REVIEW ARTICLE

Adverse events associated with the use of direct-acting oral anticoagulants in clinical practice: beyond bleeding complications

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KEY WORDS

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ABSTRACT

Non-vitamin K oral anticoagulants, also known as direct-acting oral anticoagulants (DOACs), have entered the market in 2008 with the expected breakthrough potential of circumventing limitations related to treatment with vitamin K antagonists (eg, warfarin) by virtue of their pharmacological properties. Although data derived from premarketing randomized clinical trials have largely demonstrated the clinical benefit of DOACs, especially in terms of reduced risk of intracranial bleeding, it is important to monitor the safety in the postmarketing phase, which better reflects real-world patients with comorbidities and polypharmacotherapy, in order to assess the actual risk–benefit profile. In this critical review, we aimed to evaluate the evidence on the latest debated safety issues. In the first section, we will discuss: 1) the need for pharmacovigilance (ie, the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems in the real-world setting), and 2) the importance of properly interpreting postmarketing data to avoid unnecessary alarm. In the second section, emerging and debated safety issues potentially associated with the use of DOACs in the postmarketing setting will be assessed: 1) the potential coronary risk (which emerged during the preapproval period); 2) the occurrence of liver injury (a risk undetected in clinical trials and highlighted by case reports or series); and 3) the potential for renal damage (a still unclear safety issue). It is anticipated that hepatic and renal issues still require dedicated postauthorization safety studies to ultimately assess causality.

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Introduction Non-vitamin K oral anticoagulants, now referred to as direct-acting oral anticoagulants (DOACs), are candidate to changing the therapeutic scenario for patients requiring short- and long-term anticoagulation, by virtue of their pharmacological properties: fixed-dose administration, reduced likelihood of drug–drug and drug–food interactions, and no need for coagulation monitoring, as compared to vitamin K antagonists (VKAs).[1,2]

In consolidated indications, namely, nonvalvular atrial fibrillation and venous thromboembolism (VTE, prevention and treatment), the current place in the therapy of dabigatran, rivaroxaban, apixaban, and edoxaban is recognized: in nonvalvular atrial fibrillation, the updated European Heart Rhythm Association (EHRA) and the American College of Cardiology (ACC) guidelines supported the optimization in the use of DOACs through algorithm-based approaches[3,4]; in VTE scenario, the latest American College of Chest Physicians guideline was the first recommending DOACs over VKAs for initial and long-term VTE treatment (in the absence of cancer).[5]

Although data derived from premarketing randomized clinical trials have largely demonstrated the net clinical benefit of DOACs, especially in terms of reduced risk of intracranial bleeding, there is still room for improvement to optimize appropriateness and safe use of DOACs,[6] especially in evolving and emerging therapeutic indications (eg, post-acute coronary syndrome) to assess effectiveness in the real world.[7]

In addition, recent postauthorization studies and a meta-analysis have highlighted the potential occurrence of unpredictable safety signals and

a higher than expected incidence of gastrointestinal bleeding,[8,9] which requires further evaluation and integration with real-world data to assess their actual risk–benefit profile.

In this context, the aim of this review was to critically evaluate the evidence on the latest debated safety issues (ie, coronary risk, liver and renal injury), especially considering real-world data.

Lessons from pharmacovigilance: the road towards appropriateness Pharmacovigilance has been defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems".[10] The current era has started with the pharmacovigilance legislation (Regulation [EU] No 1235/2010 and Directive 2010/84/EU), in force as of July 2012, and aims to promote and protect public health by reducing the burden of adverse drug reactions (ADRs) and optimizing the use of medicines. This can be achieved through heterogeneous sources of data, from randomized clinical trials (RCTs) to analytical observational studies, but also from health forums of patients.[11]

Although it is universally accepted that RCTs represent the highest level of evidence (and usually do have internal validity), too stringent enrollment criteria and short-term follow-up do not allow generalizability and full translation of results into clinical practice. Moreover, safety is rarely tested as a prespecified endpoint during the premarketing phase. Therefore, postmarketing safety studies are recognized as a key tool to investigate the real-world usage patterns of drugs, where multimorbidities and polypharmacology exist, in order to cover the whole spectrum of the evidence.

This is particularly the case for patients requiring DOAC administration, who are likely to be elderly, with a various degree of renal impairment, affected by multifactorial cardiovascular dysfunctions (eg, previous myocardial infarction [MI] or chronic heart failure) and other diseases (eg, cancer), as well as requiring multiple drugs likely to result in interactions. All these aspects increase the risk of predictable (ie, bleeding) and unpredictable ADRs. Different examples have been recently presented in the literature, indicating that, for both dabigatran and rivaroxaban, a large proportion of spontaneous reports of ADRs (from 34% to 89%) were associated with the use of concomitant medicines with bleeding potential.

These findings once more call for active vigilance by prescribers and careful assessment of the patient's comorbidities and comedications to minimize risks in routine clinical practice.[12,13] When properly designed (ie, with a clear research question, keeping in mind major bias and addressing major confounders), reported with transparency and disseminated through a balanced view, these studies may highlight possible foci of inappropriateness and support a safe use of drugs through early identification of safety signals, especially for rare and unpredictable ADRs.[14,15] It is important to remind here that these safety signals should not be viewed as unjustified alarms for clinicians (ie, they do not necessarily imply changes in prescribing practice), but should be interpreted as a research tool (ie, the first alert of potential drug–event association) to guide future research (analytical observational studies).

Coronary risk: a resolved safety issue? **First suspicion and the analysis of possible biases** In this section, we will describe the history of coronary risk associated with dabigatran (how and when this safety issue emerged) and guide the reader in the complex interpretation and analysis of data with the (theoretically) highest strength of evidence (ie, meta-analysis) through a perusal of the data.

The suspicion that MI could occur more frequently in patients receiving dabigatran compared with warfarin was raised by secondary results of the landmark Randomized Evaluation of Long Term Anticoagulant Therapy Trial (RE-LY),[16] which enrolled more than 18 000 patients with atrial fibrillation. MI, one of several secondary outcomes, had an annual incidence of 0.74% for patients randomized to dabigatran therapy, 150 mg twice daily, and 0.53% for warfarin, corresponding to a 38% higher risk. Since then, different meta-analyses have been published with discordant results, thus causing uncertainty as to this putative association. In particular, Uchino et al[17] performed a fixed-effects Mantel–Haenszel meta-analysis of 7 noninferiority RCTs comparing dabigatran with warfarin and found a 33% higher risk of MI or acute coronary syndrome (ACS). Several methodological pitfalls were elegantly highlighted by Correia and Lopes,[18] who hypothesized the concept of "meta-illusion": the fact that MI was a secondary endpoint (more prone to result from chance) and, especially, the remarkable influence of RE-LY may have strongly guided the meta-analytic process (ie, the relative weight of RE-LY largely exceeded that of all other RCTs). To support their theory, they meta-analyzed the same trials except RE-LY through a random-effect model, which yielded a statistically nonsignificant result (odds ratio [OR], 1.2; 95% confidence interval [CI], 0.66–1.9). We would like to remark that the RE-LY's definition of MI was as follows: "Clinical MI was defined as the presence of at least two of the following three criteria: 1) Typical prolonged severe chest pain or related symptoms or signs (eg, ST changes or T-wave inversion in the ECG); 2) Suggestive of MI elevation of troponin or creatine kinase-MB to more than the upper level of normal, or if creatine kinase-MB was elevated at baseline, reevaluation to 50% increase above the previous level; 3) Development of significant Q waves in at least two adjacent ECG leads".[16] Therefore, even nonspecific cardiac disorders resulting in the elevation of creatine kinase-MB levels and chest pain might be included according to these criteria, with a potential overestimation of the actual cases of MI.

TABLE 1 Analysis of discordant meta-analyses and possible reasons behind the detected differences (see text for details)

Main biases and fallacies	Uchino et al[17]	Douxfils et al[19]	Clemens et al[20]
included trials and relative weight in meta-analysis	7 RCTs: RE-LY (76% calculated[a]) RECOVER, RENOVATE I and II, RE-DEEM, REMODEL, PETRO	14 RCTs: RE-LY (69.83% reported), REMEDY RECOVER I and II, RENOVATE I and II, RE-DEEM, REMODEL, REMOBILIZE, RESONATE, RE-ALIGN PETRO, BISTRO II, FUJI	RE-LY (91.66 % calculated[b]), REMEDY, RECOVER I and II
MI definition in trials	secondary outcome (the authors do not discuss this issue)	secondary outcome (the authors recognize this issue: all ACSs adjudicated as MI)	secondary outcome (the authors recognize this issue)
availability of individual patient data	no	no	yes
other potential sources of bias	–	–	study and authors funded by Boehringer
primary analysis	including original RE-LY data: Peto OR, 1.29 (95% CI, 1.03–1.62)	OR, 1.41 (95% CI, 1.11–1.80; $P = 0.005$)	• 150 mg twice daily vs warfarin: OR, 1.42 (95% CI, 1.07–1.88) • 150 mg twice daily vs placebo: OR, 1.37 (95% CI, 0.50–3.70) • 110 mg twice daily vs warfarin: OR, 1.30 (95% CI, 0.96–1.76) • 110 mg twice daily vs warfarin: OR, 1.07 (95% CI, 0.36–3.20) • 220 mg once daily vs enoxaparin: OR, 0.50 (95% CI, 0.22–1.18)
sensitivity analysis without RE-LY	not performed; performed with revised RE-LY results with loss of statistical significance: Peto OR, 1.26 (95% CI, 1.00–1.58; $P = 0.05$)	performed by individual removal of RE-LY with loss of statistical significance: • vs any control: OR, 1.457 (95% CI, 1.002–2.118; $P = 0.049$) • vs warfarin: OR, 3.227 (95% CI, 1.507–6.908; $P = 0.003$)	not performed
authors' conclusion	Dabigatran increases the risk of MI or ACS in a broad spectrum of patients when tested against different controls.	Dabigatran is associated with a significantly increased risk of MI.	These analyses suggest a more protective effect of well-controlled warfarin …. These data suggest that myocardial infarction is not an adverse drug reaction associated with the use of dabigatran.

a 257 total events/20 000 total patients × 100 = 1.28; 195 events in RE-LY/20 000 total patients × 100 = 0.975; 0.975/1.28 × 100 = 76%

b 213 total events/16 073 total patients × 100 = 1.32; 195 events in RE-LY/16 073 total patients × 100 = 1.21; 1.21/1.32 × 100 = 91.66%

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction; OR, odds ratio; RCTs, randomized clinical trials

Moving towards a more critical overview of discordant meta-analyses: a meta-delusion This intriguing scenario prompted us to test other discordant meta-analyses for potential methodological bias, paying attention to sensitivity analyses. We performed a search in MEDLINE (free text strategy "dabigatran and myocardial infarction") and retrieved 2 additional systematic reviews directly comparing dabigatran with VKAs. A synopsis is provided in TABLE 1.

Douxfils et al[19] considered the potential influence of RE-LY on results and performed additional analyses, but firmly stated that "overall one-way sensitivity analysis shows that similar results are obtained regardless of which study is excluded from the primary analysis, even when RE-LY is removed". However, a supplementary table reported that RE-LY removal resulted in a Peto OR of 1.457 (95% CI, 1.002–2.118) with a *P* value of 0.049, which is within the threshold of statistical significance, as compared to other *P* values (ranging from 0.003 to 0.025) obtained when the other studies were excluded. Interestingly enough, a higher *P* value was also accepted when RE-MEDY was excluded (0.025). Furthermore, the authors report that, as in most trials the definition of MI was not available, they adjudicated all ACSs as MI if not stated otherwise, admitting that this might have led to overestimation of the rate of MI.

We believe that statistical incoherence in reporting results, lack of individual patient data, and unspecific outcome definition might have biased the conclusions drawn by the authors (ie, significantly increased risk of MI).

Clemens et al[20] meta-analyzed only 4 RCTs, all of which reported MI as a secondary outcome: RE-LY, RE-MEDY, and RECOVER I and II. The RE-LY and RE-MEDY trials strongly affected the meta-analysis as they enlisted roughly 4 times as many patients as RECOVER I and II. The reported OR was 1.42 (95% CI, 1.07–1.88), which

is very similar to the results obtained by Douxfils et al.[19] Although Clemens et al[20] had access to individual patient data, these aspects remain problematic in this sponsored study: the ambiguous outcome definition and a possible imbalance in data interpretation. Notably, the authors stated that the increase in MI events with dabigatran is due to a protective effect of warfarin against MI. To support this claim, they quoted 3 articles: the RCT SPORTIF III (comparing ximelagatran with warfarin),[21] a meta-analysis (combining RE-LY, SPORTIF-III, and SPORTIF-IV, and comparing ximelagatran with warfarin), and AMADEUS (comparing idraparinux with warfarin).[22] The third study quoted by Clemens et al[20] did not compare warfarin with DOACs and concluded that warfarin use at discharge was superior to no warfarin (a pool of drugs which included aspirin and ticlopidine/clopidogrel) in preventing a second hit in post-MI patients with atrial fibrillation.[23]

For the sake of completeness, we retrieved 3 additional meta-analyses that did not fulfill our inclusion criteria. One of them compared apixaban with different controls and did not identify an increased risk of MI (OR, 0.92; 95% CI, 0.71–1.20, as compared to other anticoagulants).[24] The other two meta-analyses indirectly compared DOACs and were concordant in concluding that dabigatran was associated with an increased risk as compared to rivaroxaban and apixaban.[25,26] However, it should be recognized that these data are mainly driven by studies in population with ACS, especially by the ATLAS ACS 2 – TIMI 51 trial[27] for rivaroxaban, which was pivotal for rivaroxaban approval in this indication.

In summary, the confusion from discordant meta-analyses has now been pruned, and we take this opportunity to call once more for proper conduction, interpretation, and communication of data derived from safety meta-analysis in order to avoid unnecessary alarm[28-30] and avoid the possibility of a meta-delusion (ie, the misinterpretation of findings that are strongly influenced by residual confounders). The current body of evidence from RCTs does not support an increased risk of MI with dabigatran (it is of borderline statistical significance and largely guided by the RE-LY study).[31] More importantly, these preapproval data (based on phase III studies) actually conflict with postmarketing cohort studies (phase IV), which failed to find an increased coronary risk[32] and even documented lower rates of MI in different propensity-matched comparisons against warfarin.[33,34] In addition, no sound pharmacologic mechanism supports the hypothesis of dabigatran-related myocardial adverse events. This is just another example of how safety signals should be handled in order to avoid unnecessary alarm for clinicians.

Liver risk: a safety issue that should not be overlooked

Drug-induced liver injury (DILI) is a leading cause of drug withdrawal worldwide and a safety topic attracting multidisciplinary interest, because of the imperfect prediction of preclinical assays and potential underestimation in clinical phases.[35]

The risk of DILI associated with DOACs is a recent safety issue, which was undetected in preclinical, underestimated in clinical phases, and only emerged during postmarketing use (**FIGURE 1**). In fact, even when suspected to be drug-related, the diagnosis is a current clinical challenge because a number of alternative causes must be excluded.[36]

It is important to remind that patients with active liver disease were not enrolled in landmark studies: liver impairment may in fact per se increase the risk of clinically relevant bleeding and increase the drug-related toxicity, considering that DOACs undergo hepatic metabolism. Therefore, current summaries of the product characteristics (SPCs) do not recommend use of DOACs in patients with liver impairment, and rivaroxaban is even contraindicated in cirrhotic patients (hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C).

Based on premarketing RCTs, DOACs can cause a transient elevation of hepatic transaminase levels in about 2% of the treated patients enrolled in phase III studies (uncommon in terms of frequency).[37] However, the idiosyncratic nature of DILI, including the undefined role of patient- and drug-related risk factors (exemplified by the case of ximelagatran)[38] and relevant limited capacity to predict its occurrence in the real-world scenario make postmarketing surveillance crucial to identify these off-target side effects. In particular, case reports still represent a key source of evidence to support regulatory measures, including drug withdrawals.[39] A number of case reports, case series, and analyses of pharmacovigilance databases has been accrued in the last year and suggest that DOACs are associated with a rare but clinically relevant risk of hepatotoxicity.[40]

An updated free text search in MEDLINE (as of May 31, 2016) yielded 13 publications: 10 case reports/case series (28 patients), 1 review providing the overall reporting frequency from international spontaneous reporting systems (SRSs), 1 pharmacovigilance study (disproportionality analysis) on the US Food and Drug Administration SRS (called FAERS), and 1 systematic review with meta-analysis of RCTs (Supplementary material online, *Table S1*).[41-53]

As expected, the meta-analytic approach by Caldeira et al,[52] did not highlight an increased risk, although a trend towards statistical significance emerged for rivaroxaban. However, data from large international SRSs highlighted that rivaroxaban is reported to cause liver damage in 3.7% to 3.9% of total reports, whereas 1.7% to 1.8% of cases submitted for dabigatran mentioned potential liver injury.[48,49] Rivaroxaban is identified as the suspect drug in all but one DILI reports published so far: most patients are characterized by hyperbilirubinemia with hepatocellular or mixed liver injury pattern, usually recovered

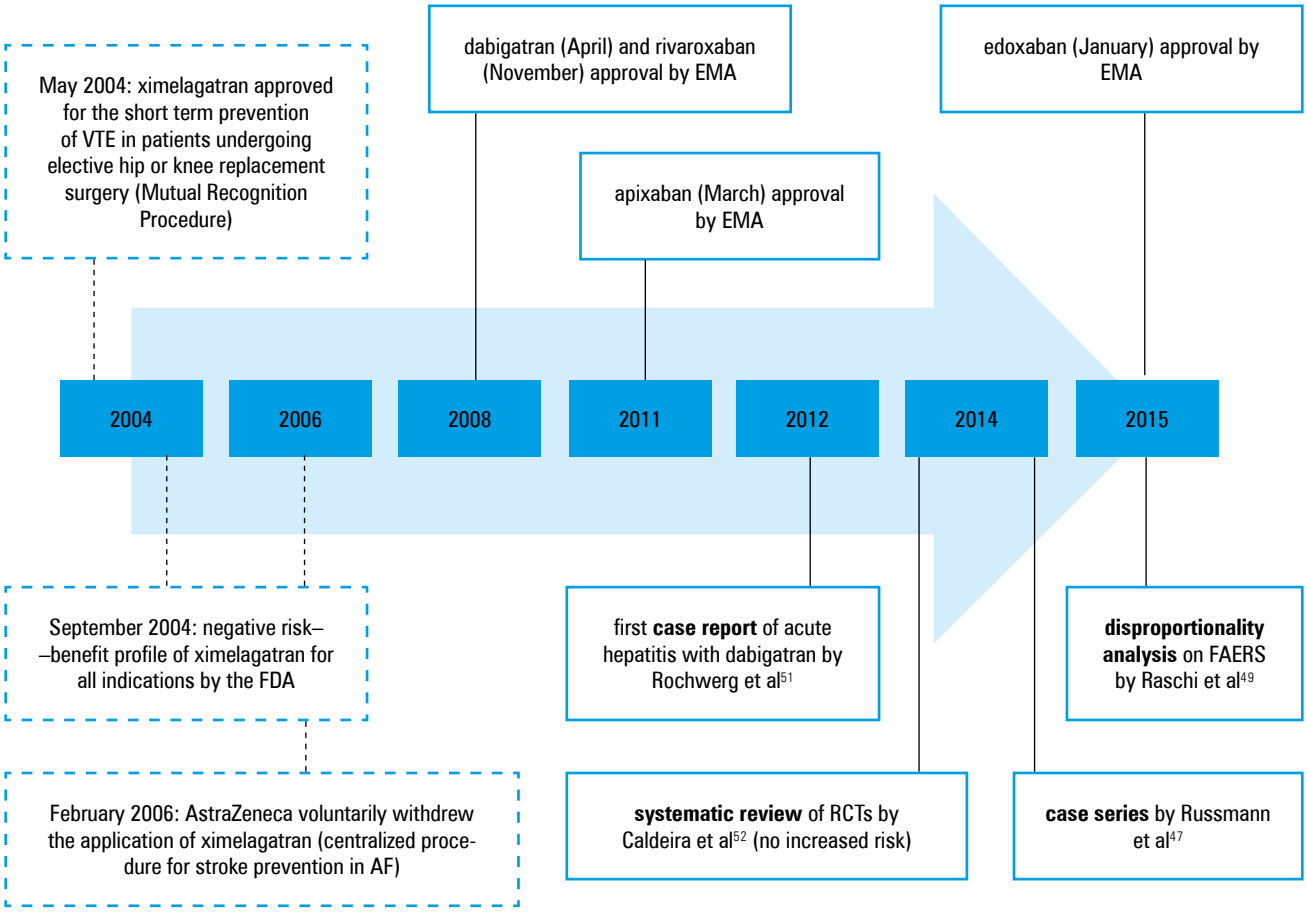

FIGURE 1 Milestones in approval history (upper panel) and liver safety data (lower panel) of direct oral anticoagulants. Information on ximelagatran is presented in boxes with dotted lines. Abbreviations: AF, atrial fibrillation; EMA, European Medicines Agency; FAERS, FDA spontaneous reporting systems; FDA, Food and Drug Administration; RCT, randomized controlled trial; VTE, venous thromboembolism

rapidly after drug discontinuation, but hepatic failure has also been described. It is interesting to note that 4 case reports/case series came from France and 2 from Switzerland. This suggests that a local reporting pattern should be further investigated, as it may have a role as a predisposing factor in the occurrence of the event. In addition, the majority of these patients have undergone knee surgery or experienced venous thrombotic events, suggesting that orthopedic and related prothrombotic conditions (instead of atrial fibrillation) may increase patient's susceptibility to DILI.

Although hepatic events associated with DOACs are clearly rare, vigilance should be maintained by both clinicians and pharmacovigilance experts. In fact, although incidence and relative risk cannot be derived from SRSs, the estimated risk could not be as uncommon as stated in the SPCs. Based on this reporting frequency, recommending close monitoring of liver function in patients treated with DOACs is not justified. However, the time-to-onset from published case reports suggests that early evaluation of hepatic enzymes (ie, within the first month) may be considered at least in patients under complex treatment regimen with comorbidities; subsequently, liver function can be monitored on a yearly basis. Patients should be instructed to timely communicate early clinical signs and symptoms to the physician, who should consider, on a case-by-case basis, the role of DOACs as well as concomitant therapies and, eventually, interrupt drug administration in patients with severe hepatotoxicity. It is also important to report suspicious cases to the national pharmacovigilance services in order to improve our understanding of DILI, especially for recently marketed apixaban and edoxaban.

The research agenda should address the issue of class effect and the mechanistic basis of DILI. In fact, although hepatotoxicity (associated with DOACs) is deemed to be idiosyncratic (ie, it may occur at therapeutic doses and cannot be explained by the pharmacological action of these drugs), the latest evidence has suggested that both host- and drug- related risk factors are likely to interact in the occurrence of DILI.[54] Among the latter, daily dose, lipophilicity, metabolic pathway mediated by cytochromes, and structural moieties with the formation of reactive metabolism have been proposed to be strong predictors of the risk in humans.[55] Notably, apixaban, rivaroxaban, and dabigatran contain structural moieties, although they are not clearly involved in the formation of known hepatotoxic reactive metabolites.[56-58] Therefore, chemical and pharmacokinetic features deserve further analyses before being considered to account for the increased reporting frequency observed for rivaroxaban. In fact, a recent case report described a 67-year-old male with atrial fibrillation receiving rivaroxaban who developed a 16-fold elevation in alanine transaminase levels; a switch to apixaban resulted in rapid resolution of laboratory

TABLE 2 Synopsis of spontaneous reports on emerging safety issues (myocardial infarction, liver injury, and renal failure) recorded in large international spontaneous reporting systems (ie, Vigibase and Eudravigilance) for oral anticoagulants (ie, direct-acting oral anticoagulants and warfarin). Data are presented as number of reports, stratified according to a specific pharmacovigilance teminology called MedDRA (Medical Dictionary for Regulatory Activities). The percentages indicate the reporting frequency of specific acute clinical events as compared to total reports.

Reports	Warfarin		Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
	Vigibase	Eudravigilance	Vigibase	Eudravigilance	Vigibase	Eudravigilance	Vigibase	Eudravigilance	Vigibase	Eudravigilance
total reports	76.793	27.581	44.952	31.714	55.054	55.578	13.914	11.418	570	457
hepatobiliary disorders	853	471	537	523	815	895	159	188	14	12
acute hepatic failure	11 (0.01%)	11 (0.04%)	24 (0.05%)	31 (0.10%)	31 (0.06%)	35 (0.06%)	7 (0.05%)	7 (0.06%)	0	0
drug-induced liver injury	19	17	18	41	68	104	12	15	1	0
hepatic failure	48	27	67	71	72	81	6	5	0	0
abnormal hepatic function	223	73	39	34	98	101	30	29	6	5
renal and urinary disorders	5.097	1.963	3.749	3.240	3.674	4.001	687	635	27	24
acute kidney injury	607 (0.79%)	286 (1.04%)	1.144 (2.54%)	1.118 (3.53%)	435 (0.79%)	544 (0.98%)	75 (0.54%)	76 (0.67%)	5 (0.88%)	4 (0.88%)
renal failure	289	164	480	493	226	259	55	70	0	1
renal impairment	164	95	294	337	272	319	82	93	1	6
chronic kidney disease	50	32	54	4	20	19	8	10	0	0
cardiac disorders	3.421	1.636	3.756	3.557	2.362	2.493	803	796	9	11
acute myocardial infarction	69 (0.09%)	59 (0.21%)	238 (0.53%)	269 (0.85%)	90 (0.16%)	87 (0.16%)	22 (0.16%)	22 (0.19%)	0	0

Vigibase: www.vigiaccess.org (accessed June 21, 2016)

Eudravigilance: www.adrreports.eu (accessed June 21, 2016; updated May 2016)

abnormalities, thus suggesting that rivaroxaban's mechanism of hepatotoxicity may be unrelated to its pharmacologic action.[59]

In summary, chemists, pharmacologists, and clinicians should join efforts to improve prediction, assess actual mechanistic basis of DILI occurrence, and establish causality.

Renal risk: a still uncertain multifaceted issue Before discussing the risk of DOACs in precipitating renal dysfunction, we briefly mention a debated aspect, that is, appropriate prescribing in patients with renal impairment. In this setting, assessment of kidney function is important to estimate their potential accumulation, which may result in increased risk of bleeding, and dose adjustment may be required depending on the extent of renal impairment and relevant kidney clearance of each DOAC.

In fact, clinicians should remind that all DOACs depend to some extent on renal function for clearance, with dabigatran being 80% excreted via the kidney. This is especially critical in patients with advanced chronic kidney disease (CKD) and end-stage renal disease requiring dialysis. These patients were excluded from all pivotal phase III trials, thus current SPCs do not recommend their use when creatinine clearance is below 15 ml/min. The reader may refer to the 2015 EHRA practical guide, which suggested a 3-month interval monitoring in elderly patients,[3] and to recent review articles, which supported close monitoring in elderly patients (at risk of tubule-interstitial injury) with comorbidities and polypharmacology, especially at the beginning of the therapy, in case of long-term use, concomitant interacting/nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs), and incidental infections that may increase the patient's susceptibility to renal injury and bleeding occurrence.[60,61] The preference over one DOAC versus another is still a matter of debate and the therapeutic choice should be made on a case-by-case basis and likely to be guided mainly by clinical experience.[62]

Anticoagulant-related nephropathy The risk of anticoagulant-related nephropathy is a recently identified clinical entity defined as an acute kidney injury (AKI), without other obvious etiology, in the setting of an international normalized ratio (INR) greater than 3.0.[63] First characterized as warfarin-related nephropathy by Brodsky et al[64] in 2009, it has been also related to dabigatran and, possibly, other DOACs. Its incidence and prevalence are difficult to be precisely estimated, although the overall evidence (mainly based on case reports and case series) suggests it is a rare clinical event. Brodsky et al[65] reported a mean incidence of 20.5% in the whole cohort of patients with an INR exceeding 3.0 and serum creatinine levels measured, rising to 33.0% in patients with CKD, while remaining at a level of 16.5% in the non-CKD cohort. These data might unduly overestimate the actual epidemiological dimension, given that patient data on AKI etiology were not available. Data on dabigatran are much more scarce, although case reports have been documented, including reports of fatal toxicity.[66]

The pathophysiological mechanisms underlying warfarin- and dabigatran-related nephrotoxicity have been investigated by Ryan et al[67] and Narasimha Krishna et al,[68] who confirmed that they resemble each other in clinical and pathological features but differ in mechanisms. Warfarin might cause damage by inhibiting GAS6 and matrix G1a protein, the vitamin K-dependent inhibitors of smooth muscle cell migration, mesangial cell proliferation, and vascular calcification. The mechanistic basis of dabigatran-related nephrotoxicity, as a non-vitamin K anticoagulant, follows a different pathway. Ryan et al[67] showed that thrombin inhibition causes a decreased thrombin activity resulting in decreased protease-activated receptor 1 activity (thrombin GPCR is expressed on endothelial cells), and this is thought to alter the glomerular filtration barrier and disrupt the endothelial lining integrity.[67]

A recent meta-analysis of 10 RCTs comparing DOACs and VKAs found no differences in the risk of renal failure associated with the use of DOACs, although rivaroxaban shows a trend for increased risk and an increased risk of creatinine elevation (relative risk, 1.25; 95% CI, 1.08–1.45).[69] As compared to DILI, it must be emphasized that no reports have been published to date suggesting the occurrence of AKI with rivaroxaban and apixaban, with only 1 nonfatal case report for dabigatran.[70]

Summary and conclusions We have addressed 3 debated safety aspects of DOACs (coronary risk, liver injury, and renal impairment), which per se represent clinically relevant ADRs and may also increase the risk of bleeding. With the aim of providing the global safety profile of DOACs and verify their actual reporting pattern for the 3 ADRs of interest, we accessed publicly available SRSs and extracted the crude number of cases submitted to the WHO-Vigibase, collecting worldwide reports (www.vigiaccess.org; accessed June 21, 2016), and Eudravigilance, collecting European data (www.adrreports.eu, accessed June 21, 2016; updated May 2016) (TABLE 2). Overall, the reporting rate of liver, renal, and myocardial failures (serious acute events) is very low as compared to other ADRs, thus suggesting the rarity of these events in clinical practice. However, the frequency of renal injury for dabigatran (2.5%–3.5%) warrants a case-by-case analysis. In fact, these data must be interpreted very cautiously, and a direct association cannot be inferred because of the inherent limitations (mainly underreporting and the lack of "nonexposed" patients). These data primarily aim at identifying further areas of research in pharmacovigilance. In conclusion, we offer the following take-home messages:

1 The current risk–benefit profile of DOACs is largely positive, but the magnitude of these ADRs in terms of clinical and epidemiological impact is

still incompletely defined. Data from SRSs worldwide highlight the importance of monitoring the postmarketing use of DOACs in clinical practice to assess comparative effectiveness and safety in different clinical settings.[71]

2 The coronary risk, described for dabigatran, is not supported by a critical evaluation of the evidence, mainly derived from RCTs. High-risk patients should be investigated to finally exclude this risk, although recent cohort studies have consistently demonstrated a reduced risk of MI in real-world clinical practice.

3 The unpredictable nature of liver damage by DOACs, especially for rivaroxaban, emerged from postmarketing real-world data and calls for awareness by clinicians, who should consider DOACs among the differential diagnoses and report suspected drug-related hepatic injuries to regulatory authorities, as well as for preclinical studies to gain insight into mechanistic basis and predict drug-related features likely to increase the occurrence of DILI in humans. Clinicians should consider to assess liver function at the beginning of administration (within the first month) and then on a yearly basis, at least in patients under a complex treatment regimen with comorbidities.

4 The potential for renal damage (ie, the possibility of precipitating kidney dysfunction in patients with or without renal impairment) remains insufficiently characterized and warrants observational data to validate the pharmacokinetic hypothesis that renal clearance may compromise clinical effectiveness and safety, and to confirm the mechanistic basis of anticoagulant-related nephropathy and actual epidemiological magnitude.

Current clinical and research efforts should be directed towards defining the precise place in therapy of DOACs in frail patients (severe renal impairment with comorbidities and polypharmacology), especially in light of evolving therapeutic uses (eg, heparin-induced thrombocytopenia, cancer, coronary artery diseases).[7]

REFERENCES

1 Riva N, Lip GY. A new era for anticoagulation in atrial fibrillation. Which anticoagulant should we choose for long-term prevention of thromboembolic complications in patients with atrial fibrillation? Pol Arch Med Wewn. 2012; 122: 45-53.

2 Kornej J, Potpara T, Lip GY. Anticoagulation management in nonvalvular atrial fibrillation: current and future directions. Pol Arch Med Wewn. 2013; 123: 623-634.

3 Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015; 17: 1467-1507.

4 Kovacs RJ, Flaker GC, Saxonhouse SJ, et al. Practical management of anticoagulation in patients with atrial fibrillation. J Am Coll Cardiol. 2015; 65: 1340-1360.

5 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016; 149: 315-352.

6 Undas A, Pasierski T, Windyga J, et al. Practical aspects of new oral anticoagulant use in atrial fibrillation. Pol Arch Med Wewn. 2014; 124: 124-135.

7 Chan NC, Eikelboom JW, Weitz JI. Evolving treatments for arterial and venous thrombosis: role of the direct oral anticoagulants. Circ Res. 2016; 118: 1409-1424.

8 Hernandez I, Baik SH, Pinera A, et al. Risk of bleeding with dabigatran in atrial fibrillation. JAMA Intern Med. 2015; 175: 18-24.

9 Romanelli RJ, Nolting L, Dolginsky M, et al. Dabigatran versus warfarin for atrial fibrillation in real-world clinical practice: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2016; 9: 126-134.

10 Raschi E, De Ponti F. Drug Utilization Research and Pharmacovigilance. In: Elseviers M, Wettermark B, Almarsdóttir AB, et al, eds. Drug Utilization Research: Methods and Applications. Chichester, UK: John Wiley & Sons, Ltd; 2016: 399-407.

11 Harpaz R, DuMouchel W, Shah NH, et al. Novel data-mining methodologies for adverse drug event discovery and analysis. Clin Pharmacol Ther. 2012; 91: 1010-1021.

12 McDonald CJ, Kalisch Ellett LM, Barratt JD, et al. A cross-country comparison of rivaroxaban spontaneous adverse event reports and concomitant medicine use with the potential to increase the risk of harm. Drug Saf. 2014; 37: 1029-1035.

13 McDonald CJ, Kalisch Ellett LM, Barratt JD, et al. An international comparison of spontaneous adverse event reports and potentially inappropriate medicine use associated with dabigatran. Pharmacoepidemiol Drug Saf. 2015; 24: 399-405.

14 Montastruc JL, Sommet A, Bagheri H, et al. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol. 2011; 72: 905-908.

15 Harpaz R, DuMouchel W, LePendu P, et al. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clin Pharmacol Ther. 2013; 93: 539-546.

16 Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361: 1139-1151.

17 Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012; 172: 397-402.

18 Correia LC, Lopes AA. Dabigatran and myocardial infarction: meta-illusion? Arch Intern Med. 2012; 172: 823.

19 Douxfils J, Buckinx F, Mullier F, et al. Dabigatran etexilate and risk of myocardial infarction, other cardiovascular events, major bleeding, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2014; 3: e000515.

20 Clemens A, Fraessdorf M, Friedman J. Cardiovascular outcomes during treatment with dabigatran: comprehensive analysis of individual subject data by treatment. Vasc Health Risk Manag. 2013; 9: 599-615.

21 Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet. 2003; 362: 1691-1698.

22 Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? Am J Med. 2010; 123: 785-789.

23 Lopes RD, Starr A, Pieper CF, et al. Warfarin use and outcomes in patients with atrial fibrillation complicating acute coronary syndromes. Am J Med. 2010; 123: 134-140.

24 Tornyos A, Vorobcsuk A, Kupo P, et al. Apixaban and risk of myocardial infarction: meta-analysis of randomized controlled trials. J Thromb Thrombolysis. 2015; 40: 1-11.

25 Loke YK, Pradhan S, Yeong JK, et al. Comparative coronary risks of apixaban, rivaroxaban and dabigatran: a meta-analysis and adjusted indirect comparison. Br J Clin Pharmacol. 2014; 78: 707-717.

26 Tornyos A, Kehl D, D'Ascenzo F, et al. Risk of myocardial infarction in patients with long-term non-vitamin K antagonist oral anticoagulant treatment. Prog Cardiovasc Dis. 2016; 58: 483-494.

27 Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012; 366: 9-19.

28 Raschi E, Salvo F, Poluzzi E, et al. Safety meta-analysis: a call for appropriate use of disproportionality measures from spontaneous reporting systems. J Am Coll Cardiol. 2016; 67: 2193.

29 Fuhr U, Hellmich M. Channeling the flood of meta-analyses. Eur J Clin Pharmacol. 2015; 71: 645-647.

30 Stoto MA. Drug safety meta-analysis: promises and pitfalls. Drug Saf. 2015; 38: 233-243.

31 Caldeira D, Ferreira JJ, Pinto FJ, et al. Safety of non-vitamin K antagonist oral anticoagulants – coronary risks. Expert Opin Drug Saf. 2016; 15: 731-740.

32 Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation. 2015; 131: 157-164.

33 Larsen TB, Gorst-Rasmussen A, Rasmussen LH, et al. Bleeding events among new starters and switchers to dabigatran compared with warfarin in atrial fibrillation. Am J Med. 2014; 127: 650-656.

34 Lauffenburger JC, Farley JF, Gehi AK, et al. Effectiveness and safety of dabigatran and warfarin in real-world US patients with non-valvular atrial fibrillation: a retrospective cohort study. J Am Heart Assoc. 2015; 4

35 Sarges P, Steinberg JM, Lewis JH. Drug-induced liver injury: highlights from a review of the 2015 literature. Drug Saf. 2016;

36 Lewis JH. The art and science of diagnosing and managing drug-induced liver injury in 2015 and beyond. Clin Gastroenterol Hepatol. 2015; 13: 2173-2189.

37 Watkins PB, Desai M, Berkowitz SD, et al. Evaluation of drug-induced serious hepatotoxicity (eDISH): application of this data organization approach to phase III clinical trials of rivaroxaban after total hip or knee replacement surgery. Drug Saf. 2011; 34: 243-252.

38 Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. Handb Exp Pharmacol. 2010; 407-418.

39 Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med. 2016; 14: 10.

40 Raschi E, De Ponti F. Drug- and herb-induced liver injury: progress, current challenges and emerging signals of post-marketing risk. World J Hepatol. 2015; 7: 1761-1771.

41 Lambert A, Cordeanu M, Gaertner S, et al. Rivaroxaban-induced liver injury: results from a venous thromboembolism registry. Int J Cardiol. 2015; 191: 265-266.

42 Cordeanu M, Lambert A, Gaertner S, et al. Apixaban-induced hepatotoxicity. Int J Cardiol. 2016; 204: 4-5.

43 Cordeanu M, Gaertner S, Bensalah N, et al. Rivaroxaban induced liver injury: a cholestatic pattern. Int J Cardiol. 2016; 216: 97-98.

44 Baig M, Wool KJ, Halanych JH, et al. Acute liver failure after initiation of rivaroxaban: a case report and review of the literature. N Am J Med Sci. 2015; 7: 407-410.

45 Aslan AN, Sari C, Bastug S, et al. Severe jaundice due to intrahepatic cholestasis after initiating anticoagulation with rivaroxaban. Blood Coagul Fibrinolysis. 2016; 27: 226-227.

46 Liakoni E, Ratz Bravo AE, Terracciano L, et al. Symptomatic hepatocellular liver injury with hyperbilirubinemia in two patients treated with rivaroxaban. JAMA Intern Med. 2014;

47 Russmann S, Niedrig DF, Budmiger M, et al. Rivaroxaban postmarketing risk of liver injury. J Hepatol. 2014; 61: 293-300.

48 Liakoni E, Ratz Bravo AE, Krahenbuhl S. hepatotoxicity of new oral anticoagulants (NOACs). Drug Saf. 2015; 38: 711-720.

49 Raschi E, Poluzzi E, Koci A, et al. Liver injury with novel oral anticoagulants: assessing post-marketing reports in the US Food and Drug Administration adverse event reporting system. Br J Clin Pharmacol. 2015; 80: 285-293.

50 Fulcrand J, Lerooy A, Giraud J, et al. [Cytolysis in an elderly patient treated with dabigatran etexilate]. Therapie. 2013; 68: 332-334. French.

51 Rochwerg B, Xenodemetropoulos T, Crowther M, et al. Dabigatran-induced acute hepatitis. Clin Appl Thromb Hemost. 2012; 18: 549-550.

52 Caldeira D, Barra M, Santos AT, et al. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart. 2014; 100: 550-556.

53 Barrett P, Vuppalanchi R, Masuoka H, et al. Severe drug-induced skin and liver injury from rivaroxaban. Dig Dis Sci. 2015; 60: 1856-1858.

54 Chen M, Suzuki A, Borlak J, et al. Drug-induced liver injury: Interactions between drug properties and host factors. J Hepatol. 2015; 63: 503-514.

55 Kalgutkar AS, Dalvie D. Predicting toxicities of reactive metabolite-positive drug candidates. Annu Rev Pharmacol Toxicol. 2015; 55: 35-54.

56 Zhang D, He K, Raghavan N, et al. Comparative metabolism of 14C-labeled apixaban in mice, rats, rabbits, dogs, and humans. Drug Metab Dispos. 2009; 37: 1738-1748.

57 Weinz C, Schwarz T, Kubitza D, et al. Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. Drug Metab Dispos. 2009; 37: 1056-1064.

58 Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet. 2008; 47: 285-295.

59 Anastasia EJ, Rosenstein RS, Bergsman JA, et al. Use of apixaban after development of suspected rivaroxaban-induced hepatic steatosis; a case report. Blood Coagul Fibrinolysis. 2015; 26: 699-702.

60 Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. J Am Coll Cardiol. 2016; 67: 2888-2899.

61 Mlodawska E, Tomaszuk-Kazberuk A, Lopatowska P, et al. Management of patients with atrial fibrillation and chronic kidney disease in light of the latest guidelines. Pol Arch Med Wewn. 2016; 126: 353-362.

62 Stollberger C, Finsterer J. Pipe dreams about apixaban for stroke prevention in renal impairment. J Clin Pharmacol. 2016; 56: 646-647.

63 Wheeler DS, Giugliano RP, Rangaswami JR. Anticoagulation-related nephropathy. J Thromb Haemost. 2015;

64 Brodsky SV, Satoskar A, Chen J, et al. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. Am J Kidney Dis. 2009; 54: 1121-1126.

65 Brodsky SV, Nadasdy T, Rovin BH, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int. 2011; 80: 181-189.

66 Maddry JK, Amir MK, Sessions D, et al. Fatal dabigatran toxicity secondary to acute renal failure. Am J Emerg Med. 2013; 31: 462.

67 Ryan M, Ware K, Qamri Z, et al. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. Nephrol Dial Transplant. 2014; 29: 2228-2234.

68 Narasimha Krishna V, Warnock DG, Saxena N, et al. Oral anticoagulants and risk of nephropathy. Drug Saf. 2015; 38: 527-533.

69 Caldeira D, Goncalves N, Pinto FJ, et al. Risk of renal failure with the non-vitamin K antagonist oral anticoagulants: systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2015; 24: 757-764.

70 Shafi ST, Negrete H, Roy P, et al. A case of dabigatran-associated acute renal failure. WMJ. 2013; 112: 173-175.

71 Larsen TB, Skjoth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2016; 353: i3189.

ARTYKUŁ POGLĄDOWY

Działania niepożądane bezpośrednich antykoagulantów doustnych w praktyce klinicznej – nie tylko krwawienia

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SŁOWA KLUCZOWE

antykoagulanty, bezpieczeństwo, ryzyko wieńcowe, uszkodzenie nerek, uszkodzenie wątroby

STRESZCZENIE

Doustne antykoagulanty niebędące antagonistami witaminy K, zwane też bezpośrednimi doustnymi antykoagulantami (*direct oral anticoagulants* – DOAC), wprowadzono na rynek w 2008 r. z nadzieją, że ich właściwości farmakologiczne pozwolą przezwyciężyć ograniczenia w stosowaniu antagonistów witaminy K (np. warfaryny). Wprawdzie korzyści kliniczne z DOAC, zwłaszcza zmniejszenie ryzyka krwawienia wewnątrzczaszkowego, wyraźnie wykazały już badania z randomizacją przed ich wprowadzeniem na rynek, ale do ustalenia faktycznego profilu ryzyka i korzyści ważne jest monitorowanie bezpieczeństwa w fazie postmarketingowej, lepiej pokazujące efekty leczenia u „prawdziwych" pacjentów – z wieloma chorobami współistniejącymi i polifarmakoterapią. Niniejszy przegląd krytyczny ma na celu ocenę danych na temat ostatnio dyskutowanych problemów bezpieczeństwa. W pierwszej części omówimy: 1) potrzebę nadzoru nad bezpieczeństwem farmakoterapii (*pharmacovigilance*; nauka i działania dotyczące wykrywania, oceny, wyjaśniania i prewencji działań niepożądanych lub innych problemów związanych z lekami w warunkach zwykłej praktyki) oraz 2) wagę właściwej interpretacji danych postmarketingowych dla uniknięcia niepotrzebnych alarmów. W drugiej części zostaną ocenione nowe i dyskutowane problemy bezpieczeństwa potencjalnie związane ze stosowaniem DOAC w fazie postmarketingowej: 1) potencjalne ryzyko wieńcowe (dostrzeżone w fazie przedrejestracyjnej), 2) wystąpienie uszkodzenia wątroby (niewykryte w badaniach klinicznych, naświetlone w opisach pojedynczych lub serii przypadków) oraz 3) możliwość uszkodzenia nerek (zagadnienie wciąż niejasne). Uznaje się, że problemy dotyczące wątroby i nerek wciąż wymagają specjalnych badań porejestracyjnych, aby ostatecznie ustalić związek przyczynowy.

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