A Medwatch review of reported events in patients who discontinued rivaroxaban (XARELTO) therapy in response to legal advertising

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Introduction

Rivaroxaban (XARELTO) is an oral Factor Xa inhibitor anticoagulant. Studied in over 85,000 patients,[1] it was initially approved by the FDA in 2011 and is indicated to treat or prevent thrombosis in a variety of clinical settings; and when appropriately prescribed, for example in patients with atrial fibrillation, rivaroxaban has similar anticoagulant efficacy, with a lower risk of intracranial hemorrhage, as compared to the historical standard of warfarin.[1]

It is well established that anticoagulant therapy is associated with an increased risk of hemorrhage, regardless of the specific anticoagulant. Therefore, in the risk–benefit balance, an appropriate anticoagulation prescription occurs in the setting of increased thrombotic risk that justifies the increased bleeding risk. This is an important consideration, as the mitigation of the thrombotic risk attained by the use of an anticoagulant is terminated if the anticoagulant is stopped. Importantly, current evidence[2] does not suggest a rebound of thrombotic risk upon anticoagulation discontinuation; rather, the patient simply resumes the thrombotic risk that existed prior to anticoagulant initiation, and the lack of rebound thrombosis with rivaroxaban is supported by longitudinal studies.[2] However, in a patient at risk for a thrombotic event, premature discontinuation of any oral anticoagulant may increase the risk of thrombotic events, as outlined in The United States Prescribing Information for all of the newer non-warfarin anticoagulants (https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf; http://packageinserts.bms.com/pi/pi_eliquis.pdf; http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf; http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true). As a class, the novel oral anticoagulants have rapid onset of action and short half-lives; as such, it is important to avoid abrupt cessation.

Rivaroxaban is currently the subject of a class action litigation. Beginning in 2014, advertising has appeared on television, on the radio, and in print media directed toward patients who may have experienced adverse clinical events while on rivaroxaban. Described here are a series of serious medical events reported in 28 submissions of 31 individual patients to Medwatch (The FDA Safety Information and Adverse Event Reporting System; http://www.fda.gov/Safety/MedWatch/default.htm).

Case report

Overall, based on the available data, the mean age of the patients was 72 (range, 45–90), and 13 patients were male. All were prescribed rivaroxaban and subsequently discontinued their anticoagulant without consulting their physician after viewing negative rivaroxaban legal advertising.

In the majority of these cases (23/31, 75%), patients experienced a stroke or a transient ischemic neurologic event; 2 patients had persistent residual paralysis. One patient, a 45-year-old man receiving rivaroxaban for treatment of a deep vein thrombosis, stopped the drug and died of a subsequent pulmonary embolism, and 1 female patient, receiving rivaroxaban for stroke prevention, stopped the drug and died of a massive stroke (Table). All these cases were considered to be serious medical events by the health care professionals that submitted the reports.

Discussion

There are obvious numerous and significant limitations to this report. These include the limited description of clinical

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KEY TEACHING POINTS

- Novel oral anticoagulants provide a new treatment option for a variety of thrombotic conditions, including nonvalvular atrial fibrillation.
- These drugs have rapid onsets and short half-lives and should not be prematurely discontinued.
- Legal advertising concerning XARELTO (rivaroxaban) has resulted in some patients stopping XARELTO therapy and experiencing adverse clinical events, such as stroke.

patients ceased their anticoagulant and suffered an adverse event that was not reported. Finally, while the language in these forms clearly states that patients viewed legal advertising and stopped their rivaroxaban, this cannot be definitively known. However, it is clear that some patients are intimidated enough by the ongoing legal campaign to stop their anticoagulant, and thus suffer an adverse event.

These cases serve to highlight the importance of following anticoagulant prescribing information, and that physicians should emphasize that patients should not stop anticoagulants without medical consultation. Continued partnership between drug manufacturers, physicians, regulators, and patients is necessary to provide sufficient education to ensure that these important medical events do not occur.[3]

Table Summary of clinical outcomes following abrupt rivaroxaban termination as reported to Medwatch

Case	Age	Sex	Anticoagulant indication	Consequence of stopping anticoagulant	Event reported
1	NR	F	NVAF	TIA/possible stroke	September 2014
2	80	F	NVAF	DVT of arm	November 2014
3	80	M	NR	Stroke	December 2014
4	NR	M	NVAF	Stroke	January 2015
5	NR	NR	NR	Stroke	January 2015
6	80	F	NVAF	Stroke	March 2015
7	NR	M	NR	Stroke	March 2015
8	55	M	NVAF	Cardiac thrombosis	April 2015
9	NR	NR	NR	Stroke	April 2015
10	NR	M	VTE	Cerebral and lower limb thrombosis	April 2015
11	60	M	NVAF	Stroke	April 2015
12	NR	NR	NR	Stroke in 2 patients	May 2015
13	NR	F	NVAF	DVT	June 2015
14	NR	F	VTE	Pulmonary embolism	June 2015
15	45	M	VTE	Death due to pulmonary embolism	June 2015
16	90	M	NVAF	Stroke	June 2015
17	NR	NR	NR	Stroke in 3 patients	June 2015
18	NR	NR	NR	Thrombosis	June 2015
19	69	F	NVAF	TIA	July 2015
20	NR	F	NVAF	Stroke	August 2015
21	NR	NR	NVAF	Stroke	September 2015
22	NR	F	NVAF	Death following stroke	September 2015
23	NR	M	VTE	Thrombosis	September 2015
24	NR	NR	NR	Stroke	October 2015
25	NR	M	AF	Stroke	November 2015
26	70	M	NR	Stroke	November 2015
27	90	M	AF	Cardiomyopathy/TIA	December 2015
28	NR	M	AF	Stroke	December 2015

AF = atrial fibrillation; DVT = deep vein thrombosis; NR = not reported; NVAF = nonvalvular atrial fibrillation; TIA = transient ischemic attack; VTE = venous thromboembolism.

characteristics of the individual cases within the Medwatch submissions, such as prior medical history, clinical risk (eg, CHADS2 score), the lack of ability to follow up on an individual case basis, the potential for bias in the reporting mechanism that cannot be controlled, and an unknown denominator of the "at-risk" population. Further, it is not known how many patients abruptly ceased rivaroxaban and did not experience a clinical event, nor is it known how many

References

1. Sarich TC, Peters G, Berkowitz SD, et al. Rivaroxaban: a novel oral anticoagulant for the prevention and treatment of several thrombosis-mediated conditions. Ann N Y Acad Sci 2013;1291:42–55.
2. Mahaffey KW, Hellkamp AS, Patel MR, et al. End of study transition from study drug to open-label vitamin K antagonist therapy: the ROCKET AF experience. Circ Cardiovasc Qual Outcomes 2013;6:470–478.
3. Have Atrial Fibrillation? Blood Thinners Can Prevent Strokes, Save Lives. Available at ⟨http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm467201.htm⟩. Accessed December 20 2015.