Research Article

Adverse Drug Reactions during Real-Life Use of Direct Oral Anticoagulants in Italy: An Update Based on Data from the Italian National Pharmacovigilance Network

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Keywords

Adverse drug reactions · Dabigatran · Rivaroxaban · Edoxaban · Apixaban

Abstract

Background: The availability of direct oral anticoagulants (DOAC) in clinical practice has transformed the health care provided to patients for the prevention and treatment of thromboembolism. Safety and efficacy data guide clinicians in the choice of the drug used. To date, no evidence is available from head-to-head trials comparing different DOAC with regard to safety and efficacy; information is mainly derived from several meta-analyses and real-life studies. Conclusions from these studies are inconsistent and unsatisfactory. The evaluation of self-reported adverse drug reactions (ADR) available from databases of drug-regulatory agencies such as the Italian Medicines Agency (AIFA) pharmacovigilance database represents a novel aid to guide decision-making. **Objective:** To analyze potential suspected ADR of DOAC using a previously described risk index (RI) in daily clinical practice in Italy. **Methods:** The National Pharmacovigilance Network database (from the AIFA website) was searched in order to retrieve information on all ADR related to oral anticoagulants occurring from 2013 to 2018. The ADR RI for each drug was calculated, where an RI = 1 indicates a balance between the

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percentage of ADR share and the percentage of market share for each DOAC; and an RI <1 indicates a rate of ADR lower than the rate of market share (safer DOAC). The following DOAC molecules were considered: dabigatran, rivaroxaban, apixaban, and edoxaban. **Results:** The results showed that rivaroxaban is the DOAC with the lowest RI among the 4 molecules available today in Italy. **Conclusions:** Based on the RI, we identified rivaroxaban as the DOAC having the best safety profile.

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Introduction

Atrial fibrillation (AF) represents the most frequent arrhythmia affecting the general population with a progressive increase in prevalence with increasing age of >10% in the population >80 years of age [1, 2]. The prevalence of AF is higher in patients with preexisting cardiovascular disease [3] and/or diabetes mellitus [4], or chronic kidney disease (CKD) [5]. In most patients, the therapeutic approach consists of the administration of an oral anticoagulant aimed at preventing the most feared complications of AF, represented by systemic thromboembolism and ischemic stroke [6].

For these reasons, the initiation of chronic anticoagulation should be strongly considered based on the individual assessment of stroke risk. Before the advent of direct oral anticoagulants (DOAC), the only pharmacological aid available was vitamin K antagonists (VKA) [7]. These drugs, although of undoubted clinical efficacy, are associated with significant limitations, such as the need for frequent monitoring of coagulation levels to adjust the therapeutic dosage, and interference with different foods and drugs [8]. Moreover, patients particularly at risk, such as those suffering from CKD, have further complications related to VKA therapy with an increased risk of major bleeding, which warrants caution [9].

The new DOAC class includes 4 molecules: “dabigatran (thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (direct inhibitors of activated factor X)” [10]. Results obtained from 4 different clinical registration trials for these molecules have shown that these DOAC have a favorable risk/benefit profile in terms of efficacy and safety [11–15]. On this basis, they are currently proposed as first-line therapy in patients with AF in preference to a VKA in the international guidelines (level of recommendation IA) [6, 16, 17].

To date, there are no clinical trials directly comparing DOAC. As pointed out by Camm et al. [18], it is not possible to accurately compare different DOAC with regard to safety and efficacy based on clinical registration trials due to significant heterogeneity of the patient populations enrolled in the various studies. Examples of this heterogeneity include the percentage of patients with impaired renal function, heart failure, or previous stroke, as well as the diversity of endpoints and outcomes [18]. For this reason, considerations on the different properties of single molecules can be extrapolated only thanks to meta-analyses, which are often characterized by a high level of heterogeneity and poor reproducibility, as well as observational studies of variable quality and robustness.

In the various studies comparing DOAC to VKA, DOAC were found to be either noninferior or superior to warfarin in terms of prevention of thromboembolic events. Safety data appear to be more fragmented and less homogeneous, except for an evident and constant reduction in intracranial hemorrhagic events in patients treated with DOAC compared to VKA [19].

One of the intrinsic problems in comparing different studies, as mentioned previously, is the heterogeneity of baseline characteristics and therefore stroke and bleeding risk among the populations enrolled. For example, in ROCKET-AF, patients with a more complex background were enrolled, with CHADS2 levels higher than the average of the other registered studies (3.5 vs. an average of 2.1–2.8) [11–14].

It should also be noted that patients enrolled in the registered trials are not exactly representative of those seen in daily clinical practice. It is for this reason that much attention has now been focused on observational studies coming from the so-called “real-world” experience. These studies provide useful additional information for several reasons: the population sample is more numerous, and patients are not selected; they generally have more comorbidities and are treated for longer time periods. In short, these subjects have more characteristics similar to those observed in daily clinical practice [20–22].

Analyzing different real-life studies present in the literature, a general tendency to a lower incidence of major bleeding in DOAC-treated patients can be observed. It should be emphasized, however, that these studies, unlike registered randomized clinical trials, show significant differences both in terms of data collection and analysis methodologies.

A high methodological standard is guaranteed by phase IV prospective observational studies aimed at verifying the safety of drugs after being placed on the market. These studies meet the requirements that the regulatory authorities (e.g., EMA, European Medicines Agency) usually demand of pharmaceutical companies for primary endpoint completion (e.g., the assessment of drug safety).

Some examples are the Xantus AF study, which also validated the safety of rivaroxaban in daily clinical practice [23] and ETNA, assessing edoxaban safety [24]. In contrast, information derived from retrospective databases is of lower quality, since often adverse event reports have administrative and nonscientific purposes [25, 26].

Two recent real-life observational studies have examined the effect of DOAC versus warfarin in CKD patients. The first study was performed in a cohort of over 340 patients (247 being treated with rivaroxaban and 100 with warfarin) and in patients with impaired renal function (CKD stage 3B–4); it clearly shows how the use of rivaroxaban at the “renal” dosage of 15 mg/day is significantly associated with a net clinical benefit both in terms of efficacy and safety [27]. The second study was performed in a limited sample of patients with the same characteristics in terms of CKD and confirmed the best risk/benefit ratio of edoxaban compared to warfarin [28].

The aim of the present retrospective descriptive study was to analyze potential suspected adverse drug reactions (ADR) of DOAC, in daily clinical practice in Italy, using a previously described risk index (RI) associated with the percentage of single molecules [29].

The official portal of the Italian Drug Association (AIFA) is publicly available, and the Adverse Reactions to Medicines (RAM) system allows the visualization of spontaneous reports signaled by health personnel since 2002. Reports sent to AIFA regarding the incidence of ADR registered in the National Pharmacovigilance Network (RNF) and available in the RAM system (Adverse Reactions to Medicines) were used as a source of data (<https://servizionline.aifa.gov.it/>) [30].

Materials and Methods

In Italy, postmarketing surveillance of different pharmacological molecules is regulated by procedures and regulations in which institutional and noninstitutional figures intervene, such as health care professionals, users, local health care authorities, drug companies, regions, and AIFA.

ADR surveillance is based on information recorded in the RNF, which has a dual function: it collects, manages, and analyzes the reports of suspected adverse reactions from users and clinicians, and, at the same time, it deals with disseminating information issued by AIFA regarding drug safety [31].

Since 2006, RNF have been connected to EudraVigilance [32], a database coordinated by the EMA [33], the agency responsible for collecting all reports of suspected ADR arriving from each member state.

Fig. 1. Definition of “risk index” (RI). RI is defined as the ratio between the serious adverse drug reaction (ADR) rate and the rate of usage of the active principle (AP). The closer the RI value approaches zero, the better the safety performance of the drug.

$$\text{ADR rate for AP} = \frac{\text{Suspected ADR for AP (n)}}{\text{Total suspected ADR for AP of a specific class (n)}} \times 100$$

Table 1. Variations in the number of serious ADR reported for the 4 direct oral anticoagulants (DOAC) between 2017 and 2018

DOAC	Variation
Rivaroxaban	+1%
Apixaban	+5%
Dabigatran	+13%
Edoxaban	+140%

With regard to Italian data, it should be noted that a specific law has been released by the Ministry of Health on April 30, 2015, which reiterated the obligation to promptly report ADR and vaccines, also providing the appropriate timing for reporting them.

These data are available to the public through the RAM system, which allows the analysis of all reports from 2002 onwards [34]. A summary of definitions of ADR and serious ADR, and how to search for ADR is shown in the online supplementary Boxes 1 and 2 (see www.karger.com/doi/10.1159/000507046 for all online suppl. material), respectively.

For what specifically concerns the molecules of interest for the present study, the presence of such a database allowed us to perform a “real-time” evaluation of the progress of the ADR reports associated with the DOAC used in clinical practice (dabigatran, rivaroxaban, apixaban, and edoxaban in strict order of availability on the market).

Subsequently, data collected from AIFA were compared with the usage rate expressed as market share obtained from the IQVIA (Institute for Human Data Science) [35].

Based on this information, we defined the RI, as the ratio between the serious ADR rate and the rate of usage of the active principle (Fig. 1) [29]. The closer the RI value approaches zero, the better the safety performance of the drug.

Results

Analysis was performed for the years 2013–2018 with particular focus on the years 2017 and 2018 (Table 1). The change in ADR reported over the past 6 years for the 4 DOAC is shown in Figure 2.

Analyzing the curve showing the incidence of reported ADR from 2013 to 2018, a greater incidence of ADR related to the use of dabigatran and a similar trend observed for rivaroxaban and apixaban can be observed (Fig. 2a). It is difficult to make a comparison with edoxaban, since it was only released in 2016, with ADR data only being available for the past 2 years. To address this difference, we focused on ADR reported for all 4 molecules from 2016 (Fig. 2b).

In the period 2016–2018, rivaroxaban was the DOAC shown to have a lower increase in the percentage of serious ADR compared to the other molecules (Fig. 2b). The percentage difference was expressed by calculating the percentage ratio between ADR relative to the single molecule and total ADR class.

For completeness of this analysis, the total ADR numbers recorded in the RNF for the years 2017 and 2018 stratified by active principle and by severity are shown in Figure 3.

Fig. 2. Total reports of adverse drug reactions (ADR) from 2013 to 2018 (**a**) and the number of serious ADR reported from 2016 to 2018 (**b**). Source of ADR: AIFA.

Fig. 3. Total number and proportion of adverse drug reactions for 2017 (**a**) and 2018 (**b**).

Fig. 4. Risk index of 2017 versus 2018 for each direct oral anti-coagulant in 2018.

Table 2. Variations in the number of serious adverse drug reactions (ADR) reported for the 4 direct oral anticoagulants (DOAC) in 2017 and 2018

DOAC	2017			2018		
	suspect ADR, %	use, %	RI	suspect ADR, %	use, %	RI
Rivaroxaban	28.2	37.5	0.75	24.7	35.6	0.69
Apixaban	29.9	32.6	0.75	27.4	31.7	0.86
Dabigatran	5.8	5.8	1.0	12.1	10.9	1.09
Edoxaban	31.6	24.1	1.5	35.8	21.8	1.63

RI, risk index.

These findings highlight that dabigatran and apixaban are the molecules leading to a higher percentage of serious than mild ADR. Comparing the percentage of ADR reported in 2017 (Fig. 3a) versus 2018 (Fig. 3b), we can observe that the number of ADR reported for dabigatran has increased (50 vs. 60%), while ADR numbers for the other 3 molecules remained largely unchanged.

Figure 4 represents the trend of ADR in the years 2017 and 2018 with the respective RI. In the year 2018, a total of 1,215 serious ADR were reported in DOAC-treated patients, with a 13.7% increase compared to 2017 (absolute number = 1,068). Therefore, although the increase in the use of DOAC was higher from 2017 to 2018 (by 30.4%), this increase was not paralleled for the number of ADR (13.7%), confirming the safety of this drug class.

Rivaroxaban was found to be the molecule showing the lowest RI of 0.69% (ADR: 300 and a market share of 35.6%), followed by apixaban with an RI of 0.86% (ADR: 332 serious ADR equal to 31.7% of all ADR) (Fig. 4). The third molecule in terms of RI is edoxaban (1.09%), for which 148 serious ADR were reported with a market share of 10.9%. Finally, dabigatran was associated with the highest RI (1.63%) and a number of reports of serious ADR equal to 435 and a market share of 21.9% (Table 2).

For the year 2018, further analysis focused on reports of serious ADR on the central nervous system (intracranial hemorrhage or ischemic stroke), which is presented in Figure 5. Regarding the absolute number of intracranial hemorrhages, the highest number of reports is related to the use of apixaban (43, equal to 12.9% of all ADR), followed by dabigatran (27, equal to 6.2% of all ADR), rivaroxaban (20, equal to 6.6% of all ADR), and edoxaban (6, equal to 4% of the total of ADR), a figure consistent with the respective RI (Fig. 5).

Fig. 5. Risk index of serious adverse drug reactions (ADR), cerebral hemorrhage, or ischemic stroke (serious ADR) in 2018.

Fig. 6. Trend for warfarin-related adverse drug reactions (ADR) reported from 2013 to 2018.

Furthermore, in regard to ischemic stroke, our results indicate that the safest drug (lowest RI) is rivaroxaban, followed by dabigatran, apixaban, and edoxaban (Fig. 5).

The change in ADR number is also presented for warfarin (Fig. 6). The number of reports, in absolute terms, is much higher (number of ADR from 2013 to 2018 = 11,000) compared to DOAC for the same period (average of 2500–3000 for the 4 DOAC; Fig. 2a).

Discussion

The introduction of DOAC in clinical practice has opened up new possibilities for the prevention of stroke in patients with AF and in the treatment of venous thromboembolism.

In recent years, this drug class represents one of the most significant therapeutic advances in the treatment of cardiovascular diseases and is characterized by a better risk/benefit profile than conventional therapy. In addition to their superior safety profile, VKA therapy often has to take the issue of reduced compliance into consideration, mainly due to numerous food-drug interactions.

The results observed in registered trials for the 4 different DOAC molecules would not seem to be homogeneous, but the variability in results obtained can be attributed to pharmacological differences between the different molecules, to different study designs, to the different populations included in these trials, to the different dosages used, and to the different endpoints and outcomes considered. The differences in the reproducibility of data, especially in terms of safety, observed between clinical trials and the results of phase IV and “real-life”

studies are largely attributable to the clinical risk profile (thromboembolic and hemorrhagic events) of the patients.

This issue has been well documented in several meta-analyses [11–14, 19], particularly in the meta-analysis performed by Ruff et al. [19], which included 71,683 patients with AF from all of the registration trials: RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48. Results from their meta-analysis have shown that treatment with DOAC instead of VKA reduced the incidence of stroke and systemic embolism by 19% (relative risk 0.81, 95% confidence interval 0.73–0.91; $p < 0.0001$) mainly due to a reduction in the incidence of hemorrhagic stroke. However, an increase in the risk incidence of gastrointestinal bleeding was also observed [19].

The authors highlight that there are important differences between the trials, especially in terms of the distribution of the various risk factors for both thromboembolic (CHADS2 score) and hemorrhagic events (HAS-BLED score). For example, the ROCKET-AF study enrolled patients at higher risk, with an average CHADS2 score of 3.5 [12] versus average CHADS2 values in the other studies ranging from 2.1 to 2.8.

Leaving aside the registration trials, which often include patient populations that are greatly different from those observed in daily clinical practice, we can confirm that the ADR data analyzed in this paper corroborate results of important international observational studies such as XANTUS and PREFER [23, 36, 37]. These studies represent patient cohorts that are more representative to those of the real world versus patients enrolled in phase 3 trials.

Interesting data have also emerged from the XANTUS study, in which over 6,000 nonvalvular AF patients treated with rivaroxaban were enrolled [23]. Patients showed an average CHADS score of 2, which corresponds to a CHA₂DS₂VASc value of 3.4, i.e., significantly lower than in ROCKET (average CHADS of 3.5) [12].

In this population characterized by a lower risk but with a better representation of the real-life scenario, the annual risk of stroke/systemic embolism, as well as that of gastrointestinal bleeding, in treated patients was significantly lower than that of the phase 3 trial ROCKET-AF [12].

These safety data were also confirmed in a retrospective postmarketing analysis involving 27,647 patients, which confirmed the excellent safety profile of rivaroxaban also demonstrated by a remarkable low frequency of fatal bleeding (0.08/100 years/person) [38].

Taken together, evidence emerging from registration studies, prospective phase IV observational studies, and “real-life” studies confirm the favorable risk/benefit profile of DOAC; this benefit also consolidated by international guidelines and a recent meta-analysis [39].

Guidelines from the European Cardiology Society indeed confirm that “the use of VKAs is limited by the narrow therapeutic interval, necessitating frequent monitoring and dose adjustments [6, 16, 17] when delivered with adequate time in therapeutic range, are effective for stroke prevention in AF patients. All DOACs have a predictable effect (onset and offset) without need for regular anticoagulation monitoring.”

Even the most recent updates from the European guidelines confirm the recommendation to use DOAC in preference to VKA, even in more compromised patient categories such as AF individuals with diabetes [40].

Data emerging from the analysis of the ADR available on the AIFA database for DOAC for the period 2013–2018 confirm previous findings, and we can say that DOAC, compared to VKA, have an excellent safety profile.

We can observe that although the trend in warfarin-related ADR reported is decreasing gradually since 2013, in absolute terms, the ADR number is much higher than that which occurs for DOAC (comprising >11,000 reports for all 4 molecules). The authors believe it

likely that the number of warfarin ADR reported is lower than the real ADR related to this drug, as it is a drug in use for a long period of time and therefore well known. This consideration is based on clinical experience rather than data from the literature.

The availability of data on the ADR registered in the RNF, even with the limits of this type of observation, has allowed us to estimate the risk of use of each drug presented in the official list of pharmaceutical drugs according to the drug quantities administered.

We therefore believe that the methodology presented and discussed in this study can be of use in providing clinicians with a practical parameter to determine the risk of severe ADR for each of the anticoagulant drugs, supporting their therapeutic choice.

Limitations

There are several limitations related to the data collected on the AIFA website that need to be mentioned. These include: (i) Lack of the possibility of distinguishing the ADR type and, above all, assessing the ADR in relation to the type of patient and the comorbidities that may be present and which could affect the ADR incidence. In addition, according to AIFA [41], it is requested to, but not mandatory, to provide information associated with the observed ADR, whether it is due to misuse, off-label use, or abuse. Therefore, it is not possible to extrapolate the indication according to therapeutic indication. (ii) The inability to make a specific analysis for the different dosages of the drugs. (iii) The RI: despite the fact that it is not a completely validated score, it was considered essential to normalize the data examined. (iv) It was not possible to include information on the number of patients who bled since this information was not available.

Although these elements of bias underline the importance of cautious interpretation of these findings, it is important to underline that such bias is inherent for all molecules examined.

Conclusions

From what emerged in our study and from data present in the literature, it is quite clear how DOAC therapy can be considered as a revolutionary treatment in the management of patients suffering from nonvalvular AF.

This survey aims to present a photograph of the Italian scenario currently present, representing an example of the real-life safety of oral anticoagulants.

The two milestones of the therapeutic response, in terms of efficacy and safety, are substantially in favor of the whole class of DOAC compared to warfarin and, more generally, to the class of VKA generally, as also evidenced by recent data on fencoprumone [40].

Data obtained from the pharmacovigilance network, which embraced what has been published in the pharmacovigilance network of the Italian Ministry of Health, confirm the safety profile and extend it further with the addition of data concerning the potential differences between the 4 molecules. The aim of the present analysis was not to make a direct comparison between the 4 DOAC of the new VKA because adequate information is not available on the patient cohorts in which they have been used.

The RI allowed us to identify rivaroxaban as the DOAC with the best safety profile. Based on evidence from previous studies and meta-analyses as well as results from the present study, we can argue that the entire DOAC class represents a step forward compared to the now obsolete VKA therapy, which, in our opinion, should be confined to a few and selected cases (e.g., AF in patients with artificial mechanical valves or patients with severe renal function impairment).

Statement of Ethics

The studies analyzed meet the requirements regulatory authorities (e.g., EMA) usually demand of pharmaceutical companies for primary endpoint completion (e.g., assessment of drug safety).

Disclosure Statement

The authors have no conflicts of interest.

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