Atrial fibrillation

Inappropriate use of antiarrhythmic drugs in paroxysmal and persistent atrial fibrillation in a large contemporary international survey: insights from RealiseAF†

Chern-En Chiang1*, Marnix Goethals2, James O. O’Neill3, Lisa Naditch-Brûlé4, Sandrine Brette5, Habib Gamra6, Oleg Zharinov7, and P. Gabriel Steg8,9,10, on behalf of the RealiseAF survey investigators

1General Clinical Research Center and Division of Cardiology, Taipei Veterans General Hospital, National Yang-Ming University, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan; 2Department of Cardiology-Electrophysiology, H.-Hartziekenhuis Roeselare-Menen, Wilgenstraat 2, Roeselare 8800, Belgium; 3Connolly/Mater Hospitals/RCSI, Dublin 15/7/2, Ireland; 4Sanofi, Paris 75008, France; 5Lincoln, Boulogne-Billancourt 92517, France; 6Department of Cardiology A, Cardiothrombosis Research Unit, Fattouma Bourguiba University Hospital, Monastir 5000, Tunisia; 7National Medical Academy of Postgraduate Education, Kiev 04112, Ukraine; 8INSERM U-698, Paris 75018, France; 9Université Paris-Diderot, Paris 75013, France; and 10Assistance Publique – Hôpitaux de Paris, Centre Hospitalier Bichat-Claude Bernard, Paris 75018, France

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Aims
International atrial fibrillation (AF) guidelines have defined optimal drugs for patients with various underlying diseases, but the extent to which real-life practice complies with these guidelines is unknown. This study aimed to evaluate the appropriate use of antiarrhythmic drugs (AADs) in patients with paroxysmal and persistent AF from the RealiseAF survey, according to the 2006 American College of Cardiology/American Heart Association-European Society of Cardiology AF guidelines.

Methods and results
RealiseAF was an international cross-sectional, observational survey of 10,523 eligible patients from 26 countries on 4 continents, with ≥1 AF episode documented by standard electrocardiogram or by Holter monitoring in the last 12 months. Participating physicians were randomly selected during 2009–10 from lists of office-based or hospital-based cardiologists and internists. Overall, 4947 patients with paroxysmal (n = 2606) or persistent AF (n = 2341) were included; mean (standard deviation) age was 64.7 (12.4) and 66.0 (11.8) years, respectively. Class Ic drugs were prescribed in 589 patients (11.9%); however, in 20.0% of these patients, the indication was not consistent with published guidelines. Similarly, for the 219 patients prescribed sotalol (4.4%), 16.0% received treatment for an indication that deviated from the published guidelines. Amiodarone was prescribed as first-line therapy in 1268 patients (25.6%), but 49.9% of these did not have heart failure or hypertension with significant left ventricular hypertrophy.

Conclusion
The use of AADs for persistent or paroxysmal AF in this large contemporary international survey showed some deviations from international guidelines. The highest discordance came with the use of amiodarone in first line. Clearly, there is a large discrepancy between published guidelines and current practice.

Keywords
Atrial fibrillation • Antiarrhythmic drugs • Guidelines
What’s new?
• The RealiseAF survey is unique in that few large-scale, international studies in patients with atrial fibrillation have evaluated the appropriateness of antiarrhythmic drugs use in real-life clinical practice.
• The findings from this subanalysis suggest that there is a large discrepancy between those management strategies recommended in the published guidelines, and those that are currently being used in ‘real-life’ clinical practice.

Fibrillation, discordance between the 2001 ACC/AHA/ESC AF guidelines and real-life practice was found.4 Despite better dissemination of the 2006 ACC/AHA/ESC AF guidelines, it is unclear whether clinical practice has changed in accordance with these published recommendations. Furthermore, many previous surveys focused primarily on the issue of antithrombotic use in a single country5,6 or continent.4 International studies on the appropriateness of antiarrhythmic drug (AAD) use in real-life practice are more limited.

The RealiseAF survey, an international, observational, cross-sectional survey of >10 000 patients with all types of AF, was established to provide reliable information regarding patient characteristics, cardiovascular (CV) risk, AF type, symptoms, medical history, impact on quality of life, and management practices in AF.7 The aim of this subanalysis was to evaluate the appropriate use of AADs in patients with paroxysmal and persistent AF from the RealiseAF survey, according to the 2006 ACC/AHA/ESC AF guidelines.

Methods

Design
As previously reported,7 RealiseAF was an international, cross-sectional, observational survey of >10 000 patients with AF from >800 sites in 26 countries.

Patient population
Patients with a history of AF (treated/untreated, notwithstanding their rhythm at the time of inclusion), who had ≥1 AF episode [documented by standard electrocardiogram (ECG) or by Holter-ECG monitoring] in the previous 12 months, or who had documented current AF, and who provided written informed consent, were enrolled. We did not define a time parameter to establish the diagnosis of AF by Holter monitoring, and the diagnosis depended on the decision of participating physicians. Exclusion criteria included mental disability (such as dementia or significant cognitive disorders), inability to provide written informed consent, patients with AF within 3 months of cardiac surgery, and participation in clinical trials in the AF or antithrombotic field in the previous month.

Investigator selection
Participating physicians were randomly selected from a global list of cardiologists and internists (office and hospital-based) in each country from 2009–10. To ensure unbiased recruitment, the ratio of cardiologists to internists was predetermined to reflect the practice in each country. The list and ratio were validated by national coordinators. The maximum duration of enrolment per centre was 6 weeks to maximize recruitment of consecutive patients. Each investigator was asked to recruit a minimum of 10 patients and a maximum of 30.

Data collection
Data on demographics, risk factors, prior medical history, symptoms, management strategy, use of antithrombetics and AADs, prior use of procedures and devices, and quality of life were collected. To ensure data quality, 10% of sites in each country were randomly selected for data quality control, and key items were source-verified for all patients at the site.

Objectives
The primary objectives of the study were to: (i) determine the frequency of AF ‘control’ (defined as being either in sinus rhythm or in AF with a resting ventricular rate ≤80 b.p.m. at the time of the visit on resting ECG); and (ii) describe the CV risk profile. Secondary objectives included describing the characteristics and management strategies of patients with AF, and to determine whether current practice adhered to the 2006 ACC/AHA/ESC AF guidelines available at the time of recruitment.3 The aim of this subanalysis was to evaluate the appropriateness of the use of AADs in patients with paroxysmal and persistent AF according to the algorithm presented in the 2006 guidelines.

Statistical analysis

Determination of sample size
We assumed that ‘AF control’ would be achieved in ~50% of patients and that ≤10% of patients would be non-evaluable. The enrolment of 450–900 patients per geographical area (country/region) would allow the calculation of a 95% confidence interval with a precision level between 3.5 and 5%. If the rate of control was higher or lower than 50%, then greater precision would be achieved. To determine the relationship between ‘AF control’ and CV risk factors or comorbidities, a sample size of 10 000 patients would allow measurement of an odds ratio of 1.2 to be ‘not controlled’ for a risk factor prevalence ranging from 15 to 85% of patients (with α = 5% and β = 15%).

Statistical methods
Population characteristics were summarized into mean, standard deviation (SD) for continuous variables, and count and percentages for qualitative variables. Comparisons between subgroups (paroxysmal AF vs. persistent AF) were made using the χ² test and Student’s t-test. Analyses were performed using the SAS® statistical software, version 9.1 (SAS Institute).

Role of the funding source
The RealiseAF survey was sponsored by Sanofi, who provided assistance with data collection. The statistical analysis was performed by a contract organization (Registat-MAPI) and by Sanofi. Editorial assistance with formatting the manuscript and preparing figures and references was provided by PPSI. Both Registat-MAPI and PPSI were funded by the sponsor.

Results
From October 2009 to May 2010, 831 sites were active in screening 11 198 patients and enrolling 10 546 patients, of whom 23 (0.2%) were found to be ineligible.7 The final dataset included 10 523 eligible patients from 26 participating countries located in Western and
Eastern Europe, the Middle East, Africa, Asia, and Central and South America.7

There were 2606 patients with paroxysmal AF and 2341 patients with persistent AF. Of the remaining 5576 patients, 4886 patients had permanent AF, 675 patients had a first episode of AF, and 32 patients had missing data regarding the type of AF and, therefore, were not included in this paper. The mean age was higher in patients with persistent AF and more patients with persistent AF had an age ≥75 years. There were slightly more men than women in both patient groups (Table 1). Patients with persistent AF had similar CV risk profiles, but higher rates of heart failure and coronary artery disease (CAD) compared with patients with paroxysmal AF.

Antiarrhythmic drugs were prescribed in 81.1% of patients with paroxysmal AF, 81.4% with persistent AF, and 81.2% of patients with either paroxysmal or persistent AF at the end of the enrolment visit. Among all AADs, Class II and Class III drugs were the most frequently used (Figure 1). Very few patients received Class Ia drugs (<1% in both groups). Class Ic drugs were more frequently prescribed in patients with paroxysmal AF (15.6 vs. 7.8%, P < 0.001), while more patients with persistent AF received Class II drugs for AF reasons (37.8 vs. 33.3%, P < 0.001). The use of Class III and Class IV drugs was more evenly distributed. Cardiac glycosides were more commonly used in patients with persistent AF (20.7 vs. 9.5%, P < 0.001). Among Class Ic and Class III drugs, propafenone, flecainide, and sotalol were more commonly used in patients with paroxysmal AF, while amiodarone was more commonly used in those with persistent AF (Figure 2).

According to the algorithm in the 2006 ACC/AHA/ESC AF guidelines,1 which recommends the most appropriate AADs for maintaining sinus rhythm in patients with paroxysmal and persistent AF, Class Ic drugs are recommended in patients with no (or minimal) heart disease or in hypertensive patients who do not have substantial left ventricular hypertrophy (LVH). Sotalol is indicated in similar conditions and in patients with CAD. Amiodarone is suggested as first-line therapy in patients with heart failure or in patients with hypertension who have substantial LVH.

Among 15.6% of patients with paroxysmal AF who received Class Ic drugs, 81.8% of patients had no (or minimal) heart disease, or had hypertension without substantial LVH, consistent with the recommendations of the 2006 ACC/AHA/ESC AF guidelines (Figure 3). However, in 17.2% of these patients, the indication was not consistent with the guidelines. Similarly, in 26.4% of patients with persistent AF who received Class Ic drugs, the prescription deviated from the guidelines. Overall, in 20.0% of patients with paroxysmal or persistent AF who received Class Ic drugs, the use did not conform to the guidelines.

Sotalol was prescribed in 5.3, 3.5, and 4.4% of patients with paroxysmal, persistent, and paroxysmal or persistent AF, respectively (Figure 4). Among these patients, 14.6, 18.3, and 16.0% were receiving the drug under conditions which did not comply with the guidelines. Amiodarone is the most commonly prescribed Class III drug. It was received as first-line therapy by 24.3% of patients with paroxysmal AF and 27.2% of patients with persistent AF (Figure 5). Around half of these patients did not have the indications suggested by the 2006 ACC/AHA/ESC AF guidelines (54.3 and 45.6%, respectively). In the combined patient population of paroxysmal and persistent AF,

Table 1 Background characteristics of patients with paroxysmal or persistent AF

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Paroxysmal (n = 2606)</th>
<th>Persistent (n = 2341)</th>
<th>Paroxysmal + persistent (N = 4947)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>64.7 (12.4)</td>
<td>66.0 (11.8)</td>
<td>65.3 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥75 years, %</td>
<td>22.4</td>
<td>25.3</td>
<td>23.8</td>
<td>0.016</td>
</tr>
<tr>
<td>Male, %</td>
<td>55.5</td>
<td>57.9</td>
<td>56.7</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Ethnicity, %</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caucasian</td>
<td>81.2</td>
<td>88.9</td>
<td>84.9</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>13.1</td>
<td>6.4</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.3</td>
<td>2.3</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.5</td>
<td>2.4</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td><strong>CV risk factors and comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>74.6</td>
<td>73.2</td>
<td>74.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>19.1</td>
<td>19.3</td>
<td>19.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Dyslipidaemia, %</td>
<td>50.4</td>
<td>48.2</td>
<td>49.4</td>
<td>0.14</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>10.3</td>
<td>11.2</td>
<td>10.7</td>
<td>0.07</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>28.0 (5.0)</td>
<td>28.7 (5.3)</td>
<td>28.3 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, %</td>
<td>12.3</td>
<td>12.7</td>
<td>12.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>32.9</td>
<td>44.3</td>
<td>38.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>30.0</td>
<td>32.9</td>
<td>31.4</td>
<td>0.028</td>
</tr>
</tbody>
</table>

*BMI, body mass index.

*P values are calculated on the differences between paroxysmal and persistent AF.
49.9% of patients also had indications which differed from those suggested by these guidelines.

The incidence of underlying heart diseases for users of Class Ic and Class III AADs is shown in Table 2. Among users of Class Ic AADs, 20.8% of patients had heart failure, 17.0% of patients had CAD, and 6.9% of patients had hypertension and LVH; for all, these drugs were considered to be contraindicated or inappropriate. Similarly, for sotalol users, 28.0% of patients had heart failure and 9.6% of patients had hypertension and LVH; again, for all, these drugs were considered to be inappropriate. In those who received amiodarone as the first-line drug, 36.7% of patients had CAD and 6.0% of patients had lone AF (data not shown in Table 2), conditions in which amiodarone is usually used as a second-line drug.

The underlying heart diseases for users of different AADs in different continents are shown in Table 3. Heart failure and CAD in users of Class Ic AADs were not uncommon in both Europe (22.6 and 17.8%, respectively) and Asia (21.6 and 20.8%, respectively). It was also common to find CAD in patients using amiodarone as the first-line drug in Europe (41.8%), Asia (35.2%), Africa (26.1%), and Central and South America (16.7%). Furthermore, in those who used amiodarone as a first-line drug, 3.9% from Europe, 6.7% from Asia, 10.1% from Africa, and 16.3% from Central and South America had lone AF (data not shown in Table 3).

Discussion

The RealiseAF survey is unique due to its large patient population compared with previous AF surveys.4–7 The investigators were randomly picked to avoid selection bias, and the appropriateness of the use of individual AADs was analysed. The major finding in this study is that the use of AADs in paroxysmal and persistent AF deviates from international guidelines, with the highest discordance coming from the use of amiodarone in first line. Around half of the patients receiving amiodarone in first line did not appear to fulfil the guideline recommendations.

It has been shown that higher adherence to evidence-based guidelines improves CV outcomes.8 However, significant disparities have been reported in the application of evidence-based guidelines in treatment of various CV disorders.9–11 Since the CAST (Cardiac Arrhythmia Suppression Trial) study showed an increased mortality with the use of Class Ic AADs in patients after myocardial infarction,12 safety has become the primary consideration in selection of AADs in clinical practice. Moreover, a rhythm-control strategy is not superior to a rate-control strategy in reducing CV events.13 The issue of safety has therefore driven the majority of international AF guidelines to recommend different AADs for patients with AF who experience a variety of structural heart diseases.2,3 Surprisingly, underlying heart disease was not uncommon in patients receiving Class Ic AADs and sotalol in this survey. Adherence to AF guidelines may decrease the risk of proarrhythmic effects, but has not been proven effective for reducing CV events. This survey shows that application of the 2006 ACC/AHA/ESC AF guidelines was suboptimal and may, in fact, suggest an unmet need for more adequate treatment. To improve adherence to AF guidelines in the future, more educational programmes and extensive dissemination of guidelines may be needed.

So far, amiodarone has been the most effective AAD for reducing AF recurrence,14,15 but there is no evidence that amiodarone...
reduces CV events.\textsuperscript{14–16} Significant long-term organ toxicity render it a second-line therapy in maintenance of sinus rhythm,\textsuperscript{17} except in patients with heart failure or hypertension with substantial LVH in whom amiodarone can be used as a first-line AAD.\textsuperscript{3} In this survey, 25.6\% of patients with paroxysmal or persistent AF received amiodarone as first-line therapy. This is surprising, given that amiodarone

Figure 3  Appropriate use of Class Ic drugs according to the 2006 ACC/AHA/ESC AF guidelines. Among patients with paroxysmal AF, 15.6\% received at least one Class Ic drug. In 17.2\% of these Class Ic users, the indication was not consistent with the guidelines. Similarly, 7.8\% of patients with persistent AF used at least one Class Ic drug, but in 26.4\% of these Class Ic users, the prescription deviated from the guidelines. In patients with paroxysmal or persistent AF as a whole, 11.9\% received at least one Class Ic drug, but in 20.0\% of these Class Ic users, the prescription did not conform to the guidelines.

Figure 4  Appropriate use of sotalol according to the 2006 ACC/AHA/ESC AF guidelines. Among patients with paroxysmal AF, 5.3\% received sotalol. In 14.6\% of these sotalol users, the indication was not consistent with the guidelines. Similarly, 3.5\% of patients with persistent AF used sotalol, but in 18.3\% of these sotalol users, the prescription deviated from the guidelines. In patients with paroxysmal or persistent AF as a whole, 4.4\% received sotalol, but in 16.0\% of these sotalol users, the prescription did not conform to the guidelines.
was not recommended in the guidelines for ~50% of the patient population of the present study. Previous studies or surveys have focused mainly on the issues of antithrombotic therapy. Very few studies have systemically reviewed whether AADs are used in accordance with international guidelines. The RealiseAF survey provided a unique snapshot of the appropriateness of AAD use in routine daily practice on an international basis. Compared with the Euro Heart Survey on Atrial Fibrillation, in which an over-representation of enrolment from highly specialized centres with a particular interest in AF was suspected, participating physicians in RealiseAF were randomly selected and validated by national coordinators to achieve unbiased recruitment. With a maximum 6-week enrolment duration per centre, and consecutive recruitment of 10–30 patients per investigator, the RealiseAF survey is more representative of real-life practice. Furthermore, we found that in the RealiseAF survey, inappropriate use of AADs appears to be a global issue, and is not limited to developed countries only.

After completion of this survey, the 2011 ACCF/AHA/HRS focused update on management of patients with AF was published. The recommendations for Class Ic AADs, sotalol, and amiodarone were the same as those in the 2006 ACC/AHA/ESC AF guidelines. The only difference is that dronedarone, a Class III AAD, is now recommended as a first-line treatment in patients with lone AF, with hypertension without substantial LVH, and with CAD. Similarly, in the 2012 focused update of the ESC guidelines for management of AF, the recommendations for Class Ic AADs, sotalol, and amiodarone were the same as those in the 2006 ACC/AHA/ESC AF guidelines and the 2011 ACCF/AHA/HRS focused update on management of patients with AF. Again, the only difference is the recommendation for dronedarone. Since the recommendations for Class Ic AADs, sotalol, and amiodarone were the same across all three AF guidelines, the conclusions drawn from this survey are probably still appropriate for current clinical practice; however, further studies may be needed to examine the appropriateness of dronedarone use in real-life practice.
Limitations

The present report should be interpreted cautiously given its observational and cross-sectional nature. Despite the wide geographic scope of this study, it does not include other geographical regions such as North America or Central Africa. There are probably major differences in patient characteristics and management in these regions. However, RealiseAF does have unprecedented geographic relevance by including many developing low- and middle-income countries.

Except for amiodarone, we did not have information for Class Ic AADs and sotalol regarding whether they were used as the first- or second-line drug. This is because, according to the 2006 ACC/AHA/ESC AF guidelines,\(^3\) they are placed as first-line drugs in patients with minimal heart diseases (or sotalol for CAD) and are not to be used as second-line drugs in patients with more significant heart diseases if the previous drugs failed. However, this kind of information would be important to find out the switching pattern of different AADs in real-life practice, and to see if physicians choose the drug as the last resort.

Conclusion

The use of AADs for persistent or paroxysmal AF in routine daily practice showed some deviations from international guidelines. The highest discordance came from the use of amiodarone in first line. Clearly, there is a large discrepancy between published guidelines and current practice.

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References


Table 3 Underlying heart diseases for users of different AADs in different continents

<table>
<thead>
<tr>
<th></th>
<th>Europe (n = 3576)</th>
<th>Asia (n = 668)</th>
<th>Africa (n = 558)</th>
<th>Central and South America (n = 145)</th>
</tr>
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<tbody>
<tr>
<td>Class Ic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>105 (22.6%)</td>
<td>11 (21.6%)</td>
<td>5 (8.6%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>CAD</td>
<td>81 (17.8%)</td>
<td>10 (20.8%)</td>
<td>6 (10.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>HT with LVH</td>
<td>30 (6.5%)</td>
<td>5 (13.2%)</td>
<td>4 (6.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Sotalol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>60 (30.6%)</td>
<td>0 (0%)</td>
<td>1 (5.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CAD</td>
<td>59 (31.2%)</td>
<td>3 (60%)</td>
<td>2 (12.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>HT with LVH</td>
<td>17 (8.7%)</td>
<td>3 (60%)</td>
<td>1 (5.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Amiodarone in first line</td>
<td>n = 725</td>
<td>n = 271</td>
<td>n = 229</td>
<td>n = 43</td>
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<tr>
<td>Heart failure</td>
<td>391 (54.1%)</td>
<td>104 (38.7%)</td>
<td>63 (27.9%)</td>
<td>15 (34.9%)</td>
</tr>
<tr>
<td>CAD</td>
<td>288 (41.8%)</td>
<td>92 (35.2%)</td>
<td>58 (26.1%)</td>
<td>7 (16.7%)</td>
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<tr>
<td>HT with LVH</td>
<td>149 (20.7%)</td>
<td>35 (17.9%)</td>
<td>9 (4.0%)</td>
<td>6 (14.0%)</td>
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<tr>
<td>Amiodarone in second line</td>
<td>n = 210</td>
<td>n = 27</td>
<td>n = 39</td>
<td>n = 4</td>
</tr>
<tr>
<td>Heart failure</td>
<td>121 (57.6%)</td>
<td>10 (38.5%)</td>
<td>19 (48.7%)</td>
<td>0 (0%)</td>
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<tr>
<td>CAD</td>
<td>88 (43.6%)</td>
<td>7 (28.0%)</td>
<td>16 (42.1%)</td>
<td>1 (25%)</td>
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<tr>
<td>HT with LVH</td>
<td>33 (15.7%)</td>
<td>8 (38.1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

HT, hypertension.
Europe: Belgium, Bulgaria, Czech Republic, Germany, Hungary, Ireland, Italy, Lithuania, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, and Ukraine.
Asia: Azerbaijan, India, Lebanon, and Taiwan.
Africa: Algeria, Egypt, Morocco, and Tunisia.
Central and South America: Mexico and Venezuela.


