

Should we CARE? Coagulation effects of Amiodarone on Rivaroxaban (Xarelto) and Apixaban (Eliquis)

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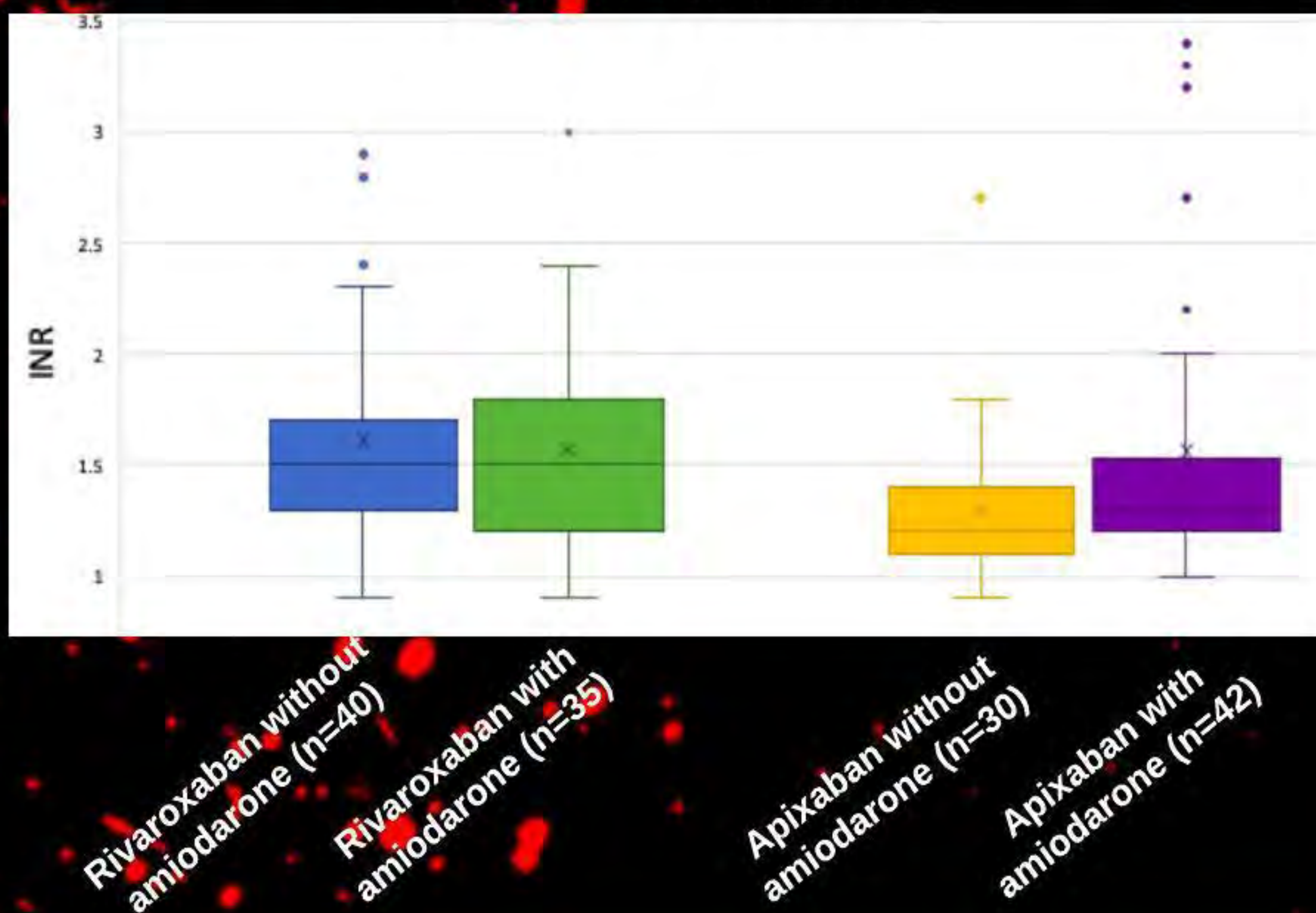
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Background: Rivaroxaban and apixaban, both have significant clearance via cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) pathways. However, impacts on bioavailability and clearance mediated by inhibition of these pathways vary between the Factor Xa inhibitors rivaroxaban and apixaban. Amiodarone, a weak CYP3A4 and strong P-gp inhibitor, has the potential to increase Factor Xa inhibitor exposure, although clinical significance of this is unclear. Despite their limitations in measuring efficacy of Factor Xa inhibitors, changes in coagulation markers such as antiXa assays, Prothrombin Time (PT) and corresponding International Normalised Ratio (INR) have some utility in determining whether amiodarone has a meaningful interaction with these drugs.

Aim: To determine whether there is a clinically significant effect of amiodarone on the coagulation markers for patients prescribed concurrent therapy with rivaroxaban or apixaban in a real world cohort.

Method: In this retrospective observational study, patients with atrial fibrillation prescribed amiodarone and rivaroxaban/apixaban (n=77) and those prescribed only rivaroxaban/apixaban (n=70) between April 2017 to December 2022 were audited. Laboratory samples were analysed for coagulation markers before and after initiation of amiodarone. We report here on INR results only.

INR Comparison of patients prescribed a factor Xa inhibitor with and without concomitant amiodarone



DID YOU KNOW?

Amiodarone does have a small drug-drug interaction with apixaban

Results: The mean INR was greater for patients prescribed both apixaban and amiodarone concurrently vs apixaban alone (1.56 vs 1.29 respectively) but not for patients prescribed rivaroxaban and amiodarone concurrently compared to rivaroxaban alone (1.57 vs 1.61 respectively). Significant interpatient variability occurred with four patients taking apixaban and amiodarone concurrently achieving INRs >3.

Figure 1: INR in patients prescribed a factor Xa inhibitor with (n=77) and without (n=70) concomitant amiodarone. There were five patients with an INR ≥ 3, four of which were prescribed apixaban. All five patients were ≥75 years, experienced hypoalbuminaemia with serum albumin levels <35g/L, and had either received high doses of amiodarone or had reached the steady state of amiodarone prior to collection of INR bloodtests. See table below.

Patient	INR	Age	Albumin (g/L)	Factor Xa	Dose (mg)
1	3.4	90	24	Apixaban	2.5mg BD
2	3.2	81	20	Apixaban	2.5mg BD
3	3.3	76	27	Apixaban	5mg BD
4	3	75	30	Rivaroxaban	20mg OD
5	3.3	94	26	Apixaban	2.5mg BD

Discussion: Our real-world data supports existing literature that amiodarone does have a small in magnitude drug-drug interaction with apixaban. However, there is significant heterogeneity in this drug interaction. Consideration of this interaction should occur in patients at high-risk of bleeding. Further research analysing other coagulation markers such as antiXa levels (and corresponding apixaban levels) is warranted to identify cohorts most at risk of this drug-drug interaction.

Depicted above is the chemical structure of apixaban