Improving Thromboprophylaxis Using Atrial Fibrillation Diagnostic Capabilities in Implantable Cardioverter-Defibrillators

The Multicentre Italian ANGELS of AF Project

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Background—Atrial fibrillation (AF) is a well-established risk factor for stroke and thromboembolism and is a frequent comorbid arrhythmia in patients with implantable cardioverter-defibrillators (ICDs). The Anticoagulation Use Evaluation and Life Threatening Events Sentinels (ANGELS) of AF project was a medical care program aimed at supporting adherence to oral anticoagulation (OAC) guidelines for thromboprophylaxis through the use of ICD AF diagnostics.

Methods and Results—Fifty Italian cardiology clinics followed 3438 patients with ICDs. In a subgroup of 15 centers (the ANGELS of AF centers), cardiologists attending to follow-up visits were supplied with specific reports describing stroke risk factors and risk scores (American College of Chest Physicians and CHADS₂ [congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack]), AF occurrence and duration, and current antithrombotic therapy for patients with AF, especially those with a CHADS₂ score > 0 and not on OAC therapy. The remaining centers represented a control group of patients as a comparison of OAC use. In the ANGELS of AF centers, 709 (36%) patients had AF described either in their clinical history (n = 426 [22%]) or as new-onset AF (n = 257 [14%]). Among 683 (96%) patients with CHADS₂ score > 0, 209 (30.6%) were not taking an OAC. Appropriate OAC therapy was prescribed in 10% (22/209) of patients after evaluation of ANGELS of AF reports. The percentage of patients on OAC therapy, as indicated by guidelines, increased during follow-up from 46.1% at baseline, to 69.4% at the stroke risk evaluation phase, to up to 72.6% at the end of the observation period. In control centers, corresponding figures were 46.9% at baseline and 56.8% at the end of the observation period (P < 0.001 versus ANGELS of AF group).

Conclusions—The ANGELS of AF project demonstrates the possibility to improve OAC use in accordance with available guidelines for stroke risk reduction in AF by supplying attending physicians with reports about patients risk factors and AF information from continuous ICD monitoring.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01007474.

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Key Words: stroke ■ cerebral ischemia ■ anticoagulants ■ atrial fibrillation ■ implantable cardioverter-defibrillators

Atrial fibrillation (AF) is the most common cardiac arrhythmia, which is increasing in prevalence and incidence. Importantly, AF has been associated with a 5-fold increase in the risk of ischemic stroke. Effective prevention of stroke and thromboembolism requires oral anticoagulation (OAC), although stroke risk is influenced by associated risk factors. Underuse of OAC therapy with warfarin has been shown to occur in real-world clinical practice in patients at moderate to high thromboembolic risk. Current guidelines for stroke prevention in AF do not differentiate between patients with symptomatic or asymptomatic AF or between paroxysmal or persistent AF. Continuous device monitoring has
shown that atrial tachyarrhythmias are frequent comorbidities in patients with implantable cardioverter-defibrillators (ICDs)\(^9\)–\(^10\) and that the majority of AF episodes are asymptomatic, including many episodes of clinically significant

**WHAT IS KNOWN**

- Atrial fibrillation (AF), either silent or clinically manifest, is associated with a 5-fold increase in the risk of ischemic stroke.
- Effective prevention of stroke and thromboembolism requires oral anticoagulation, guided by risk stratification, but underuse of oral anticoagulation with warfarin is common in real-world clinical practice in patients at moderate to high risk of thromboembolism.

**WHAT THIS ARTICLE ADDS**

- A dedicated medical care program, ANGELS (Anticoagulation Use Evaluation and Life Threatening Events Sentinels) of AF, including use of information from implantable cardioverter-defibrillator AF diagnostics on AF occurrence and duration improved oral anticoagulation use compared with standard care.
- This approach may be useful in improving appropriate warfarin use in patients with implantable cardioverter-defibrillators and concomitant AF.

AF detection was programmed to guarantee memorization of atrial tachyarrhythmia data if the atrial rate was >171 beats per minute for at least 32 ventricular events in which the AV pattern showed evidence of an atrial arrhythmia (ie, >1:1 conduction). High sensitivity and specificity of AF detection algorithms in the devices used has been previously demonstrated.\(^9\) Device diagnostics allowed for the measurement of AF occurrence and duration in each day of the observation period.

**Project Design**

Fifty Italian cardiology clinics included in the project 3438 consecutive patients with ICDs and followed them according to standard clinical practice protocols of follow-up visits. Of these clinics, 15 received reports about AF occurrence and duration, stroke risks factors, and OAC use and, thus, comprised the active intervention arm of the project (Figure 1). The remaining 35 cardiological centers prospectively followed their patients according to their center’s standard clinical practice without reports and comprised the usual care control arm of the project.

For patients involved in the active intervention arm, an automatic algorithm periodically evaluated patient AF history; this information was collected as a baseline condition or as evidence derived from device diagnostics at follow-up visits. In the latter case, a minimum daily AF duration of 6 hours was required to indicate a patient with clinically significant AF because this cutoff was considered to be associated with a relevant stroke risk, as shown in the TRENDS study.\(^12\) For each patient with AF, an automatic algorithm estimated American College of Chest Physicians\(^3\) and CHADS\(_2\) (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or TIA)\(^4\) stroke risk scores. If the patient was at high or moderate stroke risk, an automatic algorithm was used to assess current pharmacological data to evaluate whether the patient was taking appropriate antithrombotic agents according to current guidelines. In the case of a patient with AF with moderate of high stroke risk and without OAC protection, an automatic algorithm produced a report on the patient’s risk factors and on AF daily history for the last 14 months, which was submitted to physicians involved in the follow-up of that patient. During their hospital visit, physicians were requested to fill out a questionnaire confirming the absence of the OAC therapy, stating the antithrombotic therapy assigned to the patient in that visit and for patients discharged without OAC and explaining the reason for not administering the OAC therapy.

**Statistical Analysis**

Investigators had the ability to query any aspect of the data; authors had direct access to the primary data when reporting results of the research. Descriptive statistics were reported as mean±SD for normally distributed continuous variables or median with interquartile range in the case of skewed distributions. Normality of distribution was tested by calculating skew and kurtosis values. Absolute and relative frequencies were reported for categorical variables. Comparisons of categorical variables were performed by means of the Fisher exact test for extreme proportions; otherwise, the \(\chi^2\) test was used. For statistical analysis, Stata/SE version 11.0 for Windows (StataCorp) software was used.

**Results**

A total of 3438 patients were prospectively followed in this project (Figure 1) of whom 1961 (57\%) were in the active intervention arm (ANGELS of AF centers (active intervention arm) and 1477 (43\%) were in the usual care control arm (Table 1). The median follow-up duration was 25 months (interquartile range, 14–41 months), with a total follow-up of 9118 patient-years.

Figure 1 shows the flowchart of the project, whereby the active intervention arm comprised 1961 patients of whom 709 (36\%) had AF either described in their preimplant clinical history (426 [22\%]) or observed during follow-up (283 [14\%]) as a new onset of AF lasting >6 hours. In total,
683 patients were at moderate to high stroke risk, and 474 (69.4%) patients were on OAC therapy. For the remaining 209 patients who were not on OAC therapy, ANGELS of AF reports were supplied to attending physicians.

ANGELS of AF reports were the specific trigger for altering antithrombotic therapy in 24 patients (Figure 2). Specifically, appropriate OAC therapy was prescribed in 22 of 209 (10.5%) patients, and antiplatelet therapy was started in 2 (1.0%) patients. In 158 (75.6%) patients, antiplatelet therapy was confirmed as the best therapeutic choice, and in 27 (12.9%) patients, no antithrombotic therapy was prescribed. In the active intervention arm, the percentage of patients on OAC therapy, as indicated by guidelines, increased during the follow-up from 46.1% at baseline, to 69.4% in the stroke risk evaluation phase, to up to 72.6% at the end of the observation period (Figure 3). In the usual care control arm, the percentage of patients on OAC therapy was 46.9% at baseline and 56.8% at the end of the observation period (P<0.001 versus active intervention arm).

Stroke, TIA, and Embolic Events

During the follow-up period, 37 embolic events in 33 patients were recorded (17 ischemic stroke, 10 TIA, and 10 peripheral thromboembolic complications). Among 1174 patients with a history of AF or new-onset AF, 22 experienced 25 embolic events (8 ischemic strokes, 9 TIA, and 8 peripheral thromboembolic complications). The annual rate of patients with embolic events was 0.7 per 100 patient-years; in the remaining 2264 patients who never experienced an AF, in a total follow-up of 5367 patient-years, 11 experienced ischemic strokes, TIA, or thromboembolic complications, with an annual rate of 0.2 per 100 patient-years (P=0.001 versus patients with AF).

Among 33 patients with stroke, TIA, or embolic events, 21 (64%) had at least an AF lasting at least 5-minutes, as detected by ICD diagnostics, in the observation period preceding thromboembolic events. When evaluating the 30 days preceding the thromboembolic events, 11 (33%) patients experienced AF. Finally, 5 (15%) patients experienced embolic events during AF.

The annual rate of patients with embolic events in a subgroup of 1174 patients with a history of AF or new-onset AF is shown in Table 2 in relation to CHADS2 score and antithrombotic therapy. In patients with a CHADS2 score of 1 to 2, the annual rate of patients with embolic events was 2 of 934 (0.2%) with OAC and 8 of 1011 (0.8%) without OAC (P=0.11).
Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall Population (n=3438)</th>
<th>Active Intervention Arm (n=1961)</th>
<th>Control Arm (n=1477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2802 (82)</td>
<td>1608 (82)</td>
<td>1194 (81)</td>
</tr>
<tr>
<td>Age, y</td>
<td>71 ± 11</td>
<td>71 ± 11</td>
<td>73 ± 6</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>2790 (81)</td>
<td>1532 (78)</td>
<td>1258 (85)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1814 (53)</td>
<td>1022 (52)</td>
<td>792 (54)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1571 (46)</td>
<td>809 (41)</td>
<td>762 (52)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>735 (21.4)</td>
<td>389 (19.8)</td>
<td>346 (23.4)</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>135 (4)</td>
<td>81 (4)</td>
<td>54 (4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>713 (21)</td>
<td>426 (22)</td>
<td>287 (19)</td>
</tr>
<tr>
<td>Drug therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>1597 (46)</td>
<td>904 (46)</td>
<td>693 (47)</td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>364 (10)</td>
<td>202 (10)</td>
<td>162 (11)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1234 (36)</td>
<td>702 (36)</td>
<td>532 (36)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>789 (23)</td>
<td>477 (24)</td>
<td>312 (21)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3310 (96.3)</td>
<td>1891 (96.4)</td>
<td>1419 (96.1)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>2797 (81)</td>
<td>1561 (80)</td>
<td>1236 (84)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>2747 (80)</td>
<td>1571 (80)</td>
<td>1176 (80)</td>
</tr>
<tr>
<td>Antiarrhythmic therapy</td>
<td>1648 (48)</td>
<td>935 (48)</td>
<td>713 (48)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD.
TIA indicates transient ischemic attack; ACE, angiotensin-converting enzyme.

Figure 2. Antithrombotic therapy before and after the evaluation of the ANGELS (Anticoagulation Use Evaluation and Life Threatening Events Sentinels) of AF reports in the active intervention arm. A therapy upgrade was observed in 24 patients, to OAC in 22 and antiplatelet agents in 2. OAC indicates oral anticoagulation.

Post Hoc Analysis
The nonrandomized center selection might have induced a bias if centers with higher compliance in the OAC therapy implementation were involved in one or the other arm without homogeneity. To exclude this bias, we evaluated the OAC therapy implementation in the subgroup of patients who were followed up for longer than 48 months in the ANGELS of AF centers before ANGELS of AF project implementation in the centers. In 160 of these patients, 59.4% were on OAC therapy at 48 months, a value much closer to the 56.8% in the usual care control arm than to the 72.6% in the reporting arm. The difference between 59.4% and 72.6% suggests, through a comparison within the same group of centers, the possibility of OAC therapy optimization.

Discussion
The presented results demonstrate that a medical care program may improve OAC implementation in standard medical practice by supplying accurate and continuous information about stroke risk factors, AF occurrence, and burden. We also provide real-world data on thromboembolic events among patients with ICDs and their association with stroke risk scores and antithrombotic therapy.

OAC therapy implementation increased in both the arms of the project. In the usual care control arm, the percentage of indicated patients who were on OAC therapy was 46.9% at baseline and increased to 56.8% at last follow-up. In the active intervention arm, it was at 46.1% at baseline and increased to 69% before the report was provided. This increase may possibly be explained by the fact that device diagnostics make it possible to better detect AF occurrence and exactly define AF burden and type, whether paroxysmal or persistent. Awareness of physicians participating to the ANGELS of AF project is also a factor.

In the active intervention arm, the implementation of a reporting system further improved OAC uptake and guideline adherence to OAC therapy; in fact, anticoagulation therapy was upgraded in 10.5% of patients after evaluation of the ANGELS of AF reports. The net change in OAC implementation between the active intervention arm and the control arm was 15.8%, which represented a statistically significant change from 56.8% OAC implementation in the control arm to 72.6% in the active intervention arm. This result is clinically noteworthy in view of other dedicated program efforts aimed at exploring and improving adherence to recommendations for antithrombotic therapy in AF that reported either no increase in warfarin prescription for AF in heart failure at 2 and 3 years15,16 or an 11% increase in warfarin prescription in the specific setting of in-hospital management of stroke.17

The present results complement other observational studies performed in non-ICD populations.15,16,18–21 Of note, 82% of the patients in the present research experienced heart failure. Piccini et al15 found that from 2005 to 2007, the rate of OAC use among patients with AF hospitalized for heart failure was ≈60% to 65%. The IMPROVE HF (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) study16 was performed to enhance quality of care of patients with heart failure by facilitating adoption of evidence-based guideline-recommended therapies. This showed a significant improvement in 6 of 7 quality measures at 12 and 24 months, especially, in the use of angiotensin-converting enzyme inhibitors, β-blockers, aldosterone antag-
onists, cardiac resynchronization therapy, and ICD therapy, but failed to improve the compliance for OAC therapy. The percentage of indicated patients who were on OAC therapy was 69% at baseline, and this remained stable during the entire study follow-up period. In a study by Nieuwlaat et al among patients with AF and a high risk for stroke, antithrombotic treatment was consistent with the guidelines in 61% of patients, and importantly, guideline nonadherence was associated with a higher risk of thromboembolism.

The ANGELS of AF project suggests that the implementation of a quality-of-care improvement intervention enhances OAC therapy compliance and reinforces the message of the IMPROVE HF trial, which failed to enhance OAC compliance. In the specific field of OAC treatment, the present findings indicate that education and benchmark reporting should be integrated with patient-specific reports about stroke risk factors and AF characteristics (occurrence, temporal trends, and burden) as continuously monitored by ICD diagnostics.

Gaps, variations, and disparities in the use of evidence-based, guideline-recommended therapies for AF in inpatient and outpatient care settings are well documented; in particular, an important underuse of OAC therapy has been shown in numerous studies evaluating clinical practice. As a result, many patients with AF may experience embolic events, such as strokes or TIA, that might have been prevented. The present project shows that hospital-based performance improvement programs may enhance quality of care in patients with AF. In particular, in patients with ICDs, reliable and continuous AF diagnostics may be exploited to supply physicians with useful reports about AF occurrence. Such a reporting system may be of paramount importance because studies have indicated that the majority of AF episodes are asymptomatic, including many episodes of clinically significant duration. The identification of asymptomatic AF is of primary importance for guiding OAC therapy in patients with clinical risk factors, given that the risk for ischemic stroke is similar in patients with intermittent and sustained AF. Patients with infrequent paroxysms of AF are the most difficult to identify with intermittent monitoring and face a significant stroke risk in the absence of appropriate OAC therapy. Indeed, treatment guidelines recommend that we should not consider the clinical AF subtype when deciding on OAC.

Today, device data can be sent from the patient’s home through a telephone or Internet connection; therefore, physicians can have remote access to diagnostics. Clinical data similarly may be accessed through the Intranet or Internet using connectivity applications. The findings of the ANGELS of AF project may serve as a model for future performance improvement programs that link device and clinical data to

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**Table 2. Annual Rate of Stroke, TIA and Embolic Events as a Function of CHADS2 in 1174 Patients With a History of AF or a New-Onset AF**

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>Patients</th>
<th>Antithrombotic Therapy</th>
<th>Total Follow-Up, y</th>
<th>Patients With Events</th>
<th>Annual Rate of Patients With Event, per 100 Patient-y</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>37</td>
<td>All</td>
<td>102</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>242</td>
<td>All</td>
<td>743</td>
<td>3</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAC</td>
<td>369</td>
<td>1</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APA</td>
<td>185</td>
<td>1</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Null</td>
<td>189</td>
<td>1</td>
<td>0.53</td>
</tr>
<tr>
<td>2</td>
<td>436</td>
<td>All</td>
<td>1202</td>
<td>7</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAC</td>
<td>565</td>
<td>1</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APA</td>
<td>347</td>
<td>3</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Null</td>
<td>290</td>
<td>3</td>
<td>1.03</td>
</tr>
<tr>
<td>3</td>
<td>329</td>
<td>All</td>
<td>838</td>
<td>8</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAC</td>
<td>428</td>
<td>4</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APA</td>
<td>265</td>
<td>4</td>
<td>1.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Null</td>
<td>145</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥4</td>
<td>130</td>
<td>All</td>
<td>275</td>
<td>4</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAC</td>
<td>137</td>
<td>3</td>
<td>2.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APA</td>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Null</td>
<td>54</td>
<td>1</td>
<td>1.86</td>
</tr>
<tr>
<td>All</td>
<td>1174</td>
<td>All</td>
<td>3160</td>
<td>22</td>
<td>0.70</td>
</tr>
<tr>
<td>All</td>
<td>1174</td>
<td>OAC</td>
<td>1530</td>
<td>9</td>
<td>0.59</td>
</tr>
<tr>
<td>All</td>
<td>1174</td>
<td>APA</td>
<td>907</td>
<td>8</td>
<td>0.88</td>
</tr>
<tr>
<td>All</td>
<td>1174</td>
<td>Null</td>
<td>723</td>
<td>5</td>
<td>0.69</td>
</tr>
</tbody>
</table>

The number of patients for each antithrombotic therapy changed during the observation period because of changes in the administered drug and, thus, is not shown. The total follow-up period assigned to each antithrombotic therapy is calculated while taking into account the actual therapy taken by the patient and, therefore, the drug changes.

OAC indicates oral anticoagulation; APA, antiplatelet; Null, no antithrombotic therapy.
data warehouses fed by telemedicine and connectivity systems. Projects aiming to improve OAC use are warranted because they may improve patient survival and quality of life and reduce disability and hospital and social resource utilization. Furthermore, new OACs that reduce hemorrhagic risk\textsuperscript{22,23} may reduce the barriers and the concerns for instituting anticoagulation, also facilitating the optimization of patient management.

**Cerebrovascular Events and Systemic Emboli: Relationship With AF and CHADS\textsubscript{2}**

In the present population of patients with AF, the annual rate of stroke, TIA, and embolic events was 0.7 per 100 patient-years, and an increasing trend as a function of CHADS\textsubscript{2} score (from 0.4 per 100 patient-years for a CHADS\textsubscript{2} score of 1 to 1.45 per 100 patient-years for a CHADS\textsubscript{2} score of $\geq$4) was found (Table 2). Low rates of cerebrovascular events and systemic emboli in patients with ICDs have been previously shown, as in the TRENDS study,\textsuperscript{2,12} which estimated an annual rate of 1.2 per 100 patient-years. The analysis of the incidence of thromboembolic events should also consider that this 46\% of the patients were under treatment with OACs as a result of current practice guidelines.

The temporal relationship of device-detected AF and stroke, TIA, or embolic events showed that 64\% of patients had AF in any period preceding a thromboembolic event, 33\% of patients had AF in the 30 days preceding a thromboembolic event, and 15\% of patients had AF during thromboembolic events. Comparing recent findings by Daoud et al\textsuperscript{24} of 50\%, 27.5\%, and 15\%, respectively, and the present percentages confirms that AF has a causal relationship with thromboembolic events, with a rate similar to that reported in other studies.\textsuperscript{14,24–27}

**Limitations**

This research is limited by its nonrandomized observational design. Nonetheless, we report unique, to our knowledge, real-world data in a large cohort of patients with ICDs in whom asymptomatic AF episodes may develop. The main objective of the project was to implement a strategy for improvement of OAC therapy; therefore, we did not design the project to be powered to show the impact of the program on the incidence of thromboembolic end points. Our estimation of embolic events rates may also be open to underreporting of clinical outcomes and some limitations in the ascertainment of causes of death.

The amount of AF burden, as detected by the ICDs, that conveys a substantial risk of stroke has been the object of debate.\textsuperscript{2,28} In this project, we adopted the cutoff of 6 hours, but in the future, lower cutoffs may be used on the basis of new data,\textsuperscript{29} also taking into account the extent of burden in relationship with CHADS\textsubscript{2} score; the increase in stroke risk is achieved with a lower AF burden in patients at higher risk on the basis of CHADS\textsubscript{2}.\textsuperscript{11,30} We did not collect baseline information about mitral stenosis, cardiac thrombus, mechanical heart valve, blood pressure, or time from previous stroke or TIA; therefore, we could not study these variables as stroke predictors. We did not collect information about international normalized ratio values and the time in therapeutic range for patients who were anticoagulated. Finally, reasons for nonuse of OAC therapy, such as contraindications or adverse events, may not have been completely documented.

**Conclusions**

The ANGELS of AF project demonstrates the possibility of improving OAC use in accordance with available guidelines for stroke risk reduction in AF by supplying attending physicians with reports about patient risk factors and AF information from continuous digital monitoring.

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**Disclosures**

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**References**


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