Treatment with novel oral anticoagulants in a real-world cohort of patients undergoing cardiac rhythm device implantations

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Aims
The safety and efficacy of novel oral anticoagulants in patients with atrial fibrillation undergoing pacemaker or implantable cardioverter-defibrillator interventions have not been clearly defined. Therefore, we compared the incidence of bleeding and thrombo-embolic complications following cardiac rhythm device (CRD) implantations under dabigatran vs. rivaroxaban in a real-world cohort.

Methods and results
We analysed 176 consecutive procedures performed in 93 patients treated peri-interventionally with dabigatran and 83 patients with rivaroxaban, respectively. Post-operative bleeding complications and thrombo-embolic events occurring within 30 days were compared. There were no significant differences in baseline characteristics between patients in the dabigatran and the rivaroxaban group. Most of the patients in both the groups received dual chamber or cardiac resynchronization devices (71 vs. 78%) as opposed to single-chamber systems (29 vs. 22%). In the dabigatran group, two (2%) bleeding complications (two pocket haematomas) were observed in comparison with four (5%, three pocket haematomas and one pericardial effusion) in the rivaroxaban group \((P = 0.330)\). Three complications in the rivaroxaban group necessitated surgical intervention as opposed to none in the dabigatran group \((P = 0.064)\). One case of a transient ischaemic attack occurred in the dabigatran group \((P = 0.343)\).

Conclusion
Bleeding and thrombo-embolic complications in patients treated with dabigatran or rivaroxaban are rare. Further and larger studies are warranted to define the optimal anticoagulation management in patients with a need for oral anticoagulation and CRD interventions.

Keywords
Pacemaker • Implantable cardioverter-defibrillator • Dabigatran • Rivaroxaban

Introduction
Approximately 25% of patients undergoing implanta tions of cardiac rhythm devices (CRDs) require a long-term anticoagulation\(^1\) leading to increased peri-interventional bleeding rates.\(^2\) The optimal peri-procedural management and finding the delicate balance between potential risk of thrombo-embolic event and bleeding is difficult and a common clinical problem with limited evidence insuring optimal treatment.\(^2\) While uninterrupted warfarin use in patients undergoing pacemaker (PM) or implantable cardioverter-defibrillator (ICD) implantations has very recently been shown to be superior to bridging therapy with heparin,\(^3\) only very limited data exist on the safety and efficacy of novel anticoagulants.\(^4\)

We present, for the first time, a comparison of peri-interventional bleeding and thrombo-embolic complications of two widely used novel oral anticoagulants (NOACs), dabigatran and rivaroxaban, in a real-world cohort.

Methods

Patients
In this prospective, observational study, 93 consecutive patients who were peri-procedurally treated with dabigatran and 83 consecutive patients treated with rivaroxaban between January 2011 and December 2012 were included. Table 1 shows the baseline characteristics and procedural data of both groups.

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What’s new?
- The safety and efficacy of novel oral anticoagulants (NOACs) in patients undergoing cardiac rhythm devices implantation have not yet been well studied.
- The study presents a comparison of two widely used NOAC, dabigatran and rivaroxaban, in terms of post-interventional bleeding and thrombo-embolic complications.

Results

Comparison of patient characteristics

There were no significant differences in baseline characteristics between patients in the dabigatran and the rivaroxaban group. The thrombo-embolic risk, defined by the CHA2DS2-VASc score was similar in both the groups [4 (IQR 3–5) vs. 4 (IQR 3–5), P = 0.770]. Patients in the dabigatran group were more frequently co-medicated with aspirin (27 vs. 10%, P = 0.015) and thienopyridine (14 vs. 4%, P = 0.018).

The procedural parameters including mean procedural time (60 ± 30 vs. 56 ± 35 min, P = n.s.), the frequency of sub-pectoral implantations (3 vs. 2%, P = n.s.), and specification of implanted devices (71 vs. 78% of dual chamber or CRT devices, P = n.s.) were also similar in both the groups. In both the groups, the most frequent procedure was de novo implantation (79 vs. 78%, P = n.s.), as compared with generator change (10 vs. 12%, P = n.s.) and system upgrade (10 vs. 10%, P = n.s.).

Peri-procedural novel oral anticoagulant management

In the dabigatran group, anticoagulation was administered for the first time post-procedurally in 24 patients (26%) while the remainder 69 patients (74%) were on dabigatran on admission. Rivaroxaban treatment was started post-procedurally in 29 patients (35%) and 54 patients (65%) were already on rivaroxaban on admission.

The first dose of dabigatran was administered significantly earlier after the procedure than rivaroxaban (37 ± 21 vs. 27 ± 23 h, P = 0.006). In both the groups no bridging with heparin was performed.

Patients were treated with 110 mg (n = 54, 58%) or 150 mg (n = 39, 42%) dabigatran twice-daily according to their creatinine clearance and age (77 ± 26 or 79 ± 27 ml/min/1.73 qm). Forty-one patients (49%) were treated with 15 mg rivaroxaban and 42 (51%) with 20 mg according to their creatinine clearance only (54 ± 23 or 74 ± 21 ml/min/1.73 qm).

Complications

In the rivaroxaban group, we observed four (5%) bleeding complications (three pocket haematomas and one pericardial effusion) compared with two (2%) pocket haematomas in the dabigatran group (P = n.s.). Three complications in the rivaroxaban group (two pocket haematomas and one pericardial effusion) needed surgical intervention as opposed to none in the dabigatran group (P = 0.064).

In dabigatran group, one case of transient ischaemic attack without any lasting neurological deficits occurred while there were no thrombo-embolic events in the rivaroxaban group (P = n.s.).

The detailed complication characteristics are summarized in Table 2.

The hospitalization time was similar in both the groups [2 (IQR 1–3) days vs. 2 (IQR 1–3) days, P = n.s.]. During extended follow-up of 66 ± 86 days, one case of device infection after 30 days was observed in the rivaroxaban group.

Discussion

To the best of our knowledge, this is the first study comparing bleeding and thrombo-embolic complications following CRD implantation.
under dabigatran vs. rivaroxaban. Overall, the complication rate was low and in a comparable range with recent reports. Although not statistically significant, there was a trend towards an increased risk of bleeding complications with the need for surgical revision in rivaroxaban-treated patients compared with dabigatran. Interestingly, this finding was observed despite the more frequent use of antiplatelet drugs in dabigatran-treated patients. Those findings are in accordance with recently published data from the RE-LY study population, showing a low incidence of bleeding complications after different surgical procedures and other invasive interventions.

Considering our and the comparable bleeding rates in the very recently published BRUISE CONTROL study under warfarin, NOAC may even be associated with superior safety.

Although the two anticoagulation agents have many similarities concerning pharmacokinetics, low potential for drug interactions, and rapid onset of action, some significant differences may explain our results. The different levels of inhibition of coagulation cascade, factor Xa in case of rivaroxaban and thrombin in case of dabigatran might be crucial: compared with thrombin, factor Xa is more thrombogenic as a primary site of amplification and is not associated with protein C-mediated thrombin generation after withdrawal.

Therefore, deactivation of factor Xa could lead to more aggressive anticoagulation resulting in more bleeding complications, even if started after longer interval than dabigatran. In addition, the effective anticoagulation time of single rivaroxaban dose is almost two times longer than that of dabigatran. Although, in our study and clinical practice, this fact was reflected by an extended period of discontinuation, it also may contribute to a higher complication rate. Furthermore, an additional interaction of rivaroxaban with the wound healing processes cannot be excluded and has been suggested recently after orthopedic surgery.

Since surgery may induce a prothrombotic state related to inflammatory reactions, endothelial injury, and transient immobilization, an adequate protection in the form of early initiated anticoagulation is advisable. However, despite recent and this investigation in atrial fibrillation (AF) patients, the optimal peri-procedural anticoagulation management strategy according to bleeding and (rebound) thromboembolic risk is hard to determine.

### Table 1 Comparison of clinical, procedural, and outcome data of patients treated with dabigatran (n = 93) and rivaroxaban (n = 83)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (n = 93)</th>
<th>Rivaroxaban (n = 83)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age, (years ± SD)</td>
<td>72 ± 11</td>
<td>74 ± 9</td>
<td>0.179</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>60 (65)</td>
<td>57 (69)</td>
<td>0.560</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>24 (26)</td>
<td>29 (35)</td>
<td>0.187</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>28 (30)</td>
<td>22 (27)</td>
<td>0.597</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>86 (93)</td>
<td>78 (94)</td>
<td>0.693</td>
</tr>
<tr>
<td>Median CHA2DS2-VASc score, (IQR)</td>
<td>4 (3–5)</td>
<td>4 (3–5)</td>
<td>0.770</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>78 (84)</td>
<td>74 (88)</td>
<td>0.323</td>
</tr>
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<td>ACE inhibitor/angiotensin receptor blocker, n (%)</td>
<td>80 (86)</td>
<td>77 (93)</td>
<td>0.150</td>
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<tr>
<td>Diuretics, n (%)</td>
<td>70 (75)</td>
<td>65 (78)</td>
<td>0.633</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>22 (24)</td>
<td>8 (10)</td>
<td>0.015</td>
</tr>
<tr>
<td>Thienopyridine, n (%)</td>
<td>13 (14)</td>
<td>3 (4)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Procedural data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single- and dual-chamber pacemaker, n (%)</td>
<td>60 (65)</td>
<td>48 (58)</td>
<td>0.616</td>
</tr>
<tr>
<td>Cardiac resynchronization pacemaker, n (%)</td>
<td>2 (2)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Single- and dual-chamber ICD, n (%)</td>
<td>14 (15)</td>
<td>15 (18)</td>
<td></td>
</tr>
<tr>
<td>Cardiac resynchronization ICD, n (%)</td>
<td>17 (18)</td>
<td>15 (18)</td>
<td></td>
</tr>
<tr>
<td>De novo implantation, n (%)</td>
<td>73 (79)</td>
<td>65 (78)</td>
<td>0.924</td>
</tr>
<tr>
<td>Generator change, n (%)</td>
<td>10 (11)</td>
<td>10 (12)</td>
<td></td>
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<tr>
<td>System upgrade, n (%)</td>
<td>10 (10)</td>
<td>8 (10)</td>
<td></td>
</tr>
<tr>
<td>Procedure time, (min ± SD)</td>
<td>60 ± 30</td>
<td>56 ± 35</td>
<td>0.487</td>
</tr>
<tr>
<td>Sub-pectoral implantation, n (%)</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>0.745</td>
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<tr>
<td><strong>NOAC management</strong></td>
<td></td>
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<tr>
<td>NOAC at the admission, n (%)</td>
<td>69 (74)</td>
<td>54 (65)</td>
<td>0.187</td>
</tr>
<tr>
<td>Post-procedural interruption, [hours, (IQR)]</td>
<td>24 [12–48]</td>
<td>48 [24–48]</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>Bleeding, n (%)</td>
<td>2 (2)</td>
<td>4 (5)</td>
<td>0.330</td>
</tr>
<tr>
<td>Surgical revision, n (%)</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td>0.064</td>
</tr>
<tr>
<td>Thrombo-embolic event, n (%)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0.343</td>
</tr>
<tr>
<td>Mean time to discharge, days (IQR)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.722</td>
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</tbody>
</table>
The novel agents with fast onset are advantageous, but the optimal time of initiation is disputable and more evidence is needed. Perhaps, also the time of discontinuation of NOAC must be re-evaluated as we recently saw it in the case of warfarin where a continuous medication enables a so-called ‘anticoagulant stress test’ where any excessive bleeding is detectable and appropriately managed while the wound is still open, which results in a lower bleeding rate. This question will be possibly soon be answered by an ongoing trial testing the uninterrupted dabigatran regime in CRD implantations (NCT01675076).

Modern anticoagulation agents have been rapidly adopted into ambulatory practice for the treatment of AF and a further rise is to be expected. Therefore, the peri-procedural management of such patients is a rapidly growing and complex clinical problem that requires further careful evaluation.

**Limitations**

Despite the novelty and so far largest sample size, our study is still limited by heterogeneous anticoagulation management, diverse procedures, and non-randomized design. Although no association between higher dose of dabigatran and bleeding complications was observed in our study, it cannot be excluded that the application of higher dose in countries where the 110 mg dose was not approved may influence bleeding rates. The discontinuation of the NOAC was protocolized but was not adjusted for creatinine clearances as it is was not recommended at the time of the study’s beginning. The physicians assessing the incision site were not blinded to the treatment and no ultrasound imaging of the haematoma was conducted. Although, the study design is in accordance with previous trials comparing different anticoagulation regimens, an open-label design and observational nature of the study might be a potential source of type 2 error.

**Conclusions**

Bleeding and thrombo-embolic complications in patients treated with dabigatran or rivaroxaban are rare. Further and larger studies are warranted to define the optimal anticoagulation management in patients with a need for oral anticoagulation and CRD interventions.

**Conflict of interest:** none declared.

**References**


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**Post-shock oversensing by a subcutaneous defibrillator resulting in inappropriate withholding of post-shock bradycardia pacing**

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A 30-year-old woman with hypertrophic cardiomyopathy had received a subcutaneous-only implantable cardioverter defibrillator (S-ICD) before for secondary prevention of sudden cardiac death. Follow-up had been uneventful until presentation to the emergency room after transient loss of consciousness during a run to the train station. She had no recollection of the event.

Check-up of the S-ICD revealed sinus tachycardia followed by ventricular fibrillation (VF) that was adequately detected by the device and terminated after 15 s with an 80 J shock (Figure). After termination of VF and asystole of > 4 s the patient developed slow, most likely supraventricular, escape rhythm. Post-shock pacing had been programmed on but was inadequately withheld because of oversensing (S). The escape rhythm was labelled as noise (N) until after 9 s escape beats were adequately labelled (S).

This case illustrates adequate sensing and termination of VF by an S-ICD followed by oversensing and inadequate withholding of post-shock pacing. Oversensing is most likely due to very sensitive automated settings post-shock to prevent lack of redetection of VF in case of unsuccessful shock therapy. It is unlikely that this device malfunction contributed to loss of consciousness since the patient has no recollection of the shock.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/Post-shock-oversensing.pdf.

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