Value of Adding the CHA2DS2-VASc Score to the GRACE Score for Mortality Risk Prediction in Patients With Acute Coronary Syndrome

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Global Registry of Acute Coronary Events (GRACE) risk score has been routinely used for risk stratification of acute coronary syndrome (ACS) patients. We aimed to examine whether the addition of the CHA2DS2-VASc score to the GRACE score improves risk stratification. Included were patients with ACS who were divided into high (>140), intermediate (110< GRACE score ≤140) and low (<110) GRACE score. Each group was further divided into 3 subgroups categorized according to their CHA2DS2-VASc score: 0−1, 2−3, and ≥4. Management and Outcomes were compared for each GRACE score group and CHA2DS2-VASc score subgroups. Included 6,854 ACS patients, of them 3596 (52.5%) were classified as low risk, 1,937 (28.3%) were at intermediate risk and 1,321 (19.3%) were high-risk patients. In the intermediate risk group, patients with a higher CHA2DS2-VASc score more frequently underwent percutaneous coronary revascularization. For low risk patients, 30-day mortality rates were 0.8%, 1.5%, and 1.3% (p = 0.02), and 1-year all-cause mortality rates were 1.3%, 3%, and 2.6% (p = 0.002) for CHA2DS2-VASc score 0−1, 2−3, ≥4, respectively. For intermediate risk patients, 30-day mortality rates were 2.9%, 3.4%, and 3.8% (p = 0.8), and 1-year all-cause mortality rates were 6.4%, 7.8%, and 11.2% (p = 0.01) for CHA2DS2-VASc score 0−1, 2−3, ≥4, respectively. Among patients with a GRACE score <140, each 1 point increase in the CHA2DS2-VASc score was associated with a 57% increase in 1-year mortality rates. In conclusion, the addition of the CHA2DS2-VASc score to the GRACE risk score in ACS patients improves risk stratification of patients with low and intermediate risk. **(Am J Cardiol 2019;123:1751−1756)**

The Global Registry of Acute Coronary Events (GRACE) was developed for the assessment of the risk of death in patients with ACS and has become the gold standard for risk stratification of ACS patients and has been endorsed by the clinical guidelines.[1−4] The GRACE score includes age as well as clinical (heart rate, systolic blood pressure, ST segment deviation on electrocardiogram, Killip class, and cardiac arrest) and laboratory (creatinine and cardiac biomarkers) parameters assessed at presentation to the hospital. It divides ACS patients into 3 risk groups: high (≥140), intermediate (110 to 139) and low (<110). Although patients in the high-risk group clearly benefit from an early invasive approach, the population of patients in the intermediate and low risk is more diverse and may benefit from additional noninvasive ischemic assessment. Interestingly, different baseline co-morbidities such as diabetes, previous coronary, peripheral or cerebrovascular disease and previous congestive heart failure that have been clearly associated with poor outcomes in patients with ACS[5−9] were not incorporated into the GRACE score. The CHA2DS2-VASc score (congestive heart failure; hypertension; age ≥75 years [doubled]; type 2 diabetes; previous stroke or transient ischemic attack [doubled]; vascular disease; age 65 to 74 years; and sex category) has been recommended for the assessment of thromboembolic risk and guiding antithrombotic therapy in patients with atrial fibrillation or flutter.[10] Several studies have demonstrated an association between the CHA2DS2-VASc score and adverse outcomes of patients with ACS regardless of the presence of atrial fibrillation.[11−13] The present study is aimed to investigate whether the addition of the CHA2DS2-VASc score to the GRACE score improves risk stratification of patients with ACS.

Methods

The Acute Coronary Syndromes Israeli Survey (ACSIS) is a biennial, 2-month survey that was carried out in all intensive coronary care units and cardiology departments in Israel. The study population consisted of patients presenting with acute coronary syndrome (unstable angina, non−ST-elevation myocardial infarction and ST-elevation myocardial infarction) that were included in the ACSIS Surveys during 2000 to 2016. Study physicians recorded all clinical and demographic data on prespecified forms for consecutive participants. The diagnosis of acute coronary syndrome

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was based on clinical, electrocardiographic and biochemical criteria and patients were managed at the discretion of each center.

GRACE and CHA2DS2-VASc scores were calculated for each individual patient. The study cohort was initially stratified into 3 risk groups: High GRACE score (>140), intermediate GRACE score (110 to 140), and low GRACE score (<110). Each group was further divided into 3 subgroups categorized according to their CHA2DS2-VASc score: a score of 0−1, 2−3, and ≥4.

The primary outcome of the study was all-cause mortality at 30 days and at 1 year. Mortality rates were determined for all participants from hospital charts and by matching the identification numbers of the patients with the Israeli National Population Registry.

Categorical variables were expressed as percentage of available data and continuous variables were expressed as mean ± SD. Characteristics of study participants were compared using chi-square test for categorical variables and Student's *t* Test or Wilcoxon rank tests, as appropriate for continuous variables. Kaplan-Meier survival curves with the log-rank test were used to compare all-cause mortality during 1-year. Cox proportional hazard model was used to evaluate the effects of patients' characteristics on 1-year all-cause mortality. The variables that were included in the analysis were all baseline variables that were significantly different in the groups, excluding parameters that are part of the CHA2DS2-VASc score.

Results are presented as hazard ratio and 95% confidence interval (95% CI). A p value of less than 0.05 was considered significant. Statistical analyses were carried out using R version 3.2.5 (April 14, 2016).

Results

Study population included 6,854 ACS patients. Of them, 3,596 (52.5%) were classified as low risk (GRACE score <110), 1,937 (28.3%) were at intermediate risk (110< GRACE score ≤140) and 1,321 (19.3%) were high-risk patients (GRACE score >140). We further divided each GRACE score group into 3 subgroups according to CHA2DS2-VASc score (0−1, 2−3, ≥4) (Table 1). Baseline demographic and clinical characteristics of patients according to their GRACE and CHA2DS2-VASc scores are presented in Table 1. Not surprisingly, patients with higher GRACE or CHA2DS2-VASc scores were older and had higher prevalence of most coexisting co-morbidities and previous cardiovascular disease. Among the 1,321 patients in the high GRACE score group, only 228 (17.3%) had a CHA2DS2-VASc score <4. This low number precluded a meaningful subanalysis according to CHA2DS2-VASc score in this group. The distribution of CHA2DS2-VASc scores in the different GRACE score groups is presented in Supplemental Figure 1.

In hospital treatment characteristics according to GRACE and CHA2DS2-VASc scores are presented in Table 2. There was no significant association between the CHA2DS2-VASc and referral for coronary angiography regardless to the GRACE score. However, in the intermediate GRACE score group, patients with a higher CHA2DS2-VASc score more frequently underwent coronary revascularization by percutaneous coronary intervention. Medical therapy with antiplatelet agents and angiotensin-converting enzyme-inhibitors was administered more frequently in patients with a higher CHA2DS2-VASc score in both the low and intermediate GRACE score groups.

We further evaluated the additive value of the CHA2DS2-VASc score in prediction of mortality within the low and intermediate GRACE risk score groups. High CHA2DS2-VASc score was associated with increased 30-day and 1-year all-cause mortality rates in both groups. Lowest mortality rates were observed in patients with CHA2DS2-VASc score of 0−1 (Figure 1). For patients with GRACE score <110, 30-day mortality rates were 0.8%, 1.5%, and 1.3% (p = 0.02), and 1-year all-cause mortality rates were 1.3%, 3%, and 2.6% (p = 0.002) for patients with

Table 1
Baseline characteristics and clinical presentation according to GRACE and CHA2DS2-VASc scores

	GRACE >140				GARACE 110−140				GRACE <110			
CHA2DS2-VASc	0−1	2−3	≥4	P	0-1	2-3	≥4	p	0−1	2−3	≥4	p
n	10	218	1093		207	849	881		2,135	1,223	238	
Male	100%	89.0%	60.7%	<0.001	97.6%	81.9%	56.1%	<0.001	94.1%	78.5%	55.9%	<0.001
Age (mean ± SD)	66.8%	76.6%	79.7%	<0.001	64.0%	69.0%	73.5%	<0.001	52.6%	57.7%	62.2%	<0.001
Previous MI	20.0%	42.2%	63.6%	<0.001	17.9%	35.2%	43.0%	<0.001	6.5%	32.2%	29.8%	<0.001
Previous CABG	0.0%	13.8%	24.9%	<0.001	2.4%	9.3%	18.2%	<0.001	0.6%	4.7%	11.8%	<0.001
Previous PCI	20.0%	30.7%	50.2%	<0.001	16.9%	33.7%	46.8%	<0.001	7.2%	37.7%	45.8%	<0.001
COPD	0.0%	9.2%	11.9%	0.48	3.9%	10.0%	9.0%	0.09	1.8%	2.9%	9.0%	<0.001
PVD	0.0%	8.3%	20.8%	<0.001	1.0%	5.8%	15.3%	<0.001	1.0%	6.7%	14.9%	<0.001
Diabetes mellitus	0.0%	18.3%	57.4%	<0.001	5%	30.3%	64.0%	0.43	8.5%	50.2%	69.3%	<0.001
Hypertension	0.0%	48.6%	92.4%	<0.001	15.5%	69.5%	95.0%	<0.001	21.7%	82.0%	96.9%	<0.001
Dyslipidemia	30.0%	62.7%	81.0%	<0.001	62.7%	70.4%	86.1%	<0.001	56.6%	80.3%	89.3%	<0.001
Atrial fibrillation	0.0%	12.8%	12.2%	0.48	6.8%	6.8%	6.6%	0.98	1.7%	2.5%	3.4%	0.11
Unstable angina pectoris	0.0%	0.9%	2.9%	0.20	1.4%	1.2%	3.3%	<0.01	1.4%	3.8%	5.5%	<0.001
Non-ST elevation myocardial infarction	100.0%	78.8%	77.8%	0.23	65.7%	61.1%	58.6%	0.15	36.5%	39.7%	40.3%	<0.001
ST elevation myocardial infarction	0.0%	20.3%	19.3%	0.28	32.9%	37.7%	38.1%	0.36	62.1%	56.6%	54.2%	<0.01

Table 2
Management according to GRACE and CHA2DS2 scores

	GRACE >140				GRACE 110−140				GRACE <110			
CHA2DS2-VASc	0−1	2−3	≥4	p	0−1	2−3	≥4	p	0−1	2−3	≥4	p
n	10	218	1093		207	849	881		2,135	1,223	238	
In hospital treatment												
Coronary angiography	80%	67%	59.2%	0.04	87.4%	90%	90.6%	0.4	97.1%	97%	97.1%	0.98
PCI	10.0%	33.5%	35.2%	0.22	55.1%	60.9%	73.8%	<0.001	85.5%	87.0%	86.6%	0.48
CABG	30%	8.7%	3.1%	<0.001	7.7%	6.6%	3.1%	0.001	1.8%	2.2%	1.3%	0.52
Medical therapy at discharge												
Aspirin	100.0%	89.1%	87.8%	0.45	95.6%	96.3%	95.8%	0.87	98.4%	97.0%	99.2%	0.01
Antiplatelets	50.0%	65.0%	68.5%	0.30	76.1%	78.2%	86.4%	<0.001	91.2%	90.6%	92.3%	0.66
Statins	90.0%	90.5%	87.9%	0.57	93.2%	95.5%	93.8%	0.21	96.2%	95.8%	97.9%	0.31
ACE-I/ARB	60.0%	57.1%	67.1%	0.02	67.6%	79.0%	83.9%	<0.001	73.0%	86.0%	86.9%	<0.001
Beta-blockers	90.0%	71.5%	77.3%	0.12	81.3%	80.5%	84.4%	0.10	81.3%	84.5%	88.0%	0.01

CHA2DS2-VASc score 0−1, 2−3, ≥4, respectively. For patients with GRACE score 110 to 139, 30-day mortality rates were 2.9%, 3.4%, and 3.8% (p = 0.8), and 1-year all-cause mortality rates were 6.4%, 7.8%, and 11.2% (p = 0.01) for patients with CHA2DS2-VASc score 0−1, 2−3, ≥4, respectively. Kaplan-Meier curves comparing 1-year mortality rates according to the CHA2DS2-VASc score for the low and intermediate GRACE score group are presented in Figure 2. We further conducted a multivariate analysis using the CHA2DS2-VASc score as a continuous variable. The association between the CHA2DS2-VASc score and the risk for 1-year all-cause mortality remained significant following adjustment for all baseline characteristics not included in the CHA2DS2-VASc score. Among patients with a GRACE score <140, each 1 point increase in the CHA2DS2-VASc score was associated with a 57% increase in 1-year mortality rates.

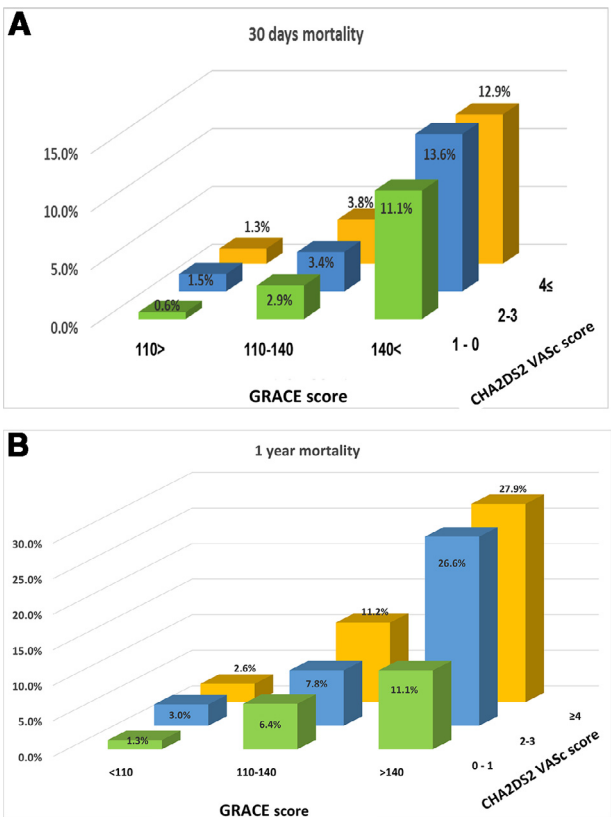

Figure 1. All-cause mortality rates in 30 day (*A*), and 1 year (*B*) in each GRACE score risk groups according to CHA2DS2-VASc score (0-1, 2-3, ≥4).

Discussion

The analysis of this large cohort from a national survey suggests that the CHA2DS2-VASc score may have an additive value to the GRACE score for mortality risk prediction in patients with ACS. Among patients in the low and intermediate GRACE score, the addition of the CHA2DS2-VASc clearly identified the higher risk patients in terms of 30-day and 1-year mortality.

Optimal management of ACS should include individualized patient risk assessment at hospital admission. Accurate risk stratification can help to identify high risk patients who would benefit the most from early invasive strategies and intensive medical therapy, while reducing unnecessary treatment complications in low risk patients. The GRACE score has been clearly established as the gold standard score for individual mortality risk estimation in patients with ACS.[1−4] It divides ACS patients into 3 risk groups: high (≥140), intermediate (110 to 139), and low (<110). Based on the GRACE score, patients in the high risk strata should be considered for an early invasive intervention within 24 hours. Thus, as opposed to low and intermediate risk patients, no further risk stratification is needed.[3,4] In contrast, intermediate and low risk patients are more diverse and may benefit from an additional risk stratification that may identify patients eligible for noninvasive cardiac imaging. The GRACE score includes age as well as laboratory (creatinine and cardiac biomarkers), electrocardiographic (ST segment deviation on electrocardiogram), and clinical (heart rate, systolic blood pressure, Killip class, and cardiac arrest) parameters assessed at presentation to the hospital. Interestingly, different baseline co-morbidities such as

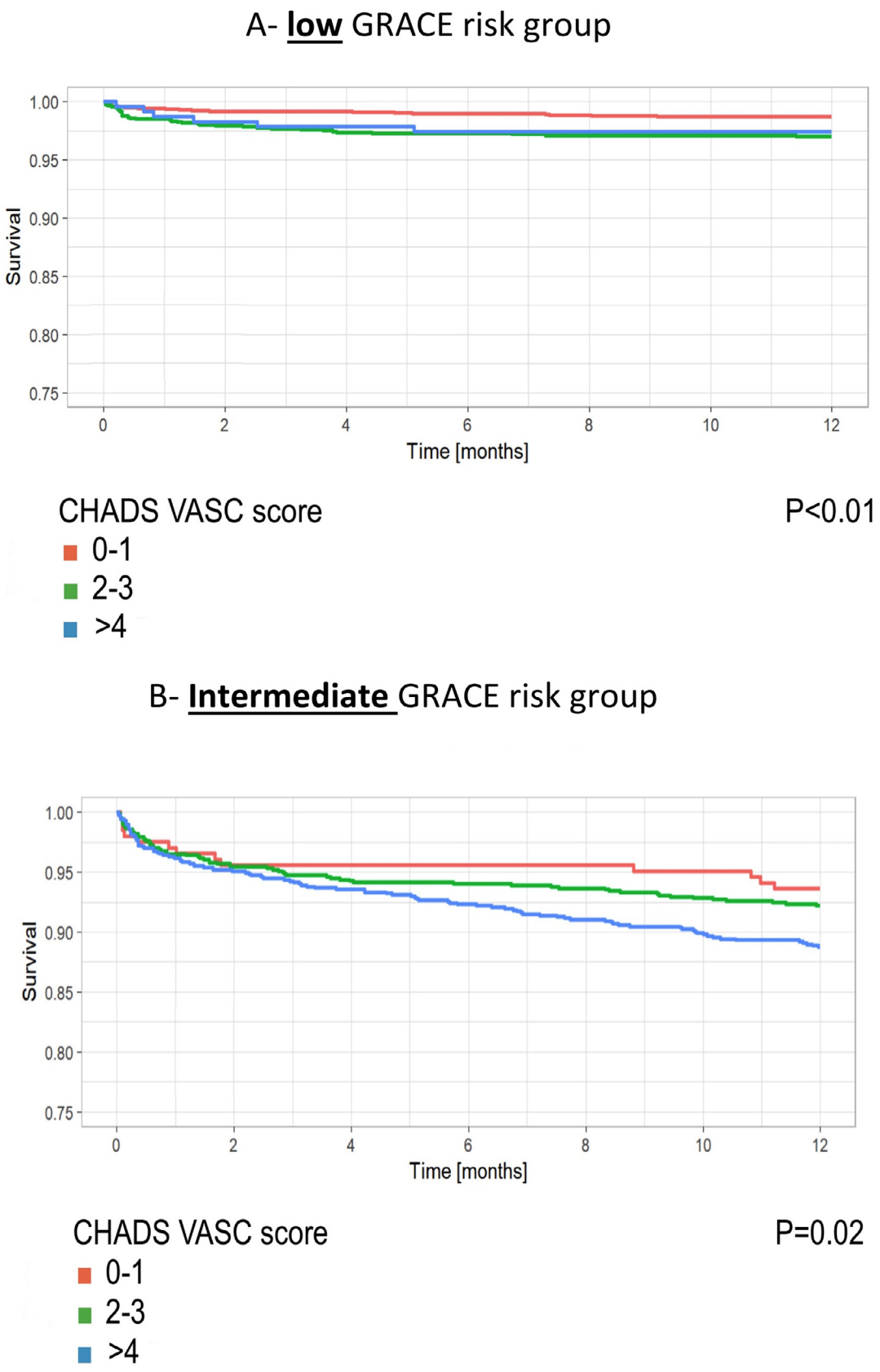

Figure 2. Kaplan-Meier 1-year survival curves of ACS patients according to CHA2DS2-VASc score (0−1, 2−3, ≥4) in low (*A*) and intermediate (*B*) GRACE risk groups.

diabetes, previous coronary, peripheral or cerebrovascular disease and previous congestive heart failure that have been clearly associated with poor outcomes in patients with ACS,[5–9] were not incorporated into the GRACE score. The CHA2DS2-VASc score (congestive heart failure; hypertension; age ≥75 years [doubled]; type 2 diabetes; previous stroke or transient ischemic attack [doubled]; vascular disease; age 65 to 74 years; and sex category) has been recommended for the assessment of thromboembolic risk and guiding antithrombotic therapy in patients with atrial fibrillation or flutter.[10] Several studies have demonstrated an association between the CHA2DS2-VASc score and adverse outcomes of patients with ACS regardless of the presence of atrial fibrillation.[11–13] However, the present study is the first to assess the additive value of the CHA2DS2-VASc score to the GRACE score. We demonstrated that among low and intermediate risk patients according to the GRACE score, higher CHA2DS2-VASc score was associated with significantly higher mortality rate. The fact that differences in mortality rates according to the CHA2DS2-VASc score remained significant even after 1 year provides further support for its relevancy for risk stratification of ACS patients in addition to the GRACE score. Given the higher variability in clinical and demographic characteristics among patients with intermediate GRACE score, differences in outcome according to the CHA2DS2-VASc score were more robust in this group. The CHA2DS2-VASc score is simple and readily available and can be calculated at bedside without a calculator. It has been used extensively in patients with atrial fibrillation and most physicians are familiar with it. Therefore, its incorporation into the routine risk stratification of low and intermediated risk ACS patients should be easy.

Despite their increased risk, patients with a higher GRACE score were less frequently selected for an invasive strategy with an early coronary angiogram and subsequent angioplasty and were less commonly treated with guideline-based medications regardless to enrollment period. This observation, referred to as the "treatment risk paradox," has been previously described.[14,15] Both patients (frailty, mental and functional status, and patient preference) and physician related factors (misjudgment of patient risk at baseline) appear to contribute substantially to this phenomenon. This paradox highlights the need to further improve the risk stratification of ACS patients.

There are several limitations to our analysis that should be considered. First, our analysis uses observational nonrandomized data and therefore the associations between baseline characteristics, treatment, and outcomes may be confounded by unmeasured variables. Second, we did not have any data regarding several important patient-level factors such as frailty, compliance and personal choices that may influence treatment decisions and clinical outcomes. Third, while the GRACE risk score was developed in a large multinational registry involving 94 hospitals in 14 countries, the present study is based on a multicenter survey from a single country. Given the possible differences in patient and treatment characteristics, our findings should be interpreted to other countries with caution. Finally, our database did not include specific causes of death. Therefore, the primary end points of our study were 30-day and 1-year all-cause mortality.

In conclusion, addition of the CHA2DS2-VASc score to the GRACE risk score in ACS patients improves risk stratification of patients with low and intermediate GRACE scores and identifies a subgroup of patients with higher short- and long-term mortality rate.

Disclosures

The authors declare no conflicts of interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.02.045.

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