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Effect of preceding medications on resuscitation outcome of out-of-hospital cardiac arrest

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ABSTRACT

As evidence regarding the impact of preceding medications on resuscitation outcomes has been inconsistent, this study aimed to analyze the association between preceding medications and resuscitation outcomes in patients experiencing out-of-hospital cardiac arrest (OHCA). This retrospective study included patients with OHCA presenting to a tertiary care hospital by emergency medical service (EMS) between January 2006 and June 2011. Using the Utstein template, data were collected from EMS and hospital medical records for prehospital care, in-hospital care, and medications which were taken continuously for at least 2 weeks preceding OHCA. Primary outcome was the proportion of patients with a survived event. Multivariable logistic regression analyses were performed to evaluate the predictors of survived events. Among the 1381 included patients with OHCA, 552 (40.0%) patients achieved sustained return of spontaneous circulation and 463 (33.5%) patients survived after resuscitation, 96 (7.0%) patients survived until discharge, and 20 (1.4%) patients had a favorable neurological outcome at discharge. The multivariable analyses revealed that use of statins preceding OHCA was independently associated with a greater probability of a survived events (OR=2.09, 95% CI 1.08 to 4.03, $p=0.028$). Use of digoxin was adversely associated with survived events (OR=0.39, 95% CI 0.16 to 0.90, $p=0.028$) in patients with OHCA. The continuous use of statins preceding OHCA was positively associated with survived events, while use of digoxin was adversely related. It deserves more attention on medications preceding OHCA because of their potential effect on resuscitation outcomes.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a profound clinical challenge worldwide. The reported incidence of OHCA ranges from 19 to 150 per 100 000 person-years, and the survival to discharge rate of OHCA is poor, at 1–20%.¹ The majority of OHCA are attributable to ischemic heart disease,^{2–3} followed by structural heart disease,⁴ and primary electrical disease.⁵ In addition to an effective and rapid chain of care for OHCA, reducing the risk of developing ischemic heart disease and preventing ventricular arrhythmia prior to OHCA greatly improve outcome.⁶ Pharmacotherapy plays an important role in pre-OHCA

Significance of this study

What is already known about this subject?

- ▶ The survival-to-discharge rate of out-of-hospital cardiac arrest (OHCA) ranges from 1% to 20% and requires improvement.
- ▶ Pharmacotherapy plays an important role in the primary prevention of OHCA, including reducing risk factors for ischemic heart disease and preventing ventricular arrhythmia.
- ▶ Questions have been raised about whether preceding medications improve or worsen prognosis after successful resuscitation.

What are the new findings?

- ▶ Preceding statin use was independently associated with better survived events in patients with OHCA (OR=2.09, $p=0.028$).
- ▶ Preceding digoxin use was adversely associated with survived events in patients with OHCA (OR=0.39, $p=0.028$).
- ▶ Preceding use of antiarrhythmics had no effect on the survived events in patients with OHCA.

How might these results change the focus of research or clinical practice?

- ▶ The most effective management of OHCA is to prevent its occurrence by lowering the risk of ischemic heart disease and preventing ventricular arrhythmia; therefore, our results suggest that more attention needs to be paid to the preceding medications because of their potential association with survival after OHCA.

managements, including anticoagulants for preventing myocardial infarction, antihypertensive and antidiabetic drugs for treating underlying risk factors of ischemic heart disease, and antiarrhythmic drugs for treating and preventing ventricular arrhythmia.⁶

While medications play a role in the primary prevention of OHCA, once sudden cardiac arrest occurs, it is unclear whether the preceding medications improve survival after resuscitation. In a prospective multicenter study including 874 patients with prehospital cardiac



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arrest, the antecedent use of antiarrhythmic drugs were associated with poor emergency room survival.⁷ Another study found that class III antiarrhythmic drugs, such as sotalol, could reduce arrhythmia recurrences but not total mortality after sudden cardiac arrest.⁸ As evidence has been inconsistent, the aim of this study is to analyze the association of preceding medications with the resuscitation outcome in patients with OHCA.

METHODS

Subjects

Subjects who presented to a tertiary care hospital by emergency medical service (EMS) after experiencing OHCA between January 2006 and June 2011 were included. Patients were excluded for any of the following: (1) age <18 years, (2) significant signs of death, (3) refusal of resuscitation, (4) traumatic cardiac arrest, or (5) implantable cardioverter defibrillator. Significant sign of death refers to postmortem changes, including rigor mortis, livor mortis, algor mortis, cadaveric spasm, decomposition, mummification, and skeletonization.⁹ Traumatic cardiac arrest refers to cardiac arrest directly caused by trauma, such as blunt, penetrating, or burn injury.¹⁰

This retrospective study was ethically approved by the local Institutional Review Board.

Data collection

The Utstein template was used for data collection.¹⁰ From EMS and hospital medical records, we retrospectively collected demographic characteristics, past medical histories, prehospital and in-hospital care data, and information on medication use during the 2 weeks prior to OHCA. Prehospital care data included place of arrest; presence of witness and bystander cardiopulmonary resuscitation (CPR); time of calls, EMS dispatching, EMS arrival at the scene, EMS starting CPR, EMS departing the scene, and EMS arrival at the hospital; use of automated external defibrillator (AED) and initial rhythm of AED; administration of advanced airway management by EMS; and administration of epinephrine by EMS. In-hospital care data included initial rhythm of 12-lead ECG, medication use during CPR, presence of ventricular tachycardia (VT) or ventricular fibrillation (VF) during CPR, and probable etiology of OHCA.

Information regarding medications that were used continuously for at least 2 weeks prior to OHCA was collected from ambulatory and insurance records of each subject. Data were collected only for drugs that have a previously reported association with sudden death and/or significant cardiovascular or respiratory effects, including antiarrhythmic drugs (class I: sodium channel blockers; class II: β -blockers; class III: potassium channel blockers; class IV: calcium channel blockers), cardiovascular drugs (aspirin, clopidogrel, statins, nitroglycerin, Q10, cilostazol), antidiabetic drugs (insulin, oral hypoglycemic agent), antihypertensive drugs (α -blockers, ACE inhibitors, angiotensin II receptor blockers, diuretics), and other relevant drugs such as warfarin, magnesium sulfate, erythromycin, N-acetylcysteine, steroid, digoxin, and QT-prolonging agents.

Statistical analysis

The primary outcome was the success of resuscitation in the emergency department, represented by the rate of

survived events. A survived event, as defined by the Utstein template, is the sustained return of spontaneous circulation (ROSC) until admission and handover to the receiving hospital.¹⁰ Continuous data are presented as mean with SD, and categorical data presented as count with percentage. The differences between patients with and without survived events for continuous and categorical data were tested using the two-sample t-test and χ^2 test, respectively. Multivariable logistic regression analyses were performed to evaluate the predictors of survived events using variables with a p value of <0.1 in the univariable analysis. A two-tailed p value of <0.05 indicated statistical significance. All statistical analyses were performed using IBM SPSS Statistics for Windows, V19.0 (Armonk, New York, USA).

RESULTS

A total of 1381 patients with OHCA were included (figure 1). Among these patient, 552 (40.0%) patients achieved ROSC and 463 (33.5%) had survived events after resuscitation. Ninety-six (7.0%) patients survived until discharge and 20 (1.4%) had favorable neurological outcomes at discharge defined as a cerebral performance category (CPC) of ≤ 2 .

Table 1 lists the comparison of demographic characteristics and medical histories between the patients with and without survived events. There was no difference regarding sex and medical histories between the two groups. Patients with survived events were older than those without survived events (68.8 vs 66.4 years, $p=0.01$).

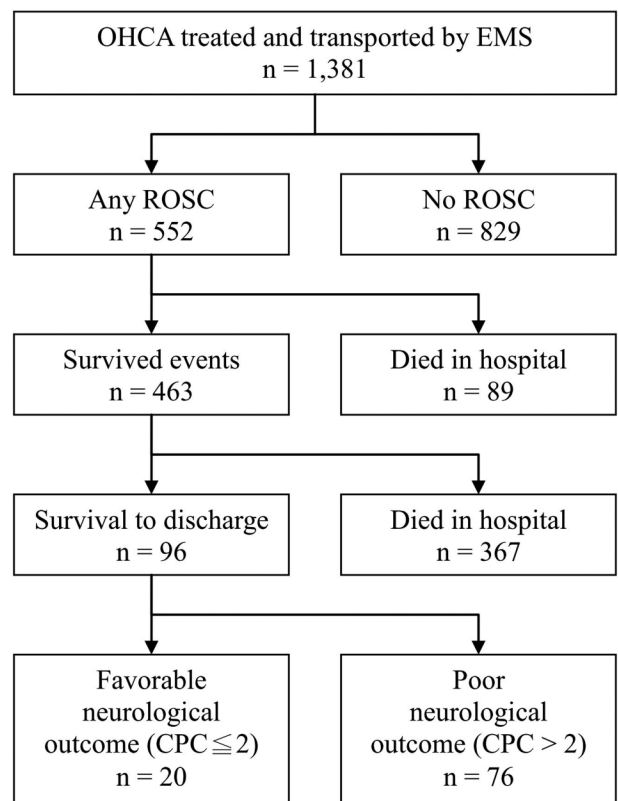


Figure 1 Outcomes of the included OHCA patients. CPC, cerebral performance category; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

Table 1 Demographic characteristics of the included patients with out-of-hospital cardiac arrest

	No survived event (n=918)	Survived event (n=463)	p Value
Age (year)†	66.4 (17.4)	68.8 (15.1)	0.010*
Sex			
Female	332 (36.2)	170 (36.7)	0.841
Male	586 (63.8)	293 (63.3)	
Medical history			
Diabetic mellitus	196 (21.4)	113 (24.4)	0.198
Hypertension	268 (29.2)	148 (32.0)	0.289
Hyperlipidemia	19 (2.1)	10 (2.2)	0.912
Heart failure	59 (6.4)	24 (5.2)	0.359
Arrhythmia	21 (2.3)	17 (3.7)	0.138
Coronary artery disease	176 (19.2)	97 (21.0)	0.433
Cancer	94 (10.2)	50 (10.8)	0.748
COPD/asthma	54 (5.9)	31 (6.7)	0.553
Stroke	97 (10.6)	65 (14.0)	0.058
Chronic liver disease	32 (3.5)	15 (3.2)	0.812
Chronic kidney disease	84 (9.2)	52 (11.2)	0.221

*p<0.05.

†Data were presented as count (percentage) or mean (SD). COPD, chronic obstructive pulmonary disease.

Clinical information regarding prehospital and in-hospital care is provided in table 2. Patients with survived events had significantly greater proportion of witnessed arrests (55.9% vs 32.6%, $p<0.001$), shorter duration between time of call and time of EMS arrival at the scene (4.9 vs 5.2 min, $p=0.04$), shorter duration between time of call and time of EMS departing the scene (16.1 vs 17.1 min, $p=0.004$), shorter duration between time of call and time of EMS arrival at the hospital (24.7 vs 26.0 min, $p<0.001$), greater proportion of shockable initial AED rhythm (13.2% vs 8.0%, $p=0.005$), and a greater proportion of patients received advanced airway management by EMS (31.7% vs 24.7%, $p=0.006$) than those without survived events. After arrival at the emergency department, significantly more patients with survived events had shockable initial 12-lead ECG rhythm (8.0% vs 3.8%, $p=0.001$), had received atropine (30.0% vs 20.9%, $p<0.001$), had received MgSO₄ (4.3% vs 1.5%, $p=0.002$), had presence of VT/VF during CPR (27.0% vs 19.7%, $p=0.002$) and fewer had cardiac etiology of OHCA (51.4% vs 72.3%, $p<0.001$) than those without survived events.

Comparison of medications uses during the 2-week period prior to OHCA between patients with and without survived events revealed that significantly more patients who survived OHCA were receiving class II antiarrhythmic drugs (5.6% vs 3.2%, $p=0.028$), statins (5.0% vs 2.8%, $p=0.043$), N-acetylcysteine (1.7% vs 0.5%, $p=0.040$), and fewer were receiving digoxin (1.7% vs 3.7%, $p=0.044$) compared with those who did not survive (table 3).

Results of multivariable logistic regression model for the predictors of survived events are summarized in table 4. After adjusting for other variables, several variables were independent predictors of survived events, including witnessed arrest (OR=2.18, 95% CI 1.70 to 2.80, $p<0.001$), response time between call and EMS arrival at the hospital

Table 2 Clinical information of patients

	No survived event (n=918)	Survived event (n=463)	p Value
Prehospital			
Arrest at home	76 (8.3)	34 (7.3)	0.544
Witnessed arrest	299 (32.6)	259 (55.9)	<0.001*
Bystander CPR	118 (12.9)	73 (15.8)	0.139
Response time (min)†			
Time to EMS arrival at the scene	5.2 (2.4)	4.9 (2.4)	0.040*
Time to EMS starting CPR	9.3 (4.9)	9.2 (5.1)	0.675
Time to EMS departing the scene	17.1 (6.0)	16.1 (6.2)	0.004*
Time to EMS arrival at the hospital	26.0 (6.5)	24.7 (7.0)	<0.001*
AED			0.005*
No AED use	44 (4.8)	27 (5.8)	
Initial AED rhythm non-shockable	801 (87.3)	375 (81.0)	
Initial AED rhythm shockable	73 (8.0)	61 (13.2)	
Advanced airway management by EMS	227 (24.7)	147 (31.7)	0.006*
Epinephrine given by EMS	175 (19.1)	101 (21.8)	0.227
Hospital			
Initial 12-lead ECG rhythm shockable	35 (3.8)	37 (8.0)	0.001*
Medications			
Epinephrine	835 (91.0)	415 (89.6)	0.427
Atropine	192 (20.9)	139 (30.0)	<0.001*
Sodium bicarbonate	273 (29.7)	151 (32.6)	0.274
Amiodarone	114 (12.4)	60 (13.0)	0.775
MgSO ₄	14 (1.5)	20 (4.3)	0.002*
Lidocaine	14 (1.5)	7 (1.5)	0.985
VT/VF during CPR	181 (19.7)	125 (27.0)	0.002*
Cardiac etiology	664 (72.3)	238 (51.4)	<0.001*

*p<0.05.

†Data were presented as count (percentage) or mean (SD).

AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; VF, ventricular fibrillation; VT, ventricular tachycardia.

(OR=0.97, 95% CI 0.95 to 0.98, $p<0.001$), performance of advanced airway management by EMS (OR=1.70, 95% CI 1.27 to 2.26, $p<0.001$), administration of atropine (OR=1.68, 95% CI 1.26 to 2.23, $p<0.001$), administration of MgSO₄ (OR=3.13, 95% CI 1.43 to 6.88, $p=0.004$), prehospital ROSC (OR=6.89, 95% CI 3.27 to 14.54, $p<0.001$), and cardiac etiology (OR=0.30, 95% CI 0.23 to 0.39, $p<0.001$). Regarding medication use preceding OHCA, the use of statins was an independent positive predictor (OR=2.09, 95% CI 1.08 to 4.03, $p=0.028$) and the use of digoxin was a negative predictor (OR=0.39, 95% CI 0.16 to 0.90, $p=0.028$) of survived events.

DISCUSSION

Most patients with OHCA had some form of underlying heart diseases, mainly ischemic heart diseases. Primary prevention of OHCA includes optimal management of ventricular arrhythmia and reduction of risk factors for ischemic heart disease. Pharmacotherapy plays an important role in the primary prevention of OHCA; however, sufficient evidence is lacking regarding the association

Table 3 Medication uses during the 2 weeks preceding out-of-hospital cardiac arrest

	No survived event (n=918)	Survived event (n=463)	p Value
Antiarrhythmics			
Class I	6 (0.7)	3 (0.6)	1.000
Class II	29 (3.2)	26 (5.6)	0.028*
Class III	7 (0.8)	3 (0.6)	1.000
Class IV	63 (6.9)	34 (7.3)	0.741
Aspirin	54 (5.9)	31 (6.7)	0.553
Clopidogrel	23 (2.5)	16 (3.5)	0.314
Statin	26 (2.8)	23 (5.0)	0.043*
Nitroglycerin	23 (2.5)	15 (3.2)	0.431
Insulin	10 (1.1)	8 (1.7)	0.323
Oral hypoglycemic agents	65 (7.1)	42 (9.1)	0.191
α-Blockers	17 (1.9)	16 (3.5)	0.065
Angiotensin receptor blockers	58 (6.3)	40 (8.6)	0.113
ACE inhibitors	19 (2.1)	9 (1.9)	0.875
Diuretics	97 (10.6)	52 (11.2)	0.707
Warfarin	9 (1.0)	4 (0.9)	1.000
Magnesium	14 (1.5)	9 (1.9)	0.566
Erythromycin	2 (0.2)	1 (0.2)	1.000
N-acetylcysteine	5 (0.5)	8 (1.7)	0.040*
Steroid	17 (1.9)	8 (1.7)	0.870
Digoxin	34 (3.7)	8 (1.7)	0.044*
Theophylline	39 (4.2)	19 (4.1)	0.899
Cilostazol	5 (0.5)	1 (0.2)	0.670
QT-prolonging drugs	10 (1.1)	5 (1.1)	0.987

Data were presented as count (percentage).

*p<0.05.

Table 4 Multivariable logistic regression model for the predictors of survival events

	OR	95% CI	p Value
Age (year)	1.01	1.00 to 1.01	0.066
Witnessed arrest	2.18	1.70 to 2.80	<0.001*
Time to EMS arrival at the hospital	0.97	0.95 to 0.98	<0.001*
Advanced airway management by EMS	1.70	1.27 to 2.26	<0.001*
AED			
No AED use	–	–	0.128
Initial AED rhythm non-shockable	0.65	0.41 to 1.02	0.063
Initial AED rhythm shockable	0.81	0.43 to 1.54	0.529
Initial 12-lead ECG rhythm shockable	1.57	0.83 to 2.98	0.170
Atropine	1.68	1.26 to 2.23	<0.001*
MgSO ₄	3.13	1.43 to 6.88	0.004*
VT/VF during CPR	1.24	0.88 to 1.74	0.221
Prehospital ROSC	6.89	3.27 to 14.54	<0.001*
Cardiac etiology	0.30	0.23 to 0.39	<0.001*
Stroke	1.30	0.89 to 1.90	0.175
Antiarrhythmics, class II	1.74	0.93 to 3.26	0.081
Statin	2.09	1.08 to 4.03	0.028*
α-Blocker	1.31	0.59 to 2.91	0.505
N-acetylcysteine	3.14	0.96 to 10.26	0.059
Digoxin	0.39	0.16 to 0.90	0.028*

*p<0.05.

AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

between medication use preceding OHCA and the resuscitation outcome. In this study, use of a statin was significantly associated with survival after OHCA (OR=2.09, 95% CI 1.08 to 4.03, p=0.028) and use of digoxin was associated with less likelihood of survival (OR=0.39, 95% CI 0.16 to 0.90, p=0.028) after adjusting for other variables.

Statins have been shown to have cardiovascular protective effects, including stabilization of atherosclerotic plaque, inhibition of systematic inflammation, antioxidative quality, improvement in endothelial function, and ability to increase nitric oxide bioavailability, which attribute to the pleiotropic and lipid-lowering effects of agents in this class.^{11–12} Some studies have observed potential antiarrhythmic effects of statins, such as improving heart rate variability and decreasing QT dispersion.^{13–14} Moreover, a meta-analysis of 25 randomized controlled trials conducted by Rahimi *et al*¹⁵ reported that statin use was associated with a 10% reduction in risk of sudden cardiac death in comparison with control (OR=0.90, 95% CI 0.82 to 0.97, p=0.01). However, very few studies have analyzed the effect of statins on resuscitation outcomes after cardiac arrest. In a prospective study by Vukmir *et al*, antecedent medication use by patients with OHCA was only briefly described as use of cardiac drugs, and antihypertensive, antiarrhythmic, pulmonary, hematological, gastrointestinal, psychiatric, or antiseizure agents.⁷ This study did not specify which agents were included as cardiac drugs, for

example, cholesterol-lowering agents or statins.⁷ Our results found that the use of statins significantly increased the rate of survived events in patients experiencing OHCA. This finding suggests that the cardioprotective effect of statins prevents cardiac arrest and cardiac death, and also might affect resuscitation outcomes of sudden cardiac arrest.

Digoxin is a standard treatment for congestive heart failure, but its cardiac safety and effect remain uncertain. In a prospective study by Teodorescu *et al* comprising 378 sudden cardiac death cases, multivariable analysis revealed that digoxin significantly increased the risk of sudden cardiac death (OR=4.74, 95% CI 2.35 to 9.53, p<0.0001).¹⁶ Conversely, a retrospective study including 6797 participants noted that digoxin was not an independent risk factor of sudden coronary death (OR=1.19, 95% CI 0.94 to 1.49, p=0.15).¹⁷ These conflicting results might have been due to interaction between digoxin and other drugs that could influence digoxin concentrations, and thus affecting its activity. Consequently, the true effect size of digoxin could be underestimated or overestimated in each study.¹⁸ In addition to these conflicting results, sufficient evidence is lacking in regard to the effect of digoxin on resuscitation outcomes of cardiac arrest. Our study found that digoxin use was associated with poor emergency room survival in patients with OHCA. The result suggests that the cardiac toxicity of digoxin remains when sudden cardiac arrest occurs and subsequently influences resuscitation outcomes.

While a better understating could be gained from a randomized controlled clinical study, the retrospective findings presented here could be a starting point. In the future,

practice guidelines for resuscitation might be modified as sufficient evidence becomes available. For example, different resuscitation processes may need to be applied, such as the administration of different drugs during CPR, for patients who are currently taking digoxin or statins.

In this study, we did not find any significant association between the empiric use of antiarrhythmic drugs and OHCA event survival. Vukmir *et al* reported that antiarrhythmic use was associated with decreased survival of patients with prehospital cardiac arrest. However, this study collected only data for four specific antiarrhythmic drugs (procainamide, quinidine, disopyramide, and mexiletine) and multivariate analysis was not performed to adjust for confounding factors.⁷ Contrastingly, a retrospective study by Dries *et al* found that the use of any antiarrhythmic agents (other than β -blockers) independently increased the risk of sudden coronary death (OR=1.33, 95% CI 1.05 to 1.69, $p=0.02$), but β -blockers were not associated with increased risk (OR=0.75, 95% CI 0.55 to 1.03, $p=0.07$). Unfortunately, this study did not specify the details of antiarrhythmic drugs and also did not evaluate the resuscitation outcomes.¹⁷ In our study, we collected data on all classes of antiarrhythmic drugs, which provides a more comprehensive view of the empiric use of antiarrhythmic drugs for cardiac arrest.

There were several limitations in this study. First, potential bias is inherent in the retrospective study design. Second, we did not consider certain time-related factors which can potentially confound outcomes, such as time of collapse, time interval from collapse to ROSC, and time interval from collapse to AED use; however, recall of precise time would be difficult in an emergency settings. Third, we only collected data on drugs which have been previously reported to have an association with sudden death and/or have significant cardiovascular or respiratory effects. Potential drug–drug interactions which could possibly affect the outcomes of OHCA were not assessed. Fourth, we did not consider physiological factors, such as renal and hepatic function, which could alter pharmacological effects. Finally, this study only focused on the predictors of survived events and did not consider other core outcomes, such as survival to discharge or discharge with favorable neurological outcomes. These outcomes also deserve further investigations for their association with medications preceding OHCA.

CONCLUSION

This study found that the continuous use of statins during the 2 weeks preceding OHCA significantly increased the likelihood of survived events. Conversely, use of digoxin was adversely associated with survived events in patients with OHCA. As pharmacotherapy plays an important role in the primary prevention of OHCA, more attention needs to be paid to medication preceding OHCA because of their potential effects on resuscitation outcomes.

Contributors S-WH, T-LW conceived and designed the study. C-MC, C-FS reviewed the charts and collected the data. L-MT performed the statistical analysis. S-WH drafted the manuscript. All authors contributed to the approval of the final version.

Competing interests None declared.

Ethics approval Institutional Review Board of the Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.

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