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.

(Circ Cardiovasc Qual Outcomes. 2012;5:182-188.)

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.1,2 Importantly, AF has been associated with a 5-fold increase in the risk of ischemic stroke.2,3 Effective prevention of stroke and thromboembolism requires oral anticoagulation (OAC), although stroke risk is influenced by associated risk factors.2,3 Underuse of OAC therapy with warfarin has been shown to occur in real-world clinical practice in patients at moderate to high thromboembolic risk.4–6 Current guidelines for stroke prevention in AF2,3,7 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) and that the majority of AF episodes are asymptomatic, including many episodes of clinically significant duration. However, it is unknown to what extent physicians actually make clinical decisions driven by the arrhythmic events detected by the implantable device.

The Anticoagulation Use Evaluation and Life Threatening Events Sentinels (ANGELS) of AF project was a medical care program aimed at improving OAC use as thromboprophylaxis through the use of information from ICD AF diagnostics. The main objectives of the ANGELS of AF project were to (1) evaluate the prevalence of AF and stroke risk factors and their association with OAC use in the followed patient population; (2) measure the annual rate of stroke, transient ischemic attacks (TIAs), and embolic complications; and (3) implement a strategy for improvement of OAC use.

**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.

**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.

**Methods**

Patients included in the present analysis were followed in a network of 50 Italian cardiological centers that participate in the Italian Clinical Service Project. This national cardiovascular data repository and medical care project aims to describe and improve the use of ICDs in Italian clinical practice. The project was approved by each site’s institutional review board or medical director and conforms with the principles outlined in the Declaration of Helsinki. Each patient signed informed consent for data collection and analysis.

**Results**

A total of 3438 patients were prospectively followed in this project (Figure 1) of whom 1961 (57%) were followed in the 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 TIAS, 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 TIAS, 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, TIAS, 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).
Among 709 patients with a history of AF or a new-onset AF in the active intervention arm, 14 experienced embolic events in 2200 patient-years, with an annual rate of 0.64 per 100 patient-years. Among 465 patients with a history of AF or a new-onset AF in the usual care control arm, 8 experienced embolic events in 960 patient-years, with an annual rate of 0.83 per 100 patient-years. Among 465 patients with a history of AF or a new-onset AF in the usual care control arm, 8 experienced embolic events in 960 patient-years, with an annual rate of 0.83 per 100 patient-years. Among 465 patients with a history of AF or a new-onset AF in the usual care control arm, 8 experienced embolic events in 960 patient-years, with an annual rate of 0.83 per 100 patient-years. Among 465 patients with a history of AF or a new-onset AF in the usual care control arm, 8 experienced embolic events in 960 patient-years, with an annual rate of 0.83 per 100 patient-years. Among 465 patients with a history of AF or a new-onset AF in the usual care control arm, 8 experienced embolic events in 960 patient-years, with an annual rate of 0.83 per 100 patient-years.

**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 years or an 11% increase in warfarin prescription in the specific setting of in-hospital management of stroke.

The present results complement other observational studies performed in non-ICD populations. Of note, 82% of the patients in the present research experienced heart failure. Piccini et al 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) study 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 antagonists and diuretics.

**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>
</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.
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 al19 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,16 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.4–6 As a result, many patients with AF may experience embolic events, such as strokes or TIAs, 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.11 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.21 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.18 Indeed, treatment guidelines recommend that we should not consider the clinical AF subtype when deciding on OAC.3

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

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>1530</td>
<td>OAC</td>
<td>9</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>907</td>
<td>APA</td>
<td>8</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>723</td>
<td>Null</td>
<td>5</td>
<td>0.69</td>
<td></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.
Cerebrovascular Events and Systemic Emboli: Relationship With AF and CHADS₂
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 CHADS₂ score (from 0.4 per 100 patient-years for a CHADS₂ score of 1 to 1.45 per 100 patient-years for a CHADS₂ score of ≥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, 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 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.

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. 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, also taking into account the extent of burden in relationship with CHADS₂ score; the increase in stroke risk is achieved with a lower AF burden in patients at higher risk on the basis of CHADS₂. 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 device monitoring.

Acknowledgments
We thank Giorgia D’Ippolito for her technical support in the management of data.

Sources of Funding
The research was performed in the framework of a medical care project sponsored by Medtronic Italia, an affiliate of Medtronic Inc.

Disclosures
Dr Santini receives research grant support from Medtronic, St. Jude Medical, and Biotronik and honoraria from Medtronic and Bayer; has a speakers’ bureau appointment with MSD, Medtronic, St. Jude Medical, and AstraZeneca; and has an advisory board relationship with Boehringer Ingelheim. Dr Gasparini has an advisory board relationship with Boston Scientific. Dr Proclemer receives research grant support and has an advisory board relationship with Medtronic. Dr Landolina has a speakers’ bureau appointment with St. Jude Medical, Medtronic, and Boston Scientific and an advisory board relationship with St. Jude Medical and Medtronic. Dr Padeletti receives research grant support and an advisory board grant from Medtronic. Dr Capucci has a speakers’ bureau appointment with St. Jude Medical and Boston Scientific. Dr Ricci receives research grant support from Medtronic, St. Jude Medical, and Biotronik and is a consultant for Medtronic. M. Vimercati and Dr Grammatico are employees of Medtronic Italia, an affiliate of Medtronic Inc. Dr Lip has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers, including Merck, AstraZeneca, Boehringer Ingelheim, Bayer, BMS/Pfizer, Astellas, Daiichi, Portola, Sanofi-Aventis, and Biotronik. The other authors report no conflicts.

References


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Circ Cardiovasc Qual Outcomes. 2012;5:182-188; originally published online February 28, 2012;
doi: 10.1161/CIRCOU10111.964205
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

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