




Determinants of left atrium thrombi in scheduled cardioversion: an ENSURE-AF study analysis

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Aims

ENSURE-AF (NCT 02072434) was the largest prospective randomized clinical trial of anticoagulation for cardioversion in atrial fibrillation (AF), which also provides the largest prospective dataset for transoesophageal echocardiography (TOE) prior to cardioversion. This ancillary analysis investigated determinants of TOE-detected left atrium thrombi (LAT) in patients scheduled for electrical cardioversion (ECV).

Methods and results

The ENSURE-AF multicentre PROBE evaluation trial compared edoxaban 60 mg once daily (QD) with enoxaparin/warfarin in 2199 subjects undergoing ECV of non-valvular AF. Patients were stratified by the use of TOE, anticoagulant experience, and selected edoxaban dose. Electrical cardioversion was cancelled or deferred when TOE-detected LAT. In total, 1183 subjects were stratified to the TOE arm and LAT was reported in 91 (8.2%). In univariate analysis, age ≥ 75 years (26.4% vs. 16.9%, $P=0.0308$), lower weight (86.5 ± 15.0 vs. 90.7 ± 18.0 kg, $P=0.0309$), lower creatinine clearance (80.1 ± 30.6 vs. 93.2 ± 33.9 mL/min, $P=0.0007$), heart failure (59.3% vs. 43.0%, $P=0.0029$), and diuretic treatment (53.9% vs. 40.1%, $P=0.0141$) were more prevalent in the LAT group. Non-significant trends were seen for higher mean CHA₂DS₂-VASc score (3.0 ± 1.41 vs. 2.7 ± 1.48 , $P=0.0571$) and more prevalent anticoagulation use prior to enrolment (60.4% vs. 50.3%, $P=0.0795$) in the LAT group. In logistic regression analysis, age ($P=0.0202$) and heart failure ($P=0.0064$) were independently associated with LAT.

Conclusion

Elective ECV is commonly cancelled or deferred due to TOE-detected LAT in patients with non-valvular AF. Age ≥ 75 years and heart failure were associated with the presence of LAT.

Keywords

Anticoagulation • Atrial fibrillation • Edoxaban • Electrical cardioversion • Left atrial thrombus • Transoesophageal echocardiography

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What's new?

- The prevalence of left atrial thrombi (LAT) was found high in a contemporary population from the largest trial on electrical cardioversion (ECV) of atrial fibrillation.
- Age and heart failure, but not the CHA₂DS₂-VASc score, were predictive of LAT.
- Left atrial thrombus was found in some patients despite optimal anticoagulation but this did not appear to necessarily translate to the development of systemic embolism in case of ECV.

Introduction

Potential risk factors for stroke in patients with atrial fibrillation (AF) have been thoroughly studied and are well established.¹ Stroke, however, may result from different mechanisms, such as left atrial thrombi (LAT) embolization or local brain thrombosis. Risk factors for LAT formation are not well understood and are not necessarily the same as the risk factors for stroke in patients with AF.² The theory of endocardial remodelling describes the underlying molecular pathophysiology of atrial thrombogenesis in AF.³ Main factors of this process appear to be oxidative stress and inflammation in the fibrillating atrial tissue, which cause up-regulation of thrombogenic proteins at the endocardial surface. Furthermore, concomitant diseases and conditions such as ageing, arterial hypertension, diabetes mellitus, or congestive heart failure appear to have an important impact. Recognition of these factors is potentially important, especially for patients who are scheduled for cardioversion because the procedure may result in thrombi dislodgement and embolization.⁴

Multiple studies have reported the incidence of LAT in several clinical settings, including prior to AF cardioversion.^{5–8} These reports include prospective trials in the setting of cardioversion, as well as single-centre retrospective studies, which found different risk factors for LAT.^{9,10} The ENSURE-AF study (NCT 02072434) is the largest prospective, multicentre, randomized clinical trial of anticoagulation for cardioversion in non-valvular AF and demonstrated a comparable efficacy and safety of the oral factor Xa inhibitor edoxaban vs. enoxaparin–warfarin.¹¹ This randomized trial also provides the largest prospective dataset for transoesophageal echocardiography (TOE) prior to cardioversion in this clinical setting.

The aim of this ancillary analysis was to investigate clinical determinants of TOE-detected LAT in patients scheduled for electrical cardioversion (ECV) of AF.

Methods

Study design

The ENSURE-AF trial design has been described elsewhere in detail.¹² In brief, this was an open-label, randomized, multicentre, multinational, parallel-group study comparing edoxaban 60 mg QD with optimized anticoagulation by enoxaparin–warfarin in subjects with indication for ECV of AF.

The primary efficacy endpoint was the composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular death from

randomization until end of study, and the primary safety endpoint was the composite of major and clinically relevant non-major bleeding after TOE- or non-TOE-guided cardioversion in both treatment arms.

The study was conducted in compliance with the protocol, the ethical principles as outlined in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and applicable regulatory requirements. The protocol and its amendments were approved by ethics committees or institutional review boards. All patients provided written informed consent prior to participation in the study.

To comply with the Transparency and Openness Promotion Guidelines, data presented in this manuscript can be obtained from the corresponding author.

Patients

Patients were enrolled if they had ongoing non-valvular AF lasting for ≥ 48 h but ≤ 12 months, and were scheduled for ECV. Exclusion criteria included recent acute coronary syndrome or coronary intervention, thrombus or mass in the left cardiac chambers, left atrial appendage exclusion, mitral valve rheumatic disease or mechanical heart valve, formal indication for conventional anticoagulation, active or high-risk bleeding, severe renal insufficiency (calculated creatinine clearance [CrCl] < 30 mL/min), treatment with dual antiplatelet therapy, or contraindication for anticoagulant agents. The sample size calculation for the main trial has been reported elsewhere,¹¹ and the present study represents a pre-specified ancillary analysis of those patients with left atrial thrombus present.

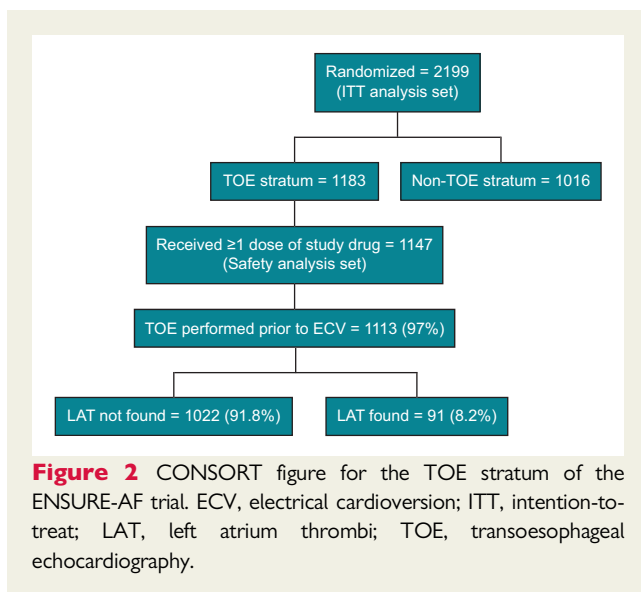
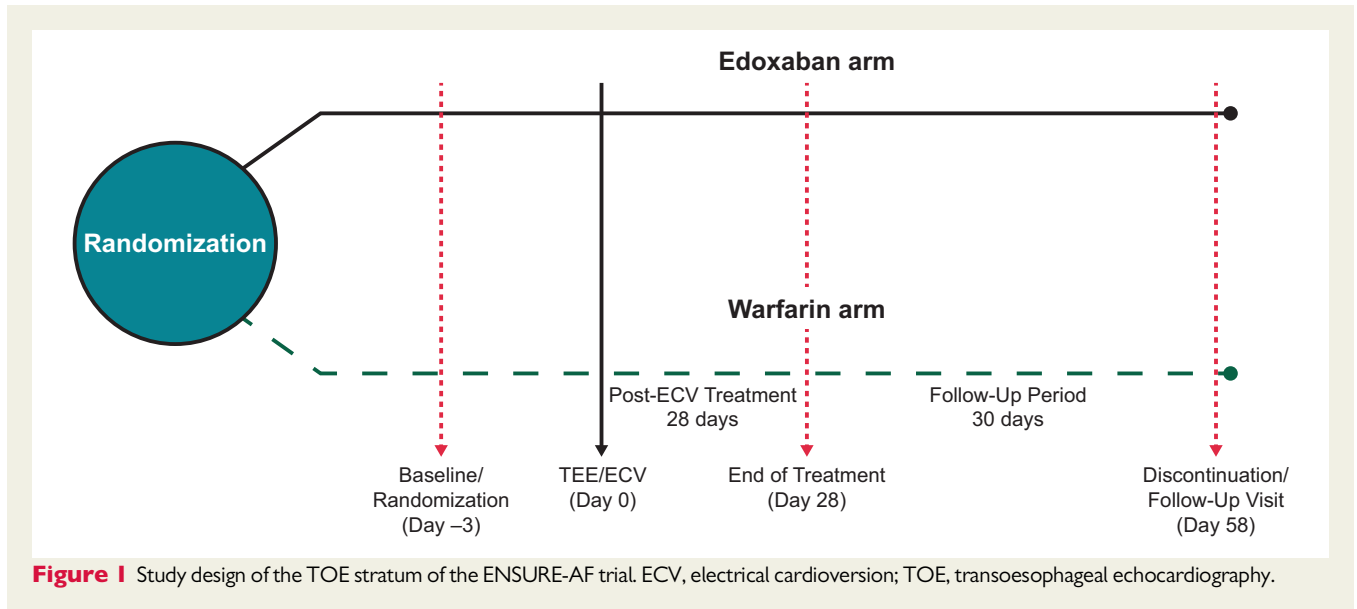
At randomization, all subjects were stratified based on the approach to cardioversion (TOE vs. non-TOE). The decision to enrol the patient in the TOE or non-TOE stratum was left to the local investigators.

Treatment and transoesophageal echocardiography

The study treatment with either edoxaban or enoxaparin–warfarin was started on the day of randomization and continued until day of ECV. Patients randomized to edoxaban received 60 mg once daily (QD) except for those with CrCl < 50 mL/min, low body weight (≤ 60 kg), or concomitant use of P-glycoprotein inhibitors (with the exception of amiodarone) who received 30 mg of edoxaban. Patients randomized to warfarin also received enoxaparin until they had international normalized ratio (INR) ≥ 2.0 . Both TOE and ECV were performed on the same day and within 3 days after randomization (Figure 1). Cardioversion was performed at least 2 h after the first dose of edoxaban or enoxaparin–warfarin. If LAT were identified during the TOE procedure, the patient was considered not eligible for subsequent cardioversion and the procedure was cancelled or postponed.

Statistical analysis

This ancillary analysis included all randomized patients in the TOE stratum who performed the TOE procedure. The data for patients in the non-TOE stratum can be found elsewhere.¹¹ Patients were divided into two groups based on whether thrombi were identified by TOE. Demographic, clinical characteristics and prior anticoagulant treatment were summarized by TOE finding. Numerical variables were described as mean with standard deviation. Categorical variables were described by numbers and percentages of patients in each category. Data were compared using one-way analysis of variance for numerical data and Fisher's exact test for categorical data. A logistic regression analysis with TOE finding as the response variable was performed. The independent variables included the demographic and baseline characteristics, which showed difference between LAT found and no LAT found groups



($P < 0.1$). Interaction term was not included in the analysis. Body weight and CrCl were excluded in the analysis due to their high correlations with age. Odds ratios and associated P -values were calculated.

Results

Some patients were excluded from the analysis because they did not receive at least one dose of the study drug (36 patients); converted spontaneously to sinus rhythm (20 patients); discontinued study treatment before TOE procedure (10 patients); or had TOE cancelled due to protocol deviation (1 patient), technical problem (1 patient), it was not tolerated (1 patient), or unknown reason (1 patient). The remaining TOE patients ($n = 1113$, 97.04%) finally

had a TOE performed before ECV, and comprised the population used for the present analysis (Figure 2). The characteristics of these patients compared with those enrolled in the non-TOE stratum of the main study, which was not included in the present analysis, can be found elsewhere.¹¹ LAT was found in 91 patients (8.2%). All these patients had ECV cancelled or delayed until LAT resolution was demonstrated. Demographic data of patients with and without LAT at TOE are shown in Table 1. Univariate analysis showed that age ≥ 75 years (26.4% vs. 16.9%, $P = 0.0308$), lower weight (86.5 ± 15.0 vs. 90.7 ± 18.0 , $P = 0.0309$), lower CrCl (80.1 ± 30.6 vs. 93.2 ± 33.9 , $P = 0.0007$), heart failure (59.3% vs. 43.0%, $P = 0.0029$), and diuretic treatment (53.9% vs. 40.1%, $P = 0.0141$) were more prevalent in the LAT group. Compared with patients with no LAT, those with LAT had a higher mean CHA₂DS₂-VASc score (3.0 vs. 2.7), but the differences were not statistically significant ($P = 0.057$); see Table 1.

Multivariable analysis showed that only age [odds ratio (OR): 1.055, $P = 0.0013$] and heart failure (OR: 1.97, $P = 0.0064$) were independently associated with the detection of LAT on TOE. Age ≥ 75 years (OR: 2.13, $P = 0.0202$) and heart failure were associated with the presence of LAT, which was found in 12.2% and 10.9% of patients with these variables, respectively. Left atrium thrombus was found in 6.0%, 7.3%, and 5.4% of patients with no heart failure, age < 75 years, or both, respectively. In contrast, LAT was found in 18.7% of patients with heart failure and age ≥ 75 years (Figure 3).

Relationship to prior anticoagulation

The prevalence of LAT was not significantly different in relation to the anticoagulation use in the 30 days prior to TOE (Table 2). Compared with patients with no LAT, those with LAT were more frequently treated with vitamin K antagonists in the 30 days prior to enrolment; see Tables 1 and 2. No statistical differences were seen for mean INR at enrolment (1.6 ± 0.70 vs. 1.5 ± 0.65 , $P = 0.3381$).

Table 1 Demographic and clinical data of patients with and without LAT detected by TOE performed for electrical cardioversion of AF

	LAT found (n = 91)	No LAT found (n = 1022)	P-value
Age (year)			
Mean ± SD	67.3 ± 9.4	64.2 ± 10.8	0.0095
65–74	33 (36.3)	357 (34.9)	0.8191
>65	53 (58.2)	500 (48.9)	0.1007
≥75	24 (26.4)	173 (16.9)	0.0308
Male	55 (60.4)	678 (66.3)	0.2515
Weight (kg)			
Mean ± SD	86.5 ± 15.05	90.7 ± 18.0	0.0309
≤60 kg	1 (1.1)	26 (2.5)	0.7188
BMI (mean ± SD)	29.9 ± 5.1	30.4 ± 5.5	0.4312
CHA ₂ DS ₂ -VASc score (mean ± SD)	3.0 ± 1.4	2.7 ± 1.5	0.0571
HAS-BLED score (mean ± SD)	1.0 ± 0.8	0.9 ± 0.8	0.3713
Current VKA user	50 (54.9)	469 (45.9)	0.1011
Current NOAC user	14 (15.4)	181 (17.7)	0.6669
CrCl (mL/min)	80.1 ± 30.6	93.2 ± 33.9	0.0007
TtTR (days)	6.4 ± 3.3	7.6 ± 5.1	0.2658
TiTR (% of time)	74.5 (32.2)	72.1 (28.9)	0.6279
TTR (% of time)	62.1 (34.2)	57.5 (33.2)	0.4219
Medical history			
CHF	54 (59.3)	439 (43.0)	0.0029
CAD	17 (18.7)	174 (17.0)	0.6647
Diabetes	19 (20.9)	188 (18.4)	0.5740
Hypertension	68 (74.7)	825 (80.7)	0.1708
Myocardial infarction	4 (4.4)	63 (6.2)	0.6477
Valvular heart disease	20 (22.0)	302 (29.5)	0.1477
Peripheral artery disease	8 (8.8)	48 (4.7)	0.1254
Ischaemic stroke/TIA	4 (4.4)	78 (7.6)	0.3989
Intracranial bleeding	0	1 (0.1)	1.0000
Life-threatening bleed	1 (1.1)	2 (0.2)	0.2260
AF history			
Paroxysmal (≤7 days)	17 (18.7)	233 (22.8)	0.4321
Persistent (>7 days, <1 year)	74 (81.3)	789 (77.2)	
Drug treatment ^a			
Aspirin	18 (19.8)	194 (19.0)	0.8892
Lipid-modifying agents	33 (36.3)	392 (38.4)	0.7365
Beta blockers	75 (82.4)	797 (78.0)	0.3556
ACEI/ARB	52 (57.1)	660 (64.6)	0.1718
Diuretics	49 (53.8)	410 (40.1)	0.0141
VKA/NOAC	55 (60.4)	515 (50.3)	0.0795

P-values are from 1-way ANOVA model for numerical data and Fisher's exact test for categorical data. Data reported as n (%) unless otherwise noted.

^aDuring the 30 days before enrolment.

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BMI, body mass index; CAD, coronary artery disease; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75, diabetes mellitus, and prior stroke or transient ischaemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; CHF, congestive heart failure; CrCl, creatinine clearance; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding history or disposition, labile INR, elderly, drugs or alcohol; INR, international normalized ratio; LAT, left atrium thrombi; NOAC, non-vitamin K antagonist oral anticoagulant; SD, standard deviation; TIA, transient ischaemic attack; TiTR, time in treatment range; TTR, time in treatment range calculated using the Rosendaal method; TtTR, time to treatment range; TOE, transoesophageal echocardiography; VKA, vitamin K antagonist.

Discussion

The main findings of this analysis, from a contemporary trial population, are the prevalence of LAT in patients scheduled for ECV. Age

and heart failure, but not the CHA₂DS₂-VASc score, were predictive of LAT. Other studies have reported slightly lower and higher rates of LAT in patients scheduled for ECV of AF. However, most of these studies are single-centre retrospective cohorts or had low numbers

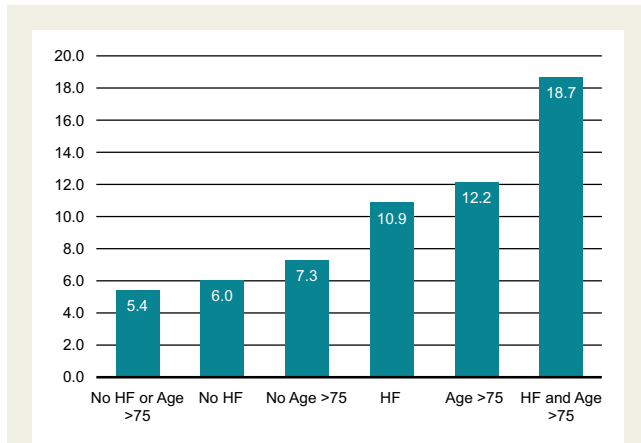


Figure 3 Prevalence of LAT according to age and history of heart failure in TOE stratum of the ENSURE-AF trial. HF, heart failure; LAT, left atrium thrombi; TOE, transoesophageal echocardiography.

Table 2 Differences in anticoagulation treatment between patients with and without LAT detected by TOE performed for electrical cardioversion of AF

	LAT found (n = 91)	No LAT found (n = 1022)	P-value
Anticoagulation, n (%)			
Experienced	69 (75.8)	745 (72.9)	0.6221
Naïve	22 (24.2)	277 (27.1)	
Prior 30-day anticoagulation	55 (60.4)	514 (50.3)	0.0795
VKA, n (%)	43 (47.3)	340 (33.3)	0.0081
NOAC, n (%)	14 (15.4)	183 (17.9)	0.6671
INR at enrolment ^a			
Mean ± SD	1.6 ± 0.7	1.5 ± 0.6	0.3381
≥2, n (%)	22 (27.2)	213 (23.5)	0.4955

Suboptimal anticoagulation was defined as missing ≥1 dose of NOAC or enoxaparin-warfarin with INR <2.

^aDenominators are the number of patients who took VKAs.

AF, atrial fibrillation; INR, international normalized ratio; LAT, left atrium thrombi; NOAC, non-vitamin K antagonist oral anticoagulant; SD, standard deviation; TOE, transoesophageal echocardiography; VKA, vitamin K antagonist.

of patients.^{5–8,13,14} Other randomized trials—such as the ACUTE trial, which enrolled 1222 patients with AF for ECV—included 549 patients who underwent TOE prior to ECV and found a higher rate of LAT (13.8%).¹⁵ However, this trial was terminated almost 20 years ago when the use of oral anticoagulation was less common and the non-VKA oral anticoagulants were not available. More recent trials, such as the X-VerT trial,¹⁶ found LAT in 2.7% in 564 patients who underwent TOE prior to ECV of AF. The population of this trial was slightly younger, with lower prevalence of heart failure and prior stroke than that included in the ENSURE-AF trial, which may explain the three-fold higher prevalence of LAT in the ENSURE-AF trial.¹⁶ Data evaluating TOE prior to ECV of AF were obtained from more

than 1100 patients from 239 study sites in 19 countries in Europe and the US in the ENSURE-AF trial. Therefore, it provides a contemporary and well-represented sample of the general population of patients scheduled for ECV. In addition, the EMANATE trial,¹⁷ which studied 840 patients with TOE prior to ECV of AF, found LAT in 7.3%, a figure similar to the present study. Age (64.5 ± 12.8 and 64.7 ± 12.2 years for heparin/warfarin and apixaban, respectively) and CHA₂DS₂-VASc score (2.4 ± 1.7 and 2.4 ± 1.7 for heparin/warfarin and apixaban, respectively) were slightly lower in the general population enrolled in the EMANATE trial compared with the ENSURE trial.

Older age and heart failure were the only independent factors associated with LAT in this study. These were also among the most powerful determinants of LAT in a recent meta-analysis in patients with non-valvular AF.⁷ In contrast, previous stroke is the most powerful risk factor for stroke in the general population of patients with AF. This emphasizes that risk factors for stroke in AF are not necessarily the same as those for LAT development in AF patients scheduled for ECV. Some studies,^{5,13,14} but not others,¹⁸ have found the CHADS₂ and CHA₂DS₂-VASc scores are the best determinants of LAT prior to ECV. Although there was a trend toward higher CHA₂DS₂-VASc in the present study, this was not statistically significant.

In addition, patients already treated with warfarin in the previous 30 days had significant higher prevalence of LAT than those naïve to it. Several factors could explain this apparent paradox. One reason could be that the decision of enrolment of patients in the TOE or non-TOE strata was left to the investigator; hence, there could be a potential bias that patients with higher perceived risk were placed in the TOE stratum despite prior optimal or close-to-optimal anticoagulation due to the fear of potential LAT. Indeed, patients enrolled in the TOE stratum have significantly higher CHA₂DS₂-VASc score than those enrolled in the non-TOE stratum.¹⁹ This probably was not the case for those not already treated with warfarin—either because of a low-risk profile or first AF episode—who could be equally enrolled in the TOE or non-TOE strata.

Left atrium thrombus was found in some patients despite optimal anticoagulation, as was found in other studies.^{13,14} This raises concerns about the safety of the non-TOE approach for ECV compared with the TOE approach. Indeed, there were non-significant trends towards lower cardiovascular events in the TOE strata compared with the non-TOE strata despite more cardiovascular risk factors in the former.¹⁹

Limitations

The main limitation of this study is that the decision to enrol patients in the TOE or non-TOE strata was left to the investigator. Therefore, the incidence of LAT in patients scheduled for ECV may have been overestimated due to the potential bias of patients with worse risk profile enrolled in the TOE stratum. A second limitation comes from an inconsistent follow-up of INR levels, time in therapeutic range and duration of anticoagulation before patient enrolment. Therefore, this study does not clarify the risk of LAT formation despite proper anticoagulation regime at the time of ECV and is unclear if age and heart failure will be more important determinants. Finally, TOE could have been performed up to 72 h after anticoagulation initiation. This may have resulted in some LATs having resolved prior to the TOE.

Conclusion

Elective ECV is commonly cancelled or deferred due to occurrence of TOE-detected LAT in patients with non-valvular AF. Age ≥ 75 years and heart failure are associated with the presence of LAT in these patient populations.

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