Predictors of clinically relevant bleeding and overdose in prospectively followed cohort of dabigatran treated stroke patients

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Background

Dabigatran is direct thrombin inhibitor approved in the prevention of stroke in patients with AF. It was shown in the RELY trial substudy (1) that genetic variants could contribute to interindividual variability in concentrations of the active metabolite of dabigatran and influence the safety of treatment. Carriage of the **CES1 rs2244613** minor allele was in RE-LY pharmacogenetics substudy associated with lower exposure to active metabolite and with a **lower bleeding risk** compared to wild-type allele (1).

Aim of the study

To determine the influence of *CES1* polymorphism rs2244613 on occurrence of clinically relevant bleeding (CRB) or higher plasmatic levels in dabigatran treated stroke patients.

Methods

Prospective observational monocentric (Comprehensive stroke centre) study in consenting cardioembolic stroke patients initiated on dabigatran.

Primary outcome was clinically relevant bleeding (CRB) defined as composite of major bleeding (ISTH criteria), clinically relevant non-major bleeding and/or dabigatran through plasmatic level $c_{min} > 300$ ng/ml.

Secondary outcomes were death from any cause, recurrent ischemic stroke/TIA/myocardial infarction.

Bleeding definitions

ISTH major bleeding in non-surgical patients:

1) Fatal bleeding. 2) Bleeding in a critical area or organ, 3) Bleeding causing a fall in haemoglobin level of 20 /L or leading to transfusion of 2 or more units

Clinically relevant non-major bleeding: Bleeding episode not meeting ISTH definition of major bleeding but does meet at least 1 of the following criteria: 1) requiring medical intervention by a healthcare professional. 2) leading to hospitalization or increased level of care. 3) prompting a face-to-face healthcare professional evaluation.

DNA analysis of *CES1* polymorphism rs2244613 was done with RFLP analysis.

Through concentration of dabigatran (c_{min}) was measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS) at least 7 days after initiation, therapeutic range 50-200 ng/ml. Overdose was defined as $c_{min} > 300$ ng/ml.

Statistical analysis – T-test, Chi2, Fisher exact, Mann Whitney U test, Cox regression, Kaplan Meier (SPSS 24, IBM).

Results

110 patients after cardioembolic stroke were enrolled and followed up for mean 19.9 months.

	Clinically relevant bleeding and overdose group (n=12)	Group without clinically relevant bleeding and overdose (n=98)	Difference between groups
Age, years; mean (SD)	75.1 (7.9)	69.6 (13.0)	0.109
Male sex	6 (50%)	50 (51%)	1.0
Weight, kg; mean (SD)	79.9 (16.0)	80.4 (1.5)	
Follow-up time, months; mean (SD)	8.6 (10.3)	21.3 (19.6)	0.007*
CHA ₂ DS ₂ -VASC; mean (SD)	5.8 (1.1)	4.8 (1.9)	0.032*
HAS-BLED; mean (SD)	3.7 (1.5)	3.2 (1.6)	0.819
Hypertension	11 (91.7%)	71 (72.4%)	0.290
Diabetes mellitus	4 (33.3%)	32 (32.7%)	1.0
Heart failure, ejection fraction of left ventricle <35%	3 (25.0%)	13 (13.3%)	0.208
Serum creatinine, umol/L; mean (SD)	88.4 (20.6)	80.2 (22.5)	0.898
CES1 variant allele	1 (8.3%)	41 (41.8%)	0.028*
Ischemic stroke/TIA/MI	2 (16.7%)	10 (10.2%)	0.618
Mortality, any cause	2 (16.7%)	4 (4.1%)	0.445
Dosage 150 mg bid	6 (50.0%)	72 (73.5%)	0.104

There were 8 episodes of CRB and 4 patients with c_{min} above 300 ng/ml. There were **8 episodes of clinically relevant bleeding, all in patients with wild-type genotype**: 3x gastrointestinal, retroperitoneal, intracerebral, 2x subcutaneous and hemoptysis. **5 patients died**: intracerebral bleeding, cardiac arrest, 2x sepsis + pneumonia, 1x unknown cause.

Carriers of minor allele were less likely to have the outcome:

HR 0.124 (95% CI 0.02 – 0.96, p = 0.046).

Conclusion

Patients with minor allele had significantly lower risk of CRB or increased level of dabigatran. Dabigatran dosing based on pharmacogenetics should be studied in future trials with aim to increase the safety of treatment.