Thrombotic events associated with low baseline direct oral anticoagulant levels in atrial fibrillation: the MAS study

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Background

- Over the last years, clinical trials, meta-analyses, and clinical practice records confirmed the efficacy and safety of direct oral anticoagulants (DOACs) for stroke prevention in patients with nonvalvular atrial fibrillation (AF).
- However, a nonnegligible incidence of thrombotic and bleeding events has been recorded in clinical trials and in observational studies in patients receiving DOACs.
- In addition, very recent studies showed a relationship among low DOAC levels (generally measured after the events), the risk of ischemic stroke and its severity and the risk of stroke recurrences.

AIM of the study

To investigate whether low DOAC plasma levels, assessed at steady-state within the first month of treatment, are associated with thrombotic events during a 1-year follow-up.

Methods

- The Measure and See study (MAS) is an observational, prospective cohort, multicenter study of patients with AF, who started treatment with DOACs.
- Consecutive patients with AF, without rheumatic mitral valve disease or mechanical heart valves, aged >18 years, were enrolled in the study.
- The study required a mandatory plasma collection to measure the DOAC level for each enrolled patient.
- Venous blood sampling was performed at a steady state (within the first 2-4 weeks of initiation of treatment) and obtained immediately before the subsequent drug intake.
- The predefined study outcomes were all thromboembolic complications, including objectively documented ischemic cerebral vascular events, systemic emboli, the occurrence of acute venous thromboembolism (VTE), acute myocardial infarction, and thrombotic and cardiovascular deaths.

Results (I)

- A total of 1657 patients had blood sampling for DOAC level measurement.
- During a total follow-up of 1606 years, thromboembolic outcomes occurred in 21 patients (incidence of 1.31% pt/y).
- DOAC plasma levels were the most important independent predictor of the occurrence of the primary study outcome, even after adjustment for other possible confounders and enrollment centers.

Table 3. Effect of standardized plasma DOAC levels on the primary thrombotic outcome end point, adjusted for potential confounders

	First model (C-trough), n = 1657		Second model (C-peak), n = 1298	
Characteristic	**HR**	**95% CI**	**HR**	**95% CI**
Standardized C-trough DOAC	0.56	0.37-0.86	-	-
Standardized C-peak DOAC	-	-	0.19	0.06-0.66
CHA_2DS_2VASc score	2.01	1.02-3.97	2.07	1.26-3.39
BMI, kg/m^2	0.93	0.80-1.08	0.95	0.82-1.09
Glomerular filtration rate, mL/min	1.02	1.00-1.05	1.02	0.99-1.05
Low-dose vs standard dose DOAC	3.49	0.76-16.0	2.72	0.55-13.5
Antiplatelet treatment (yes vs no)	0.28	0.03-2.53	0.25	0.03-1.81

Both models were estimated using the Fine and Gray competitive risk regression model. The Akaike information criteria was 118.4 and 106.1 for the models using C-trough and C-peak, respectively.

The inclusion of enrollment center as a potential confounder was not significant ($P > 0.9$ for both models) and it is not reported because it did not materially change estimates.

CI, confidence interval; HR, hazard ratio.

Results (II)

- Patients with thrombotic outcomes had C-trough DOAC values below the mean value for each drug in 17 (1.7% pt/y) cases, whereas 4 (0.69% pt/y) cases had values above the mean value.
- The highest incidence of thrombotic events (4.82% pt/y) occurred among 89 patients with standardized DOAC values in the lowest class (−1.00 or less) compared with the mean value; the incidence of events decreased sharply in the other classes.

Figure 2. Measured C-trough DOAC levels assessed at steady-state in atrial fibrillation patients who experienced thrombotic outcomes within 1 year follow-up. Blue dots represent the values and dotted lines represent the mean values of each drug.

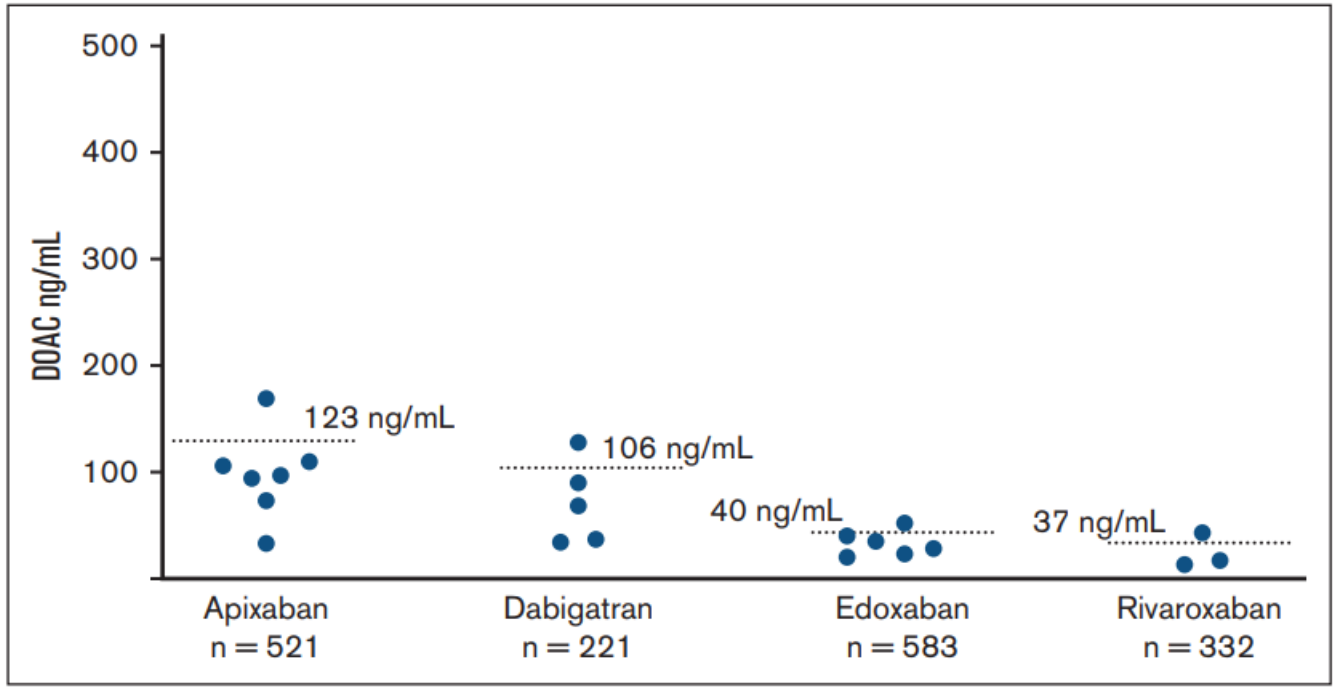
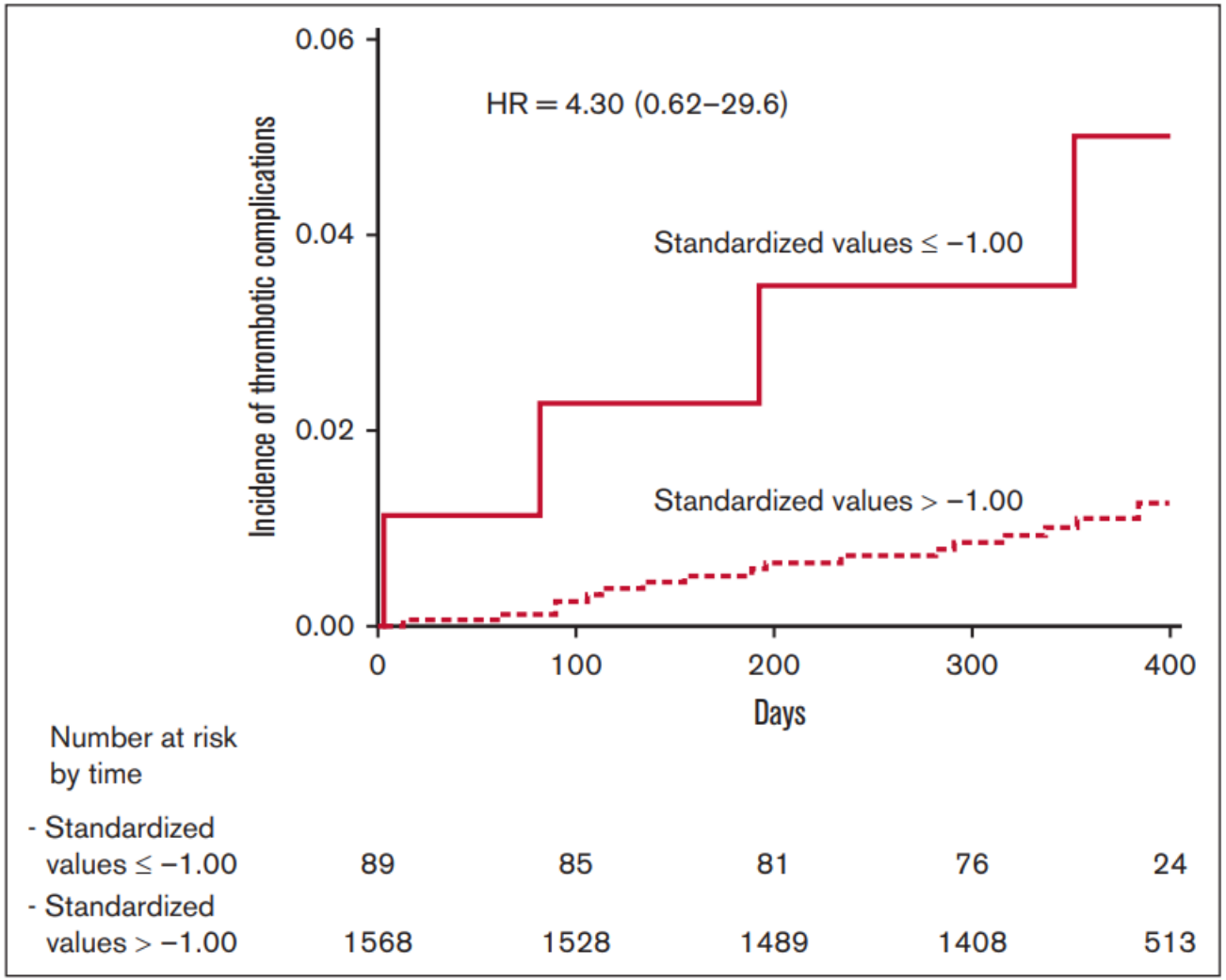


Figure 3. Cumulative event rates for thrombotic outcomes. The Kaplan-Meier cumulative event rates for the thrombotic outcomes in patients with DOAC levels in the standardized class of −1.00 or less (continuous line) and in patients with DOAC levels in the standardized classes of more than −1.00 (dotted line) at C-trough. HR, hazard ratio.



Conclusions

- In conclusion, the trial show a clear relationship between low DOAC levels measured at steady state and the occurrence of stroke, TIA, VTE and other thrombotic cardiovascular events in patients with AF.
- These findings may pave the way to future studies aimed to definitively assess whether measuring DOAC plasma levels at steady state in selected patients may reduce the incidence of thrombotic complications during follow-up in the setting of patients with AF.