# 5PSQ - 107 ASPIRIN AND NOVEL ORAL ANTICOAGULANTS: REPORTING OF ADVERSE DRUG REACTIONS

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## 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: apixaban, 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.**

**2) A questionnaire was developed to collect information related to ADRs encountered by patients while taking aspirin or NOACs. Fifty patients were recruited (25 taking aspirin, 25 taking rivaroxaban).**

**3) Documented ADRs from PV reports were compared to patient-reported ADRs.**

**4) Consumption trends for the NOACs were analysed from literature.**

## RESULTS

- **For the fifteen ADRs analysed, 51,391 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).**

| | | Aspirin | Apixaban | Dabigatran | Rivaroxaban |
|---|---|---|---|---|---|
| | | % (no. of PV reports) | % (no. of PV reports) | % (no. of PV reports) | % (no. of PV reports) |
| ADRs | Bleeding-related | 74.5 (9424) | 67.6 (3112) | 70.4 (6551) | 79.5 (19739) |
| | Gastrointestinal | 16.0 (2026) | 17.0 (781) | 20.0 (1864) | 10.2 (2533) |
| | CNS-related and hypotension | 9.5 (1208) | 15.4 (4602) | 9.6 (884) | 10.3 (2560) |

**Figure 1: Comparison between aspirin and NOACs for ADRs documented in ICSRs.**

- **Reported ADRs were highest for rivaroxaban (n=24,832).**
- **Gastrointestinal bleeding (n=25,892) was the commonest reported ADR for aspirin and the three NOACs (Figure 2).**

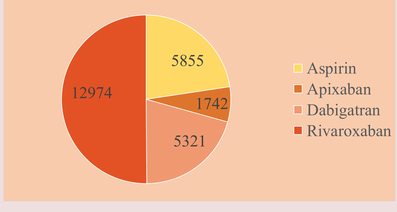


**Figure 2 : Number of reports for gastrointestinal bleeding.**

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

| Medication Pair | ADR | p-value |
|---|---|---|
| Aspirin versus Apixaban | Abdominal pain | 0.000 |
| Aspirin versus Dabigatran | Epistaxis | 0.005 |
| Aspirin versus Rivaroxaban | Dizziness | 0.001 |
| Apixaban versus Rivaroxaban | Gastrointestinal Haemorrhage | 0.009 |
| Apixaban versus Dabigatran | Dyspepsia | 0.000 |

**Figure 3: Examples 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=5) showing statistically significant differences.**
- **Gastrointestinal haemorrhage – the most commonly reported ADR, statistical significance difference observed only between rivaroxaban and apixaban (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 (14.3%)).**
- **Patients reported ADRs as being either mild or moderate.**
- **Consumption trends show that rivaroxaban is the most used NOAC in patient populations.**

## DISCUSSION

- **The comparative analysis suggests a bias in the reporting of ADRs to PV databases in terms of selective reporting or under-reporting.**
- **ADRs reported to PV databases do not reflect the amount of ADRs which occur following medication use.**
- **Bleeding-related ADRs were the most reported ADRs in PV reports and the lowest reported ADRs in patient questionnaires. ADRs which were considered minor or less serious when compared to bleeding-related ADRs were reported less in PV reports.**

- **Comparison of the three NOACs : The high numbers of ADRs reported for rivaroxaban compared to dabigatran and apixaban possibly reflect the consumption trends for rivaroxaban. High consumption trends for rivaroxaban may account for higher number of reported ADRs for rivaroxaban. An increase in the prescribing of medications causes an increase in the possibility of identifying an ADR, which may result in an increase in reporting of ADRs to PV databases.**

- **Comparison of aspirin to NOACs : ADRs are more likely to be reported for novel medications such as NOACs when compared to the more conventional drugs such as aspirin. Information on the safety profile of medications obtained from clinical trials is limited. Data from ADR reports submitted to PV databases may contribute to new information on the safety profile of medication.**

## 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.**