Monitored Atrial Fibrillation Duration Predicts Arterial Embolic Events in Patients Suffering From Bradycardia and Atrial Fibrillation Implanted With Antitachycardia Pacemakers

Alessandro Capucci, MD,* Massimo Santini, MD,† Luigi Padeletti, MD,‡ Michele Gulizia, MD,§ GianLuca Botto, MD,|| Giuseppe Boriani, MD,¶ Renato Ricci, MD,† Stefano Favale, MD,# Francesco Zolezzi, MD,** Natale Di Belardino, MD,†† Giulio Molon, MD,‡‡ Fabrizio Drago, MD,§§ Giovanni Q. Villani, MD,* Elena Mazzini, MS,||| Marco Vimercati, MS,||| Andrea Grammatico, PhD||| on behalf of the Italian AT500 Registry Investigators

Piacenza, Rome, Florence, Catania, Como, Bologna, Bari, Velletri, Bari, Vigevano, and Milan, Italy

OBJECTIVES
The aim of our study was to evaluate arterial embolism (AE) occurrence rates and predictors in patients suffering from bradycardia and wearing a pacemaker with antitachycardia pacing therapies.

BACKGROUND
Atrial fibrillation (AF) is associated with a high incidence of AE.

METHODS
A total of 725 patients (360 men, age 71 ± 11 years) were implanted with a DDDR-P pacemaker (Medtronic AT500, Medtronic Inc., Minneapolis, Minnesota). At baseline 225 (31.0%) patients received antiplatelet therapy and 264 (36.4%) patients received anticoagulation agents.

RESULTS
Over a median 22-month follow-up (25th to 75th interquartile range 16 to 30 months), AE occurred in 14 (1.9%) patients; 7 patients suffered a nonfatal ischemic stroke (0.6% per year), 4 patients had transient ischemic attack (0.34% per year), and 3 patients had embolic complications. Among baseline patients' characteristics, multivariate logistic analysis showed that embolic events are independently associated to ischemic heart disease (7.0 odds ratio [OR], 95% confidence interval [CI] 2.3 to 21.3, p = 0.001), prior embolic event (7.3 OR, 95% CI 1.2 to 43.9, p = 0.029), diabetes (5.0 OR, 95% CI 1.1 to 15.7, p = 0.032), and hypertension (4.1 OR, 95% CI 1.1 to 15.6, p = 0.036). The risk of embolism, adjusted for known risk factors, was 3.1 times increased (95% CI 1.1 to 10.5, p = 0.044) in patients with device-detected atrial fibrillation episodes longer than one day during follow-up.

CONCLUSIONS
In a cohort of patients with bradycardia and AF, arterial embolism was common in patients with ischemic cardiopathy, hypertension, diabetes mellitus, and in patients with known stroke risk factors. Atrial fibrillation occurrences longer than one day were independently associated with embolic events.

From the *Cardiology Department, Civil Hospital, Piacenza, Italy; †Cardiology Department, S. Filippo Neri Hospital, Rome, Italy; ‡Cardiology Department, Clinica Medica, University of Florence, Florence, Italy; §Cardiology Department, San Luigi-S. Currò Hospital, Catania, Italy; ¶Cardiology Department, S. Anna Hospital, Como, Italy; ||Institute of Cardiology, University of Bologna, Bologna, Italy; |||Cardiology Department, Policlinico Hospital, Bari, Italy; #Cardiology Department, Civil Hospital, Velletri, Italy; **Cardiology Department, Civil Hospital, Bari, Italy; ††Cardiology Department, S. Cuore Hospital, Negrar, Italy; ‡‡Cardiology Department, Bambino Gesù Hospital, Rome, Italy; and |||Clinical Department, Medtronic Italy, Milan, Italy. Elena Mazzini, Marco Vimercati, and Dr. Andrea Grammatico are employees of Medtronic, Inc.

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Atrial fibrillation (AF) is very common in patients with bradycardia undergoing cardiac pacemaker implantation (1–4). Nonvalvular AF has been recognized as a cause of mortality (5) and in particular it has been associated to a five-fold increase in the risk of ischemic stroke, probably associated to atrioembolic mechanism (6–9). Atrial fibrillation is present in 6% to 24% of patients who have an ischemic stroke, and in up to 50% of patients with cardioembolic strokes (10,11). Annual rate of embolic events in bradycardia patients has been measured in the range between 6% and 10% (12–14). Yearly incidence of ischemic stroke in pacemaker patients with sinus node disease has been recently measured between 1% (3) and 1.4% (15).

The Mode Selection Trial (MOST) atrial diagnostics ancillary study (16) recently showed that atrial high rate episodes detected by an implanted pacemaker in sinus node disease patients are associated with a two-fold increase in the risk of death or stroke. Thus, early identification of patients with AF recurrences may have clinical importance.

The aim of this prospective multicenter observational study was to assess the incidence of arterial embolic events in patients suffering from bradycardia and symptomatic paroxysmal or persistent AF and therefore implanted with pacemakers able to deliver antitachycardia therapies. We also aimed to find predictors of arterial embolic events and to evaluate the clinical significance of AF as detected by pacemaker diagnostics.

METHODS
Patients suffering from bradycardia, having at least a class I or II American College of Cardiology/American Heart...
Association indication for dual-chamber pacing (17) and a history of symptomatic atrial tachyarrhythmias (at least three symptomatic episodes within the last year before implant, one episode in the last month before implant, and electrocardiogram or 24-h Holter monitoring documentation of at least one of these episodes) were eligible for study participation.

**Antithrombotic therapy.** The choice of drug treatment to prevent embolism was performed by each attending physician, who decided according to the patient’s clinical condition and his own experience and preferences.

**Device characteristics and programming.** The Medtronic AT500 (Medtronic Inc., Minneapolis, Minnesota) is a dual-chamber rate-responsive pacemaker, with advanced algorithms designed for rhythm discrimination and prevention and treatment of atrial arrhythmias, as previously described (18,19). Programming of conventional pacemaker parameters were left to physician discretion. Paced and sensed atrioventricular delays were programmed with the aim of promoting intrinsic atrioventricular conduction as much as possible.

**Detection of atrial arrhythmias.** The implanted devices continuously classify the rhythm status of each patient: it bases the classification on the PR Logic (Medtronic Inc.) algorithm (20,21), which has been previously tested on this device and showed 100% sensitivity, 97% specificity (18), and 100% positive predictive value (95% confidence interval [CI] in the range 96% to 100%) (21) for atrial tachyarrhythmia detection.

**Data analysis.** Data about arterial embolic events were obtained at follow-up visits and, when necessary, by a telephone contact. An outcome committee of two physicians evaluated arterial embolic events, defined as the occurrence of ischemic stroke, transient ischemic attack (TIA), or peripheral arterial embolism. Ischemic stroke was defined as a neurological deficit with sudden onset, persisting for more than 24 h.

We considered as risk factors for embolic events: prior ischemic stroke or TIA, age >75 years, ejection fraction <35%, left atrium diameter >50 mm, ischemic heart disease, hypertension, heart failure, and diabetes. Patients were stratified according to the number of such risk factors at enrollment.

The possible association between AF occurrence and embolic events was studied by stratifying patients according to their device-calculated duration of AF recurrences observed at follow-up. Prespecified AF duration were at least 5 min of AF (recognized as an appropriate cutoff to select AF episodes and discard premature atrial contraction runs or spurious events [22]), and 1 day duration (which is the new measurement used in device diagnostics that daily collects long-term information about AF), during the whole observational period. An episode review committee of three physicians evaluated atrial electrograms of AF episodes saved in device diagnostics to verify detection appropriateness.

**Statistical analysis.** Descriptive statistics were calculated using mean and standard deviation for normally distributed continuous variables, or median with 25th to 75th inter-quartile range (IQR) in case of skewed distributions. Skewness and kurtosis values were calculated, in order to document a normal distribution of each studied parameter. Absolute and relative frequencies were calculated for categorical variables.

Logistic models were fitted to evaluate patients’ clinical characteristics associated with embolic events. Odds ratios (OR) and their 95% CIs were computed. Odds ratio expresses the increased (OR >1) or decreased (OR <1) embolism risk, according to the examined characteristic. Variables that showed a p < 0.2 when compared for homogeneity between groups of patients with and without embolic events were included in the univariate analysis. After checking for collinearity, variables that showed a significant (p < 0.05) correlation with embolic events at univariate analysis were considered in the multivariate logistic models.

Cox proportional hazards models were used to examine the association between occurrence of AF episodes, longer than 5 min and longer than 1 day, and the occurrence of embolic events. Atrial fibrillation recurrences contributed to the models as time-dependent covariates, with patients entering the AF risk class at the time of the first AF episode. Models were adjusted for other known embolism predictors.

Comparisons of continuous variables were performed by two-tailed unpaired Student t test for normally distributed variables and by Mann-Whitney test for variables with skewed distribution. Comparisons of categorical variables were performed by means of Fisher exact test for extreme proportions or chi-square otherwise.

Curves for survival to embolic events were calculated using the Kaplan-Meier method and displayed for the entire patient population and for patients subgroups selected as a function of AF recurrence in the follow-up. Kaplan-Meier curves comparison was performed by log-rank test. All reported p values are two-tailed. SPSS software (version 11.5 statistical package, SPSS Inc., Chicago, Illinois) was used for all the statistical analysis.

**RESULTS**

Between September 1999 to December 2003, 725 patients were enrolled in 83 cardiology departments (Appendix)
Table 1. Clinical and Diagnostics Characteristics of All 725 Patients, 711 Patients Without, and 14 Patients With Cerebral Ischemia Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>725 Patients</th>
<th>711 Patients With No Embolic Events</th>
<th>14 Patients With Embolic Events</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>360 (49.7%)</td>
<td>351 (49.4%)</td>
<td>9 (64.3%)</td>
<td>0.268†</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>71 ± 11</td>
<td>71 ± 11</td>
<td>73 ± 6</td>
<td>0.515§</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56 ± 10</td>
<td>56 ± 10</td>
<td>54 ± 12</td>
<td>0.582§</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>43.6 ± 6.7</td>
<td>43.5 ± 6.8</td>
<td>46.1 ± 3.0</td>
<td>0.280§</td>
</tr>
<tr>
<td>NYHA functional class I, n (%)</td>
<td>306 (42.2%)</td>
<td>302 (45.8%)</td>
<td>4 (28.6%)</td>
<td>0.414*</td>
</tr>
<tr>
<td>NYHA functional class II, n (%)</td>
<td>317 (43.7%)</td>
<td>310 (47.0%)</td>
<td>7 (50.0%)</td>
<td>0.632*</td>
</tr>
<tr>
<td>NYHA functional class III, n (%)</td>
<td>50 (6.9%)</td>
<td>47 (7.1%)</td>
<td>3 (21.4%)</td>
<td>0.065*</td>
</tr>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>447 (61.7%)</td>
<td>436 (61.3%)</td>
<td>11 (78.6%)</td>
<td>0.189†</td>
</tr>
<tr>
<td>Valvular disease, n (%)</td>
<td>53 (7.3%)</td>
<td>51 (7.2%)</td>
<td>2 (14.3%)</td>
<td>0.273*</td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>632 (87.2%)</td>
<td>619 (87.1%)</td>
<td>13 (92.9%)</td>
<td>1.000*</td>
</tr>
<tr>
<td>Atrial flutter, n (%)</td>
<td>142 (19.6%)</td>
<td>138 (19.4%)</td>
<td>4 (28.6%)</td>
<td>0.492*</td>
</tr>
<tr>
<td>Atrial tachycardia, n (%)</td>
<td>83 (11.4%)</td>
<td>80 (11.3%)</td>
<td>3 (21.4%)</td>
<td>0.434*</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>304 (42.6%)</td>
<td>297 (42.1%)</td>
<td>7 (50.0%)</td>
<td>0.434*</td>
</tr>
<tr>
<td>Persistent AF, n (%)</td>
<td>103 (14.2%)</td>
<td>100 (14.1%)</td>
<td>3 (21.4%)</td>
<td>0.434*</td>
</tr>
<tr>
<td>Preimplant atrial cardioversions, n (%)</td>
<td>299 (41.2%)</td>
<td>292 (41.1%)</td>
<td>7 (50.0%)</td>
<td>0.501†</td>
</tr>
<tr>
<td>Preimplant AF-related hospitalizations, n (%)</td>
<td>366 (50.5%)</td>
<td>356 (50.1%)</td>
<td>71.4% (10)</td>
<td>0.113†</td>
</tr>
<tr>
<td>Number of AF-related symptoms per patient</td>
<td>1.6 ± 1.0</td>
<td>1.6 ± 1.0</td>
<td>1.7 ± 1.1</td>
<td>0.754§</td>
</tr>
<tr>
<td>Number of symptomatic AF episodes per month</td>
<td>2 (1–8)</td>
<td>2 (1–8)</td>
<td>4 (1–9)</td>
<td>0.544§</td>
</tr>
<tr>
<td>Anticoagulant therapy, n (%)</td>
<td>264 (36.4%)</td>
<td>255 (35.9%)</td>
<td>9 (64.3%)</td>
<td>0.029†</td>
</tr>
<tr>
<td>Antiplatelet therapy, n (%)</td>
<td>225 (31.0%)</td>
<td>220 (30.9%)</td>
<td>5 (35.7%)</td>
<td>0.772*</td>
</tr>
<tr>
<td>Antiarrhythmic therapy, n (%)</td>
<td>378 (52.1%)</td>
<td>371 (52.2%)</td>
<td>7 (50.0%)</td>
<td>0.827‡</td>
</tr>
<tr>
<td>Ischemic cardiopathy, n (%)</td>
<td>105 (14.5%)</td>
<td>98 (13.8%)</td>
<td>7 (50.0%)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>348 (48.0%)</td>
<td>337 (47.4%)</td>
<td>11 (78.6%)</td>
<td>0.021†</td>
</tr>
<tr>
<td>Age &gt;75 yrs, n (%)</td>
<td>235 (32.4%)</td>
<td>230 (34.0%)</td>
<td>5 (38.5%)</td>
<td>0.771*</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>56 (7.7%)</td>
<td>53 (7.5%)</td>
<td>3 (21.4%)</td>
<td>0.086†</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>59 (8.1%)</td>
<td>55 (7.7%)</td>
<td>4 (28.6%)</td>
<td>0.021†</td>
</tr>
<tr>
<td>EF ≤35%, n (%)</td>
<td>10 (1.4%)</td>
<td>10 (1.4%)</td>
<td>0 (0.0%)</td>
<td>1.000*</td>
</tr>
<tr>
<td>LAD &gt;50 mm, n (%)</td>
<td>31 (4.3%)</td>
<td>31 (10.3%)</td>
<td>0 (0.0%)</td>
<td>1.000*</td>
</tr>
<tr>
<td>Prior embolic events, n (%)</td>
<td>13 (1.8%)</td>
<td>11 (1.5%)</td>
<td>2 (14.3%)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Stroke risk factors, n (%)</td>
<td>549 (75.7%)</td>
<td>535 (75.2%)</td>
<td>14 (100.0%)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Number of risk factors</td>
<td>1.2 ± 0.9</td>
<td>1.2 ± 0.9</td>
<td>2.3 ± 1.2</td>
<td>0.004§</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or median value (25th to 75th percentile) for continuous variables and number and percentage of patients. *Fisher exact test; †chi-square test; ‡Mann-Whitney test; §t test.

AF = atrial fibrillation; EF = ejection fraction; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

after they received a DDDR pacemaker (AT500, Medtronic Inc.). Pacing indication was sinus node disease in 600 (82.8%) patients, atrioventricular block in 34 (4.7%) patients, drug-induced bradycardia in 32 (4.4%) patients, other in 59 (8.1%) patients. A review of patients clinical characteristics is shown in Table 1.

Arterial embolic events. During a median 22-month follow-up (IQR from 16 to 30 months), 14 patients had arterial embolic events. In particular, seven patients suffered an ischemic stroke, four patients a TIA, and three patients had other embolic complications. Thus, we observed a 1.2% annual rate of arterial embolism in a total follow up of 1,166 patient-years. The annual rates of ischemic stroke and TIA were 0.6% and 0.34%, respectively. A survival curve from embolic events is shown in Figure 1. One patient suffered a hemorrhagic stroke: he was not considered in the following analyses.

Predictors of arterial embolic events. The comparison of different clinical and diagnostic characteristics among patients with and without embolism is shown in the third and fourth columns of Table 1. The percentage of patients with prior embolism, ischemic heart disease, hypertension, diabetes, stroke risk factors was higher in patients with embolic events as compared to patients without them. The number of stroke risk factors was also significantly higher in patients who exhibited embolic events.

Results of univariate and multivariate analysis are shown in Table 2. Among patient baseline characteristics, univariate analysis associated ischemic heart disease, prior embolic events, diabetes, hypertension, and anticoagulant use as those associated with a significantly higher risk of embolic events. Furthermore, for each additional stroke risk factor, we observed an increase by a factor of 2.7 in the risk of embolic events. Multivariate logistic analysis showed that embolic events are independently associated with ischemic heart disease (7.0 OR, 95% CI 2.3 to 21.3, p = 0.001), prior embolic event (7.3 OR, 95% CI 1.2 to 43.9, p = 0.029), diabetes (5.0 OR, 95% CI 1.2 to 15.7, p = 0.032), and hypertension (4.1 OR, 95% CI 1.1 to 15.6, p = 0.036). Cox multivariate analysis, adjusted for previously shown embolism predictors, demonstrated that the occurrence of AF episodes longer than one day was independently associated...
with arterial embolism (3.1 hazard ratio, 95% CI 1.1 to 10.5, p = 0.044). Occurrence of AF episodes longer than 5 min was not associated with a significantly higher risk of embolic events.

The percentages of patients with at least one device-detected AF recurrence during the whole observational period longer than, respectively, 5 min and 1 day are shown in Table 3, subdividing the patients according to the presence or absence of arterial embolism in the follow-up. The percentage of patients with device-detected AF recurrences longer than one day was higher (71.4% vs. 41.2%, p < 0.03 with Fisher exact test) in patients with arterial embolism as compared to patients without it. No significant differences were found when limiting the analysis to shorter observational periods (i.e., to the first 3 months, the first 6 months, or the first 12 months of follow-up).

Kaplan-Meier survival from embolic events comparing the two groups of patients with and without AF episodes longer than one day during the follow-up is shown in Figure 2. Log-rank statistics showed an incidence of arterial embolism significantly (p = 0.03) higher in patients with such AF recurrences than in patients without them. We did not observe any significant difference by comparing with the same method the two groups of patients with and without AF episodes longer than 5 min.

**Antithrombotic therapy and risk factors.** After implantation, 489 (67.4%) patients were discharged with a pharmacological therapy to prevent thromboembolism. In particular, 264 patients were treated with oral anticoagulant (70% warfarin and 30% acenocumarol) to maintain the international normalized ratio in the range between 2 and 4, while 225 patients were treated with antiplatelet agents (76%...

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**Table 2. Results of Univariate and Multivariate Analysis**

<table>
<thead>
<tr>
<th>Patient Characteristics*</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value</td>
<td>OR</td>
</tr>
<tr>
<td>NYHA functional class III</td>
<td>0.058</td>
<td>3.55</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.201</td>
<td>2.31</td>
</tr>
<tr>
<td>Prior hospitalizations</td>
<td>0.126</td>
<td>2.49</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>0.038</td>
<td>3.22</td>
</tr>
<tr>
<td>Ischemic cardiopathy</td>
<td>0.001</td>
<td>6.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.032</td>
<td>4.07</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.067</td>
<td>3.39</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.010</td>
<td>4.77</td>
</tr>
<tr>
<td>Prior embolic event</td>
<td>0.004</td>
<td>10.6</td>
</tr>
<tr>
<td>Number of risk factors†§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All patient characteristics that were associated to p values lower than 0.2 in the homogeneity comparison between patients with and without embolic events (Table 1) were considered for univariate analysis. †When considering the number of stroke risk factors, the OR represents the increase in the risk of having an embolic event associated with increasing by one the number of risk factors (i.e., one risk factor more means increasing the embolism risk by a factor of 2.7). For all other patient characteristics, the OR represents the risk of embolism associated with the presence of the considered patient characteristic or disease. ‡All patients’ characteristics that were associated with p values lower than 0.05 at univariate analysis were considered for multivariate analysis. §The number of stroke risk factors was not considered in multivariate analysis because it was significantly correlated with ischemic cardiopathy, hypertension, and prior embolic events.

NYHA = New York Heart Association; OR = odds ratio.
aspirin, 14% indobufene, and 10% ticlopidine); 236 patients (32.6%) did not receive any anticoagulant or antiplatelet treatment.

The distribution of enrolled patients, of patients treated with antiplatelet agents, of patients treated with anticoagulation therapy, of patients who suffered embolic events, and the distribution of embolism annual rate is shown in Table 4 as a function of the number of embolism risk factors exhibited at baseline. During follow-up, anticoagulation therapy was started in two patients at the time of embolic events.

**Diagnostic data.** Several characteristics measured by device diagnostics were compared among two groups of patients: 14 patients with arterial embolic events and 711 patients without arterial embolic events. In order to build a control group more homogeneous than the general population to the group of subjects with the event, we also subselected a third group of 535 patients who had stroke risk factors but who did not suffer arterial embolic events during follow-up. These groups did not differ in terms of atrial pacing percentage (69 ± 34 vs. 74 ± 26 vs. 74 ± 26), ventricular pacing percentage (72 ± 32 vs. 70 ± 32 vs. 70 ± 31), AF burden (280 ± 498 vs. 151 ± 298 vs. 150 ± 294 min per day), number of AF episodes (2,185 ± 4,719 vs. 1,560 ± 4,240 vs. 1,615 ± 4,523), or device-defined percentage of ATP success (40 ± 29 vs. 47 ± 30 vs. 46 ± 30).

**DISCUSSION**

**Main study findings.** This study is the first to report on embolic events during a long-term follow-up (1,166 patient-years) on a large cohort of patients paced for bradycardia, suffering from AF, and implanted with a pacemaker capable of atrial therapies delivery. About 36% of the patients were anticoagulated with warfarin and acenocumarol according to the usual clinical practice (23).

Our data confirm that prior embolism, ischemic cardiomyopathy, hypertension, diabetes mellitus, and the presence of any stroke risk factor are independently associated with embolic events. Furthermore, our results show that, in a population of pacemaker patients suffering from AF, device-detected AF recurrences longer than one day are independently associated with embolic events. Atrial fibrillation duration longer than one day could certainly be a simple parameter to be used in clinical practice to guide anticoagulation therapy.

**Arterial embolism annual rates.** Embolic risk has been extensively studied in the general population of patients with AF treated with conventional pharmacological agents (6,7,24,25). On the other hand, only limited and recent data are available (3,15) about patients with bradycardia and coexisting AF. Our data show a yearly incidence of arterial embolism in general and of ischemic stroke in particular of 1.2% and 0.6%, respectively.
Investigators of the Canadian Trial Of Physiologic Pacing (CTOPP) (3) enrolled 2,568 patients and observed an annual stroke rate of 1.1% in the patient group with ventricular pacing and of 1.0% in the group with physiological pacing. Investigators of the MOST study (15) observed an annual rate of ischemic stroke equal to 1.4%, with no clear differences according to pacing mode.

Anticoagulant therapy may explain the observation of a lower annual rate for stroke observed in our study compared with the MOST study (15). As a matter of fact, 32% of patients in our study and 24% in the MOST study had anticoagulant therapy. The percentage of anticoagulated patients (34%) in the CTOPP study (3) was similar to ours. An alternative hypothesis could be that atrial pacing, with preventive algorithms and/or antitachycardia therapies, may have some protective action against thromboembolism, by preventing or suppressing AF triggers and terminating regular and slow atrial tachyarrhythmias. There are no published data to support this hypothesis, which should be tested in a prospective randomized trial. Unfortunately, such a study would require in practice a very large sample size, due to the very low expected event rate (3,15) and to the possible occurrence in an elderly population of stroke with etiologies other than left atrium cardiogenic embolism (which may be hypothetically affected by atrial pacing), such as left ventricle embolism, carotid and aortic atherosclerosis, or hypoperfusion of small arteriolar beds.

Predictors of embolic events. Previous studies (25,26) about AF patients without bradycardia identified ischemic cardiopathy, hypertension, diabetes mellitus, increasing age, previous TIA or stroke, heart failure, low ventricular function, and large left atrium dimensions as independent predictors of stroke. Our data confirm that ischemic cardiopathy, hypertension, diabetes mellitus, and prior embolism are independently associated with embolic events for our population.

Embolic events and AF. The percentage of patients with device-detected AF recurrences longer than one day was significantly higher among patients who suffered arterial embolism than among patients without embolism. Multivariate analysis, adjusted for embolism prognostic factors, demonstrated that patients with AF recurrences longer than one day were 3.1 × more likely to suffer arterial embolism. Finally, Kaplan-Meier survival analyses showed that embolic events were significantly more frequent in patients with AF episodes longer than one day when compared with patients without AF or with shorter AF recurrences.

Glotzer et al. (16) recently showed that device-detected AF episodes longer than 5 min are associated with a two-fold increase in risk of death or stroke. In our results occurrence of AF episodes longer than 5 min was not associated with higher embolic risk: this is probably due to the fact that in our patient population (i.e., bradycardia patients with history of frequent symptomatic AF episodes) short AF recurrences were very common, occurring in about 80% of our patients. Considering the results of the present study, and the findings by Glotzer et al. (16), antithrombotic therapy should be considered in patients with device-detected AF recurrences.

Clinical implications of our study. Greenspon et al. (15) showed a higher risk of embolism in patients found in AF during follow-up visits. There could be important limitations associated to limiting the selection of clinically evident AF (i.e., symptomatic or discovered by chance during a routine follow-up) as a supplementary risk factor to guide anticoagulant therapy, because patients may be exposed to the risk of embolism by persistent asymptomatic and undetected AF episodes. Our results show that, in patients paced for bradycardia and suffering from frequent AF recurrences, simple device daily diagnostics showing the time spent in AF could be useful to guide anticoagulant therapy. In particular, it could suggest that the clinician start anticoagulation in patients with no other risk factors but with long periods of arrhythmia, or to request accurate international normalized ratio control, or to add antiplatelet drugs to anticoagulant agents in specific patients. Device diagnostic capabilities may be of particular importance in pacemaker patients because pacing often results in rate smoothing, usually decreasing patients’ symptomaticity.

Embolism and risk factors. Our data show that embolism occurred only in patients with stroke risk factors, that embolism risk is directly correlated to the number of risk factors, and finally that the yearly incidence of embolism is <1% in patients with ≤1 risk factor and increases as a function of the number of cardiac or noncardiac risk factors.

Embolism and antithrombotic therapy. Warfarin has been shown as highly effective, in particular more effective than antiplatelet agents, in preventing stroke in patients with AF in several randomized trials (24,26–28), most likely by minimizing the formation of atrial thrombi.

Guidelines about antithrombotic therapy recommend preventive oral anticoagulation in patients with valvular heart disease, in patients ≥65 years old, or in the presence of additional risk factors for thromboembolic events (23).
Among 14 patients who suffered arterial embolism, 9 were on anticoagulant therapy, even if we cannot state if international normalized ratio values were in the expected range at the time of embolic events.

The choice of antithrombotic treatment in this study was left to the decision of the attending cardiologists who are used to managing anticoagulation therapy. The percentage of patients on antiplatelet therapy, but not the percentage of patients on anticoagulant agents, increased as a function of patient stroke risk factors.

Among patients indicated for anticoagulation, those who actually were on anticoagulant agents were only 32.2% at baseline and 41.2% at the end of the follow-up. This percentage is lower than those described in previous studies (29–34) outlining an important underutilization of anticoagulation therapy. However, in the arterial embolic group, the percentage of anticoagulated patients was up to 64%, which is average for this patient population (Table 1).

**Study limitations.** The incidence of some embolic events, such as asymptomatic ischemic attacks, could have been underestimated because no systematic neurological imaging procedures were requested by the study. Underestimation of the embolism risk, associated to AF episodes or other known stroke risk factors, cannot be excluded because the patients with the greatest numbers of risk factors were also selected for anticoagulation by their clinicians.

Low frequency of embolic events leaves considerable room for statistical error associated with the estimation of arterial embolism annual rate or risk associated with predictors of embolic events. Our study did not record systematically the level of anticoagulation, which was left to the attending cardiologist; therefore, we cannot discuss the adequate anticoagulation level at the time of stroke. This study did not collect information about contraindications to the anticoagulation therapy; therefore, we were only able to observe the low use of anticoagulation agents in the referred patients.

Our data should be limited to this studied population. **Conclusions.** Our study is the first to report thromboembolic complications on a long-term follow-up of a large cohort of patients paced for bradycardia and suffering from AF, and therefore implanted with a pacemaker capable of atrial therapies delivery. Our data show a 0.6% annual stroke risk among 14 patients who suffered arterial embolism, 9 were on anticoagulant therapy, even if we cannot state if international normalized ratio values were in the expected range at the time of embolic events.

Patients with device-detected AF recurrences longer than one day had a risk of embolism 3.1 times increased as compared to patients without or with shorter AF recurrences, showing that AF recurrences longer than one day are independently associated with arterial embolism. Anticoagulation therapy was underused in our patient population; moreover, arterial embolic events were observed also in anticoagulated patients. This datum suggests either a stricter international normalized ratio monitoring or an addition of antiplatelet therapy.

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**Reprint requests and correspondence:** Dr. Alessandro Capucci, Institute of Cardiology, Civile Hospital, Divisione di Cardiologia, Ospedale “Guglielmo da Saliceto,” Via Taverna 49, 29100 Piacenza, Italy. E-mail: progettovita@hotmail.com.

**REFERENCES**


APPENDIX

For a list of the investigators and centers participating in the Italian AT500 Registry, please see the online version of this article.