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REVIEW ARTICLE

Hepatotoxicity of New Oral Anticoagulants (NOACs)

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Abstract Case reports and analyses of clinical studies and of pharmacovigilance data suggest that new oral anticoagulants (NOACs) are associated with a small risk for hepatotoxicity. The objective of this publication is to summarize the current data about this subject, with a special emphasis on pharmacovigilance data in the World Health Organization (WHO) Global Individual Case Safety Reports (ICSR) database and on potential mechanisms of hepatotoxicity. For that, all available case reports as well as published analyses of clinical studies were obtained with a detailed search in PubMed. In addition, pharmacovigilance data from VigiBase®, the WHO Global ICRS database, were extracted and analyzed. The data show that liver injury associated with NOACs was reported in clinical studies and in pharmacovigilance databases. Several case reports described potentially life-threatening hepatotoxicity in patients treated with rivaroxaban or dabigatran. For rivaroxaban, most affected patients were symptomatic and liver injury was most often hepatocellular or mixed. The frequency was between 0.1 and 1 % in clinical studies and was by trend lower than for comparators (mostly enoxaparin or warfarin). Comparing the pharmacovigilance reports for the individual NOACs, more hepatic adverse events were reported for rivaroxaban than for dabigatran or apixaban. With the exception of edoxaban, for which only few reports are available, patients with acute liver failure have been reported for every NOAC, but most patients had concomitant drugs or diseases. So far, there are no clear mechanisms explaining the hepatotoxicity of these drugs. We conclude that hepatotoxicity appears to be associated with all NOACs currently on the market. Hepatotoxicity associated with NOACs is idiosyncratic; it appears at therapeutic doses, is rare and the mechanism is not related to the pharmacological action of these drugs. Prescribers should inform patients about possible symptoms of hepatotoxicity and stop these drugs in patients presenting with severe liver injury.

Key Points

Liver injury has been reported in case reports, clinical studies or in the World Health Organization (WHO) pharmacovigilance database of spontaneous reports for every currently marketed new oral anticoagulant (NOAC).

For rivaroxaban, apixaban and dabigatran, 1.8–3.9 % of the spontaneous reports in the WHO database concerned liver injury, with 3–12 % of these reports implying potentially fatal liver failure.

The small risk for potentially serious liver injury should be known to prescribers and adequately be communicated to patients treated with NOACs.

Some data for this work were obtained from the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. Data from spontaneous reporting are inhomogeneous as a result of different reporting policies worldwide and are vulnerable to underreporting and reporting bias. The information contained in this work is therefore not homogeneous, at least with respect to origin and also to likelihood that the pharmaceutical product caused the adverse reaction. The conclusions drawn on the basis of these data do not necessarily represent the opinion of the WHO.

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1 Introduction

After many years of vitamin K antagonists as the only oral drug class for preventing thromboembolic events, several new oral anticoagulants (NOACs) that directly target the enzymatic activity of thrombin or factor Xa have been developed and brought to the market over the past few years. These new substances offer advantages over vitamin K antagonists; for instance, they are active already after the first dose and have predictable pharmacokinetics, enabling a fixed dose and making laboratory monitoring in the majority of patients unnecessary.

The first NOAC on the market was ximelagatran, which was approved in many countries for primary prophylaxes of deep vein thrombosis after orthopedic surgery. Similar to dabigatran, ximelagatran was an orally administered direct thrombin inhibitor [1]. The protective effect of ximelagatran after orthopedic surgery had been shown in large clinical trials [2, 3]. Ximelagatran was a prodrug that had to be converted to melagatran to be systemically available and to be clinically active. During short-term trials, the safety was acceptable. However, when indications with a longer treatment duration such as treatment and secondary prophylaxis of deep vein thrombosis or stroke prevention in atrial fibrillation (AF) were investigated, approximately 8 % of the patients treated with ximelagatran developed alanine aminotransferase (ALT) elevations greater than three times the upper limit of normal (ULN) [4]. In patients with liver injury, the increase in transaminases occurred in more than 90 % between 1 and 6 months after the start of treatment. In most patients, transaminases normalized irrespective of whether the treatment was stopped or continued, suggesting that patients could become tolerant to liver injury associated with this drug. The mechanism of this type of toxicity is still now not entirely clear. Ximelagatran and melagatran showed no relevant toxicity in vitro and in experimental animals [5]. Since some workers producing the drug developed skin eruptions during the production process and ALT elevations were more frequent in the Scandinavian than in the Asian population, immunological mechanisms were postulated [6]. A genome-wide pharmacogenetic study in 74 patients with ALT elevations and 130 patients exposed to ximelagatran without ALT elevation revealed an association with the major histocompatibility complex (*MHC*) alleles *DRB1**07 and *DQA1**02, suggesting an immunological mechanism [6]. In favor of an immunological mechanism were also the abovementioned ethnic differences in the frequency of ALT elevations, which correlated with the distribution of *DRB1**07, skin reactions of workers producing ximelagatran, species specificity and positive lymphocyte transformation tests in some affected individuals [6]. The company producing ximelagatran also performed a metabolomic and proteomic study in the plasma of 46 patients with ALT elevation and in 94 patients exposed to ximelagatran but without ALT elevation [7]. They found an increased plasma concentration of CSF1R, the receptor for the macrophage colony stimulating factor 1 (CSF1), a cytokine that controls macrophage proliferation, differentiation and function. This finding indicated macrophage activation, and further favored an immunological mechanism, taking into account also the abovementioned association with the *MHC* alleles *DRB1**07 and *DQA1**02 [7]. On the other hand, the plasma pyruvate concentration was lower in affected compared with non-affected patients, a finding compatible with a metabolic cause for the observed hepatotoxicity of ximelagatran [7]. Taking into account the possible risks associated with hepatotoxicity of ximelagatran, the company withdrew the drug from the market and stopped all investigations in 2006.

The new NOACs were therefore preclinically and clinically thoroughly investigated regarding the possibility of hepatic and, of course, other toxicities. The NOACs currently approved and in use in many countries are the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban. Rivaroxaban is approved for prevention of atherothrombotic events after an acute coronary syndrome; all four are approved for deep venous thrombosis/pulmonary embolism (DVT/PE) treatment and prevention and for prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors. In addition, all four are approved for the prevention of DVT/PE in adult patients undergoing hip/knee replacement surgery, except edoxaban, which is approved for this indication only in Japan. The four currently marketed NOACs are pharmacokinetically characterized in Table 1.

Dabigatran is a hydrophilic drug that shows almost no intestinal absorption and therefore has to be administered as the prodrug dabigatran etexilate, reaching an oral bioavailability in the range of 7 %. Dabigatran is partially glucuronidated and is not a substrate of cytochrome P450 enzymes (CYPs). Both dabigatran and its glucuronide metabolite are active and are eliminated by the kidneys. Furthermore, dabigatran is a substrate of P-glycoprotein (P-gp). Dose adjustment therefore has to be considered in patients with impaired renal function and in patients treated with strong P-gp inhibitors. Since studies in patients with liver cirrhosis are lacking, dabigatran should not be used in this group of patients.

In comparison to dabigatran, the factor Xa inhibitors are more lipophilic drugs and are therefore CYP substrates, mainly of CYP3A4. They all have a good oral bioavailability and the metabolites generated are inactive. Despite

Table 1 Pharmacological characterization of NOACs

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Application	Oral (q24 h)	Oral (q12 h)	Oral (q24 h)	Oral (q12 h)
Bioavailability (%)	80–90	60–70	60	7
T_{max} (h)	2–4	3–4	1–2	1–3
Protein binding (%)	95	85	50	35
Metabolism	CYP3A4 substrate (inactive metabolite)	CYP3A4 substrate (inactive metabolite)	Carboxylesterase 1, CYP3A4 (minor)	Hydrolysis and glucuronidation (glucuronide is active)
P-gp substrate	Yes	Yes	Yes	Yes
Half-life (h)	5–9 (young adults) 10–13 (elderly)	8–15	10–14	12–17
Elimination	~40 % of bioavailable dose unchanged renally (Q_0 ~0.60)	~40 % of bioavailable dose unchanged renally (Q_0 ~0.60)	~50 % of bioavailable dose unchanged renally (Q_0 ~0.5)	~70 % of bioavailable dose unchanged renally (Q_0 ~0.30)
Interaction potential	CYP3A4/P-gp inhibitors	CYP3A4/P-gp inhibitors	P-gp inhibitors	P-gp inhibitors

The data are mainly based on the publications of Ufer [45], Gong and Kim [39], Mueck et al. [46], Harder and Graff [40] and the FDA labeling of the respective drugs

CYP cytochrome P450 enzyme, *NOAC* new oral anticoagulant, *P-gp* P-glycoprotein, Q_0 extrarenal dose fraction ($1-Q_0$ is the fraction of a drug which is eliminated non-metabolized renally), T_{max} the time after administration of a drug until the maximum plasma concentration is reached, *q24h* dosing interval 24 h, *q12h* dosing interval 12 h

metabolism by CYP3A4, approximately 40 % of the absorbed drug is eliminated unchanged by the kidneys. Dose adjustment therefore has to be considered in patients with impaired renal function and also in patients treated with strong CYP3A4 inhibitors or inducers. Although the half-life of the four currently marketed NOACs is in a similar range (8–17 h in adults), rivaroxaban and edoxaban were developed for once- and apixaban and dabigatran for twice-daily dosing. As expected, the amplitude of the plasma concentration–time curve is larger for the compounds with once- as compared with those with twice-daily dosing [8]. The factor Xa inhibitors can be used in patients with Child A or B liver cirrhosis but are contraindicated in Child C cirrhosis.

2 Definition and Principle Mechanisms of Hepatotoxicity

Drug-induced liver injury (DILI) is one of the most common drug-related adverse reactions and can result in acute liver failure, which may require emergency liver transplantation or may end fatally. The diagnosis of DILI is challenging, since specific clinical and biochemical biomarkers are lacking, the evaluation of liver histology may not be diagnostic, and there are other causes that can be associated with similar findings, such as treatment with other drugs or concomitant liver diseases [9]. The assessment of suspected DILI cases consists therefore of two major diagnostic processes: the exclusion of other causes that may result in similar clinical and biochemical pictures and the identification of a pattern of disease manifestations that is temporally related to exposure to the suspected drug [10].

A first, rather broad definition of DILI included a twofold or greater elevation above the ULN of ALT activity (hepatocellular liver injury), a twofold or greater elevation above the ULN of the activity of alkaline phosphatase activity (cholestatic liver injury) or a value of the ratio of the elevation above the ULN for ALT and for alkaline phosphatase of <5 and >2 (mixed liver injury) [11].

This definition turned out to be too sensitive for hepatocellular liver injury and was therefore modified in 2011 by an international DILI expert working group [12]. This group defined hepatocellular injury as a fivefold or greater elevation above the ULN for ALT, whereas the definitions of cholestatic (twofold or greater elevation above the ULN for alkaline phosphatase with concomitant elevation of the activity of 5′-nucleotidase or γ-glutamyltranspeptidase) and of mixed liver injury were the same as proposed by Benichou [11].

These classifications provide information about the clinical picture of liver injury, but not about the underlying mechanisms. With rare exceptions, e.g., for liver injury associated with paracetamol overdose, drug-induced liver injuries are idiosyncratic (or type B) adverse drug reactions [13]. Idiosyncratic drug-induced liver injuries are adverse drug reactions that are rare, appear at therapeutic doses and are not related to the pharmacological action of a specific drug. Since idiosyncratic drug reactions appear at therapeutic doses, affected patients must carry susceptibility factors that are rendering them more susceptible.

Mechanistically, there are two large groups, namely immunological and non-immunological (also called metabolic) idiosyncratic adverse drug reactions [13]. As shown for flucloxacillin [14, 15], abacavir [16] or lumiracoxib [17], certain human leukocyte antigen (*HLA*) constellations, e.g., the presence of *HLA-B**5701, are known susceptibility factors for immunological idiosyncratic adverse drug reactions. Regarding metabolic idiosyncratic adverse drug reactions, susceptibility factors include, for instance, underlying metabolic diseases, mainly causing disturbances of mitochondrial metabolism. As an example, impaired function of the mitochondrial respiratory chain [18] and impaired function of DNA polymerase γ [19] have been reported to be susceptibility factors for valproate-associated liver failure. In experimental animals, impaired mitochondrial β-oxidation has been reported to be a risk factor for valproate [20] or for dronedarone-associated [21] liver injury. Another example is liver inflammation, which has been reported to be a susceptibility factor for liver injury associated with fluoroquinolones in experimental animals [22].

3 Hepatotoxicity of NOACs in Clinical Trials

The first safety alerts associated with new drugs can, in many cases, already be made during the clinical phase of drug development. Dose-dependent (type A or intrinsic) adverse drug reactions are usually known already from preclinical and early clinical (phase I and phase II) studies. Since idiosyncratic reactions are rarer and are not predictable by the pharmacological properties of a certain drug, they are much more difficult to detect during the clinical development phase of a drug. The "rule of three" states that if a certain event did not occur in a sample of 3000 subjects, it can be concluded with 95 % confidence that fewer than one subject in 1000 (3/3000) will be affected [23]. This means that large populations have to be studied to detect events with a frequency of 1:1000 up to 1:10,000, which is typical for idiosyncratic drug reactions. Such reactions are therefore mostly detected when the drug is on the market.

Nevertheless, hepatotoxicity has been described as an adverse event in clinical studies with NOACs. Watkins et al. [24] studied adverse events of four randomized controlled studies in which patients were randomized to rivaroxaban or enoxaparin after knee or hip replacement surgery for primary prevention of DVT. A total of 12,262 patients were included, approximately 6000 in each group. The authors analyzed the data using the eDISH approach (evaluation of Drug-Induced Serious Hepatotoxicity). For that, they calculated the maximal values for ALT activity and serum bilirubin (both expressed per ULN) for every patient and plotted the values in a diagram with log serum ALT activity on the abscissa and log serum bilirubin on the ordinate. According to Aithal et al. [12], ALT activities $\geq 3 \times$ ULN and bilirubin concentrations $\geq 2 \times$ ULN were judged as pathological. Like that, they could group the values in four quadrants. A total of 143 patients treated with rivaroxaban (2.3 %) had an ALT elevation $\geq 3 \times$ ULN with normal bilirubin (3.6 % in the enoxaparin group). Importantly, nine patients treated with rivaroxaban and eight patients treated with enoxaparin had an ALT with concomitant bilirubin elevation, potentially fulfilling Hy's rule [25, 26]. In six out of the eight patients in the rivaroxaban group, alternative explanations were likely, but two of them were judged as probably rivaroxaban associated. The study therefore suggested that rivaroxaban may rarely be associated with potentially severe liver injury in patients treated with this drug.

In a recent systematic review and meta-analysis of phase III randomized controlled trials [27], the liver safety of NOACs was evaluated. The NOACs evaluated were apixaban, dabigatran, darexaban, edoxaban and rivaroxaban. Only phase III randomized controlled trials were included, in order to avoid bias by small size and therefore underpowered studies. The primary outcome was the frequency of DILI, defined as the combined increase of serum transaminases (defined as $\geq 3 \times$ ULN of ALT or AST) and total bilirubin ($\geq 2 \times$ ULN). Secondary outcomes were the frequency of transaminase elevation $\geq 3 \times$ ULN, and the frequency of bilirubin elevation $\geq 2 \times$ ULN. The patients' mean age varied between 55 years and 71 years, and approximately 30 % of the patients had AF. The mean follow-up was 16.4 months (range 2 weeks to 2 years). Low-molecular weight heparin (LMWH) was the most common control group, as it was included in 41 % of the studies. The pooled analysis of 25 studies showed that NOACs as a group did not show an increased risk of DILI compared with the control group (LMWH, vitamin K antagonists, placebo or non-pharmacological treatment, depending on the study). Similar results were obtained for each individual NOAC. The frequency of DILI in patients treated with NOACs was in the range of 0.1–1 %, which was, by trend, lower than in active control groups. NOACs were less likely than the combined control treatments to be associated with transaminase elevations $\geq 3 \times$ ULN [relative risk (RR) 0.79; 95 % confidence interval (CI) 0.70–0.90]. This 'protective' effect was larger if compared only with LMWH. Pooled results from trials with LMWH as a control treatment showed a 29 % risk reduction (RR 0.71; 95 % CI 0.59–0.85) of transaminase elevations in patients treated with NOACs. In comparison, the frequency of bilirubin elevation $\geq 2 \times$ ULN was not different between patients treated with NOACs compared with the combined control treatments (RR 0.93; 95 % CI

0.59–1.48). According to these results, NOACs do not appear to be associated with a higher risk of DILI than the control treatments and may have a lower risk for ALT elevation compared with treatment with LMWH.

However, according to the "rule of three," the number of patients included in clinical trials is often insufficient to reliably detect risks of rare idiosyncratic adverse reactions such as drug-induced liver disease. Further limitations of the evaluation of clinical trials' results include that patients with potential risk factors such as pre-existing liver disease are often excluded from the trials and that the duration of treatment in trials is usually shorter than when the drug has been approved.

Therefore, although important data can be derived from the premarketing phase, postmarketing surveillance including postmarketing studies are required to overcome the limitations mentioned above and to provide more comprehensive safety data.

4 Postmarketing Hepatotoxicity of NOACs

Since NOACs are new drugs and only rarely associated with hepatotoxicity, there are only few postmarketing data concerning hepatotoxicity of these drugs. There are more data for rivaroxaban than for the other NOACs, which is understandable taking into account that rivaroxaban has currently the highest market share of all NOACs [28].

Postmarketing data can be communicated in several ways. One way is to publish case reports, case series or case control studies. Another way is to obtain and analyze data from spontaneous reports to drug authorities or to the pharmaceutical companies marketing these drugs. Regarding hepatotoxicity associated with NOACs, both ways have been pursued.

4.1 Search of Databases for Postmarketing Safety Data of NOACs

Case reports and case series were searched in PubMed using the terms (rivaroxaban OR apixaban OR edoxaban OR dabigatran OR NOAC) AND (liver disease OR liver injury OR liver toxicity OR liver failure OR hepatitis) without any restriction regarding language. The search was performed on May 23, 2015, and yielded 45 references, which were checked manually for relevance. Seven references [29–35] were considered to be relevant concerning postmarketing liver injury data.

Concerning spontaneous reports, we searched VigiBase®, the World Health Organization (WHO) Global Database of Individual Case Safety Reports (ICSR), using VigiLyze™ as a search tool. The search was performed on February 6, 2015. For each NOAC, we identified all spontaneous reports and filtered them for the WHO Adverse Reaction Terminology (WHO-ART) System Organ Class "liver and biliary disorders". For more precise filtering down the hierarchy of WHO-ART, we applied four high-level terms (HLTs) containing the indicated preferred terms (PTs): HLT "hepatic failure," containing PTs coma hepatic, hepatic failure; HLT "hepatic function abnormal," containing PTs alkaline phosphatase decreased/increased, ALT increased, AST increased, gamma-GT increased, hepatic enzymes increased, hepatic function abnormal; HLT "hepatocellular damage," containing PTs cirrhosis biliary, hepatic cirrhosis, hepatic necrosis, hepatitis, hepatitis cholestatic, hepatitis chronic active, hepatocellular damage, hepatorenal syndrome, liver fatty; and HLT "jaundice," containing PTs bilirubinemia, jaundice. The HLTs "biliary tract disorder," "gallbladder disorder," "hepatitis infectious" and "other liver and biliary disorders" were omitted. For each NOAC, the reports were analyzed for gender distribution, age, seriousness, fatal outcome and the respective NOAC being the sole reported suspected drug. From these data, death rates among spontaneous reports were calculated and stratified for specific HLTs where applicable.

4.2 Case Reports and Case Series

For rivaroxaban, four case reports or case series have appeared, reporting in total 22 independent patients with possible or probable liver injury.

In a first publication, 14 patients with rivaroxaban-associated liver injury that had been reported to a regional Pharmacovigilance Center in Switzerland were described [35]. The patients had a median age of 71 years (range 41–91 years), nine were female and five male. Four patients were treated because of AF and ten patients for knee joint replacement or leg surgery. The median dose was 10 mg/day (range 10–20 mg/day), and the latency period was 15.5 days (range 3–62 days). All but one patient had symptoms of liver disease; 11 of them were jaundiced. The ALT was $>2 \times$ ULN in all patients, with a median of $7.8 \times$ ULN (range 2.5–53.7). The alkaline phosphatase was $<2 \times$ ULN in five patients and $>2 \times$ ULN in nine patients, median $2.5 \times$ ULN (range 1–7.8). Eight patients had hepatocellular, four cholestatic and one mixed liver injury. The serum bilirubin concentration was determined in ten patients; the median was $6.6 \times$ ULN (range 1–21.6). The causality assessment using the Roussel Uclaf Causality Assessment Method (RUCAM) score was highly probable in four, probable in seven and possible in three patients. One patient died, while all other patients recovered.

Two patients were biopsied; both of them had cholestatic liver injury. In agreement with the clinical judgment, major findings were centroacinar cholestasis with focal ballooning of hepatocytes, portal infiltration with mainly

lymphocytes and eosinophilic granulocytes and alterations in the biliary epithelium with lymphocyte infiltration.

The authors also performed searches in three large international pharmacovigilance databases. The database of the WHO [WHO Uppsala Monitoring Centre (UMC) VigiBase®] contained 179 reports that were compatible with DILI for which rivaroxaban was reported as a suspected cause. The database of the European Medicines Agency (EMA) (Eudra-Vigilance) contained 375 events within 21 selected hepatobiliary MedDRA reaction terms for which rivaroxaban was a suspected cause. Finally, the database of the US Food and Drug Administration (FDA) [FDA Adverse Event Reporting System (FAERS)] contained 87 cases within the 21 MedDRA terms mentioned above.

In a second case report, again from Switzerland, two patients with liver injury associated with rivaroxaban were described [32]. Both patients, a 52-year-old man and a 73-year-old woman, were treated with 10 mg of rivaroxaban after leg surgery and knee joint replacement, respectively. They presented with jaundice 1–2 months after starting rivaroxaban. Both had massively increased transaminases and a slight increase in alkaline phosphatase. One of them had hepatocellular and the other one mixed liver injury. The causality was judged as probable for one and possible for the other one. Both had a full clinical recovery 2 weeks after stopping rivaroxaban.

A liver biopsy was performed in the patient with hepatocellular liver injury. The lobular architecture was preserved, and there was a minimal lymphocytic infiltrate in the portal fields without disturbance of the architecture or lymphocytic infiltration of the bile ducts. The key finding, which explains the hepatocellular pattern in this patient, was a confluent centroacinar necrosis of hepatocytes, which was associated with infiltration of macrophages.

In a third publication, five patients with possible, probable or highly probable liver injury associated with rivaroxaban have been described [31]. Only one of them had symptomatic liver injury; three of them had a hepatocellular and two a cholestatic pattern. The onset of liver injury was between 2 and 3 days after initiation of treatment in all patients. All patients recovered without sequelae.

In an additional publication, a 77-year-old man with a history of antiphospholipid antibody syndrome was switched from warfarin to rivaroxaban [29]. After 6 weeks, he presented with unspecific symptoms of liver disease, morbilliform skin eruptions and arthralgia. Co-medication included ezetimibe, valsartan and hydrochlorothiazide. He had increased serum transaminases, alkaline phosphatase, bilirubin and creatinine values, as well as leukocytosis and eosinophilia (600 cells/μL). The liver biopsy revealed non-zonal areas of necrosis without viral inclusions and a mild inflammatory infiltrate in portal fields with sporadic eosinophils or plasma cells. A diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome was made and the patient treated with prednisone. The patient clinically and biochemically improved or even normalized over the subsequent 3 weeks.

For dabigatran, so far, two patients who developed liver injury while being treated with this drug have been reported. A 71-year-old man with AF was treated with dabigatran for stroke prevention [34]. After 1 month of treatment, he presented with jaundice and malaise. ALT activity was 14 × ULN, alkaline phosphatase 5 × ULN and serum bilirubin 21 × ULN, allowing the clinical diagnosis of mixed liver injury with bilirubin elevation. Allergic features such as eosinophilia or skin eruptions were not reported, and a liver biopsy was not obtained. Treatment with dabigatran was stopped, and the patient recovered within the following 2 weeks. The second patient was an 86-year-old lady who was hospitalized with pyelonephritis and acute renal failure [30]. She was treated with dabigatran because of permanent AF. During hospitalization, she developed hepatocellular injury with slight elevation of serum bilirubin. Dabigatran was stopped, and she recovered within days. Allergic features were not described, and a liver biopsy was not obtained in this patient.

To the best of our knowledge, no reports have been published for apixaban or edoxaban.

4.3 Spontaneous Reports

Spontaneous reports originate mostly from health professionals and are transmitted to regional or national pharmacovigilance centers or to the pharmaceutical companies marketing the drugs. The national pharmacovigilance centers collect all spontaneous reports and send them to the WHO Collaboration Centre for International Drug Monitoring in Uppsala (UMC). The causality of these reports is judged by the pharmacovigilance centers and/or the pharmaceutical companies marketing these drugs. However, spontaneous reports are often incomplete, rendering the causality assessment difficult. Furthermore, the frequency of a certain adverse reaction cannot be estimated on the basis of spontaneous reports, since neither the number of patients affected by an adverse event nor the number of patients exposed to a certain drug is usually known. Nevertheless, spontaneous reports can generate signals of possible adverse reactions, which can subsequently be followed more closely.

Most recently, an analysis of spontaneous reports concerning hepatic adverse events associated with NOACs that have been transmitted to the FAERS (mainly containing spontaneous reports from the USA) has been published [33]. First, all reports concerning NOACs were extracted, and then the reports describing DILI were obtained and

assessed. Reports about acute liver failure were investigated as a special subgroup. In total, 17,097 reports associated with NOACs were extracted. A total of 13,096 reports were associated with dabigatran, 3985 with rivaroxaban and 16 with apixaban. The fraction of the reports concerning DILI was 3.7 % (147 reports) for rivaroxaban and 1.7 % for dabigatran (223 reports). For apixaban, the total number of reports was too small to draw firm conclusions. Females and elderly patients (>65 years of age) were overrepresented in the cohort with DILI compared with patients without DILI. Concomitant use of potentially hepatotoxic and/or interacting drugs (in particular, paracetamol, statins, amiodarone and other CYP3A4/P-gp inhibitors) was reported in more than one-third of the DILI cases for both rivaroxaban and dabigatran. A disproportionality analysis indicated a higher risk for DILI for rivaroxaban than for dabigatran or warfarin, which served as a control. In total, there were 41 cases with acute liver failure for dabigatran (18 % of all cases with DILI) and 25 for rivaroxaban (17 % of all cases with DILI). Thirteen patients treated with dabigatran (32 % of the cases with acute liver failure) had no other drug treatment. For rivaroxaban, eight patients (32 % of the cases with acute liver failure) had no other drug treatment. The number of patients with acute liver failure who died was 21 (51 %) for dabigatran and ten (40 %) for rivaroxaban.

Since Raschi et al. [33] analyzed and reported US data, we were interested to compare these data with the reports from the WHO database VigiBase®. The results from our search of the WHO database are shown in Table 2.

For dabigatran, the WHO database contained a total of 33,369 reports, among them 605 (1.8 %) reporting liver or biliary disorders. After narrowing the search to hepatic failure, hepatic function abnormal, hepatocellular damage or jaundice, there were still 546 reports. Approximately two thirds of the reports (361 reports) were labeled "serious."

Concerning rivaroxaban, 801 reports with liver or biliary injury were found out of a total of 20,295 reports regarding this drug (3.9 % of all reports). Narrowing the search resulted still in 775 reports. In 652 cases, the injury was graded "serious."

Regarding apixaban, the WHO database contained a total of 3710 reports, among them 79 (2.1 %) concerning liver or biliary disorders. After narrowing the search, 73 cases remained. In 56 reports, the condition was graded as "serious."

Concerning edoxaban, the WHO database contained only 63 reports, among them seven (11 % of all reports) falling into the category liver or biliary injury. All of the seven cases of liver or biliary injury were reports from Japan, since, until January 2015, Japan was the only country where edoxaban was approved for clinical use. Six of the seven cases were reported to be "serious."

Sixty patients treated with rivaroxaban (7.7 % of the patients with a specific hepatic event) developed liver failure and 17 patients died (28 % of the patients with liver failure). For dabigatran, 67 patients developed liver failure (12 % of the patients with a specific hepatic event) and 22 of these patients died (33 % of patients with liver failure). Two patients treated with apixaban and none of the patients treated with edoxaban developed liver failure. In more than a third of the patients, the NOAC was the only drug in patients developing liver failure, and in more than 80 %, the only suspected drug. It has to be taken into account, however, that most patients developing liver failure while being treated with an NOAC had concomitant diseases that may have contributed to liver injury.

5 Potential Mechanisms of NOAC-Associated Liver Toxicity

So far, there are no published data regarding possible mechanisms of hepatotoxicity associated with NOACs. In the assessment report of rivaroxaban of the EMA (EMA CHMP assessment report for Xarelto®, Procedure No. EMEA/H/C/000944), liver toxicity was observed in all three animal species investigated (mice, rats and dogs) after repetitive dosing. Mice were the most sensitive species, showing increased transaminases and focal liver necrosis already at the lowest doses. In the rat, a transient increase in transaminases with periacinar hepatocellular lesions and a periportal inflammatory infiltrate were the main findings at high doses. In the dog, increased transaminases were observed in both a 4-week and 52-week study. Histologically, periportal vacuolation and centrilobular fat was detectable.

Four liver biopsies from four patients with liver injury associated with rivaroxaban have so far been reported. In two biopsies, centroacinar cholestasis in combination with bile duct injury and lymphocytic and eosinophilic portal infiltrates were the main findings [35]. In a third biopsy, focal non-zonal areas of hepatocyte necrosis and mild portal infiltrates with sporadic eosinophil granulocytes were the main findings [29]. This patient had eosinophilia, skin eruptions and impaired renal function, compatible with a DRESS syndrome. The fourth biopsy showed centroacinar confluent necrosis with only a mild lymphocytic portal infiltration [32].

The findings in the report of Russmann et al. [35] with a dominant portal lymphocytic and eosinophil infiltrate were compatible with an allergic reaction. This is supported by the findings of Barrett et al. [29], who diagnosed a DRESS syndrome in their patient, which is considered as an HLA-associated cellular hypersensitivity reaction [36, 37]. On the other hand, exposure-dependent hepatotoxicity was a clearly

Table 2 Adverse events reported to the WHO Collaboration Centre for International Drug Monitoring in Uppsala (Uppsala Monitoring Centre)

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Total reports, *n*	20,295	3710	63	33,369
Liver and biliary disorders, *n* (% of total)	801 (3.9)	79 (2.1)	7 (11)	605 (1.8)
SHEs				
Number (% of total reports)	775 (3.8)	73 (2.0)	7 (11)	546 (1.6)
Gender, F/M/unknown	389/343/43	27/41/5	7/0/0	241/273/32
Age, mean (range)	70 (20–98)	72 (48–95)	77 (65–78)	73 (18–93)
Death rate, *n* (%)	37 (4.8)	4 (5.5)	0	51 (9.3)
Liver failure				
Number of patients, *n* (% of SHEs)	60 (7.7)	2 (2.7)	0	67 (12.3)
Recovered or recovering, *n* (% liver failure)	18 (30.0)	0	NA	22 (32.8)
Died, *n* (% liver failure)	17 (28.3)	0	NA	22 (32.8)
Unknown, *n* (% liver failure)	25 (41.7)	2 (100)	NA	23 (34.3)
NOAC only suspected drug, *n* (% liver failure)	51 (85.0)	2 (100)	NA	56 (83.6)
NOAC monotherapy, *n* (% liver failure)	22 (36.7)	1 (50)	NA	29 (43.3)

Listed events include total reports for each NOAC, liver-related adverse events (System Organ Class "liver and biliary disorders"), combined events for the four specific HLTs "hepatic failure," "hepatic function abnormal," "hepatocellular damage" and "jaundice" (SHE) and the HLT "liver failure." The date of analysis was February 6, 2015

F female, *HLT* high-level term, *M* male, *NA* not applicable, *NOAC* new oral anticoagulant, *SHEs* specific hepatic events

identified preclinical finding in several animal species, suggesting non-allergic toxicity. Non-allergic idiosyncratic toxicity is compatible with the fourth liver biopsy finding, showing centroacinar necrosis [32]. Centrocainar necrosis is compatible with the formation of toxic metabolites, since CYPs are located in this area [38]. Since the main metabolic pathway of rivaroxaban involves CYP3A4-associated dealkylation [39, 40], such a mechanism is plausible. In comparison, *N*-dealkylated metabolites of amiodarone show a more accentuated hepatotoxicity than the parent substance [41, 42]. Although the patient described by Liakoni et al. [32] had no concomitant drugs inducing CYP3A4, the variability of CYP3A4 activity is so large in the population that also non-induced patients may show this type of hepatotoxicity.

In contrast to rivaroxaban, no significant increase in transaminases or other markers of liver function and no histological changes in livers from different animal species were detected after single or repetitive application of apixaban (EMA CHMP assessment report for Eliquis®, Procedure No. EMEA/H/C/002148), edoxaban (FDA Medical Review for edoxaban, application number 206316Orig1Orig2s000) or dabigatran (EMA CHMP assessment report for Pradaxa®, Procedure No. EMEA/H/C/829). This was also the case for ximelagatran, the first clinically used direct thrombin inhibitor, which was hepatotoxic in 5–10 % of the patients treated for longer than 1 month [4, 43]. For ximelagatran, HLA-dependent allergic toxicity is a likely mechanism [6, 7]. In the only case report about dabigatran-associated hepatotoxicity, no allergic features were reported [34]. This does not support, but does also not exclude, an allergic mechanism. For apixaban and edoxaban, there are too few reports to allow speculations about possible mechanisms of hepatotoxicity.

Idiosyncratic hepatic adverse drug reactions appear to be less probable for drugs with a small daily dose [44]. For drugs with a daily dose of <10 mg, a low frequency is expected, but such reactions cannot be excluded. Taking into account the bioavailability, the daily exposure of all NOACs is in the range of 10 mg. This was also the case for ximelagatran, with its clearly documented hepatotoxicity [4]. For the long-term treatments, the daily dose of ximelagatran was 72 mg. Taking into account the drug's bioavailability of 20 %, the estimated daily exposure was approximately 15 mg [1]. This shows that a low exposure may decrease the probability for idiosyncratic liver injury, but does not eliminate it.

6 Conclusions

Recent case reports, case series, analyses of pharmacovigilance data and of data from clinical studies suggest that NOACs are associated with a small risk of hepatotoxicity. Concerning rivaroxaban, most patients affected present with hyperbilirubinemia and a hepatocellular or mixed liver injury pattern. Most of them recover rapidly after stopping the drug, but hepatic failure has been described. In comparison to ximelagatran, the first direct thrombin inhibitor, which has been withdrawn because of

hepatotoxicity, hepatic events associated with the new NOACs are clearly rarer. Hepatotoxicity associated with the currently marketed NOACs is idiosyncratic; it is rare, appears at therapeutic doses and cannot be explained by the pharmacological action of these drugs. For rivaroxaban, the currently available data are compatible with both an allergic or non-allergic (metabolic) toxicity. For the other NOACs, insufficient data are available to propose mechanisms. The frequency of hepatotoxicity associated with NOACs appears to be too low to recommend routine monitoring of liver function in patients treated with these drugs. On the other hand, it is important that patients treated with NOACs know that they should visit their physician immediately if they develop jaundice and malaise. For the treating physicians, it is important to realize that hepatotoxicity is possible with these drugs and that NOACs should be stopped in patients with severe hepatotoxicity. It is important to communicate such cases to the national pharmacovigilance services in order to improve our understanding about this potentially life-threatening adverse drug reaction.

Compliance with ethical standards

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