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Liver injury with novel oral anticoagulants: assessing post-marketing reports in the US Food and Drug Administration adverse event reporting system

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drug-induced liver injury (DILI) represents a serious clinical event unlikely to be predicted from clinical trials, thus making spontaneous reporting systems a valuable tool to detect post-marketing safety signals.
- Novel oral anticoagulants (NOACs) have been on the market for 5 years, with only limited and partial post-marketing data in terms of DILI risk.

WHAT THIS STUDY ADDS

- DILI reports in the US-FDA adverse event reporting system (FAERS) highlighted a disproportionality signal for rivaroxaban, with consistent findings against different reporting bias (i.e. drug- and event-competition bias).
- Concomitant hepatotoxic and/or interacting agents were recorded in 39% of DILI reports, thus warranting clinical judgment on a case-by-case basis.

AIM

We assessed the hepatic safety of novel oral anticoagulants (NOACs) analyzing the publicly available US-FDA adverse event reporting system (FAERS).

METHODS

We extracted reports of drug-induced liver injury (DILI) associated with NOACs, including acute liver failure (ALF) events. Based on US marketing authorizations, we performed disproportionality analyses, calculating reporting odds ratios (RORs) with 95% confidence interval (CI), also to test for event- and drug-related competition bias, and case-by-case evaluation for concomitant medications.

RESULTS

DILI reports represented 3.7% (n = 146) and 1.7% (n = 222) of all reports for rivaroxaban and dabigatran, respectively. No statistically significant association was found for dabigatran, in primary and secondary analyses. Disproportionality signals emerged for rivaroxaban in primary analysis (ALF: n = 25, ROR = 2.08, 95% CI 1.34, 3.08). In a large proportion of DILI reports concomitant hepatotoxic and/or interacting drugs were recorded: 42% and 37% (rivaroxaban and dabigatran, respectively), especially statins, paracetamol and amiodarone. Among ALF reports, fatal outcome occurred in 49% of cases (44% and 51%, rivaroxaban and dabigatran, respectively), whereas rapid onset of the event (<1 week) was detected in 46% of patients (47% and 44%, respectively).

CONCLUSIONS

The disproportionality signal for rivaroxaban calls for further comparative population-based studies to characterize and quantify the actual DILI risk of NOACs, taking into account drug- and patient-related risk factors. As DILI is unpredictable, our findings strengthen the role of (a) timely pharmacovigilance to detect post-marketing signals of DILI through FAERS and other data sources, (b) clinicians to assess early, on a case-by-case basis, the potential responsibility of NOACs when they diagnose a liver injury.

Introduction

Drug-induced liver injury (DILI) covers a broad spectrum of liver manifestations, ranging from asymptomatic liver enzyme elevation to severe liver failure requiring transplantation [1]. Over the past 50 years, DILI has been a leading cause of various regulatory actions, including drug non-approvals or withdrawals. Despite significant improvement in DILI recognition during drug development and clinical trials, there are still significant limitations in our ability to predict, recognize and diagnose DILI [2].

The post-marketing phase is pivotal to monitor high priority adverse events and gain insight into real drug safety profiles, by reflecting concrete clinical practice where comorbidities and poly-pharmacotherapy exist. Spontaneous reporting systems (SRSs) represent a primary source of information to detect safety signals (i.e. possible drug–event associations), especially for newly marketed drugs and rare events with a strong drug-related component [3]. Notably, the diagnostic potential of statistical algorithms commonly applied to SRSs to identify safety signals is reasonably efficient and accurate to discriminate true drug–event associations from those that are likely to be spurious [4]. Very recently, the US Food and Drug Administration adverse event reporting system, now termed the FAERS database, has been exploited to advance the 'real-time' hepatotoxic risk profiles of new agents [5].

In the last 5 years, different novel oral anticoagulants (NOACs, dabigatran, rivaroxaban and apixaban) have entered the European and US markets [6]. Because of a more predictable pharmacokinetic/pharmacodynamic profile than warfarin [7–11], these agents are expected to change prescribers' habits. However, scant information on their actual safety profile is available, especially in terms of DILI risk. A recent systematic review on phase III randomized clinical trials failed to demonstrate a significant risk of DILI for NOACs [12]. However, the experience gained from the history of ximelagatran suggested that caution is needed before considering NOACs free from DILI risk [13]. Despite warfarin being on the market for decades, only sporadic reports of acute liver failure have been documented [14–17].

Dabigatran, a direct thrombin inhibitor, on the US market since October 2010 for stroke prevention in non-valvular atrial fibrillation (NVAF), received EU marketing authorization in 2008 for prevention of venous thromboembolism (VTE) after hip/knee replacement surgery (HKRS) and in 2011 for NVAF. No post-marketing data on hepatotoxic potential have been published so far. Rivaroxaban, a direct inhibitor of factor Xa, received an early marketing approval for VTE prevention after HKRS in 2008 (EU) and 2011 (US) and is also indicated for NVAF (December 2011 in EU and October 2011 in US), VTE treatment and prevention of recurrent VTE (2011 and 2012, EU and US, respectively). Very recently, case series analyses suggested a possible signal for DILI [18–20]. Apixaban is the latest approved inhibitor of factor Xa (on the US market since December 2012 for NVAF), without data on post-marketing hepatic safety.

In this context, we investigated the association between NOACs and the risk of DILI by systematically assessing spontaneous reports submitted to the largest publicly available source of pharmacovigilance data, the FAERS database. This study may contribute to inform clinicians on the current DILI profile of NOACs emerging from post-marketing (real-world) clinical practice.

Methods

Data source, acquisition and processing

The FAERS database is one of the largest repositories of reports of adverse reactions and medication errors associated with chemical and biological agents spontaneously submitted by healthcare professionals, patients and manufacturers. It currently collects more than 7 million reports worldwide (including European reports potentially related to serious events and other non-US non-European data), with public data availability since 2004, thus offering an emerging opportunity in signal detection and characterization, especially for newly marketed drugs and rare events with high drug-attributable risk such as DILI [5].

Reports submitted to the FAERS database require data management to select the most accurate dataset and make sure only reports above a pre-specified level of quality are included. As detailed in a book chapter [21], duplicates were detected and removed, missing data handled and active substances properly mapped. Considering the importance of the event date in the causality assessment, reports with missing event dates, age and gender were not eligible for analysis.

From the first quarter (Q1) of 2004 (representing the beginning of FAERS data with free availability) through to the third quarter (Q3) of 2013 (last available FDA data files, last accessed June 19 2014), tables including drug information (DRUG file), event date, age and gender of the patient (DEMO file) and adverse events coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology (REACTION file) were extracted. Because FAERS is mainly based on US reports, we used the US marketing dates as references to select the adequate post-marketing period.

Case and exposure definition

Building on previous multidisciplinary collaborative work from the DILI Network [22] and considering the two existing standardized MedDRA queries (SMQ: drug related hepatic disorders – comprehensive search; drug related hepatic disorders - severe events only), we identified the occurrence of a liver injury, both acute and chronic, as overall liver injury (OLI). According to the severity of the

disease, which has different clinical implications, we also identified an additional sub-category, named acute liver failure (ALF), a severe liver injury potentially reversible in nature and with onset of encephalopathy [23, 24], which may also include acute on chronic liver failure, a distinct clinical entity from ALF arising in patients with pre-existing chronic liver disease [25].

To this aim, we identified a list of MedDRA preferred terms (PTs), which are likely to represent medical events attributed to the drug by the reporter and codified in the FAERS database as DILI. Two groups of exposure of interest were considered: 1) exposure to NOACs (apixaban, dabigatran, rivaroxaban) and 2) exposure to warfarin, which served as a reference group. In this study, exposure assessment considered drugs recorded as 'primary suspect', 'secondary suspect' or 'interacting'.

Primary disproportionality analysis

First, a descriptive analysis of reports included in FAERS for the period of interest and mentioning NOACs or warfarin as primary suspect, secondary suspect or interacting was performed (i.e. total number of reports and other demographic information, including age and gender, reporter country and indication of use as recorded by reporters).

Second, disproportionality analyses were performed using the case-non case approach [26], which can be generally viewed as a case–control study, where controls are represented by all case reports unrelated to the event of interest (i.e. DILI) [27]. When used in a more advanced way (e.g. by dealing with selective reporting), disproportionality techniques provide valuable data to generate new knowledge, especially for rare and/or unpredictable safety issues [28, 29]. In our analysis, cases were reports with any pre-specified PT of interest (see above), and non-cases were all other reports without such PTs. As a measure of disproportionality, the reporting odds ratio (ROR) with relevant 95% confidence interval (95% CI) was calculated. The ROR is the ratio of the odds of reporting one specific event *vs*. all other events for a given drug compared with this reporting odds for other drugs present in the database. Basically, the higher the ROR value, the stronger the disproportion appears to be. A statistically significant ROR was formally defined as a lower limit of the 95% CI exceeding 1 [30]. We carried out different disproportionality analyses by using the US marketing approval as reference for selecting relevant datasets: Q3-2010 to Q3-2013 for dabigatran (3 year period), Q3-2011 to Q3-2013 for rivaroxaban (2 year period) and Q1-2013 to Q3-2013 for apixaban (9 month period). Analyses on warfarin were performed separately considering two time periods: 1) Q1-2004 to Q2-2010 (i.e. before dabigatran market approval in the US) and 2) Q3-2010 to Q3-2013 (after dabigatran market approval in the US).

Secondary disproportionality analysis

The reporting of bleeding events for dabigatran in the first year after US marketing approval was recently shown to be higher than expected (from pre-marketing pivotal trials) [31]. Therefore, the number of these reports may compromise the effective identification of other safety issues by under-estimating ROR. This is known as event competition bias [32]. To test this hypothesis, all reports mentioning bleeding were removed, no matter the exposure. We adopted a conservative approach without discriminating haemorrhagic events as to their clinical relevance (i.e. minor *vs*. major bleeding) or site of bleeding (gastrointestinal vs intracranial haemorrhage). These 'bleeding reports' were described with the following PT terms: 'haemorrhage', 'haemorrhagic', 'haemotoma', 'hematoma', 'bleed', 'haemoptysis', 'exsanguination' or 'haematoma', included in the SMQ haemorrhages [31]. In case both DILI PTs and bleeding PTs were simultaneously recorded in a given report, this report was retained, also considering the fact that bleeding could be a clinical manifestation of liver injury, especially in case of ALF.

We also tested for drug competition bias, potentially caused by the presence of reports related to well-established drug–event associations [33]. Specifically, we removed reports from FAERS related to amiodarone and dronedarone because they are widely known to be strongly associated with DILI, and they are expected to be frequently co-prescribed with NOACs in patients with NVAF and they may cause potential drug interactions (see below).

Case-by-case analysis

To assess qualitatively each individual DILI report, we carried out a case-by-case evaluation by focusing on concomitant medications. Three groups of drugs were identified:

1. Concomitant drugs with possible hepatotoxic potential (Group A drugs). Apart from amiodarone and dronedarone, additional hepatotoxic agents were identified according to the joint top 10 ranking obtained from previous publications on FAERS and Vigibase: paracetamol, atorvastatin, simvastatin, duloxetine, interferon beta-1, lamivudine, methotrexate, amoxicillin/clavulanate, bosentan, sorafenib, valproic acid, rifampicin, isoniazid, carbamazepine, erythromycin and cotrimoxazole [22, 24].
2. Concomitant drugs used as anti-hepatitis agents (Group B drugs). These compounds may cause an indication bias because they are prescribed to treat hepatic disease, which may cause *per se* liver dysfunction: boceprevir, telaprevir, ribavirin, lamivudine and interferon alfa.
3. Concomitant drugs that may cause potential drug interactions (Group C drugs). Different agents may increase plasma concentrations of NOACs by acting as P-gp and/or CYP3A4 inhibitors: azole antifungals, macrolide antibiotics, HIV protease inhibitors, ciclosporin, tacrolimus, dronedarone, amiodarone, quinidine, verapamil and diltiazem.

This analysis was automatically applied to all DILI reports, with a subsequent in-depth assessment of ALF on: outcome, other codified PTs, complete list of co-reported agents (no matter their suspected role in the DILI occurrence), dose, dechallenge and time to onset (i.e. by considering the date the event was recorded in comparison with the date the drug was started).

Results

Based on our selection criteria, 17 097 reports were extracted from FAERS where at least one NOAC was recorded as a suspect agent: 13 096 (dabigatran), 3985 (rivaroxaban) and 16 (apixaban). Overall, a slight female preponderance was found and most reports (approximately 75%) involved elderly patients (>65 years of age). Atrial fibrillation was the most frequent indication, especially for dabigatran (84% of total reports).

OLI reports represented 1.7% ($n = 222$) of all submitted reports for dabigatran, corresponding to 1.3% of all OLI reports recorded in FAERS during the relevant time period ($n = 17\,268$). For rivaroxaban, OLI reports ($n = 146$) represented 3.7% of all reports and 1.4% of all OLI reports ($n = 10\,222$) recorded in FAERS during relevant time period (Table 1). Only one case of liver injury was identified within the 16 total reports mentioning apixaban.

For dabigatran, primary disproportionality analysis found non-significant ROR, both for OLI (ROR = 0.65, 95% CI 0.57–0.75) and ALF definition (0.92, 95% CI 0.66–1.25). Conversely, for rivaroxaban, significant disproportionality was found for both groups of liver injuries: ROR = 1.59 (95% CI 1.34–1.88) and 2.08 (95% CI 1.34–3.08), OLI and ALF, respectively (Table 2).

Bleeding reports represented 31% of all reports for dabigatran. There was no evidence of a possible event competition bias (no modification in ROR estimates in secondary disproportionality analyses). As for rivaroxaban,

Table 1

Demographic information extracted from FAERS on NOACs and warfarin

Drug	Number of reports*	DILI reports (% total reports)	Age (% F/M)	Age (mean) (years)	Age >65 years (% on total reports)	Main recorded indications (% out of missing data)	Reporter country (%)
Dabigatran (Q3-2010 to Q3-2013)	13 096	222 (1.7%)	51/49	75	10 976 (84%)	Atrial fibrillation (84%), cerebrovascular accident prophylaxis (9%), anticoagulant therapy (5%), thrombosis prophylaxis (3%), other (1% each). Missing data in 9%.	US (68), EU (15), other (12), missing (5)
Rivaroxaban (Q3-2011 to Q3-2013)	3985	146 (3.7%)	52/48	71	2907 (73%)	Atrial fibrillation (49%), cerebrovascular accident prophylaxis (38%), thrombosis prophylaxis (23%), unknown indication (19%), knee arthroplasty and DVT (9%), hip arthroplasty (5%). Missing data in 2%.	US (53), EU (38), other (9)
Apixaban (Q1-2013 to Q3-2013)	16	1 (6.3%)	69/31	77	14 (88%)	Thrombosis prophylaxis (57%), unknown indication (57%), percutaneous coronary intervention (21%), atrial fibrillation (9%). Missing data in 13%.	US (50), EU (50)
Warfarin (Q1-2004 to Q2-2010)	9242	235 (2.5%)	42/58	69	6086 (66%)	Atrial fibrillation (47%), unknown indication (29%), DVT (14%), thrombosis prophylaxis (12%), anticoagulant therapy (11%), pulmonary embolism (9%). Missing data in 15%.	US (62), EU (14), other (5), missing (19)
Warfarin (Q3-2010 to Q3-2013)	4068	94 (2.3%)	43/57	71	2868 (71%)		

DVT, deep vein thrombosis. *Number of reports recorded for each drug under study (i.e. dabigatran, rivaroxaban, apixaban, warfarin) according to the period of interest.

Table 2

Primary disproportionality analysis

	Primary analysis: FAERS reports (different for each time period)				
	Number of total reports*	Number of reports ALF	ROR (95% CI) ALF	Number of reports OLI	ROR (95% CI) OLI
Dabigatran (Q3-2010 to Q3-2013)	676 335	41	0.92 (0.66–1.25)	222	0.65 (0.57–0.75)
Rivaroxaban (Q3-2011 to Q3-2013)	435 115	25	2.08 (1.34–3.08)†	146	1.59 (1.34–1.88)†
Warfarin (Q1-2004 to Q2-2010)	1 163 050	38	0.79 (0.56–1.09)	235	0.62 (0.55–0.71)
Warfarin (Q3-2010 to Q3-2013)	676 335	12	0.87 (0.45–1.52)	94	0.90 (0.73–1.11)

*Number of reports recorded in FAERS for all drugs in the database, according to the period of interest. †Statistically significant ROR (i.e. lower limit of the 95% confidence interval >1). ALF, acute liver failure; OLI, overall liver injury (see methods for details).

bleeding reports accounted for 36% of all reports. Removal of bleeding reports led to remarkably increased ROR for ALF (ROR = 3.10; 95% CI 2.00–4.61) and OLI (2.39; 2.02–2.84) associated with rivaroxaban. There was also no evidence of a drug-related competition bias for either dabigatran nor rivaroxaban (Table 3).

The case-by-case analysis on OLI reports revealed that furosemide was the most frequent agent ($n = 22$) co-recorded with both dabigatran (19% of OLI reports) and rivaroxaban (15% of OLI reports). While no mention was found for Group B drugs (i.e. anti-hepatitis agents) for either NOACs, many OLI reports contained at least one compound belonging to Group A or C (i.e. drugs with hepatotoxic potential or those that may cause drug interaction): 37% ($n = 83$) and 42% ($n = 61$) for dabigatran and rivaroxaban, respectively. As regards dabigatran, statins were recorded in 19% of reports (22 for simvastatin, 20 for atorvastatin), followed by amiodarone in 9% (a P-gp inhibitors found in 19 reports), paracetamol (6%, $n = 14$) and dronedarone (4%, $n = 9$). Concerning rivaroxaban, the top five ranking was paracetamol (14%, $n = 21$) simvastatin (10%, $n = 14$), amiodarone and clarithromycin (6%, $n = 9$) atorvastatin (6%, $n = 8$). Also acetylsalicylic acid (10%, $n = 21$) for dabigatran and pantoprazole (14%, $n = 20$), acetylsalicylic acid (13%, $n = 19$) and metoprolol (11%, $n = 16$) for rivaroxaban were frequently co-reported.

Detailed case-by-case analyses of reports where ALF events were recorded are provided as supplementary material (Supplementary Tables 1 and 2). Death occurred in 21 and 11 ALF reports (dabigatran and rivaroxaban, respectively), although it should be acknowledged that this clinical event may not be necessarily related to the drug. Although concomitant agents were recorded in most of reports, dabigatran was reported as a single suspect medication in 13 out 41 cases (32%), and rivaroxaban in eight out of 25 cases (32%). The latency of the event was recorded in 53% of ALF reports (39% for dabigatran and 76% for rivaroxaban). For dabigatran, a very rapid onset (i.e. <1 week) could be identified in seven out of 16 cases, of which four patients experienced an ultra-rapid onset (within the first day of administration), a rapid onset (i.e. 1 week to 1 month) in four cases and delayed onset (i.e. >1 month) in five reports. As regards rivaroxaban, we found a very rapid onset in nine out of 19 cases (four patients experiencing ultra-rapid onset), rapid and delayed onset in seven and three reports, respectively.

Discussion

To the best of our knowledge, this is the first post-marketing comparative safety study among NOACs on spontaneous reports of DILI. Only some recent case series analyses are becoming available for individual products [18, 34]. We exploited the largest publicly available SRS to gain insight into the current DILI profile of NOACs. While post-marketing reports for apixaban are still insufficient to draw firm conclusions (only 16 reports during initial 9 months of surveillance), there is a considerable amount of data for dabigatran and rivaroxaban. Based on our analysis, a disproportionality signal of DILI emerged for rivaroxaban, that was not found for dabigatran, even when potential competition biases were tested. For warfarin, we found a remarkable amount of bleeding reports (almost 50%), with a decline in the number of DILI reports after marketing approval of NOACs, which may be also be compatible with a documented decrease in US outpatient prescriptions [35].

Although actual incidence cannot be inferred from SRSs, the fact that dabigatran and rivaroxaban were reported in 1.7% and 3.7% of total reports of DILI extracted from FAERS suggests that the estimated risk could not be so uncommon as stated in the Summary of Product Characteristics (SPC). Relevant sections on adverse effects of the US and EU labels provide imprecise mention of their DILI profile. For dabigatran, the EU SPC includes liver enzyme alterations among uncommon side effects, whereas the US label does not mention this. Concerning

Table 3

Secondary disproportionality analysis

	Event-related competition bias (bleeding)				Drug-related competition bias (amiodarone/dronedarone)			
	Number of total reports*	ROR (95% CI) ALF	ROR (95% CI) OLI	Number of bleeding reports/total (%)	Number of total reports*	Number of cases (ALF/OLI)	ROR (95% CI) ALF	ROR (95% CI) OLI
Dabigatran (Q3-2010 to Q3-2013)	637 899	1.28 (0.91–1.74)	0.91 (0.79–1.04)	4115/13 096 (31%)	669 848	34/195	0.86 (0.59–1.20)	0.64 (0.55–0.74)
Rivaroxaban (Q3-2011 to Q3-2013)	409 983	3.10 (2.00–4.61)†	2.39 (2.02–2.84)†	1434/3985 (36%)	431 577	23/137	2.07 (1.31–3.13)†	1.61 (1.35–1.92)†
Warfarin (Q1-2004 to Q2-2010)	1 098 364	1.37 (0.97–1.88)	1.08 (0.95–1.24)	4101/9242 (44%)	1 153 623	29/210	0.65 (0.45–0.94)	0.59 (0.52–0.68)
Warfarin (Q3-2010 to Q3-2013)	637 899	1.62 (0.83–2.84)	1.70 (1.38–2.09)†	1983/4068 (49%)	669 848	6/80	0.47 (0.21–1.06)	0.83 (0.67–1.04)

*Number of reports recorded in FAERS for all drugs in the database, according to the period of interest. Data are different from those presented in Table 2, because of removal of certain reports to test competition bias (see methods for details). †Statistically significant ROR (i.e. lower limit of the 95% confidence interval >1). ALF, acute liver failure; OLI, overall liver injury (see methods for details).

rivaroxaban, hepatic dysfunction is listed as an uncommon reaction in the EU SPC, whereas the US prescribing information mentions unspecified post-marketing reports of jaundice and cholestasis [36–39]. According to published pre-marketing data on phase III studies, a featured analysis on eDISH plots including 6131 patients exposed to rivaroxaban found liver enzymes increased (ALT>3 × ULN) in 2.3% of patients [40]. Thus, the frequency of DILI reports for rivaroxaban highlighted in our post-marketing analysis is higher than expected and the ROR approximates that of drugs receiving warnings and/or precautions for serious liver injury (e.g. diclofenac, telithromycin) [5]. Notably, according to the latest US prescriptions [35] and our data, the raw reporting rates (i.e. the ratio between the number of DILI reports and dispensed prescriptions over the same time period) of rivaroxaban and dabigatran are broadly comparable (~150–400/1 000 000 prescriptions), suggesting DILI as rare/very rare events. Therefore, based on our findings, the SPCs of both drugs could be harmonized. As regards warfarin, our findings are in line with previous data from the German SRS, showing that hepatitis was documented in approximately 2% of adverse event reports, with a reporting rate of 16/1 000 000 [16].

When looking at the LiverTox database (http://livertox.nih.gov/, last accessed December 15 2014), a standard reference for clinicians, it is stated that '*Chronic therapy with dabigatran is associated with moderate ALT elevations…in 1.5% to 3% of patients, an overall rate which is slightly lower than with low molecular weight heparin and similar to the rates with warfarin*'. Our findings are in line with these data. However, it is also mentioned that '*Liver injury attributed to dabigatran… is usually mild and self-limited, resolving within 4 weeks of stopping*'. We found a non-negligible fraction of reports, especially ALF events, which resulted in death, without concomitant drugs increasing the likelihood of DILI occurrence, with very rapid time to onset, all clinical elements suggesting the importance of early recognition of signs/symptoms suggestive of liver injury (e.g., fatigue, jaundice), especially at the beginning of treatment. As regards rivaroxaban, the website does not actually provide any information.

This study, based on spontaneous reports, indicates a signal of liver injury with rivaroxaban. Therefore, because of its inherent limitations [41], signal detection is a hypothesis-generating approach and asks *per se* for additional analytical studies. These formal studies, such as population-based investigation, are needed to confirm and quantify the signal before any regulatory action other than information can be envisioned. In particular, this study cannot be used to quantify DILI risk because of (a) under-reporting and the lack of data on population exposure do not actually allow calculation of incidence rate and (b) the diagnosis mainly depends on a number of criteria, including the temporal relationship and the exclusion of other causes, which cannot be obtained with absolute certainty. This is especially true when time to onset is very short (e.g. less than 1 day), which almost always leads to the consideration that the drug responsibility hypothesis is less likely than any other potential aetiology. Moreover, additional drugs with underlying (but unknown) hepatotoxic potential cannot be ruled out, as well as residual confounders. A direct unbiased comparison between rivaroxaban and dabigatran is therefore challenging based on our data, especially because, as highlighted by the demographic information detailed in Table 1, dabigatran is more frequently reported in patients with NVAF, whereas an important proportion of reports for rivaroxaban occurred in patients with HKRS. This partially different clinical setting may explain the higher proportion of DILI reports and the disproportionality signal found for rivaroxaban. Our case-by-case analysis did not highlight additional elements that may increase the likelihood of DILI occurrence in patients undergoing rivaroxaban therapy.

Nonetheless, our analysis has some strengths. It corroborated a recent analysis on spontaneous reports [18] and confirmed a DILI signal for rivaroxaban, both for ALF and OLI. In addition, we gained insight into the reporting pattern of NOACs in a consolidated clinical setting. Notably, SRSs also represents a hypothesis-generating source of information to highlight foci of possible inappropriate drug prescriptions [42]. Our data denoted that more than one third of DILI reports of rivaroxaban and dabigatran co-listed possible hepatotoxic and/or interacting drugs. This is in line with a recent pharmacovigilance study by McDonald *et al*. [34], which found that in 30 to 50% of reports submitted to the FDA, Canada and Australia, at least one concomitant prescription may have increased the risk of bleeding in patients receiving dabigatran therapy. From a pharmacological standpoint, this suggested that pharmacodynamic and pharmacokinetic drug interactions, as well as comorbidities, may have a contributing role in the occurrence of DILI in a large proportion of cases. From a clinical standpoint, it denotes how actual practice is complicated and sometimes differs from precautions stated in the SPC (the label emphasized that the use of concomitant strong P-gp/CYP inhibitors is not recommended for dabigatran, and should be even avoided for rivaroxaban on a pharmacokinetic basis [43]). As a matter of fact, patients with NVAF are likely to be treated with amiodarone or dronedarone as well as furosemide for AF-related worsening heart failure.

The mechanisms of possible NOAC-related hepatotoxicity are unknown but it is likely to be an idiosyncratic and/or immune-mediated reaction. Considering that DILI is unpredictable according to the drug's mechanism of action and that NOACs are essential medicines for which no antidote is currently available, physicians should focus on recognition of signs/symptoms suggestive of severe liver

injury (e.g. fatigue, jaundice) especially in complex patients taking multiple medications, who should be re-assessed for concomitant treatments that may pose possible hepatotoxic/interacting potential. In the case where a diagnosis of DILI is formulated and potential responsibility is attributed to rivaroxaban, physicians should immediately discontinue the drug, paying attention to the possible need of continued anticoagulation.

Conclusion

In summary, the spontaneous reporting pattern of DILI with NOACs results in (1) a previously unreported disproportionality signal for rivaroxaban, (2) a non-negligible fraction of DILI reports attributed to dabigatran and rivaroxaban with fatal outcome (49% of ALF reports) and (3) a substantial proportion of DILI reports (39%) with concomitant hepatotoxic and/or interacting drugs, which may require clinical judgment on a case-by-case basis.

These signals should not be intended as alarms or even alerts [19], but should stimulate continued vigilance with NOACs, and further research to establish actual event rates and identify risk factors that might lead to proper risk management. In the meantime, the variegate marketing launch of the different NOACs and their increasing utilization in the outpatient setting suggest that further monitoring is warranted (especially for apixaban) and strengthens the role of SRSs as a crucial source to detect rare and previously undocumented drug-related hepatotoxicity.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). ER, EP, AK, FS, AP, MB, UM, FDP declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. NM has had interactions with many pharmaceutical companies in the previous 3 years, both personal and for the department of Pharmacology of Bordeaux (see www.pharmacoepi.fr), but none relevant to this paper.

Contributors

ER conceived and designed the study, provided guidance on data analysis during the whole study and drafted the first version of the manuscript, EP, FS, AP, MB, UM, NM provided substantial contribution to the study design and data analysis, AK extracted data and performed statistical analysis and FDP supervised the project and is guarantor for the study. All authors provided substantial contribution to data interpretation and their discussion. They critically revised the content and approved the final version of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1
Tabular listing of information extracted for ALF reports where dabigatran was recorded as suspect.
Appendix S2
Tabular listing of information extracted for ALF reports where rivaroxaban was recorded as suspect.