Baseline CHADS2 Score and Risk of Cardiovascular Events in the Population Without Atrial Fibrillation

Chunpeng Ji, MD[a,b], Shouling Wu, MD[b], Jihong Shi, MD[b], Zhe Huang, MD[b], Shuohua Chen, MD[b], Guodong Wang, MD[b], and Wei Cui, MD[a,*]

The association between CHADS2 score and stroke has been confirmed in patients with atrial fibrillation. But the majority of cardiovascular events occurred primarily in population without atrial fibrillation. Therefore, we performed this cohort study to evaluate the association between baseline CHADS2 score and cardiovascular events in the population without atrial fibrillation. A total of 99,755 Chinese adults with complete baseline data were followed for up to 10 years. The primary outcomes were cardiovascular event (a composite endpoint of myocardial infarction, cerebral infarction, and cerebral hemorrhage) and all-cause death. The area under the receiver operating characteristic curve was calculated for each kind of outcome. The adjusted cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals. The results showed the incidence of cardiovascular events and all-cause death increased with CHADS2 score. The area under the receiver operating characteristic curve for myocardial infarction, cerebral infarction, cerebral hemorrhage, cardiovascular events and all-cause death was 0.66, 0.67, 0.66, 0.67, and 0.69, respectively in participants without atrial fibrillation. Each 1 point increase in CHADS2 score was associated with the risk of all the outcomes in participants without atrial fibrillation after adjusting for age, sex, and other conventional cardiovascular confounders, the hazard ratio (95% confidence interval) for cardiovascular event and all-cause death was 1.17 (1.13 to 1.22) and 1.12 (1.08 to 1.15), respectively. In conclusion, baseline CHADS2 score is an independent risk factor for cardiovascular events and all-cause death in the population without atrial fibrillation. **(Am J Cardiol 2020;129:30−35)**

As is well known to all, atrial fibrillation (AF) is an important risk factor for cardiovascular events. But in fact, most of cardiovascular events occurred primarily in population without AF.[1] Therefore, it is urgent to establish or seek an effective tool to evaluate cardiovascular risk in non-AF population. As a classic tool to assess the risk of stroke in patients with AF, CHADS2 score has also been proved to be an independent predictor for stroke in non-AF population.[2−4] However, the outcome in those studies was only limited to stroke, and there were few studies on other cardiovascular events. In view of this, we analyzed the associations between baseline CHADS2 score and multiple cardiovascular outcomes and all-cause death in non-AF population based on Chinese Kailuan cohort study.

Methods

Detailed information on the Kailuan cohort study has been described previously.[5] In brief, the Kailuan cohort study including 101,510 Chinese adults (81,110 men and 20,400 women) aged 18 to 98 years was established when detailed information on health status and lifestyle was collected in 2006 to 2007. Participants receive a health examination every 2 years to update information on potential risk factors and to ascertain newly diagnosed disease. In this study, the 99,755 participants with a complete baseline data were included in the final statistical analysis after an exclusion of those with missing value of blood pressure (n = 1,182) and fasting blood glucose (n = 573).

The study was performed according to the guidelines of the Helsinki Declaration and was approved by the Ethics Committee of the Kailuan General Hospital. Written informed consent was obtained from all participants.

CHADS2 score included 5 items, namely congestive heart failure (1 point), hypertension (1 point), age ≥75 years old (1 point), diabetes mellitus (1 point), and a history of stroke (2 points), with a total score of 6 points. According to the CHADS2 score at baseline, the study participants were divided into 3 groups: low-risk group (CHADS2 score: 0), intermediate-risk group (CHADS2 score: 1), and high-risk group (CHADS2 score: 2 to 6).

Questionnaires were used to collect information about demographic, socioeconomic, and medical data. A corrected mercury sphygmomanometer was used to measure the blood pressure of the left arm with a cuff of appropriate size following the standard recommended procedures. The participants were examined by a professional medical staff with a 12-lead electrocardiogram (ECG-9130p, Japan) after a break of at least 5 minutes. The examination was completed after tracing to 10 QRS complex. Height and weight

[a]Department of Cardiology, The Second Hospital of Hebei Medical University, Shijiazhuang Hebei 050000, China; and [b]Department of Cardiology, Kailuan General Hospital, Tangshan, Hebei, China. Manuscript received April 29, 2020; revised manuscript received and accepted May 25, 2020.

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*Corresponding author: Tel: +86 (311) 6600-2115.

E-mail address: cuiwei21c@163.com (W. Cui).

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were measured by a corrected body mass scale (RGZ-120, China). Body mass index was calculated as weight (kg)/ height $(m)^2$.

Blood samples were collected in EDTA tubes in the morning between 7:00 and 9:00 after an overnight fasting period. Then, the blood samples were centrifuged for 10 minutes at 3000 r/min at 25°C within 30 minutes after collection. All biochemical variables, such as fasting blood glucose, blood lipids, C-reactive protein and uric acid, were measured by an autoanalyzer (Hitachi 747; Hitachi, Tokyo, Japan) at the central laboratory of the Kailuan General Hospital. The specific methods of measurement refer to the published literature of our research group.[6]

The 2018 ESC/ACC/AHA/WHF universal definition of myocardial infarction was adopted for the diagnosis of acute myocardial infarction, including detection of an increase and/or decrease of cardiac troponin values with at least 1 value above the 99th percentile upper reference limit and the presence of any one of the following: (1) symptoms of myocardial ischemia; (2) new ischemic electrocardiogram changes (ST-T changes or new left bundle branch block) or new pathologic Q wave formation; (3) imaging evidence; (4) identification of a coronary thrombus by angiography or autopsy.[7] The diagnosis of cerebral infarction and cerebral hemorrhage was mainly based on symptoms, signs, and performance of computed tomography or magnetic resonance imaging. The specific diagnostic criteria refers to the 1989 world health organization recommendations on stroke prevention, diagnosis, and therapy.[8] The diagnosis of congestive heart failure was mainly based on symptoms (such as dyspnea and fatigue), signs (such as cardiac murmurs, pulmonary rales, and lower limb edema) and objective evidence (such as abnormalities of echocardiography, chest radiographs, B-type natriuretic peptide, etc.). The specific diagnostic criteria refer to the 2018 Chinese heart failure guidelines.[9] According to the 2018 Chinese hypertension guidelines,[10] hypertension was defined as: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or a history of hypertension, or taking antihypertensive drugs. According to the diagnostic standard of diabetes released by world health organization in 1998,[11] diabetes was defined as: fasting blood glucose ≥7.0 mmol/L, or a history of diabetes, or taking antidiabetic drugs. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2 or a positive urinary protein. According to 2014 AHA/ACC/HRS atrial fibrillation management guidelines,[12] the diagnostic criteria for AF were as follows: (1) 12 lead electrocardiogram: P wave disappeared, replaced by small irregular f wave of different sizes and shapes, and R-R intervals were absolutely unequal. The atrial excitation frequency was usually 300 to 600 beats/min, (2) a definite AF history.

The primary outcomes were cardiovascular event (a composite endpoint of myocardial infarction, cerebral infarction and cerebral hemorrhage) and all-cause death. If 2 or more events occurred, the first event was regarded as the end point of observation. The time of 2006 to 2007 health examination was regarded as the beginning of follow-up. The follow-up continued through December 31, 2016 or until the occurrence of cardiovascular events or the date of death. Outcome events were ascertained by the government health care system. Then, the trained researchers further identified outcome events by checking medical records from hospitals every 6 months.

SAS software (Version 9.2, SAS Institute, Cary, NC) was used for statistical analyses. All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. Continuous variables with a normal distribution were expressed as the mean plus or minus standard deviation and compared using independent-sample *t* test. Due to the skewed distribution of C-reactive protein and triglyceride in our study, logarithmic transformation was followed by *t* test, and they were expressed as median (quartile 1 to quartile 3). Categorical variables were described as percentages and compared using Chi-square test. The area under the receiver operating characteristic curve (AUC) was calculated for each kind of outcome. Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals of cardiovascular outcome and all-cause death after adjustment for age, gender, smoking, alcohol drinking, exercise, education level, income level, history of myocardial infarction, CKD, antihypertensive drugs, antidiabetic drugs, antiplatelet drugs, systolic blood pressure, body mass index, fasting blood glucose, triglyceride, low density lipoprotein, high density lipoprotein, serum uric acid, and C-reactive protein.

Results

Of the 99,755 participants, 79 728 were male (79.9%). The average age was 51.9 years. Table 1 showed that the prevalence of AF at baseline was 0.52%. The prevalence of hypertension, diabetes, stroke, heart failure and CKD was significant higher in patients with AF than that in those without AF. Moreover, patients with AF were older and were more likely to be men, to exercise, to take antihypertensive, antidiabetic, and antiplatelet drugs and have higher level of blood pressure, body mass index, C-reactive protein, and uric acid. But the participants without AF were more likely to be smoker and drinker, to have higher level of education, blood lipids and estimated glomerular filtration rate.

To analyze the predictive value of CHADS2 score for cardiovascular events and all-cause death, receiver operating characteristic curve analysis was conducted with CHADS2 score as the independent variable and each kind of outcome as the dependent variable. Table 2 showed that the AUC for each outcome both in AF and non-AF population was greater than 0.60. Moreover, the AUC for cardiovascular events and all-cause death in non-AF population was slightly higher than that in AF population.

After a follow-up of 10 years, a total of 22, 64, 13, 99, and 215 patients with AF and 1,619, 4,642, 1,079, 7,006, and 9,761 participants without AF developed myocardial infarction, cerebral infarction, cerebral hemorrhage, cardiovascular event, and all-cause death, respectively. The incidence of cardiovascular events and all-cause death increased with the CHADS2 score in both AF and non-AF population. But in each subgroup of CHADS2 score, the incidence in patients with AF was significantly higher than that in non-AF population (Table 3).

In baseline AF population, the risk of myocardial infarction increased by 107% (hazard ratio [HR] 2.07, 95%

Table 1
Baseline characteristics

Variables	With Atrial Fibrillation		t/χ^2	P
	No (n=99,240)	Yes (n=515)		
Age (year)	51.8±12.6	66.4±10.8	−30.4	<0.001
≥75 years	3711(3.7%)	115(22.3%)	480	<0.001
Men	79264(79.9%)	464(90.1%)	33.4	<0.001
Systolic blood pressure (mmHg)	131±21.1	137±21.4	−6.77	<0.001
Diastolic blood pressure (mmHg)	83.5±11.8	85.0±11.7	−2.81	0.005
Body mass index (kg/m^2)	25.1±3.49	25.6±3.84	−3.49	<0.001
High school or above	19290(20.1%)	65(13.9%)	11.2	0.001
Average monthly income ≥1000 RMB	6417(6.7%)	38(8.2%)	1.60	0.21
Current smoker	33368(34.5%)	134(27.6%)	10.1	0.002
Current drinker	36210(37.4%)	143(29.5%)	13.0	<0.001
Exerciser	87411(91.2%)	438(94.2%)	5.07	0.024
History of myocardial infarction	1329(1.4%)	18(3.8%)	20.5	<0.001
History of stroke	2147(2.2%)	39(7.6%)	69.9	<0.001
Heart failure	69(0.1%)	10(1.9%)	46.2	<0.001
Hypertension	44068(44.4%)	320(62.1%)	65.2	<0.001
Diabetes mellitus	12215(12.3%)	105(20.4%)	30.9	<0.001
Chronic kidney disease	21084(21.3%)	232(45.1%)	173	<0.001
Taking antihypertensive drugs	11095(11.8%)	120(26.5%)	94.3	<0.001
Taking antidiabetic drugs	2438(2.6%)	23(4.9%)	10.6	0.001
Taking antiplatelet drugs	1014(1.0%)	20(3.9%)	40.9	<0.001
Estimated glomerular filtration rate (mL/min/1.73m^2)	82.0±25.7	70.8±20.0	9.88	<0.001
Total cholesterol (mg/dL)	192±44.5	181±42.5	5.43	<0.001
Triglyceride (mg/dL)	113(79.7-172)	103(75.3-140)	6.14	<0.001
Low density lipoprotein (mg/dL)	90.9±35.3	85.8±39.3	2.95	0.003
High density lipoprotein (mg/dL)	59.9±15.6	58.6±17.4	1.88	0.06
Fasting blood glucose (mg/dL)	98.6±30.4	98.1±27.3	0.43	0.67
Serum uric acid (mg/dL)	4.88±1.41	5.71±1.68	−11.2	<0.001
C-reactive protein (mg/L)	0.80(0.30-2.20)	1.62(0.57-4.28)	−9.09	<0.001

confidence interval [CI] 1.17 to 3.66) and the risk of cardiovascular events increased by 45% (HR 1.45, 95%CI 1.07 to 1.98) for each 1 point increase in CHADS2 score after adjusting for age, gender, smoking, alcohol drinking, exercise, education level, income level, history of myocardial infarction, CKD, antihypertensive drugs, antidiabetic drugs, antiplatelet drugs, systolic blood pressure, body mass index, fasting blood glucose, triglyceride, low density lipoprotein, high density lipoprotein, serum uric acid, and C-reactive protein. While the risk of cerebral infarction, cerebral hemorrhage and all-cause death did not increase significantly. Compared with the low-risk group, the risk of myocardial infarction in the high-risk group was significantly higher. But as for other outcome events, there was no significant difference between the 2 groups.

In baseline non-AF population, each 1 point increase in CHADS2 score increased the risk of myocardial infarction by 9% (HR 1.09, 95%CI 1.00 to 1.18), cerebral infarction by 21% (HR 1.21, 95%CI 1.15 to 1.27), cerebral hemorrhage by 13% (HR 1.13, 95%CI 1.02 to 1.26), cardiovascular events by 17% (HR 1.17, 95%CI 1.13 to 1.22), and all-cause death by 12% (HR 1.12,95% CI, 1.08 to 1.15) after adjusting for above confounders. Compared with the low-risk group, the risk of cerebral infarction, cerebral hemorrhage, cardiovascular events, and all-cause death was significantly higher in the intermediate-risk group and high-risk group. After further excluding 897 patients with new-onset AF during the follow-up, the results did not change obviously.

Discussion

The current study showed that baseline CHADS2 score was an independent risk factor of cardiovascular events and

Table 2
Area under the receiver operating characteristic curves of the association between baseline CHADS2 score and outcome events

Outcome	Cohort with Atrial Fibrillation		Cohort without Atrial Fibrillation	
	AUC(95%CI)	*P*	*AUC(95%CI)*	*P*
Myocardial infarction	0.67(0.56-0.78)	0.008	0.66(0.64-0.67)	<0.001
Cerebral infarction	0.60(0.53-0.68)	0.009	0.67(0.66-0.68)	<0.001
Cerebral hemorrhage	0.62(0.46-0.79)	0.13	0.66(0.64-0.68)	<0.001
Cardiovascular events	0.63(0.57-0.69)	<0.001	0.67(0.66-0.68)	<0.001
All-cause death	0.60(0.55-0.65)	<0.001	0.69(0.69-0.70)	<0.001

AUC: area under the receiver operating characteristic curve

Table 3
The incidence of cardiovascular events and all-cause death

Outcome	CHADS2 score	Cohort with atrial fibrillation		Cohort without atrial fibrillation	
		No. of cases	Incidence rate/1000 person-years	No. of cases	Incidence rate/1000 person-years
Myocardial infarction	0	2 (1.6%)	1.69	394 (0.8%)	0.75
	1	6 (2.7%)	2.94	773 (2.0%)	1.87
	2-6	14 (8.3%)	10.6	452 (4.1%)	4.23
Cerebral infarction	0	9 (7.4%)	7.79	1055 (2.2%)	2.01
	1	26 (11.6%)	13.3	2330 (5.9%)	5.73
	2-6	29 (17.3%)	22.7	1257 (11.4%)	12.2
Cerebral hemorrhage	0	2 (1.6%)	1.69	222 (0.5%)	0.42
	1	4 (1.8%)	1.96	611 (1.6%)	1.48
	2-6	7 (4.2%)	5.19	246 (2.2%)	2.29
Cardiovascular event	0	11 (9.0%)	9.69	1623 (3.3%)	3.10
	1	34 (15.1%)	17.8	3529 (9.0%)	8.81
	2-6	44 (26.2%)	36.4	1854 (16.8%)	18.4
All-cause death	0	37 (30.3%)	31.0	2217 (4.5%)	4.19
	1	89 (39.6%)	43.1	4445 (11.3%)	10.7
	2-6	89 (53.0%)	64.5	3099 (28.0%)	28.5

all-cause death in non-AF population. After adjusting for conventional cardiovascular confounders, each 1 point increase in CHADS2 score was significantly associated with a higher risk of cardiovascular events and all-cause death.

Similar to our study, a large cohort study from Israel[2] showed that each 1 point increase in CHADS2 score was significantly associated with a 34% and 73% increase in the risk of stroke, respectively in participants with and without AF. The result from another cohort study[3] showed that, of all the prediction models (such as CHADS2, CHA2DS2-VASc, Framingham risk score, etc.) for stroke, the CHADS2 score had the best predictive power (C-statistic: 0.728) in non-AF population. Ntaios G et al[4] also found that compared with low-risk group (CHADS2 score: 0),

Table 4
The hazard ratios (95% confidence intervals) for cardiovascular events and all-cause death

Outcome	CHADS2 score				*P* for trend
	Per 1 point increase	0	1	2-6	
Myocardial infarction					
Model†	2.07 (1.17-3.66)*	Ref	2.28 (0.35-14.6)	15.9 (2.08-122)**	0.002
Model‡	1.09 (1.00-1.18)*	Ref	1.16 (0.99-1.36)	1.16 (0.93-1.44)	0.18
Model§	1.09 (1.00-1.19)*	Ref	1.15 (0.98-1.35)	1.16 (0.93-1.45)	0.18
Cerebral infarction					
Model†	1.19 (0.81-1.74)	Ref	0.91 (0.36-2.30)	0.91 (0.28-2.97)	0.89
Model‡	1.21 (1.15-1.27)**	Ref	1.34 (1.22-1.47)**	1.55 (1.36-1.77)**	<0.001
Model§	1.21 (1.15-1.27)**	Ref	1.34 (1.23-1.48)**	1.56 (1.37-1.78)**	<0.001
Cerebral hemorrhage					
Model†	1.39 (0.54-3.62)	Ref	0.40 (0.04-4.02)	0.69 (0.04-13.4)	0.96
Model‡	1.13 (1.02-1.26)*	Ref	1.64 (1.35-2.00)**	1.47 (1.11-1.96)**	<0.001
Model§	1.13 (1.01-1.26)*	Ref	1.63 (1.34-1.99)**	1.47 (1.10-1.96)**	<0.001
Cardiovascular event					
Model†	1.45 (1.07-1.98) *	Ref	1.15 (0.51-2.61)	2.07 (0.76-5.59)	0.09
Model‡	1.17 (1.13-1.22)**	Ref	1.33 (1.23-1.43)**	1.45 (1.30-1.61)**	<0.001
Model§	1.17 (1.13-1.22)**	Ref	1.33 (1.23-1.43)**	1.45 (1.30-1.62)**	<0.001
All-cause death					
Model†	1.14 (0.92-1.41)	Ref	0.98 (0.61-1.58)	1.14 (0.61-2.11)	0.64
Model‡	1.12 (1.08-1.15)**	Ref	1.19 (1.12-1.27)**	1.30 (1.20-1.42)**	<0.001
Model§	1.12 (1.08-1.16)**	Ref	1.20 (1.12-1.27)**	1.31 (1.20-1.43)**	<0.001

*P <0.05 and **P<0.01.

Model adjusted for age (yrs), sex, smoking (never and past, current, ≥1 cigarettes/ d), alcohol drinking (never and past, current, ≥1 times/ d), exercise (none, occasionally or frequently, ≥1 times/ wk), education level (elementary school, high school or above), income level (<1,000 yuan/ month and ≥1,000 yuan/ month), history of myocardial infarction (yes or no), chronic kidney disease (yes or no), antihypertensive drugs (yes or no), antidiabetic drugs (yes or no), antiplatelet drugs (yes or no), systolic blood pressure, body mass index, fasting blood glucose, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, serum uric acid, and C-reactive protein.

† Participants with atrial fibrillation at baseline.

‡ Participants without atrial fibrillation at baseline.

§ Further excluding 897 cases of new-onset atrial fibrillation during the follow-up on basis of model‡.

intermediate-risk group (CHADS2 score 1 point) and high-risk group (CHADS2 score: 2 to 6) were associated with a higher risk of recurrence of stroke. These studies were all based on large scale cohort study. However, their study participants were specific individuals (those aged ≥50, or aged ≥35, or with a history of stroke) other than general population, and the outcome was limited to stroke which was not specified, so their reference value is not very high.

In addition, the associations between CHADS2 score and cardiovascular events also had been confirmed in some other specific non-AF population (such as coronary heart disease,[13–15] heart failure,[16] coronary bypass graft,[17] hypertension,[18] etc.). Of those, the result from a multicenter cohort study showed that CHADS2 score (per 1 point) was an independent risk factor of cardiovascular events (HR 1.31; 95%CI 1.17 to 1.47) in coronary artery disease patients without AF.[15] The participants in this study were older and had significantly higher prevalence of hypertension, diabetes and CKD. These made it difficult to extend to other populations. However, the results from multicenter large-sample study still had an irreplaceable reference value.

The current study also found that the results did not change significantly after further excluding the patients with new-onset AF during the follow-up. To some extent, it suggested that the association between 5 risk factors in CHADS2 score and cardiovascular events may not be mediated by AF. Studies have shown that left atrial remodeling is an independent risk factor for stroke, myocardial infarction, and all-cause death in elderly non-AF population.[19] While the left atrial remodeling could be caused by all the 5 risk factors in the CHADS2 score.[20] Therefore, we can speculate that the association between the 5 risk factors in CHADS2 score and cardiovascular events may be mediated by left atrial remodeling in non-AF population, but the specific mechanism is still unclear. While Tabata N et al thought that hypertension, diabetes and other risk factors included in the CHADS2 score may lead to cardiovascular events through endothelial dysfunction and platelet activation in non-AF population.[15]

Saliba W et al[2] suggested that about 22% of non-AF population were at a high risk of stroke and anticoagulant should be recommended. However, it still needs to be further verified. Also, the bleeding risk from anticoagulants should not be ignored. According to our study, of all the outcome events, the risk of stroke (especially hemorrhagic stroke) was the greatest in the intermediate and high-risk group in the non-AF population. Therefore, we should treat the antithrombotic therapy with more caution in non-AF population. In addition, lifestyle improvements, especially moderate physical activity, may reduce both cardiovascular and AF risk. The results from Kuopio Ischemic Heart Disease Study showed that higher cardiorespiratory fitness (CRF), a high reflection of physical activity, was associated with decreased risk of all-cause mortality, cardiovascular mortality, sudden cardiac death or AF.[21,22]

Our study has some limitations. First, the participants were limited to active and retired workers of the Kailuan group, of which male accounted for more than 3-quarters. This fact limited the extension of our results. Second, the study lacked information on anticoagulant drugs, which may have a certain effect on the results. However, our results did not change significantly after excluding the patients with new-onset AF who were the potential users of anticoagulants. Third, we diagnosed AF only based on previous medical history and 12-lead electrocardiogram in the clinic, which may lead to a certain rate of missed diagnosis. Fourth, due to the lack of relative data, we cannot exclude patients with valvular heart disease and cardiomyopathy which could have an influence on the outcome.

The current study confirms that baseline CHADS2 score is an independent risk factor for cardiovascular events and all-cause death in the population without AF. Its predictive value in non-AF population may not be inferior to that in patients with AF. Easy to remember and simple to calculate, the CHADS2 score can help clinicians quickly identify those at a high risk of cardiovascular disease in non-AF population and make appropriate prevention strategies. But more studies are needed to evaluate the role of anticoagulants in stroke prevention in non-AF population.

Authors' Contributions

Chunpeng Ji: Methodology, Writing - Original draft preparation; Shouling Wu: Supervision; Jihong Shi: Data curation, Investigation; Zhe Huang: Investigation; Shuohua Chen: Validation, Investigation; Guodong Wang: Software, Investigation; Wei Cui: Conceptualization, Writing - Reviewing and Editing.

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