

## БЛИЖАЙШИЕ И ОТДАЛЕННЫЕ РЕЗУЛЬТАТЫ КАРОТИДНОЙ ЭНДАРТЕРАКТОМИИ В РАЗНЫЕ ПЕРИОДЫ ИШЕМИЧЕСКОГО ИНСУЛЬТА

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**Цель.** Анализ госпитальных и отдаленных результатов каротидной эндартерэктомии (КЭЭ) в разные периоды острого нарушения мозгового кровообращения (ОНМК).

**Материалы и методы.** Настоящее исследование являлось ретроспективным и проводилось методом сплошной выборки пациентов. За период с 2010 по 2019 гг. в было отобрано 1113 пациентов с ОНМК в анамнезе, которым в последствии выполнялась КЭЭ. В зависимости от срока между последним ОНМК и КЭЭ все больные были распределены на 4 группы: 1-ая группа – в острейшем периоде (1-3 сут.) ОНМК (n=24; 2,2%); 2-ая группа – в остром периоде (до 28 сут.) ОНМК (n=493; 44,3%); 3-ая группа – в раннем восстановительном периоде (до 6 мес.) ОНМК (n=481; 43,2%); 4-ая группа – в позднем восстановительном периоде (до 2-х лет) ОНМК (n=115; 10,3%). Отдаленный период составил 34,8±12,5 месяцев.

**Результаты.** В госпитальном периоде наблюдения были выявлены следующие осложнения: летальный исход (группа 1 – 0%; группа 2 – 0,4% (n=2); группа 3 – 0,2% (n=1); группа 4 – 0%; p=0,16); инфаркт миокарда (группа 1 – 0%; группа 2 – 0,4% (n=2); группа 3 – 0%; группа 4 – 0,9% (n=1); p=0,35); ОНМК / транзиторная ишемическая атака (ТИА, группа 1 – 4,2% (n=1); группа 2 – 0,4% (n=2); группа 3 – 0,2% (n=1); группа 4 – 0%; p<sub>1-2</sub>=0,01; p<sub>1-3</sub>=0,009; p<sub>1-4</sub>=0,01). Комбинированная конечная точка, состоящая из летального исхода + инфаркт миокарда + ОНМК/ТИА, составила к концу госпитального этапа в группе 1 – 4,2% (n=1), в группе 2 – 1,2% (n=6), в группе 3 – 0,4% (n=2), в группе 4 – 2,6% (n=3), p=0,08. В отдаленном периоде наблюдения были выявлены следующие осложнения: летальный исход от всех причин (группа 1 – 25% (n=6); группа 2 – 5,5% (n=27); группа 3 – 7,3% (n=35); группа 4 – 14% (n=16); p<sub>1-2</sub>=0,002; p<sub>1-3</sub>=0,008; p<sub>2-4</sub>=0,012); летальный исход от кардиоваскулярных причин (группа 1 – 4,2% (n=1); группа 2 – 3,6% (n=18); группа 3 – 4,8% (n=23); группа 4 – 5,2% (n=6); p=0,79); инфаркт миокарда (группа 1 – 12,5% (n=3); группа 2 – 3,6% (n=18); группа 3 – 5,4% (n=26); группа 4 – 6,1% (n=7); p=0,15); ОНМК/ТИА (группа 1 – 16,6% (n=4); группа 2 – 6,3% (n=31); группа 3 – 6% (n=29); группа 4 – 11,3% (n=13); p=0,05); комбинированная конечная точка летальный исход + инфаркт миокарда + ОНМК/ТИА (группа 1 – 54,2% (n=13); группа 2 – 15,4% (n=76); группа 3 – 18,7% (n=90); группа 4 – 31,3% (n=36); p<sub>1-2</sub>=0,0001; p<sub>1-3</sub>=0,0001; p<sub>1-4</sub>=0,005; p<sub>2-4</sub>=0,0006; p<sub>3-4</sub>=0,012).

**Заключение.** Выполнение КЭЭ продемонстрировало эффективность и безопасность в остром и раннем восстановительном периоде ОНМК.

**Ключевые слова:** каротидная эндартерэктомия; ОНМК; госпитальные осложнения; отдаленные осложнения; инсульт.



## IMMEDIATE AND LONG-TERM RESULTS OF CAROTID ENDARTERECTOMY IN DIFFERENT PERIODS OF ISCHEMIC STROKE

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**Aim.** Analysis of hospital and long-term results of carotid endarterectomy (CEA) in different periods of acute cerebrovascular event (ACVE).

**Materials and Methods.** The given study was retrospective and was conducted using the method of patients sampling. In the period from 2010 to 2019, 1113 patients with ACVE in history who were later conducted CEA, were selected. Depending on the time interval between the last ACVE and CAE, all the patients were divided into 4 groups: the 1<sup>st</sup> group – in the acutest period of ACVE (1-3 days) (n=24; 2.2%); the 2<sup>nd</sup> group – in the acute period of ACVE (up to 28 days) (n=493; 44.3%); the 3<sup>rd</sup> group – in the early rehabilitation period of ACVE (up to 6 months) (n=481; 43.2%); the 4<sup>th</sup> group – in the late rehabilitation period of ACVE (up to 2 years) (n=115; 10.3%). The long-term period was 34.8±12.5 months.

**Results.** In the hospitalization period of observation the following complications were found: lethal outcome ((group 1 – 0%; group 2 – 0.4% (n=2); group 3 – 0.2% (n=1); group 4 – 0%; p = 0.16)); myocardial infarction ((group 1 – 0%; group 2 – 0.4% (n=2); group 3 – 0%; group 4 – 0.9% (n=1); p = 0.35)); ACVE/transient ischemic attack (TIA), ((group 1 – 4.2% (n=1); group 2 – 0.4% (n=2); group 3 – 0.2% (n=1); group 4 – 0%; p<sub>1-2</sub>=0.01; p<sub>1-3</sub>= 0.009; p<sub>1-4</sub>=0.01)). By the end of hospitalization period the composite endpoint consisting of lethal outcome + myocardial infarction + ACVE/TIA made in group 1 – 4.2% (n=1), in group 2 – 1.2% (n=6), in group 3 – 0.4% (n=2), in group 4 – 2.6% (n=3), p=0.08. Complications of the long-term follow-up period were: lethal outcome from all causes ((group 1 – 25% (n=6); group 2 – 5.5% (n=27); group 3 – 7.3% (n=35); group 4 – 14% (n=16); p<sub>1-2</sub>=0,002; p<sub>1-3</sub>=0,008; p<sub>2-4</sub>=0,012)); lethal outcome from cardiovascular causes ((group 1 – 4.2% (n=1); group 2 – 3.6% (n=18); group 3 – 4.8% (n=23); group 4 – 5.2% (n=6); p = 0.79)), myocardial infarction ((group 1 – 12.5% (n=3); group 2 – 3.6% (n=18); group 3 – 5.4% (n=26); group 4 – 6.1% (n=7); p = 0.15)), ACVE/TIA ((group 1 – 16.6% (n=4); group 2 – 6.3% (n=31); group 3 – 6% (n=29); group 4 – 11.3% (n=13); p = 0,05)); composite endpoint including lethal outcome + myocardial infarction + ACVE/TIA ((group 1 – 54.2% (n=13); group 2 – 15.4% (n=76); group 3 – 18.7% (n=90); group 4 – 31.3% (n=36); p<sub>1-2</sub>=0.0001; p<sub>1-3</sub>=0.0001; p<sub>1-4</sub>=0.005; p<sub>2-4</sub>=0.0006; p<sub>3-4</sub>=0.012)).

**Conclusion.** Application of CEA demonstrated effectiveness and safety in the acute and early rehabilitation period of ACVE.

**Keywords:** carotid endarterectomy, ACVE, hospital complications, long-term complications, stroke.

Despite the fact that it is clearly stated in the effective recommendations that carotid endarterectomy (CEA) should be performed in two weeks after a partial stroke and in 6-8 weeks after a complete stroke, the discussion of the effectiveness and safety of surgical intervention in different periods of ACVE

does not stop [1-3]. There exist some works demonstrating the results of CEA performed in the acute period of ACVE, but there is deficit of works comparing outcomes of the correction performed in different periods after stroke [4-6]. Besides, in the effective recommendations, no indications are postulated for

performing CEA just in the acutest period of ACVE which creates uncertainty in choice of the time of revascularization [7-9].

*Aim* – comparative analysis of hospital and long-term outcomes of carotid endarterectomy in different periods of an acute cerebrovascular event.

### Materials and Methods

The given cohort, comparative, retrospective, open study covering the period from 2010 to 2019 included 1113 patients with symptomatic stenosis of the internal carotid artery (ICA) in whom CEA was conducted. Depending on the time interval between the last ACVE and CEA, all the patients were divided to 4 groups:

*1<sup>st</sup> group* – in the acutest period (1-3 days) of ACVE (n=24; 22%);

*2<sup>nd</sup> group* – in the acute period (up to 28 days) of ACVE (n=493; 44.3%);

*3<sup>rd</sup> group* – in the early rehabilitation period (up to 6 months) of ACVE (n=481; 43.2%);

*4<sup>th</sup> group* – in the late rehabilitation period (up to 2 years) of ACVE (n=115; 10.3%).

Criteria of choice of the time of revascularization were determined by a multidisciplinary team (cardiovascular surgeon, endovascular surgeon, neurosurgeon, cardiologist, neurologist) on the basis of the effective clinical recommendations, and included evident neurologic deficit (CEA is possible on achievement of 2 points on Rankin scale), instability of atherosclerotic plaque, stenosis of different extent of evidence, dimensions of ischemic focus, presence of decompensated comorbid pathology requiring correction.

The brain was protected by elevation of systolic arterial pressure up to 180-200 mm Hg with the absence of indications for placement of temporary bypass. Decision on use of temporary bypass was taken with the value of retrograde pressure in ICA less than 60% of systemic pressure, with the open Circle of Willis ((all patients underwent multispiral computed tomography (MSCT) of the extra- and intracranial arteries)).

Control points were recorded in hospital and long-term postoperative periods (34.8±12.5

months). Information about the structure of complications in the long-term postoperative period was obtained from the data of repeated examination of the patients in the vascular center of the institution.

Interventions were performed within the frames of the effective clinical recommendations. On admission to hospital, the patients or their legal representatives signed the informed consent in the form approved at the institution.

The groups were comparable in the majority of characteristics, however, most patients with angina pectoris of 1-2 functional classes (FC) were concentrated in the 2<sup>nd</sup> and 3<sup>rd</sup> groups. The absolute majority of patients were men. Each fifth patient had MI in history, the current ACVE was a recurrent one in each sixth patient (Table 1).

Results of the study were processed using the application software package Graph Pad Prism (USA). The type of distribution of variables was determined using Kolmogorov-Smirnov test. Comparison between the groups was implemented using Kruckall-Wallis test. The survival curves were constructed using Kaplan-Meier analysis. For comparison of the curves, Mantel-Cox test was used. The differences were considered statistically significant at  $p < 0.05$ .

### Results and Discussion

Coronarography in all the groups revealed a mild degree of lesion because of a high percent of past revascularizations of the myocardium in history. Hemodynamically significant stenoses of ICA on both sides were most commonly noted in group 4, and contralateral occlusion and unstable atherosclerotic plaque in the ipsilateral and contralateral ICA – in group 2 (Table 2).

In most patients, classic CEA was conducted with plastics of the revascularization zone with a xenopericardium patch. In single cases, hybrid revascularization (percutaneous coronary intervention + CEA) was conducted. The time of compression of ICA was comparable in all the groups (Table 2).

Table 1

**Clinical-Demographic Characteristics and Neurological Status  
of the Studied Cohort of Patients**

Parameter	Group 1 (Acutest period)	Group 2 (Acute period)	Group 3 (Early rehabilitation period)	Group 4 (Late rehabilitation period)	P
n	24	493	481	115	-
<b>Clinical-Demographic Parameters</b>					
Age, years	64.2±5.7	63.4±3.8	66.3±6.1	64.5±4.7	0.1
Male gender, %	66.6	56.4	51.1	60.0	0.12
Angina pectoris 1-2 FC, %	83.3	88.2	86.9	71.3	p <sub>2-4</sub> =0.0001 p <sub>3-4</sub> =0.0001
PICS, %	20.8	17.4	20.4	12.2	0.2
DM, %	12.5	5.9	8.5	4.3	0.17
COPD, %	4.2	0.6	0.4	0.9	0.15
MFA involving three arterial territories, %	33.3	45.2	52.2	39.1	0.01
Left ventricular ejection fraction, %	59.4±6.7	61.0±3.6	58.2±3.8	63.9±5.4	0.32
Pulmonary hypertension, %	4.2	0.6	0.4	0.9	0.15
Postinfarction aneurysm of LV, %	0	0.4	0.4	0	0.9
PCI in history, %	16.6	14.8	18.5	10.4	0.14
CBS in history, %	4.2	2.6	1.9	1.7	0.75
<b>Neurological status</b>					
NIHSS scale, points	1.86±0.70	1.75±0.32	1.81±0.53	1.88±0.59	0.2
Rivermead mobility index	13.5±2.2	12.4±1.5	13.1±1.8	13.2±3.3	0.2
Modified Rankin scale, points	1.60±0.45	1.64±0.63	1.69±0.80	1.70±0.73	0.1
Barthel scale, points	89.6±7.2	93.5±6.1	93.4±6.6	91.5±7.2	0.3
Repeated ACVE/TIA, %	16.6	17.2	15.8	12.2	0.6

*Note:* PICS – postinfarction cardiosclerosis, DM – diabetes mellitus, COPD – chronic obstructive pulmonary disease, MFA – multifocal atherosclerosis, LVEF – left ventricular ejection fraction, LV – left ventricle, PCI – percutaneous coronary intervention, CBS – coronary bypass surgery, TIA – transient ischemic attack

Significant differences obtained in the hospital period of observation were only in the frequency of ACVE/transient ischemic attack (TIA). The highest amount of neurological disasters happened in the acutest period group – 4.2% (Table 3). In the long-term follow-up, the numbers of lethal outcomes from all causes and ACVE/TIA were maximal in the 1<sup>st</sup> group (the acutest period of ACVE); the frequency of composite endpoint (lethal outcome + myocardial infarction + ACVE/TIA) was significantly higher in the 1<sup>st</sup> and 4<sup>th</sup> groups (the acutest and late rehabilitation periods of ACVE) (Table 3).

In comparison of Kaplan-Meier curves, similar parameters of intergroup differences were obtained: lethal outcome from all causes

– p=0.0001; lethal outcome from cardiovascular causes – p=0.91; myocardial infarction (MI) – p=0.14; ACVE/TIA – p=0.04; composite endpoint – p=0.0001.

As it was shown by earlier works, the benefit of revascularization of the brain after past ACVE depends on the balance between the long-term risk of vascular complications in drug treatment and perioperative risk of development of adverse cardiovascular events [1,3,10]. Meta-analysis of two studies showed that advantages of CEA are most evident in patients operated on within 2 weeks after ACVE [3], while emergency CEA in the acutest period of the disease is associated with high operative risk [3,4,11]. However, according to some authors, in stable patients

with a minor stroke or TIA, the operation may be effective in the acutest and at the begin-

ning of acute period of ACVE, therefore early CEA is considered justified [12-14].

Table 2

### Angiographic and Perioperative Characteristics of Studied Cohort of Patients

Parameter	Group 1 (Acutest period)	Group 2 (Acute period)	Group 3 (Early rehabilitation period)	Group 4 (Late rehabilitation period)	P
n	24	493	481	115	-
<b>Angiographic Characteristics</b>					
Hemodynamically significant stenosis of ICA on two sides, %	20.8	25.9	30.6	38.3	0.04
Occlusion of contralateral ICA, %	4.2	15.6	8.7	10.4	0.005
Unstable ASP in iICA, %	45.8	51.1	37.2	54.8	$p_{3-4}=0.004$
Unstable ASP in cICA, %	8.3	33.8	25.1	24.3	$p_{1-2}=0.04$ $p_{2-3}=0.01$
SYNTAX scale, points	13.5±4.2	12.9±6.1	14.6±5.1	13.6±4.5	0.1
<b>Perioperative Characteristics</b>					
CEA with use of xenopericardium patch, %	100.0	86.4	65.5	80.8	$p_{1-3}=0.0005$ $p_{2-3}=0.0001$ $p_{3-4}=0.002$
Eversion CEA, %	0	13.6	25.8	19.1	$p_{1-3}=0.01$ $p_{2-3}=0.0001$
CEA with use of temporary bypass, %	8.4	17.2	12.3	22.6	0.01
Hybrid revascularization PCI+CEA, %	0	4.5	6.0	6.1	0.43
Time of ICA compression, min.	27.5±4.3	26.1±6.2	26.9±2.4	25.1±4.4	0.2

Note: ASP – atherosclerotic plaque, iICA – ipsilateral ICA, cICA – contralateral ICA

Table 3

### Hospital and Long-Term Complications in the Studied Cohort of Patients

Parameter	Group 1 (Acutest period)	Group 2 (Acute period)	Group 3 (Early rehabilitation period)	Group 4 (Late rehabilitation period)	P
n	24	493	481	115	-
<b>Hospital Complications</b>					
Death, %	0	0.4	0.2	1.7	0.16
MI, %	0	0.4	0	0.9	0.35
Repeated ACVE/TIA, %	4.2	0.4	0.2	0	$p_{1-2}=0.01$ $p_{1-3}=0.009$ $p_{1-4}=0.01$
Significant hemorrhage (BARC ≥3 degree), requiring revision, %	0	0.8	0.4	0.9	0.83
Damage to CN, %	8.3	5.1	6.4	8.7	0.46
Composite endpoint*, %	4.2	1.2	0.4	2.6	0.08
<b>Long-Term Complications</b>					
Follow-up period, months	28.1±15.3	35.5±21.4	36.7±18.2	31.5±12.7	0.3
Death from all causes, %	25.0	5.5	7.3	14.0	$p_{1-2}=0.002$ $p_{1-3}=0.008$ $p_{2-4}=0.012$
Death from cardiovascular causes, %	4.2	3.6	4.8	5.2	0.79
Myocardial infarction (non-lethal), %	12.5	3.6	5.4	6.1	0.15

ACVE/TIA (non-lethal), %	16.6	6.3	6	11.3	0.05
Hemodynamically significant restenosis in CEA zone (more than 60%), requiring CreEA, %	0	1.6	1.5	3.5	0.42
Progression of atherosclerosis on the contralateral side requiring CEA %	8.4	5.1	6.2	11.3	0.09
Composite endpoint*, %	54.2	15.4	18.7	31.3	p <sub>1-2</sub> =0.0001 p <sub>1-3</sub> =0.0001 p <sub>1-4</sub> =0.05 p <sub>2-4</sub> =0.0006 p <sub>3-4</sub> =0.012

Note: CN – cranial nerve, CreEA – carotid re-endarterectomy, \* – death from all causes + non-lethal ACVE/TIA + non-lethal MI

The results of our work showed that patients sent to CEA, may differ only in some parameters. In particular, the most evident symptomatic damage to the coronary circulation is seen in patients in the acute period of ACVE. Nevertheless, these patients have the lowest result on SYNTAX scale in comparison with other groups, which can be explained by a complete revascularization of the myocardium in history. Moreover, these patients are characterized by a more frequent ( $p=0.005$ ) development of occlusion of the contralateral ICA. Generalizing the presented data, the conclusion can be made about *a more severe course of multifocal atherosclerosis in this group*. However, patients who underwent revascularization in the acute period of ACVE, have *lowest parameters of long-term postoperative complications*. This tendency is attributed to complete revascularization of the myocardium in history, and to a stronger adherence to doctor's recommendations. We think that higher compliance is formed due to the fact that CEA was actually performed in the accelerated manner. The patient is delivered to clinic in a life-threatening condition with already existing cardiovascular event, and after conservative treatment and aggressive surgical tactics his status completely or partially recovers. A certain «fear for life» and a correct dialogue with the doctor permit to establish in him a conscientious attitude to the administered treatment and recommendations. More stable patients

sent to revascularization of the brain from the outpatient clinic in the early and late rehabilitation periods of ACVE, are likely to demonstrate opposite peculiarities and distrust in medical indications, which results in increased significance of composite outcome ((death from all causes + CVE/TIA (non-lethal) + MI (non-lethal)) proportionally to the period after stroke: in the acute period – 15.4%, in the early rehabilitation period – 18.7%, in the late rehabilitation period – 31.3%. A similar trend is seen in the parameters of lethality from all causes and ACVE/TIA.

A special small cohort is patients in the acutest period of ischemic stroke. On the one hand, a low statistical power of this group does not permit to fully evaluate risks of hospital and long-term complications. On the other hand, at present there is a deficit of studies on CEA just in the acutest period of ACVE, which attaches additional importance to studying these, although scarce, data. To note, it is these patients that develop the highest percent of ACVE/TIA in the hospital period of observation (Table 3). In one case the cause of neurologic disaster was hyperperfusion syndrome that caused hemorrhagic transformation of the ischemic focus with subsequent evident neurologic deficit. According to the literature data, this mechanism of ACVE is most common in the patients of this cohort [10-12]. Here, it should be noted that the diameter of ischemic focus was 3.2 cm which prevented us in future from

resorting to emergency or accelerated CEA in case of the diameter of ischemic focus more than 2.5 cm [13-15].

No lethal outcomes and MI were recorded among the patients who underwent revascularization in the acutest period of the observation. This was due to a thorough screening examination of all arterial territories of the patient, of comorbid conditions, peculiarities of structure of Circle of Willis, and, finally, to a thorough selection of patients for urgent CEA by a *multidisciplinary team* (cardiovascular surgeon, neurosurgeon, endovascular surgeon, cardiologist, neurologist). In our opinion, revascularization of the brain in the acutest period of ACVE is possible with the existence of ischemic focus of any diameter less than 2.5 cm determined by MSCT, with regression of neurologic focus to 2-3 points on Rankin scale, unstable atherosclerotic plaque or floating thrombus in the bifurcation of carotid arteries. Special attention should be given to diagnosis of contralateral occlusion of ICA and the open Circle of Willis, which influences compensatory capacities of cerebral hemodynamics in compression of the carotid arteries. With the existence of these factors we recommend a temporary bypass to be installed irrespective of the level of retrograde blood flow in ICA. Thus, a complex of these actions permits to maintain the parameter of composite endpoint of the hospital period on a statistically comparable level ( $p=0.08$ ) among all the patients' groups (Table 3).

However, it should be noted that in the long-term period it is patients of the first group that have the highest parameter of composite endpoint (Table 3). A significant contribution to this point is made by deaths from non-cardiovascular complications: 16.6% ( $n=4$ ) of cases of the onset of an oncological disease and 4.2% ( $n=1$ ) of cranial traumas. Besides, the highest quantity of non-lethal ACVE in the long-term postoperative period was seen in the patients operated on in the acutest period of ischemic stroke. However, by that moment no signs of restenosis or

hemodynamically significant progression of atherosclerosis on the contralateral side were recorded, which puts to the forefront the existence of fibrillation of atria as the main predictor of development of neurological disaster in these patients. Thus, the fact of CEA in the acutest period could not influence higher parameters of complications in the long-term period.

Analysis of the amount of non-lethal ACVE in the long-term follow-up period in other groups did not reveal any statistically significant differences in their frequency. In total, 77 (7.1%) neurological disasters were recorded caused by: hemodynamically significant restenosis in 19 (24.7%) cases, hemodynamically significant progression of atherosclerosis in the contralateral ICA in 29 (37.6%) cases, fibrillation of atria in 18 (23.4%) cases, non-appearance at CEA on the contralateral side in 6 (7.8%) cases, with 5 (6.5%) cases of unclear etiology.

Discussing the necessity of performing CEA in the acute and acutest period of ACVE, some publications justify it by a vividly positive dynamics in the neurological status after the intervention, already seen as early as by the moment of discharge from hospital [15-17]. However, in our study, with examination of neurologist, on the 6<sup>th</sup> day after CEA, the presentation of neurologic deficit did not show regression. In our opinion, early rehabilitation of the patient with subsequent follow-up within 6 months is an impulse to preconditions for recovery of the patient. In this condition it is possible to achieve a confident success in partial or full regression of neurologic symptoms which is also confirmed by the literature data [4,18].

### Conclusion

A group of patients operated on in the acute period of ischemic stroke is at highest risk for development of complications of carotid endarterectomy. Thus, carotid endarterectomy may be safe only in the acute, early and late rehabilitation periods of ACVE. However, emergency carotid endarterectomy

should be performed only on strict indications including unstable atherosclerotic plaque and floating thrombus. In other conditions the risk

for development of hyperperfusion syndrome followed by hemorrhagic transformation of ischemic focus, is extremely high.

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