OBJECTIVE
To conduct a comparative analysis of adverse drug reactions (ADRs) reported for aspirin and the three novel oral anticoagulants (NOACs): apixaban, dabigatran and rivaroxaban.

STUDY DESIGN

1) Pharmacovigilance (PV) reports from Eudravigilance were used to compare fifteen ADRs listed as commonly occurring in the Summaries of Product Characteristics, for aspirin and the three NOACs: aspirin, dabigatran and rivaroxaban.

- Individual Case Safety Reports (ICSRs) reported between January 2013 and September 2017 were analysed.
- Reported ADRs were divided into 3 categories – (A) Bleeding-related ADRs, (B) Gastrointestinal ADRs and (C) Central nervous system related ADRs and hypotension.
- Pairwise comparisons between medications (aspirin vs apixaban, aspirin vs dabigatran, aspirin vs rivaroxaban, apixaban vs dabigatran, apixaban vs rivaroxaban, dabigatran vs rivaroxaban) for ADRs documented in PV reports were carried out.

RESULTS

For the fifteen ADRs analysed, 51,991 ICSRs were identified in Eudravigilance.

Bleeding-related ADRs (contusion, epistaxis, eye haemorrhage, gastrointestinal haemorrhage, gingival bleeding) were the commonest reported ADRs (38,826/51,391 or 75.6%) for all four medications (Figure 1).

Reported ADRs were divided into 3 categories - (A) Bleeding-related ADRs, (B) Gastrointestinal ADRs and (C) Central nervous system related ADRs and hypotension.

Three groups of patients were recruited (25 taking aspirin, 25 taking rivaroxaban).

- The four medications differ significantly in terms of reported ADRs.
- A statistically significant difference between at least one medication pair was observed for each of the fifteen ADRs investigated (Figure 3).

DISCUSSION

- The comparative analysis suggests a bias in the reporting of ADRs to PV databases in terms of different medication types and consumption trends.
- Consumption trends show that rivaroxaban is the most used NOAC in Malta.
- The four medications differ significantly in terms of reported ADRs.
- A statistically significant difference between at least one medication pair was observed for each of the fifteen ADRs investigated (Figure 3).

CONCLUSIONS

- Differences in reporting of ADRs to PV databases could be due to differences in consumption trends, differences in safety profiles of medication or reporting bias.
- Studies on post-marketing safety data based on spontaneous ADR reporting are essential for comparing information between different medications and to help in determining the risk-benefit ratio of therapy.
- Healthcare professionals should accept the responsibility of assuring that ADR reporting is done systematically and consistently for all suspected ADRs.

<table>
<thead>
<tr>
<th>Medication Pair</th>
<th>ADR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin vs Apixaban</td>
<td>Abdominal pain</td>
<td>0.000</td>
</tr>
<tr>
<td>Aspirin vs Dabigatran</td>
<td>Epistaxis</td>
<td>0.005</td>
</tr>
<tr>
<td>Aspirin vs Rivaroxaban</td>
<td>Dizziness</td>
<td>0.001</td>
</tr>
<tr>
<td>Apixaban vs Rivaroxaban</td>
<td>Gastrointestinal haemorrhage</td>
<td>0.009</td>
</tr>
<tr>
<td>Apixaban vs Dabigatran</td>
<td>Dyspnoea</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Figure 3: Example of medication pairs showing statistically significant differences between the numbers of reported cases of ADRs.

- Epistaxis - the ADR with the largest number of medication pairs (N=9) showing statistically significant differences.
- Gastrointestinal haemorrhage – the most commonly reported ADR, statistical significance observed only between rivaroxaban and aspirin (p-value = 0.009).
- Thirty-six patients who completed the questionnaire reported at least one ADR following intake of either aspirin or rivaroxaban (aspirin=18, rivaroxaban=18).
- Bleeding-related ADRs were the least reported types of ADRs from respondents of the questionnaire (aspirin=11 (23.4%), rivaroxaban=4 (17.4%).
- Patients reported ADRs as being either mild or moderate.
- Consumption trends showed that rivaroxaban is the most used NOAC in patient populations.