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Possible timing for anticoagulation therapy initiation in ischemic stroke patients with atrial fibrillation: further analysis of the hemorrhagic transformation index

Objective: *to assess the risk of hemorrhagic transformation (HT), by taking into account an appropriate scale (the hemorrhagic transformation index (HTI)) to clarify the possible timing of anticoagulant therapy (AT) initiation in patients with atrial fibrillation (AF) and ischemic stroke (IS) in the middle cerebral artery (MCA) bed.*

Patients and methods. *The admission data of 304 consecutively selected patients (111 men and 193 women aged 32 to 94 years (mean age, 72.7 years) with any form of AF and IS in the MCA basin were analyzed. The end point of the study was any HT according to brain computed tomography findings in the first 2 weeks after the development of IS. The HTI scores were divided into categories based on their predicted HT probabilities, thus yielding four models. Their comparison with the standard (the Diener rule) and the choice of the most appropriate model were done using the binary logistic regression and appropriate analysis (receiver operating characteristic, ROC). The final HTI model and the Diener rule were further used in the Royston–Parmar survival analysis to predict the risk of HT by days after the onset of IS. This was used to plot hazard function and survival, as well as the number of patients to be treated (number needed to treat, NNT) and the number of patients who can be harmed (number needed to harm, NNH). Possible periods for AT initiation were determined by the NNT and NNH plots.*

Results and discussion. *All the HTI models under study were superior to the Diener's rule in the accuracy of HT prediction. However, the HTI model with 0–1, 2–3, 4–5, 6–8 score arrangements was found to be the best one, as shown by the results of tests; it could additionally identify patients at very high (>0.8) risk for HT and somewhat better differentiate patients at low (0.05–0.1) risk. A survival analysis showed that the hazard function peaked on 1 and 3 days after the onset of IS. There was a progressive NNT drop in patients with a HTI score of 0–1 on 1 to 3 days; their curves reached a plateau on day 4. In patients with a HTI score of 2–3, NNT declined on days 1 to 4, with a plateau on day 5. In those with a HTI score of 4–5, NNH was minimal within the first 3 days following the onset of IS, and then there was a significant NNH rise until the end of the second week. In patients with a HTI score of 6–8, NNH remained very low throughout the follow-up period with a significant increase on days 4 to 9, with a subsequent exit to the plateau.*

Conclusion. *The greatest risk of HT is observed on 1 and 3 days after the onset of IS. AT is recommended to patients with a HTI score of 0–1 on day 4 after the onset of IS, to those with a HTI score of 2–3 on day 5, and to those with a HTI score of 4–5 following 2 weeks. AT may be initiated in patients at very high risk for HT (a HTI score of 6–8) on 9 days, provided that HT is absent.*

Keywords: *ischemic stroke; hemorrhagic transformation; atrial fibrillation; anticoagulants, prognosis; survival analysis.*
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Background

Atrial fibrillation (AF) remains the leading cause of acute ischemic stroke (AIS) worldwide. Recent studies have shown that AF is revealed in 20%P30% of patients before, during, or soon after a cerebral cardioembolic event. Moreover, about 13%P26% of AIS cases are associated with non-valvular AF [1, 2]. In non-valvular AF the risk of AIS is 5-fold increased, and in AF with mitral stenosis – 20-fold. AF-related AIS is often associated with a high rate of hemorrhagic transformation (HT), stroke recurrences and a poor functional outcome [3, 4].

Anticoagulation therapy (AT) is the cornerstone of AIS primary and secondary prevention in AF patients [1, 3]. However, its immediate initiation after the onset of AIS may increase HT risk, but a delay in AT might be associated with a high rate of stoke recurrences. The evidence-based data on AT timing in AIS patients with AF are still missing. For example, the American Heart Association/American Stroke Association (AHA/ASA) guidelines advise an individual-based approach to initiate AT for the majority of AIS patients with AF within 4P14 days after AIS onset taking into account possible cardioembolic and hemorrhagic risks, and for patients with a high risk of HT – beyond that time frame [3, 5, 6]. Since 2013, the European Heart Rhythm Association practical recommendations on non-valvular AF have been based on the consensus opinion known as the 1P3P6P12-

day rule (the Diener's rule), which considers only one criterion – clinical severity of stroke according to the National Institutes of Health Stroke Scale (NIHSS) [7, 8]. As far as this criterion is concerned, it is not obvious enough for the decision-making, taking into account that HT in its phenomenology is a complex and multifactorial pathological process, which includes the degree of brain ischemia, coagulopathy, blood-brain barrier disruption, and reperfusion injury. Thus, HT prediction may exert considerable influence on AT timing.

Recently, we have developed and validated the Hemorrhagic Transformation Index (HTI) score, which predicts HT in patients with AIS in the middle cerebral artery (MCA) territory within 2 weeks after the onset [9]. Although there are a variety of similar scores, their prediction effects on possible AT timing in AIS patients with AF have not been studied yet.

The main objective of our study was HT risk assessment with the HTI score to infer possible AT timing in patients with MCA AIS and AF.

Methods

The research was a post hoc analysis of our previous study [9]. Using our prior database consisting of 783 MCA AIS patients who were admitted to our stoke unit within 12 h after the onset, we selected 304 consecutive patients with AF (111 men, 193 women, aged 32 P 94 years old; mean age 72.7 years). The eligible patients underwent diagnostic tests and received treatment in accordance with the current National Stroke Guidelines. The permissible hospital length of stay was at least 14 days, which was determined by the state mandatory medical insurance standard for AIS patients.

Clinical baseline variables, including age, sex, risk factors, antithrombotic medication, stroke subtype according to the Trial of ORG 10172 in Acute Stroke Treatment classification, NIHSS score, vital signs, blood tests, electrocardiogram (ECG) and echocardiogram findings on admission were extracted from the medical charts. The HT day was considered as a day from the AIS onset when HT was clinically and/or radiologically documented. The term Tnon-valvular АFУ referred to AF in the absence of a mechanical prosthetic heart valve or moderate to severe mitral stenosis (usually of rheumatic origin) [7].

Brain non-contrast computed tomography (CT) was routinely performed for all AIS patients to assess the Alberta Stroke Program Early CT score (ASPECTS), hyperdense MCA sign, and leukoaraiosis [9]. A follow-up CT scan was usually repeated on hospitalization day 7 and 14 or at any time if required by a treating neurologist. All patients had at least one follow-up CT scan.

The endpoint was retrospectively analyzed based on the prospectively collected data. Any HT on a follow-up CT scan within 14 days after AIS onset was taken into account. A hemorrhage was considered clinically relevant if it was not seen on a previous CT scan and there was subsequently either a suspicion of hemorrhage or any decline in neurologic status [10]. According to ECASS study data [11], HT was further classified into either hemorrhagic infarction type 1 or type 2, or parenchymal hematoma type 1 or type 2.

This study was approved by the Local Ethics Committee of the Kazan State Medical University, Kazan, Russia. The informed consent was not required since the study was observational and retrospective in nature.

Statistical analysis

The descriptive statistics included median values (M) with the interquartile range (IQR) and percentage for continuous (the distribution was not normal) and categorical data respectively. The NIHSS, ASPECTS, and HTI data were treated as continuous variables because of multiple categories. The baseline data were compared between groups of patients using the MannPWhitney U test or Pearson ?2 test for continuous and categorical variables respectively.

To simplify the HTI score for the prediction of AT timing, the HTI points were arranged into categories based on their predicted probabilities of HT. As a result, 4 models were created. Their predictive abilities were compared against each other and against the Diener's rule using binary logistic regression (BLR). Bootstrapping was performed with 1000 pseudosamples with subsequent computing of odds ratio and bias-corrected and accelerated (BCa) confidence intervals (CIs) to reduce sampling bias, overfitting, and prediction errors. Once the BLR coefficients were obtained, the marginal effects were estimated: the category mean predicted probabilities of HT and Sidak-adjusted for multiple comparison 95% CIs were calculated using the delta-method.

The final HTI model was chosen based on the results of the post-estimation tests and receiver operating characteristic (ROC) analysis. The strength of the evidence against the model with a higher Bayesian information criterion (BIC) value was as follows: 0–2 – weak; 2–6 – positive; 6–10 – strong; >10 – very strong [12]. Each area under the ROC-curve (AUC) was compared against the standard, the Diener's rule. For each comparison, a Sяid?k-adjusted p-value was reported. AUC equality was evaluated by using the DeLong algorithm [13]. The AUC with corresponding 95% CIs were calculated with the 10-fold cross-validation method [14].

Once the final HTI model was selected, HT timing was predicted using the Royston–Parmar (RP) parametric survival analysis* [15]. The predictors were either the chosen HTI model or the Diener's rule. The proportional hazard assumption was assessed with the Schoenfeld residuals test using the Cox regression. If the assumption was violated, the time-dependent effects were included into the RP regression. The scale of the RP regression coefficients (hazard, odds, probit, or proportions), and the degree of freedom of the baseline function and time-dependent effects were estimated in an exploratory manner with minimal values of the Akaike information criterion (AIC) and BIC. Goodness of fit of the HTI model and the Diener's rule was assessed with the Harrell's C and Somers' D index of con-

*Survival analysis is a type of statistics for analyzing the expected duration of time until one or more events happen. In this regard, we use some special terms: the hazard function is the instantaneous rate at which HT occurs given no previous events; the survival function is the probability that a patient will not have HT by a certain time point; the baseline function is the hazard or survival function calculated with no predictors; the number needed to treat (NNT) is the average number of patients prevented from HT provocative factors needed for saving one additional patient from having HT; the number needed to harm (NNH) is the average number of patients exposed to HT provocative factors needed for developing HT in one additional patient. Obviously, the less the NNT, the better, and vice versa, the less the NNH, the worse. The hazard and survival functions, the NNT and NNH are reciprocal terms.

Table 1. Baseline data of AIS patients with AF on admission.

	Any HT, *n* = 117	No HT, *n* = 187	*p*
Risk factors, *n* (%)			
Age, y, M (IQR)	75 (67–80)	75 (66–80)	0.757
Male sex	38 (32.5)	73 (39.0)	0.248
Hypertension	112 (95.7)	171 (91.4)	0.152
Dyslipidemia	33 (28.2)	67 (35.8)	0.169
Diabetes mellitus	40 (34.2)	54 (28.9)	0.330
Recurrent stroke/TIA	56 (47.9)	89 (47.6)	0.963
Myocardial infarction	10 (8.6)	9 (4.8)	0.191
Alcohol abuse	4 (3.4)	11 (5.9)	0.335
Blood tests, M (IQR)			
Random blood sugar, mmoL/L	7.69 (6.54–10.10)	6.75 (5.75–8.01)	<0.001
Platelets, × 10^9/L	231 (182–271)	230 (189–275)	0.503
White blood cells, × 10^9/L	8.4 (6.3–10.2)	7.7 (6.3–9.3)	0.095
INR	1.06 (1.02–1.20)	1.09 (1.02–1.29)	0.146
APPT, s	32.0 (29.3–35.5)	32 (28.3–35.3)	0.826
Creatinine, µmoL/L	87.0 (77.2–104.9)	92.9 (80.1–110.5)	0.094
ALT, U/L (*n* = 117/186)	21 (16–33)	20 (14–30)	0.162
AST, U/L (*n* = 113/169)	27 (21–25)	24 (19–33)	0.050
Bilirubin, total, µmoL/L (*n* = 113/175)	13.1 (9.4–20.3)	12.6 (9.1–18.5)	0.618
Cholesterol, total, mmoL/L (*n* = 100/156)	4.68 (4.15–5.52)	4.97 (4.25–5.79)	0.079
Clinical data, M (IQR)			
Onset-to-admission time, h	3.0 (1.5–8.0)	4.5 (2.0–10.0)	0.005
CHA_2DS_2-VASC (before current stroke)	6 (5–6)	5 (4–6)	0.120
HTI	5 (4–7)	1 (1–2)	<0.001
NIHSS	20 (16–24)	8 (5–14)	<0.001
ASPECTS	4 (1–6)	7 (6–9)	<0.001
Hyperdense MCA sign, *n* (%)	84 (71.8)	33 (17.7)	<0.001
AF on ECG, *n* (%)	99 (84.6)	142 (75.9)	0.069
Non-valvular AF, *n* (%)	109 (93.2)	164 (87.7)	0.126
Prosthetic valve, *n* (%)	0 (0)	10 (5.35)	0.011
Leukoaraiosis (on CT), *n* (%)	84 (71.8)	122 (65.2)	0.234
ECG heart rate, bpm	93 (77–111)	86 (70–100)	0.007
EF, % (*n* = 114/175)	53 (46–58)	55 (47–60)	0.107
Systolic blood pressure, mm Hg	160 (140–180)	150 (135–170)	0.119
Diastolic blood pressure, mm Hg	90 (80–100)	90 (80–100)	0.741
Treatment, *n* (%)			
IV rtPA	20 (17.1)	21 (11.2)	0.145
Antiplatelet	68 (58.1)	111 (59.4)	0.831
Anticoagulant	6 (5.1)	24 (12.8)	0.028
Antiplatelet + anticoagulant	23 (19.7)	31 (16.6)	0.494
Poor outcome, *n* (%)			
Death	27 (23.1)	11 (5.9)	<0.001
Dependency	108 (92.3)	121 (64.7)	<0.001
HT detection day, M (IQR)	2 (1–4)		
HT types, *n* (%)			
Symptomatic	70 (59.8)		
Hemorrhagic infarction, type 1	10 (8.6)		
Hemorrhagic infarction, type 2	73 (62.4)		
Parenchymal hematoma, type 1	11 (9.4)		
Parenchymal hematoma, type 2	23 (19.6)		

Note — *ALT*: alanine aminotransferase; *AST*: aspartate aminotransferase; *APPT*: activated partial thromboplastin time; *IV rtPA*: intravenous recombinant tissue plasminogen activator; *INR*: international normalized ratio; *TIA*: transient ischemic attack; *EF*: ejection fraction of the left ventricle (echocardiogram, Simpson method).

cordance, AIC and BIC, and explained variation (R2D). The hazard functions for each HTI and Diener's category were plotted. If the curves were below the baseline hazard function, the NNT was calculated: 1 / (category survival function – baseline survival function). Respectively, the NNH was computed, if the graphs were above the baseline hazard function: 1 / (category hazard function – baseline hazard function). Possible timing for AT was inferred by using the NNT and NNH charts.

Results

The baseline data of the AIS patients with AF are listed in Table 1.

There were statistical differences between the HT-positive and negative groups in the HT predictors (AT, random blood sugar, ECG heart rate, NIHSS, ASPECTS, HTI, and hyperdense MCA sign), poor outcome (death, or dependency defined as the modified Rankin scale >2 at discharge), and onset-to-admission time. However, further multivariate BLR adjustment for the random blood sugar, AT, ECG heart rate, poor outcome, and onset-to-admission time variables exerted no significant effect on odds ratio (OR) (Table 2). Patients with AF and prosthetic valves were absent in the HT-positive group due to a small sample size. Therefore, they were excluded from the multivariate analysis.

The HTI score arrangement into categories and the models of their comparison with the Diener's rule for predicted probabilities of HT are demonstrated in Table 3 and Figure 1.

The BLR analysis showed that the Diener's rule and the HTI models were well-fitted and statistically significant in HT prediction; their link functions were chosen correctly. However, the BIC

Table 2. BLR (Binary logistic regression). Crude and adjusted odds ratio (OR). The adjustment was made for random blood sugar, ECG heart rate, onset-to-admission time, AT, and poor outcome.

	Crude		Adjusted		Difference	
	OR (95% BCa CI)	*p*	OR (95% BCa CI)	*p*	$\chi^2(1)$	*p*
Diener's rule	5.08 (3.52–7.36)	<0.001	4.09 (2.39–6.41)	<0.001	3.57	0.059
Model 1	6.92 (4.72–10.56)	<0.001	6.26 (3.85–9.57)	<0.001	1.01	0.316
Model 2	4.62 (3.44–6.60)	<0.001	4.43 (2.88–6.37)	<0.001	0.20	0.657
Model 3	5.96 (4.23–8.67)	<0.001	5.79 (3.59–8.31)	<0.001	0.08	0.775
Model 4	8.08 (5.30–13.87)	<0.001	7.29 (4.05–12.60)	<0.001	0.71	0.399

Table 3. HTI score arrangement into categories and their matching to the Diener's rule by predicted probabilities of HT.

Diener's rule			Model 1		Model 2		Model 3		Model 4	
AT timing, day	NIHSS category	PP (95% CI)	HTI category	PP (95% CI)	HTI category	PP (95% CI)	HTI category	PP (95% CI)	HTI category	PP (95% CI)
1	TIA									
3	<8	0.079 (0.025–0.133)	0	0.020 (0.000–0.041)	0–1	0.052 (0.006–0.098)	0–1	0.055 (0.012–0.098)	0–1	0.050 (0.006–0.094)
6	8–16	0.303 (0.222–0.384)	1–2	0.121 (0.053–0.189)	2	0.202 (0.110–0.294)	2–3	0.257 (0.165–0.348)	2–3	0.299 (0.205–0.392)
≥12	>16	0.689 (0.594–0.783)	3–4	0.488 (0.389–0.587)	3–4	0.539 (0.442–0.636)	4–5	0.673 (0.571–0.775)	4–8	0.775 (0.688–0.862)
			5–8	0.868 (0.787–0.950)	5–8	0.844 (0.765–0.923)	6–8	0.925 (0.869–0.980)		

Note — *PP*: predicted probability of any HT over the next 2 weeks after AIS onset.

differences between the Diener's rule and each HTI model exceeded 10. Hence, there was a strong evidence for superiority of all HTI models. HTI model 3 proved to be the best in the post-estimation tests and ROC-analysis. Therefore, it was chosen for further survival analysis (Table 4).

The HTI 0–1 and 2–3 categories of model 3, and the NIHSS <8 and 8–16 categories of the Diener's rule were similar in predicted probabilities of HT as well as in the distribution of patients. However, the HTI was superior to the Diener's rule in the detection of patients with a low HT probability (Figures 1 and 2). The HTI 4–5 category and the NIHSS >16 were similar only in their predicted probabilities of HT. The BLR marginal effects demonstrated that the Diener's rule could not predict HT probability of >80%. By contrast, HTI model 3 could detect such patients; there was also the HTI 6–8 category which encompassed the remaining 20% of the patients.

The NIHSS >16 category was heterogenous – it included patients with low and high HTI scores (Figure 3A). There was a clear overlap in the distribution of NIHSS scores between the categories of all HTI models, which could be an indirect evidence that using a complex model for HT prediction was more accurate than a simple one (Figure 3B–F).

In the survival analysis, the proportional hazard assumption was violated in HTI model 3 (the Schoenfeld residuals test: ?2(1) = 18.58, p <0.001), but was met in the Diener's rule (?2(1) = 1.48, p = 0.224). The baseline hazard function had minimal values of the AIC and BIC at the degree of freedom of 4 on the hazard scale. The time-dependent effects of HTI model 3 had minimal values of the AIC and BIC at the degree of freedom of 2. HTI model 3 as well as the Diener's rule were statistically significant predictors of HT risk (HTI model 3: exponential coefficient, 2.85, 95% CI, 2.34–3.45, p <0.001; the Diener's rule: exponential coefficient, 3.58, 95% CI, 2.66–4.83, p <0.001). However, the goodness-of-fit statistics confirmed the superiority of HTI model 3 over the Diener's rule (Table 5).

As a result of RP survival analysis predictions, the baseline hazard function peaked on day 1 and 3 after the AIS onset then it logarithmically declined over the remaining days. The category hazard functions of HTI model 3 and the Diener's rule mirrored the baseline configuration. However, the hazard function of the HTI 0–1 and 2–3, and NIHSS <8 and 8–16 categories was below the baseline function, but was above it in the HTI 4–5, 6–8, and NIHSS >16 groups (Figure 4 A–B).

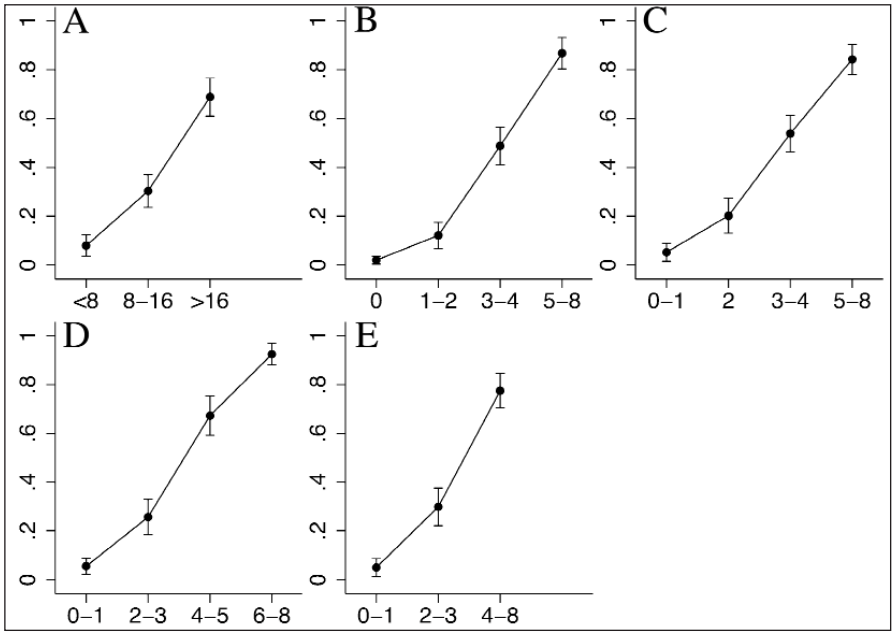

Figure 1. *BLR marginal effects. Black circles — mean value of HT predicted probability; whiskers — 95% CIs; Y-axis — predicted probability; X-axis — NIHSS (A) and HTI (B–E) score arrangement into categories (Table 3). A. Diener's rule. B. Model 1. C. Model 2. D. Model 3. E. Model 4.*

Although the HTI 4–5 and NIHSS >16 categories were similar in their predicted HT probability (Table 3, Figure 1), they were different in the hazard function — half of the patients in the former group would develop HT by day 6 whereas in the latter one — by day 3 (Figure 4C–D).

From day 1 to 3, there was a progressive NNT decline in the HTI 0–1 and NIHSS <8 categories followed by the plateau from day 4 onwards (Figure 4E). Hence, it seemed to be safe to initiate AT in those patients on day 4 since further delay would not gain any benefit for HT risk reduction. The similar pattern was seen in the HTI 2–3 and NIHSS 8–16 categories — the NNT was falling from day 1 to 4 followed by a level-off over the remaining days. Therefore, AT could be started on day 5 in those patients.

In the HTI 4–6 and NIHSS >16 categories, the NNH was minimal over the first 3 days after AIS onset then it rose sharply over the remaining days. Indeed, there was a 5.4-fold absolute HT risk

Table 4. BLR post-estimation tests and ROC-analysis.

	Diener's rule	Model 1	Model 2	Model 3	Model 4
Likelihood ratio test					
Deviance (d.f. = 92)	312.48	256.49	252.54	239.57	262.20
Wald χ^2 (d.f. = 1)	67.17	77.21	76.77	89.49	71.17
p	<0.001	<0.001	<0.001	<0.001	<0.001
Pseudo-R^2					
McFadden	0.229	0.367	0.377	0.409	0.353
Cox–Snell	0.263	0.387	0.395	0.420	0.375
Nagelkerke	0.357	0.525	0.536	0.570	0.510
McKelvey and Zavoina	0.355	0.506	0.514	0.551	0.495
Tjur's *D*	0.279	0.445	0.448	0.479	0.424
Information criteria					
AIC	316.48	260.49	256.54	243.57	266.20
BIC (d.f. = 2)	323.91	267.92	263.97	251.01	273.63
Variance					
Error, ε	3.290	3.290	3.290	3.290	3.290
Latent variable, *y**	5.103	6.659	6.768	7.321	6.518
Goodness of fit					
Hosmer–Lemeshow χ^2 for 10 groups (d.f. = 1/1/2/2/1)	0.02	0.58	3.35	2.59	1.00
p	0.875	0.448	0.187	0.274	0.317
Pearson χ^2 (d.f. = 1/2/2/2/1)	0.02	1.23	3.35	2.59	1.00
p	0.875	0.542	0.187	0.274	0.317
Pregibon link test					
Linear predicted value, *p*	<0.001	<0.001	<0.001	<0.001	<0.001
Linear predicted value squared, $\hat{p}$	0.875	0.299	0.133	0.201	0.320
ROC-analysis					
AUC (95% CI)	0.760 (0.704–0.816)	0.831 (0.779–0.882)	0.855 (0.809–0.902)	0.862 (0.816–0.908)	0.831 (0.781–0.882)
χ^2 (d.f. = 1)	–	14.63	24.52	25.57	12.75
p	–	<0.001	<0.001	<0.001	0.001

Note: *d.f.* — degree of freedom

reduction in the HTI 4–5 category from day 1 to 5 followed by a 2.2-fold decrease from day 6 to 14 (Figure 4A, F). Thus, a two-week delay of AT could be reasonable for HT risk mitigation.

In patients with a predicted probability of HT >80% (the HTI 6–8 category), the NNH remained very low throughout the entire observation. Half of those patients would develop HT by day 2. However, there was a slight NNH increase from day 4 to 9 followed by the plateau with an absolute HT risk reduction by only 1.2 times (Figure 4A, C, F). Hence, it could be reasonable to initiate AT in those patients who survived on day 9 since further delay would insignificantly reduce the HT risk.

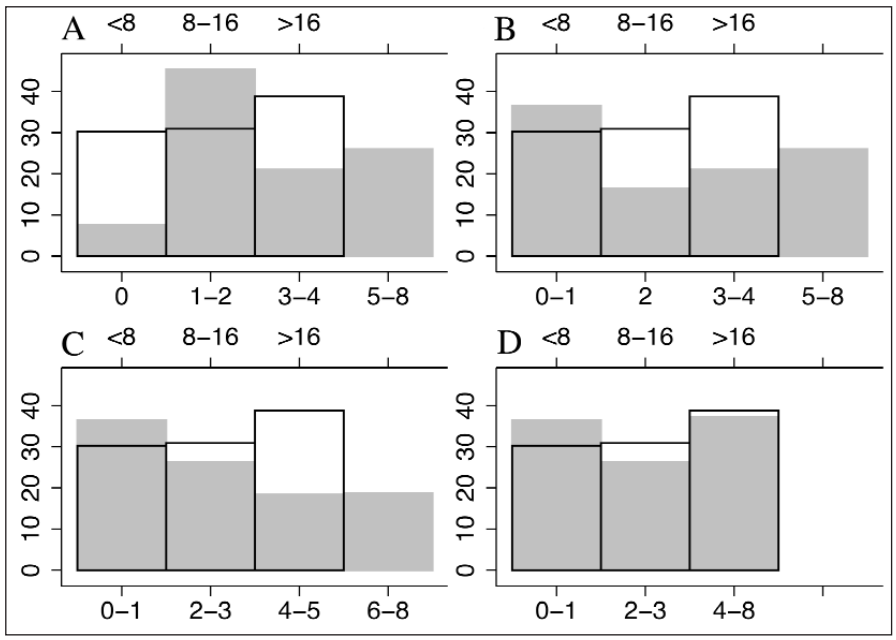

Figure 2. *Histograms of patients distribution into categories. Y-axis – percentage; X-axes – NIHSS (upper axis) and HTI (lower axis) score arrangement into categories (Table 3); outlined histograms – Diener's rule; grey histograms – HTI models. A. Model 1. B. Model 2. C. Model 3. D. Model 4.*

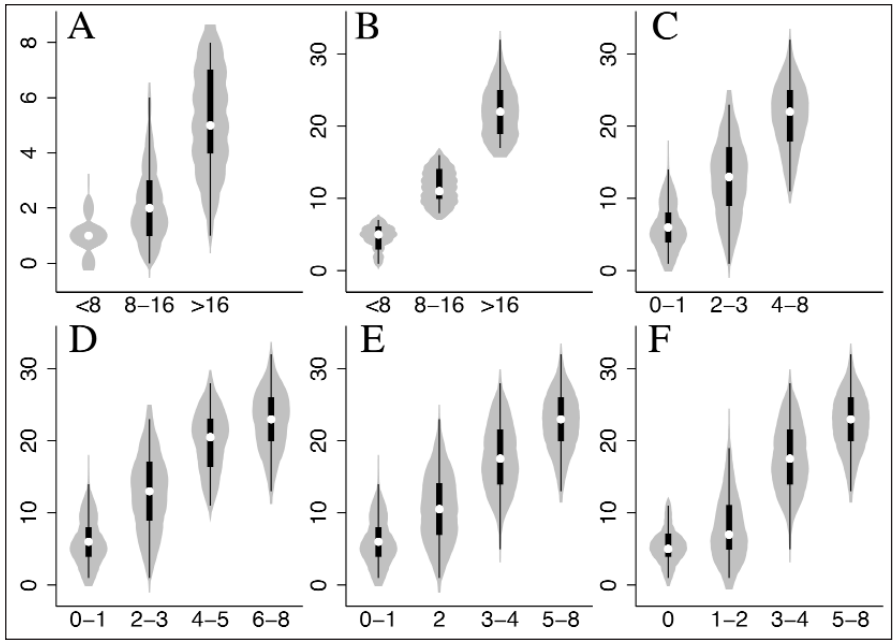

Figure 3. *Violin plots. White circles – median values; black rectangles – IQR; upper whiskers – 75th percentile + 1.5 IQR; lower whiskers – 25th percentile – 1.5 IQR; grey areas – kernel density estimates; Y-axis – HTI (A) and NIHSS (B–F) scores; X-axis – NIHSS and HTI score arrangement into categories (Table 3). A–B. Diener's rule. C. Model 4. D. Model 3. E. Model 2. F. Model 1.*

Discussion

As far back as 1980s, observational studies showed that the risk of stroke recurrences in patients with AF who were not on AT could be 8–12% within the first week after a cerebral cardioembolic event [16]. Theoretically, early AT might be effective in preventing secondary AIS in such patients. However, meta-analyses of randomized clinical trials (RCTs) on heparin use in subgroups of AF patients within 48 h after AIS onset did not demonstrate a substantial reduction in the risk of stroke recurrences, but did reveal a considerable increase in HT rate [17]. Based on these findings, the paradigm that urgent AT is harmful for secondary stroke prevention has been dominating [5].

However, some observational studies have recently reported a low HT rate after starting AT in selected patients within 7 days after AIS onset. In another work, the rate of symptomatic HT within 14 days was 1.5% among 260 consecutive patients who were on AT and had no HT high-risk factors (a large infarct size, uncontrolled hypertension, HT revealed by neuroimaging on admission, and tendency to bleeding) [6].

There is scarce RCT evidence of effectiveness of vitamin K antagonists (VKAs) in AIS patients [2]. Since 2010, non-VKA oral anticoagulants (NOACs) have been approved for the use in clinical practice. Cochrane systematic reviews and meta-analyses have found that NOACs are as effective as VKAs in primary and secondary stroke prevention, but are associated with a twice less rate of intracranial hemorrhages. However, no RCT comparing NOACs with VKAs included AIS patients with AF, probably due to concern about increased HT risk [2].

A favorable safety profile of NOACs prompted researches on their earlier initiation in AIS patients. A few prospective observational studies and two small RCTs analyzed risks and benefits of the NOAC early use (in 3–5 days) in patients with

Table 5. RP (Royston-Parmer) survival analysis. Goodness-of-fit statistics (n = 304).

	Model 3	Diener's rule
Information criteria		
AIC	517.36	576.75
BIC (d.f. = 6)	539.66	599.05
Concordance indexes		
Harrell's *C*	0.792	0.737
Somers' *D*	0.585	0.473
Explained variation		
R^2_D (95% CI)	0.546 (0.449–0.625)	0.460 (0.333–0.564)

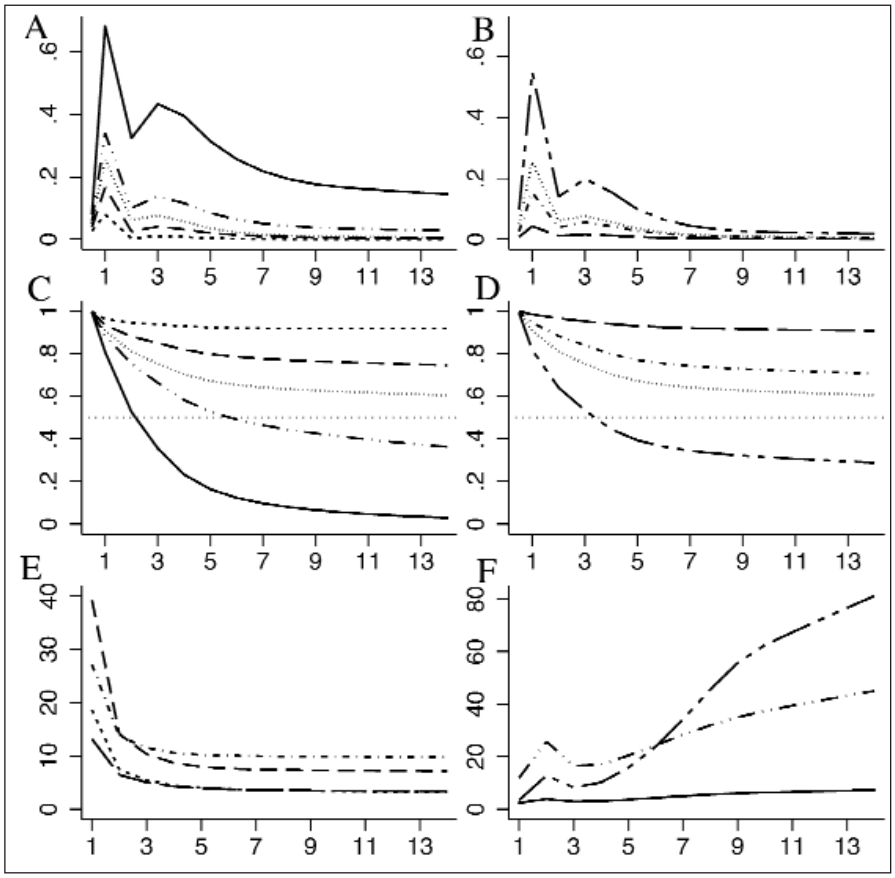

Figure 4. *RP survival analysis. Tight dot line – baseline function; very short dash line – HTI 0–1; dash line – HTI 2–3; dash – dot–dot line – HTI 4–5; solid line – HTI 6–8; long dash line – NIHSS <8; short dash–dot line – NIHSS 8–16; long dash–short dash–short dash line – NIHSS >16; reference dot line – median probability. Y-axis – probability (A–D) or number of patients (E–F); X-axis – days after AIS onset. A, C. HTI score (model 3). B, D. Diener's rule. A–B. Hazard function. C–D. Survival function. E. NNT. F. NNH.*

mild-to-moderate AIS and AF. The early use was found to be associated with a low rate of symptomatic and asymptomatic HT, whereas the delayed start (>7–14 days after the event) increased the rate of stroke recurrences. Large RCTs comparing early and delayed initiation of AT in AIS patients with AF should confirm safety and efficacy of this strategy. Currently, four RCTs with a total number of participants nearly 9,000 are being conducted, and their results are expected by 2021 [2].

Following the prospective observational study RAF which included 1,029 AIS patients with AF, the AHA/ASA updated their guidelines on the management of AIS patients in 2018, specifying possible timing to initiate AT from 4 to 14 days after AIS onset [5]. The study found that higher CHA2DS2-VASC and NIHSS scores, larger infarct size, and AT type (heparins and bridging with heparins) were associated with poorer outcomes [18]. The follow-up RAF-NOACs study revealed that starting NOACs between the 3rd and the 14th day after AIS onset was associated with the least composite rate of thromboembolic recurrences (AIS, TIA, symptomatic systemic thromboembolism) and major hemorrhages compared with the early (first 2 days) and delayed (>14 days) initiation [19].

Our results are entirely consistent with the aforementioned studies. The HT hazard function soars to the maximum in all patients within the first 3 days after AIS onset. Therefore, withholding AT for as long as 3 days would be the best management option. Moreover, pathogenesis of early and delayed HT could perfectly explain the observed hazard peaks [20]. Depending on the HTI score, AT initiation on day 4, 5, or 14 seems quite logical in the light of the discussed evidence. In this regard, the patients with the HTI score of 4–5 could gain the maximum benefit from AT delay.

In patients with a very high HT risk (the HTI score of 6–8), the AHA/ASA recommended starting AT beyond 2 weeks using an individual-based approach [3]. However, based on our own results, we assume that this strategy could not always be appropriate. By day 9, as many as 93.4% of such patients will have developed HT (Figure 4C), and starting AT beyond 14 days may be fairly reasonable in such cases. In those who survived without HT by day 9, a further delay insignificantly reduces HT risk (about 0.63% per day, Figure 4A), but may remarkably increase probability of thromboembolic events (0.5–1.3% per day [2]). Therefore, we would advise initiation of AT for such patients on day 9.

The majority of patients in our cohort had non-valvular AF (Table 1). However, we deliberately kept the patients with valvular AF for analysis – on the one hand, the AHA/ASA guidelines did not separate them from other AF patients [5], and on the other hand, the definition of valvular AF is still under debate [21].

There are a few limitations in our research. Our predictions of possible AT timing were solely based on HT risk analysis and no real data on timing and types of AT were taken into account. The study was retrospective in nature; hence, we were not blinded to the outcome. The sample size was relatively small, but sufficient for making statistical inferences. Moreover, it was a single-center study. There was neither racial nor ethnic diversity among the admitted patients. For the most part, the cohort included Russian, Tatar, and Jewish patients from our local community. There were no patients of African, Asian or Hispanic origin. Therefore, our results require further multicenter prospective validation.

Conclusions

HT risk is the highest on day 1 and 3 after AIS onset. The Diener's rule as well as the HTI score are reliable tools for prediction of possible AT timing. However, the HTI score could detect patients with very high HT probability and could better differentiate low-risk patients. In patients with the HTI score of 0–1, anticoagulation could be initiated on day 4, with the HTI score of 2–3 – on day 5, with the HTI score of 4–5 – in 2 weeks. In very high-risk patients (the HTI score of 6–8), AT administration may be reasonable on day 9 given they have had no HT.

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Disclosure

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