Real-world comparison of standard versus reduced dose apixaban in stroke prevention and bleeding risk in atrial fibrillation patients with chronic kidney disease: A retrospective analysis of TriNetX data.

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Introduction:

- Atrial fibrillation (AF) is prevalent in 2% of the population worldwide. Chronic kidney disease (CKD) is an independent risk factor for AF.
- Both conditions lead to a prothrombotic state, and both independently increase the risk of stroke.
- ARISTOTLE trial has demonstrated the superiority of apixaban over warfarin in thromboembolic risk mitigation and reduced bleeding risk.
- Apixaban dose reduction criteria were implemented to account for the variability in the drug's renal metabolism.
- From a Pharmacokinetic perspective exposure times is variable for different CKD, age and weight groups
- Thus the inconsistency and unclarity of the rationale behind the specific cutoffs in the dose reduction criteria
- Our study aims to examine the efficacy of reduced dose apixaban in stroke and bleeding risk mitigation in comparison to standard dosing in AF patients with CKD.
- As well as examining clinical outcomes derived from suggested cutoffs for ages and weights from pharmacokinetic studies.

Methods:

- This is a retrospective cohort study utilizing the TriNetX database
- Outcomes are risk, risk difference and risk ratio (RR) of developing ischemic stroke and bleeding in atrial fibrillation patients with CKD after apixaban initiation.
- Two cohorts were selected based on the use of apixaban 2.5 mg twice a day (bid) and 5.0 mg bid dose.
- Propensity score matching (PSM) was performed by age, BMI and confounding comorbidities.
- Further analysis was performed after stratification by CKD staging.
- Propensity score matching (PSM) is performed using a greedy nearest-neighbor matching algorithm to account for confounding variables.
- PSM in TriNetX uses a caliper of 0.1 pooled standard deviations of the propensity scores in aggregate.

Acknowledgment:
Deidentified data query and analysis through the TriNetX database
IRB Exempt

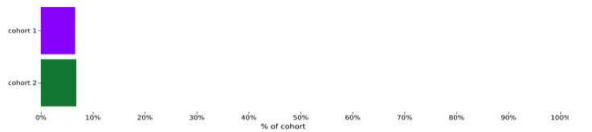
Reduced dose apixaban is just as efficacious in Stroke Mitigation for AF patients with CKD with lower risks of bleeding than full dose apixaban

Risk of Stroke

Risk analysis excluding patients with outcome prior to the time window

Cohort	Patients in cohort	Patients with outcome	Risk
2.5 mg	71,657	4,746	6.6%
5 mg	71,536	4,892	6.8%

		95% CI	z	p
Risk Difference	-0.002	(-0.005, 0.000)	-1.626	0.104
Risk Ratio	0.969	(0.932, 1.007)	N/A	N/A
Odds Ratio	0.966	(0.927, 1.007)	N/A	N/A

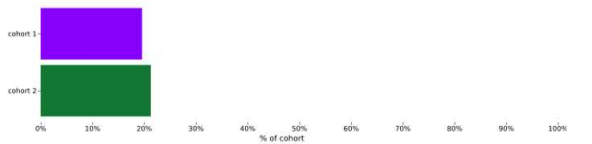


Risk of bleeding

Risk analysis excluding patients with outcome prior to the time window

Cohort	Patients in cohort	Patients with outcome	Risk
2.5 mg	59,352	11,639	19.6%
5 mg	61,207	13,037	21.3%

		95% CI	z	p
Risk Difference	-0.017	(-0.021, -0.012)	-7.270	0.000
Risk Ratio	0.921	(0.900, 0.941)	N/A	N/A
Odds Ratio	0.901	(0.876, 0.927)	N/A	N/A



Results

- After matching, the cohort included 84,032 patients in 2.5 mg bid (Cohort 1) and 5.0 mg bid groups (Cohort 2).
- The risk of stroke was not significantly different between the groups.
- The risk of stroke was 6.62 % in the 2.5 mg bid group and 6.83% in the 5.0 mg bid group with a risk difference (RD) of -0.215% (95% CI= -0.475%, 0.044%) p= 0.104.
- The risk of bleeding was significantly higher in the 5.0 mg bid group. The risk of bleeding in the 2.5 mg bid group was 18.84% and 20.411% in the 5.0 mg bid group.
- The RD is -1.57 % (95% CI =-2.023%, -1.119%) P< 0.0001. Risk ratio between groups is 0.923 (95% CI = 0.902,0.945).
- Further subgroup stratification by CKD staging have found increased bleeding risk for apixaban 5 mg bid for stages III, IV and V with consecutive risk differences of -1.682 % (95% CI = -2.206%,-1.05%) P<0.001, -4.193% (95%CI = -5.239%, -3.147%) P<0.001, -2.481% (-4.465%,-0.498%) P=0.0143.
- There was no significant difference in the risk of stroke except for stage IV where the risk of stroke was lower in the 2.5 mg bid group than the 5 mg bid group -0.653% (95% CI= -1.238%, -0.68%) P= 0.0286.
- Further stratification by age and weight have shown that they are effect modifiers
- The above age 80 group the risk of stroke was lower in the 2.5 mg group with a RD of -0.435 (-0.857,-0.013)P=0.0431.
- However, in the below 65 year old group the risk of stroke in higher in the 2.5 group in CKD stage III with a RD of 1.495 (0.062,2.928) P=0.0408 and CKD stage V RD of 2.585 (0.181,4.988)P=0.0353.
- For weight above 264 the risk of stroke was higher with a RD of 3.196 (0.24,6.151)P=0.032. Bleeding risk after stratification by age and weight was lower across the board for the 2.5 mg group.

Conclusion

- Our results are from a purely clinical real-world perspective support the efficacy of both doses in stroke mitigation with lower risks of bleeding in the reduced dose apixaban.
- As regards to Bleeding risk dose reduced apixaban is superior to standard dose in CKD patients regardless of age and weight.
- Reduced dose is efficacious for stroke risk mitigation, however obesity and younger age correlate with statistically higher risk of stroke albeit with weak significance.