by events (>444 events) from two co-primary endpoints, the first being "cardiovascular mortality or myocardial infarction or stroke", and the second being "overall mortality or hospitalization for cardiovascular causes".

After a mean follow-up of 3.5 months and the inclusion of 3236 patients, the study had to be stopped for an excess of events, 43 with dronedarone versus 19 for placebo for the first outcome, and 127 versus 67, respectively, for the second outcome. The three main cardiovascular events were heart failure hospitalization or episode (n = 115 vs. 55), cardiovascular mortality (n = 21 vs. 10), and stroke (n = 23 vs. 10) in the dronedarone group versus the placebo group. The usual effects of the drug were nevertheless found, exhibiting decreases in ventricular rate (−7.6 beats per minute) and systolic arterial pressure (−3.5 mmHg) and a small increase in QTc (+8 ms). But even during this short follow-up, tolerance was not satisfactory as the rate of premature discontinuation was high, at 21%, with side effects including usual digestive disorders along with leg oedema and dyspnoea.

The results from the PALLAS trial are the exact opposite of those from the ATHENA study [8]. The latter showed a remarkable 20–30% decrease in several morbidity and mortality endpoints (cardiovascular death, myocardial infarction, cardiovascular hospitalization, hospitalization for AF), while the findings from PALLAS were negative, with a highly significant hazard ratio of 2–3.

Why do the results from PALLAS differ from those of ATHENA?

As shown in Table 1 [9], patients in PALLAS were at higher cardiovascular risk in terms of age, cardiovascular risk factors, underlying heart disease and history of heart failure; only some had a low ejection fraction (below 45% or 40%): 12% in ATHENA and 21% in PALLAS; use of treatments was similar in the two studies, but with a greater use of anti-coagulant therapy in PALLAS. All subgroup analyses were negative, including those for age, history of heart failure, ejection fraction and heart disease. It is not possible to attribute the negative results of PALLAS to some higher-risk subgroup of patients, and similarly the benefits in ATHENA were present in all subgroups and did not decrease in higher-risk patients. The only significant interaction was with digoxin, received by one-third of the patients in PALLAS and clearly associated with a mortality increase; the known pharmacokinetic interaction of digoxin and dronedarone was probably deleterious in this population. Another point concerns the very rapid occurrence of the events, including those of the primary outcome: most strokes occurred during the first month, without clear explanation: systolic blood pressure decreased, and the quality of anticoagulation at baseline was not an issue. The high discontinuation rates, in the treatment group (21%) but also in the placebo group (11%), evoke a frail population. Regarding the second primary endpoint, the large number of heart failure events may indicate a negative inotropic effect of dronedarone, significant in this population of elderly patients treated with a uniform and standard dose of 800 mg per day.

The rationale of the PALLAS study should also be questioned, as was the rationale of another negative study (ANDROMEDA) [10], which involved treatment with dronedarone in patients without atrial arrhythmia but with heart failure with a low ejection fraction and recent (less than 1 month) left ventricular decompensation. Indeed, PALLAS was not a rhythm-control study because the atrial arrhythmia was already permanent, nor was it a rate-control study because the ventricular rate was not particularly fast, but only an add-on use of an antiarrhythmic drug in patients...
Table 1  Comparison of the ATHENA, PALLAS and ANDROMEDA populations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ATHENA</th>
<th>PALLAS</th>
<th>ANDROMEDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient demographic and clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (years)</td>
<td>72</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>Women (%)</td>
<td>47</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>Baseline atrial fibrillation (%)</td>
<td>25</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>86</td>
<td>83</td>
<td>37</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>30</td>
<td>41</td>
<td>65</td>
</tr>
<tr>
<td>CHF class II or III (%)</td>
<td>21</td>
<td>54</td>
<td>97</td>
</tr>
<tr>
<td><strong>Treatment (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Beta-blocker</td>
<td>71</td>
<td>74</td>
<td>61</td>
</tr>
<tr>
<td>Digoxin</td>
<td>14</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>70</td>
<td>78</td>
<td>86</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>60</td>
<td>84</td>
<td>31</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.84</td>
<td>1.94</td>
<td>2.13</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.71</td>
<td>2.11</td>
<td>2.75</td>
</tr>
<tr>
<td>Death for arrhythmia</td>
<td>0.55</td>
<td>3.26</td>
<td>1.68</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.66</td>
<td>2.32</td>
<td>NA</td>
</tr>
<tr>
<td>CHF (hospitalization or event)</td>
<td>0.86</td>
<td>1.89</td>
<td>1.22</td>
</tr>
</tbody>
</table>

Nattel S. [9].
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CHF: congestive heart failure.

at high cardiovascular risk. Indeed, the success of ATHENA has suggested several mechanisms for the drug, along with rhythm- and rate-control benefits, such as hypotensive and antianginal effects due to the properties of beta-blockers and calcium-channel blockers; so a post-hoc subgroup of 343 patients with permanent AF in ATHENA also benefited from the drug [11]. But the true question in permanent AF—an undeniable public health problem—is “rate control”, and it might have been better to select only those patients with a rapid ventricular rate, for example more than 80 beats per minute, as in two previous “rate control” drug trials [4,5]. The question of the optimal rate remains relevant, and significantly the success of ivabradine in heart failure was shown in patients with a rapid ventricular rate (more than 70 beats per minute) in sinus rhythm [12]. Finally, we do not know what the results will be of a randomized controlled trial of digoxin or calcium-channel blockers in a PALLAS-like population.

What remains now for dronedarone?

The indications of dronedarone in paroxysmal or persistent AF have recently been restricted, excluding any patient with a history of heart failure or left ventricular dysfunction, along with any patients with previous liver or lung intolerance on amiodarone, and those with permanent AF [13]. However, the levels of evidence of PALLAS—a warning signal carried by a prematurely stopped study—could not be compared with those of ATHENA, which involved 4600 high cardiovascular risk patients with up to 30 months of follow-up: for example, the ischaemic patient with a maintained left ventricular function and paroxysmal or persistent AF may be now the ideal recipient of dronedarone.

The role of dronedarone in the antiarrhythmic armamentarium will probably be clarified in the coming years, similarly to class I antiarrhythmic drugs, which, despite the Cardiac Arrhythmia Suppression Trial (CAST) study [14], have gradually found their place confirmed by recent international registries of patients with paroxysmal or persistent AF [15]. Dronedarone has indeed been widely studied in thousands of patients in several studies, which it is not the case with currently available but older antiarrhythmic drugs. On the contrary, amiodarone, rightly acclaimed for its remarkable efficacy and cardiac tolerance, still raises some doubts, demonstrated by the lack of any long-term benefit on morbidity and mortality shown in several meta-analysis.

So, let’s trust that despite the findings from PALLAS, the “odyssey” of dronedarone [16] will continue.

Disclosure of interest

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References


