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Comparison of the Cost-Effectiveness of Transesophgeal and Transthoracic Echocardiographies to Detect Cardioembolic Causes of Stroke in Non-Selected Patients

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ABSTRACT

Background: Both Transthoracic Echocardiography (TTE) and Transesophgeal Echocardiography (TEE) are effective investigation tools to detect cardioaortic sources of embolism in ischemic stroke. Nevertheless, there are still uncertainties about the cost-effectiveness of these methods in non-selected patients with acute stroke.

Objectives: This study aimed to investigate the cost-effectiveness of TTE and TEE using a decision analytic model in non-selected patients with acute ischemic stroke with or without clinical and radiological signs of embolic pattern.

Patients and Methods: This cross-sectional cost-effectiveness study was performed in Nemazee hospital affiliated to Shiraz University of Medical Sciences from January 2014 to April 2014. TTE and TEE were performed for all 65 consecutive patients with ischemic stroke (51.3% male, mean age of 69.7 ± 17.9 years). The required data were direct costs related to performance of TTE and TEE, which were obtained from the patients' bills in their charts. A decision analytic model was implemented to assess the cost-effectiveness of these two methods, which demonstrated an Incremental Cost-Ef-fectiveness Ratio (ICER). Effectiveness was determined based on the number of disorders diagnosed using each of the two echoes confirmed by two cardiologists. All analyses were done using Tree Age Pro 2011.

Results: The results showed that TEE was more expensive than TTE in non-selected patients. Performing TEE increased the cost by 1494 USD and the effectiveness by 7%. As per ICER equation, for each increment unit in the effectiveness, performing TEE would increase the cost by 213.4 USD compared to TTE. TEE was cost-effective in comparison to TTE regardless of age factor considering the cutoff of Gross Domestic Product (GDP) by three for ICER. Moreover, TTE was cost-effective in 41-60- and 61-80-year-old age groups, while TEE was cost-effective in the 41-60-year-old age group. However, none of the techniques was cost-effective in patients above 81 years old.

Conclusions: The results of this study can help reduce the unnecessary use of echocardiography by considering the age group and their corresponding risk factors for developing ischemic stroke.

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1. Background

Cerebrovascular diseases are among the most common causes of mortality and morbidity particularly in developing

countries (1). Ischemic stroke is the most common cause of cerebrovascular diseases (2). At least one out of every four patients with ischemic stroke had a cardioembolic source in our previous series (3).

Both Transthoracic Echocardiography (TTE) and Transesophageal Echocardiography (TTE) are the most commonly used methods to investigate the cardioembolic causes of stroke. However, TEE has been mentioned to be better than TTE for finding some speculated causes of embolization, such as aortic arch Atheroma, Patent Foramen Ovale (PFO), Atrial Septal Aneurysm (ASA), and left atrial thrombus (4). Nevertheless, there are still uncertainties about the sensitivity, specificity, and cost-effectiveness of TTE and/or TEE in detection of cardio-aortic causes of stroke (5).

Cost-effectiveness analysis is the most prevalent form of economic evaluation in the health sector. Cost-effectiveness analysis compares the outcome of two or more therapeutic interventions according to their costs and effectiveness. Incremental Cost-Effectiveness Ratio (ICER) is defined as subtracting the costs of the current intervention from the costs of the new intervention divided by subtraction of the effectiveness of the current intervention from that of the new one. Consequently, different interventions can be compared according to the cost per unit of effectiveness. Cost-effectiveness analysis can help policymakers to optimally use the limited resources in the health sector (6).

Despite paramount importance of medico-economic studies in low-to-intermediate income developing countries, there is scarce data about the cost-effectiveness of TTE and/or TEE in patients with ischemic stroke in these countries.

2. Objectives

The present study aimed to investigate the cost-effectiveness of TTE and TEE using a decision analytic model in non-selected patients with acute ischemic stroke with or without clinical and radiological signs of embolic pattern.

3. Patients and Methods

This cross-sectional, cost-effectiveness study was conducted in Nemazee hospital affiliated to Shiraz University of Medical Sciences from January 2014 to April 2014. This hospital is a referral center for stroke in Southwestern Iran.

The inclusion criteria of the study were aging above 18 years, suffering from ischemic stroke defined according to the Recognition of Stroke in the Emergency Room (ROSIER) scale (7), and signing the informed consent form. The included patients had to undergo both TEE and TTE on the same day or at most within 7 days in a single admission. All patients with ischemic stroke were included non-selectively regardless of the presence or absence of the above-mentioned clinical and imaging findings indicating a cardioembolic source for stroke. Patients with intracranial hemorrhage, vasculitis, connective tissue disease, cerebral venous thrombosis, aortic dissection, and incomplete medical charts were excluded from the study.

According to a previous study (8) and by using the following formula assuming p0 = 0.17, p1 = 0.37, α = 0.05, and β = 0.8, the sample size was estimated as 65 patients. All consecutive patients were recruited.

$$n = \frac{\left[Z_{1-\alpha/2}\sqrt{2\,\bar{p}\,(1-\bar{p})} + Z_{1-\beta}\sqrt{P_0\,(1-P_0) + P_1\,(1-P_1)}\right]^2}{(P_1 - P_0)^2}$$

$$\bar{p} = \frac{p_1 + p_0}{2}$$

Two-dimensional transthoracic and color Doppler echocardiography were performed using 2.5 MHZ probe. Besides, TEE was performed by omniplane probe. The procedure was performed without sedation in conscious patients. Lidocaine spray was used for local pharyngeal anesthesia. TEE was performed according to a standardized protocol including adequate visualization of all cardiac structures with emphasis on both atria, left atrial appendage, interatrial septum, mitral valve apparatus, and thoracic aorta. In addition, intravenous sterile isotonic saline was administered to assess atrial septal defects. Echo contrast with air (9:1 ratio) with a subsequent Valsalva maneuver was used to evaluate the right to left shunt. All cardio-aortic structures were tried to be adequately visualized. Agitated saline test was done for all TEE patients. In so doing, 9 cc normal saline was mixed with 0.5 cc of patient's own blood and 0.5 cc air and was injected through a large venous line. Echocardiograms were recorded on DVDs.

Two echocardiographers separately evaluated the recorded TTEs and TEEs and completed a designated questionnaire for each patient. The cardiologists were completely blind to the clinical diagnoses, age, sex, and number of patients in each diagnostic group. If there was inter-observer disagreement, it was settled by ombudsman opinion of a third cardiologist who was also blind to clinical diagnoses. Left atrial thrombosis, left atrial appendage thrombus, left ventricular thrombus, valvular heart disease, bioprosthetic or mechanical heart valves, Ejection Fraction (EF) < 28%, dilated cardiomyopathy, atrial myxoma, PFO, spontaneous echo contrast in the left atrium, spontaneous echo contrast in the left ventricle, mobile atheroma in ascending aorta and aortic arch, grade 4 atheroma in ascending aorta and aortic arch, and aneurysm of inter atrial septum Septum were the disorders for which echo was used.

In this study, using decision tree model, the expected costs and effectiveness of TEE and TTE were estimated and ICER was measured. A decision tree model is a systematic quantitative method used for decision-making under uncertain conditions in which at least two decision options and their respective consequences are evaluated and compared in terms of their expected costs and outcomes. ICER has been defined as the ratio of the difference between the costs of two options to the difference between their effectiveness. If ICER is negative, one of the options is dominant in comparison to the other. On the other hand, if ICER is positive, the maxi¬mum willingness to pay (threshold) would be required for decision making (9). Cost-effectiveness threshold is essentially a level of ICER that any intervention should meet if it is to be regarded as a cost-effective one. In this study, World Health Organization's (WHO) method was used to calculate the threshold. Although this recommendation of WHO about threshold is mostly used for the cost utility analyses with "cost per

QALY gained" or "cost per DALY averted" as outcome, because there is not any threshold calculated or accepted for Iran, we used it as our threshold. Therefore, if ICER is three times lower than the GDP per capita, the studied method will be cost-effective. This model can be used to compare screening strategies, treatment proposals, and diagnostic methods in order to help policymakers and clinicians for better decision making (10-12). In addition, to increase the accuracy of the study, one-way deterministic sensitivity analysis (Tornado diagram) and probabilistic sensitivity analysis were performed (13). In the probabilistic sensitivity analysis, values for parameters were randomly selected from their probability distributions and 95% Confidence Intervals (CIs) were calculated using non-parametric bootstrapping approach for cost and effectiveness. The non-parametric bootstrap is a method for estimating uncertainty using the empirical estimation of the sampling distribution. This involves re-sampling from the data set with replacement while preserving the original structure of the data (e.g. same size, same numbers in each treatment group, etc.). The advantage of such non-parametric bootstrap CIs is that they do not depend on parametric assumptions of the sampling distribution of ICER (14).

3.1. The Effectiveness Outcome

In this study, due to lack of a gold standard, the studied effectiveness was determined based on the number of disorders diagnosed by each of the two echoes confirmed by the two cardiologists (true positives).

3.2. Costs

In this study, only the direct costs of TTE and TEE paid by the patients were recorded. The data related to the direct costs were obtained from the patients' bills in their charts. Therefore, this study was carried out from the patients' perspective. For the purpose of international comparison, the costs were converted to US dollar using the exchange rate of each US dollar equal to 2510 Rials in 2014 (15). Furthermore, as the duration of the study was less than one year, the discount rate was not calculated for the costs (16). After drawing the decision tree, ICER was calculated. As all economic studies are associated with an inherent uncertainty, the robustness and generalizability was assessed using one-way and probabilistic sensitive analyses in this study. In one-way sensitivity analysis, each of the study variables were increased by 20% and the results were shown by the Tornado diagram.

This research was approved by the Ethics Committee of Shiraz University of Medical Sciences (No. 92-6801) and informed consents were obtained from all participants.

3.3. Economic and Statistical Analyses

In this study, Tree Age Pro 2011 was used to analyze the collected data and create the related decision tree, calculate the cost-effectiveness ratio of using TTEs or TEEs in the studied patients, calculate the ICER, perform the probabilistic sensitivity analysis, and draw the cost-effectiveness and Tornado diagrams.

3.4. Ethics of Study

Informed consents were obtained from all participants. This research was approved by the Ethics Committee of Shiraz University of Medical Sciences (No. 92-6801).

4. Results

This study was performed on 65 patients (51.3% male, mean age of 69.7 ± 17.9 years). Among the patients, 9.2%, 20%, 40%, and 30.8% belonged to 21 - 40, 41 - 60, 61 - 80, and more than 80 years age groups, respectively. The effectiveness of each studied echo has been presented in Table 1.

The costs of TTE and TEE for all the patients was 527$ (13227700 IRR) and 2021$ (50727100 IRR), respectively. The decision tree model related to the costs, effectiveness, and probabilities of performing TTE and TEE has been shown in Figure 1. As can be seen in this figure, the studied patients with stroke were divided into two groups of TEE and TTE. Then, the patients were divided into true- and false-positive cases. The values below the tree lines represent the probabilities and the values at the right hand of the tree indicate the values of cost and effectiveness. The results of economic evaluation of TEE in comparison to TTE showed that performing TEE would increase the costs by 1494 USD and the effectiveness by 7%. According to the ICER results, for each increment unit in the effectiveness, performing TEE would increase the costs by 213.4 USD compared to TTE.

The results of analysis of cost-effectiveness of TTE versus TEE in different age groups have been depicted in Figure 2. Accordingly, while TTE was cost-effective in 41-60- and 61-80-years age groups, TEE was cost-effective in 41-60-years age group. However, none of the techniques

Table 1. The Effectiveness of Each Studied Echo

Studied Echoes	Patients' Age Group (Year)	Disorders Diagnosed by Echoes	True Positives	False Negatives	Effectiveness (True Positives/True Positives + False Negatives)
TTE	20 - 40	0	0	0	0
	41 - 60	15	9	6	0.6
	61 - 80	15	13	2	0.86
	81 - 100	6	3	3	0.5
	Total	36	25	11	0.69
TEE	20 - 40	0	0	0	0
	41 - 60	15	15	0	100
	61 - 80	15	14	1	0.93
	81 - 100	6	5	1	0.83
	Total	36	34	2	0.94

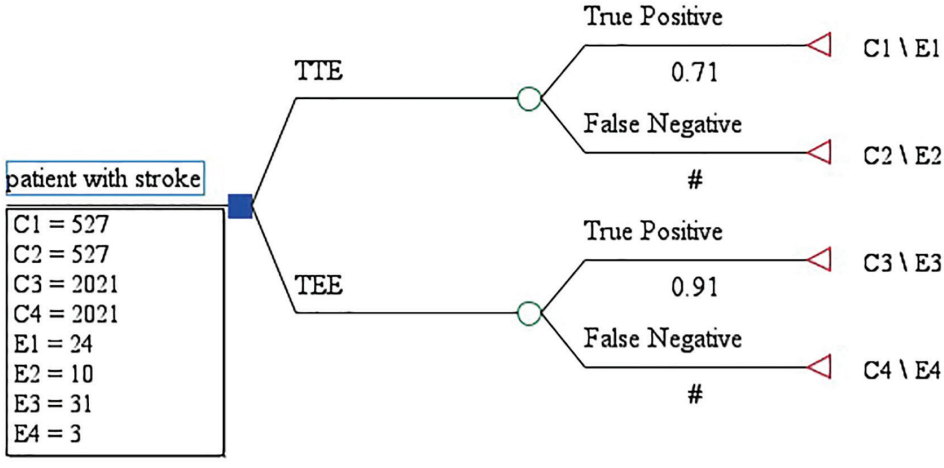

Figure 1. The Decision Tree Model for Comparing TEE to TTE

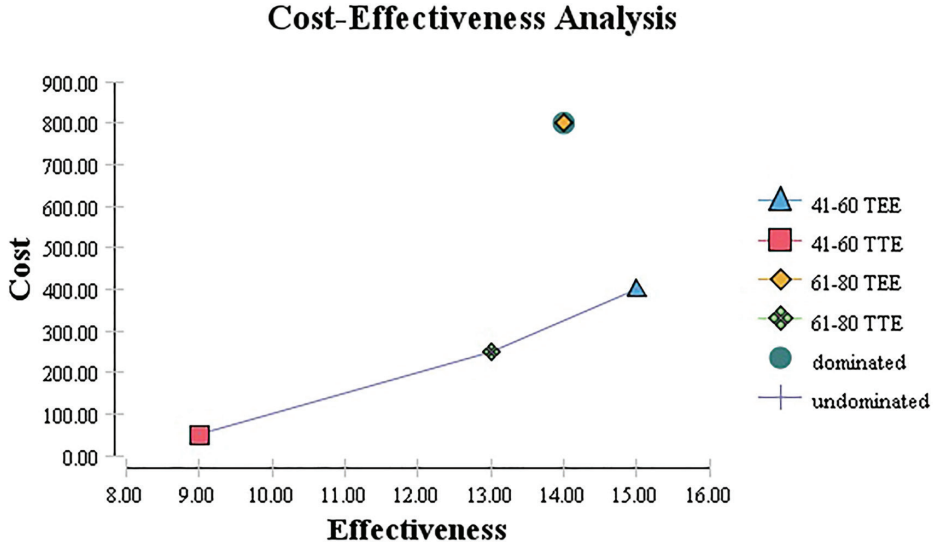

Figure 2. The Results of Comparison of Cost-Effectiveness of TTE and TEE in Different Age Groups

was cost-effective in ages above 81 years. In patients under 40 years old, cost-effective analysis was not feasible due to the small number of true positives.

One-way sensitive analysis using Tornado diagram showed that changes in most of the input parameters had few effects on the outcome. Moreover, ICER had the highest and lowest sensitivities to the increases in the effectiveness and costs of TTE, respectively (Figure 3).

The results of probabilistic sensitivity analysis using Monte Carlo simulation of incremental costs and effectiveness of TEE vs. TTE have been presented in Figure 4. For each one of the 10,000 iterations, values for parameters were randomly selected from their probability distributions. The results showed that TEE was more cost-effective than TTE with maximum willingness to pay (threshold) in 97% of the iterations.

5. Discussion

In the present study, the researchers investigated the cost-effectiveness of transesophgeal and transthoracic echocardiographies to detect cardioembolic causes of stroke in non-selected patients. ICER for performing TEE compared to TTE (213.4 $) was less than three times of Iran's GDP per capita in 2014 (17, 18). It should be mentioned that "cost per QALY gained" or "cost per DALY averted" should be considered as outcomes in medico-economic studies. Since these measures have not been calculated for the Iranian population, we considered the cutoff of GDP by three for ICER according to WHO's recommendation (19).

The study results revealed that although considering the impact of age, both TTE and TEE were cost-effective in the 40-60-years age group, only TTE was cost-effective in the 60-80-years age group. In the patients aged more than 81 years, neither TTE nor TEE was cost-effective. Besides, data were inconclusive for the patients under 40 years old. These results can be justified by the fact that the etiologies responsible for ischemic stroke differ in different age groups. The rate of atherosclerotic cardiac diseases and dilated cardiomyopathy is higher among patients aged 61-80 years. Accordingly, TTE would yield more advantages over TEE. However, non-atherosclerotic risk factors, such as aortic dissection, PFO, endocarditis, and vulvular heart diseases such as rheumatic heart disease are regarded as a major cause of Acute Ischemic Stroke (AIS) in patients

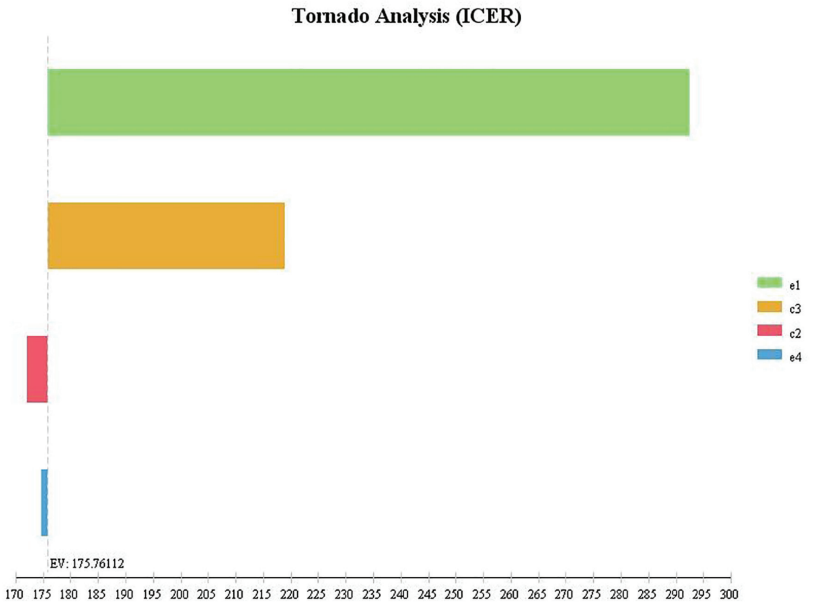

Figure 3. Tornado Diagram for One-Way Sensitivity Analysis

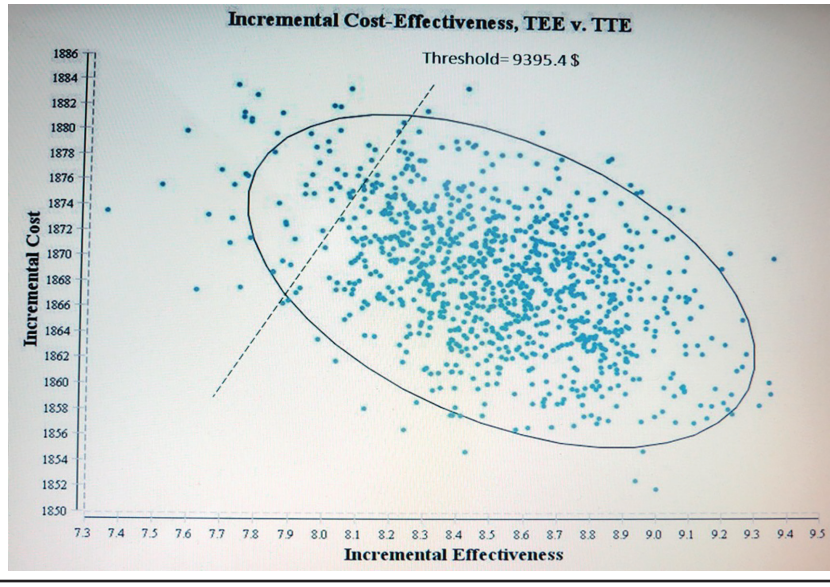

Figure 4. The Results of the Probabilistic Sensitivity Analysis (Each Point Indicates the Differences in the Costs and Effectiveness of TEE vs. TTE)

aged 41 - 60 years compared to older ones (20). This can suggest why TEE infers more benefits in this age group. Considering those older than 81 years, the etiologic factors responsible for AIS are atrial clots due to atrial fibrillation and aortic atheroma (21).

According to de Bruijn et al. (8), TEE is better than TTE in detecting the source of emboli in patients with stroke. Blum at el. (22) also concluded that in half of the patients with stroke, TEE was able to detect a serious lesion not detected by TTE. They have suggested that performing TEE is crucial in patients with stroke. Similarly, Takeda et al. (23) showed that TEE could have more clear results in cardiac disorders compared to TTE. The results of the study by Cook et al. (24), too, indicated that using TEE in surgical ICU is more cost-effective than TTE. However, Leung et al. (25) found a very low yield for TEE in 824 consecutive patients after stroke or other suspected embolic events that were in sinus rhythm and had normal TTEs. Harloff et al. (26) also found that TEE was unlikely to change management in cardioembolic patients as most patients already had an indication for oral anticoagulation.

There are some clinical and radiological findings indicating more probable cardioembolic sources of stroke. They include sudden onset of presentations, absence of preceding transient ischemic attack, severe stroke (NIHSS > 10 in the elderly, history of ischemic stroke in different arterial territories, synchronous new ischemic lesions in different arterial territories, metachronous lesions in imaging, signs of embolism to other organs (kindney, spleen, and/or extremities), presence of territorial (cortical plus subcortical) infarct or large lenticulostriate infarction in imaging, presence of hyperdense signs in major vessels,

and signs of rapid recanalization in transcranial Doppler sonographies (4). Thus, performing TTE and TEE in selected groups of patients with ischemic stroke and these embolic patterns may increase the yield of TTE and TEE.

As no stratification was done based on clinical and radiological features indicating embolic phenomenon in this study, the results regarding the cost-effectiveness of TTE and TEE could be subjected to change if a selected group of patients was included. Hence, performing TTE and TEE in selected groups of patients with ischemic stroke and these embolic patterns may increase the yield of TTE and TEE.

There are controversies about major, minor, or uncertain contributions of cardioaortic sources of embolic stroke. For instance, PFO and aneurysm of the interatrial septum which were considered as potential sources of embolism in the current study had minor or unclear importance in other studies. Furthermore, the current study included non-selected population of stroke patients. If the stroke patients had been selected according to these criteria, the cost-effectiveness results would have been different.

The current study findings were also consistent with some studies indicated that TEE could be a useful investigation tool in younger patients with ischemic stroke (3, 27).

As both TTE and TEE can be performed simultaneously in referral centers in Iran, the results of this study can be generalized to other Iranian centers. As to other countries, other factors such as selecting the effectiveness index, the degree of expenses covered by insurance companies, maximum tendency of the government to pay the costs of echo methods, and incidence and prevalence of stroke (28) should be considered.

One of the limitations of this study was lack of a gold standard to determine the effectiveness index. As a result, the effectiveness index was determined based on the number of diagnoses of each of the two tests confirmed by the two cardiologists. In addition, new ultrasound modalities, such as second harmonic imaging and Doppler tissue imaging, were not used in the current study.

In conclusion, although TEE is cost-effective in general, it is mostly recommended in patients aged 41 - 60 years. Similar medico-economic studies with larger sample sizes and/or in selected patients with higher probability of embolic stroke are highly recommended.

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Authors' Contribution

Afshin Borhani Haghighi, Ramin Ravangard, Abdolsaleh Jafari, Golnaz Yadollahikhales: concept and design, drafting the article, critical revision of article, approval of article. Iman Rahgoshai, Mahmoud Zamirian, Kamran Aghasadeghi, Alireza Moarref: data collection, drafting the article. Ramin Ravangard, Abdolsaleh Jafari: data analysis, interpretation

Salvador Cruz-Flores: critical revision of article.

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The authors would like to declare no any conflict of interests.

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