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Determinants of invasive strategy in elderly patients with non-ST elevation myocardial infarction

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Abstract

Background   Knowledge gaps across literature prevent current guidelines from providing the profile of elderly patients most likely to derive benefit from invasive strategy (IS) in non ST-elevation myocardial infarction (NSTEMI). Furthermore, the benefit of IS in a real-world elderly population with NSTEMI remains unclear. The aims of this study were to determine factors that lead the cardiologist to opt for an IS in elderly patients with NSTEMI, and to assess the impact of IS on the 6-month all-cause mortality. **Methods**   This multicenter prospective study enrolled all consecutive patients aged ≥ 75 years old who presented a NSTEMI and were hospitalized in cardiology intensive care unit between February 2014 and February 2015. Patients were compared on the basis of reperfusion strategy (invasive or conservative) and living status at six months, in order to determine multivariate predictors of the realization of an IS and multivariate predictors of 6-month mortality. **Results**   A total of 141 patients were included; 87 (62%) underwent an IS. The strongest independent determinants of IS were younger age [odds ratio (OR): 0.85, 95%-confidence interval (CI): 0.78–0.92; $P < 0.001$) and lower "Cumulative Illness Rating Scale-Geriatric" number of categories score (OR: 0.83, 95%CI: 0.73–0.95; $P = 0.002$). IS was not significantly associated with 6-month survival (OR: 0.80, 95%CI: 0.27–2.38; $P = 0.69$). **Conclusions**   In real-world elderly patients with NSTEMI, younger patients with fewer comorbidities profited more often from an IS. However, IS did not modify 6-month all-cause mortality.

1   Introduction

Development of modern treatment strategies, especially revascularization, has led to a significant decrease of mortality from non-ST elevation myocardial infarction (NSTEMI) over the last two decades.[1]

However, results from the few studies assessing the benefit of invasive strategy (IS: diagnostic angiography, with intent to perform revascularization if appropriate) in elderly patients with NSTEMI differ, depending on the population,

the definition of IS (i.e., diagnostic angiography within the first 48 h after onset of symptoms or during hospitalization) and the study's endpoints.[2–4]

Thus, although current guidelines recommend that all patients with NSTEMI, including older patients, should be assessed for IS,[5] these guidelines are unable to (1) provide the profile of elderly patients most likely to derive benefit from IS,[6] and (2) define the benefit of IS in a real-world elderly population (i.e., patients with multi-morbidity, frailty or limited life expectancy).[7] Consequently, physicians are merely suggested that management decisions for older patients with NSTEMI should be patient centered, and consider patient preferences, comorbidities, functional and cognitive status, and life expectancy.[6]

The main objective of this study was to determine precise factors that lead the cardiologist to opt for an IS in community patients aged 75 years or older with NSTEMI. The

secondary objective was to assess the impact of IS on the 6-month mortality in this real-world setting community population with NSTEMI.

2 Methods

2.1 Study design

We performed a multicenter (two sites), prospective, observational study (from February 1, 2014 to February 1, 2015). Informed consent was obtained from all patients. The study was approved by the ethical committee (CPP Pitié-Salpêtrière, Ile-de-France VI, Paris, France).

2.2 Participants

All consecutive patients aged ≥ 75 years old who presented a NSTEMI and were hospitalized in a cardiology intensive care unit (CICU) were prospectively included. A local cardiologist assessed patient eligibility. NSTEMI was defined as the combination of a raised blood concentration of troponin T or I (i.e., value exceeding the 99th percentile of a normal population at the local laboratory at each participating site) with at least one of the following: chest pain > 10 min, significant ST-segment depression or T wave changes on ECG, imaging evidence of new loss of viable myocardium or regional wall motion abnormality, and intracoronary thrombus detected on angiography. Patients presenting with ST-segment elevation on ECG were ineligible.

2.3 Procedures

A complete cardiac evaluation was performed by cardiologists. Characteristics of NSTEMI were recorded: delay from the beginning of symptoms to the CICU, clinical presentation, systolic blood pressure, heart rate, KILLIP class, Global Registry of Acute Coronary Events (GRACE) and CRUSADE risk scores, initial ECG and echocardiography description. In-hospital management (drug treatments, coronary angiography and revascularization if appropriate) and in-hospital outcomes were monitored. If coronary angiography was not performed, the treating physician was asked to indicate the reason(s). A prospective chart review was performed by a geriatrician who collected social characteristics (nursing home, malnutrition, falls, number of medications) and assessed activities of daily living (ADL) and instrumental activities of daily living (IADL) using the Katz[8] and Lawton[9] scales. Detailed comorbid conditions were also collected [hypertension, dyslipidemia, diabetes mellitus, current smoking, weight and body mass index, congestive heart failure, coronary artery disease (CAD), peripheral vascular disease (PVD), renal disease, atrial fibrillation, stroke, dementia, depression, chronic pulmonary disease

(CPD), liver disease, leukaemia, lymphoma, neoplasia and acquired immunodeficiency syndrome]. Dementia was defined by a diagnosis of dementia previously made by a clinician, or the existence of symptoms consistent with Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria for dementia reported by the patients' family. This collection enabled calculation of the Charlson Comorbidity Index (CCI) and the Cumulative Illness Rating Scale-geriatric (CIRS-G).[10,11] These scores estimate the risk of death according to comorbidities. The CIRS-G rates 14 body systems on a five-point severity scale (0–4: no/mild/moderate/severe/extremely severe). Scoring in the CIRS-G leads to five scores: the total number of categories endorsed (CIRS-G number of categories), the total score (CIRS-G total score), the ratio of total score/number of endorsed categories (CIRS-G severity index), and the number of categories at level 3 and 4. Although no golden standard for measuring multi-morbidity has been established so far, the CCI and the CIRS-G were chosen because of their wide use and their excellent ability to predict adverse outcomes in the elderly.[12,13]

2.4 Study variables

IS was defined by the realization of a coronary angiography during the index hospitalization—regardless of the time delay from admission to procedure—whether it was followed by revascularization or not. Patients with a conservative strategy (CS) did not undergo coronary angiography and received only medical therapy.

2.5 Patient follow-up

In-hospital outcomes, hospital length of stay (stays in CICU but also in rehabilitation center), and patient orientation at discharge (home, rehabilitation or nursing home) were recorded. All investigations, including vital status, were continuously assessed through feedback by phone and written reports from the local hospitals. Follow-up lasted six months.

2.6 Statistical analysis

Continuous variables were expressed as median and 25th to 75th percentile. Categorical variables were presented as absolute numbers and percentages. Two criteria were used in this study: IS (primary criterion) and 6-months survival. The two criteria were analyzed using the same statistical methodology: in a first step, a univariate analysis was performed by Mann-Whitney tests for continuous variables and Chi-square or Fisher's exact tests for qualitative ones. In a second step, variables with a *P*-value lower than 10% in the univariate analysis were included in a stepwise logistic regression. Only

the variables with a multivariate *P*-value lower than 5% by the Wald test were retained in the final model. The differences between the two analyses were that an evaluation of the model was assessed by a Receiver Operating Characteristic (ROC) curve only for the primary criterion and the IS variable was forced for the analysis of the second criterion that is it was retained in the final model regardless its *P*-value. All tests were two-tailed. Statistical analysis was performed using the SAS 9.3 statistical package (SAS Institute Inc., Cary, NC, USA).

3 Results

3.1 Baseline characteristics

A total of 141 consecutive patients were included. Median age was 84 years old (80–89 years). Patients had eight simultaneous pre-existing comorbid conditions. Seventy nine percent of the population had hypertension; 54% had dyslipidemia; 33% had diabetes mellitus; 44% and 28% had an history of CAD and stenting, respectively; 43% and 27% had an history of heart failure and atrial fibrillation, respectively; 37% had PVD; 10% had a history of stroke; 40% and 22% had dementia and depression, respectively; 30% had CPD.

Median Cockroft glomerular filtration rate (eGFR) and serum creatinine level were 49 (32–64) mL/min and 90 (69–125) μmol/L, respectively. Median GRACE score was 189 (172–215) and median CRUSADE score was 54 (42–65).

3.2 Factors associated with invasive strategy

Eighty seven patients (62%) underwent an IS (Table 1). Among patients who had a coronary angiography, athero-

Table 1.   Univariate and multivariate analysis of predictors of invasive therapy.

Variables	Univariate analysis			Multivariate analysis	
	IS, *n* = 87	CS, *n* = 54	*P*	Odds Ratio (95% CI)	*P*
Age, yrs	83 (78–86)	88 (93–91)	< 0.001	0.85 (0.78–0.92)	< 0.001
Male sex	48 (55.2%)	23 (42.6%)	0.15		
Geriatric evaluation					
Nursing home resident	2 (2.3%)	8 (14.8%)	0.007	*	
ADL	6 (5–6)	4 (3–6)	< 0.001	*	
Hypertension	69 (79.3%)	42 (77.8%)	0.83		
Dyslipidemia	52 (59.8%)	24 (44.4%)	0.076	*	
Diabetes mellitus	33 (37.9%)	14 (25.9%)	0.14		
BMI, kg/m²	23 (21–29)	22 (20–25)	0.08	*	
History of heart failure	32 (36.8%)	28 (51.9%)	0.079	*	
Atrial fibrillation	19 (21.8%)	19 (35.2%)	0.08	*	
Dementia	25 (28.7%)	31 (57.4%)	< 0.001	*	
Mean Mini Mental State Examination	23 (20–27)	20 (16–24)	0.003	*	
CIRS-G total score	13 (9–18)	18 (14–26)	< 0.001	*	
CIRS-G number of categories	7 (5–10)	10 (7–12)	< 0.001	0.83 (0.73–0.95)	0.002
Charlson comorbidity index	8 (6–10)	9 (7–11)	0.03	*	
At admission					
Pre-CICU delay (hours) (95% CI)**	12 (6–48)	12 (4–29)	0.74		
Chest pain	65 (74.7%)	25 (46.3%)	< 0.001	*	
Heart rate, beats/min	80 (67–95)	93 (80–105)	0.002	0.98 (0.96–0.99)	0.03
LV ejection fraction, %	50 (40-60)	43 (30–55)	0.03	*	
Creatinine, μmol/L	87 (68–110)	101 (70–140)	0.09	*	
Cockroft glomerular filtration rate, mL/min	54 (38–65)	37 (27–60)	0.002	*	
CRUSADE score	51 (42–61)	56 (45–68)	0.37		
GRACE score	181 (166–201)	205 (179–236)	< 0.001	*	

Categorical data are presented as *n* (%) and continuous data as median (inter-quartile range), unless stated otherwise. *Variables selected to enter in the multivariate analysis; **Time elapsed from symptom onset to CICU. ADL: activities of daily living; BMI: body mass index; CICU: cardiac intensive care unit; CIRS-G: cumulative illness rating scale for geriatrics; CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the guidelines; CS: conservative strategy; GRACE score: Global Registry of Acute Coronary Events score; IS: invasive strategy; LV: left ventricular.

sclerosis was found in 80 patients (92%), and percutaneous intervention was performed in 60 patients (69%). No patient underwent coronary artery bypass surgery. Patients who were given an IS tended to be younger (median age 83 *vs*. 88 years; *P* < 0.001), had a greater autonomy (median ADL 6 *vs*. 4; *P* < 0.001) and lived less frequently in nursing home (*P* = 0.007). They had less dementia and higher Cockroft eGFR. Both CIRS-G (number of categories and total score) and CCI were lower. Patients who underwent an IS were more likely to present with chest pain, with lower heart rate and lower GRACE risk score.

Univariate and multivariate predictors of IS are presented in Table 1. In the multivariate analysis, younger age, lower CIRS-G number of categories score and lower heart rate were associated with IS. The most commonly cited reasons for avoiding this approach were significant comorbidities (33%) and bleeding or other safety concerns (20%) (Table 2). Area under the ROC curve is 0.80 (0.73–0.88).

3.3 Process of care

During the acute phase, patients treated with an IS were more likely to receive aspirin (95.4% *vs*. 85.2%; *P* = 0.03) and anticoagulation (84.0% *vs*. 53.7%; *P* < 0.001). At discharge, they were given statins more often (91.4% *vs*. 68.9%; *P* = 0.001).

3.4 Outcome

Patients receiving an IS tended to have lower in-hospital mortality (5.8% *vs*. 14.8%; *P* = 0.07) and lower hospital length of stay (12 *vs*. 16.5 days; *P* = 0.07) (Table 3). Follow-up at 6 months was completed in all patients. A total of 31 patients (22.0%) died within 6 months of the index

hospitalization. Univariate and multivariate predictors of 6-month mortality are presented in Table 4. IS was not an independent factor associated with 6-month mortality: OR 0.80 (95% CI: 0.27–2.38; *P* = 0.69). The only multivariate predictor of 6-month mortality was the GRACE risk score with OR 1.03 (95% CI: 1.01–1.04; *P* < 0.001).

Table 3.   In-hospital complications and clinical outcomes.

Complications/Outcomes	IS, *n* = 87	CS, *n* = 54	*P*
Complications			
Cardiogenic shock	8 (9.2%)	6 (11.1%)	0.74
Cardiac arrest	3 (3.5%)	5 (9.3%)	0.32
Acute heart failure	25 (28.7%)	24 (44.4%)	0.057
Supra-ventricular tachycardia	16 (18.4%)	6 (11.1%)	0.33
Ventricular dysrhythmias	5 (5.8%)	1 (1.9%)	0.37
Bleeding complications	10 (11.4%)	9 (16.8%)	0.46
BARC 1	2 (2.2%)	1 (1.9%)	NA
BARC 2	4 (4.6%)	2 (3.7%)	NA
BARC 3	4 (4.6%)	5 (9.3%)	0.34
BARC 4	0	0	NA
BARC 5	0	1 (1.9%)	NA
Hemoglobin at admission, g/dL	11.3 (9.8–12.7)	11.0 (9.3–12.4)	0.62
In-hospital hemoglobin nadir, g/dL	9.3 (8.2–9.7)	8.9 (7.4–10.6)	0.81
Loss of hemoglobin, g/dL	2.2 (0.5–4.5)	2.5 (1.7–2.5)	0.94
Transfusion	11 (12.6%)	5 (9.3%)	0.58
Venous thromboembolism	1 (1.2%)	1 (1.9%)	0.76
Acute kidney failure	28 (32.2%)	22 (40.7%)	0.32
Acute tubular necrosis	7 (8.1%)	4 (7.4%)	0.91
Confusion	14 (16.1%)	22 (40.7%)	0.001
Stroke	3 (3.5%)	1 (1.9%)	0.63
Sepsis	15 (17.2%)	14 (25.9%)	0.24
Outcomes			
In-hospital death	5 (5.8%)	8 (14.8%)	0.07
30-day death from any cause	9 (10.3%)	11 (20.4%)	0.097
6-month death from any cause	16 (18.4%)	15 (27.8%)	0.19
6-month myocardial infarction	17 (19.5%)	10 (18.5%)	0.94
6-month stroke	5 (5.7%)	4 (7.4%)	0.73
General data			
CICU length of stay (days), (95% CI)	8 (4–14)	10 (5–15)	0.44
Hospital length of stay (days), (95% CI)	12 (5–25)	16.5 (9–37)	0.07
Returning home	53 (60.9%)	21 (39.6%)	0.01
Rehabilitation center	15 (17.2%)	18 (34.0%)	0.02
*6-month nursing home entry	1 (1.2%)	5 (10.9%)	0.02

Categorical data are presented as number of patients with events (%) and continuous data as median (inter-quartile range), unless stated otherwise. *Non-nursing home residents at admission only. BARC: bleeding academic research consortium; CICU: cardiac intensive care unit; CS: conservative strategy; IS: invasive strategy; NA: not applicable.

Table 2.   Physician-reported reasons (not mutually exclusive) for not following an invasive approach.

Variables	Reasons percents (54 patients/66 reasons)
Significant co-morbidity	33.3%
Bleeding or other safety concerns	19.7%
Clinically unstable	12.1%
Patient/Family refusal	9.1%
Patient not high risk	7.6%
GRACE score of patients not catheterized because "not high risk"	206 ± 19
Short-life expectancy < 1 year	7.6%
Anatomy previously defined as unsuitable	4.6%
Other acute problem	3.0%
Advanced age alone	3.0%
No reason given	0

Data are presented as percents or mean ± SD. GRACE score: global registry of acute coronary events score.

Table 4. Univariate and multivariate analysis of risk factors of 6-month death.

Variables	Univariate analysis			Multivariate	
	Dead (*n* = 31)	Living (*n* = 110)	*P*	Odds ratio (95% CI)	*P*
Age, yrs	86 (82–90)	83 (79–88)	0.24	*	
Male sex	18 (58.1%)	53 (48.2%)	0.33		
Geriatric evaluation					
ADL	4 (3.5–6)	5.5 (4–6)	0.099	*	
Denutrition	16 (53.3%)	40 (38.1%)	0.14		
Chronic comorbid conditions					
Hypertension	26 (83.9%)	85 (77.3%)	0.43		
Dyslipidemia	18 (58.1%)	58 (52.7%)	0.59		
Diabetes mellitus	10 (32.3%)	37 (23.6%)	0.89		
History of heart failure	17 (54.8%)	43 (39.1%)	0.12		
Atrial fibrillation	8 (25.8%)	30 (27.3%)	0.87		
History of stroke	6 (19.4%)	8 (7.3%)	0.047	*	
Dementia	12 (38.7%)	44 (40.0%)	0.89		
Mean Mini Mental State Examination	17 (12–23)	23 (20–27)	0.001		
CIRS-G total score	20 (11–25)	14 (10–19)	0.016	*	
CIRS-G number of categories	10 (6–12)	8 (6–11)	0.127	*	
CIRS-G severity index	2.1 (1.9–2.3)	1.9 (1.6–2.2)	0.003	*	
Charlson comorbidity index	9 (8–11)	8 (6–10)	0.003	*	
At admission					
Chest pain	15 (48.4%)	75 (68.2%)	0.043	*	
Systolic blood pressure, mmHg	128 (113–150)	137 (117–153)	0.29		
Heart rate, beats/min	88 (75–101)	86 (71–102)	0.84		
LV ejection fraction, %	45 (35–56)	46 (37–55)	0.51		
Cockroft glomerular filtration rate, mL/min	46 (31–58)	50 (35–64)	0.46		
GRACE score	209 (180–238)	185 (169–202)	0.001	1.03 (1.01–1.04)	< 0.001
Invasive strategy	16 (51.6%)	71 (64.6%)	0.19	0.80 (0.27–2.38)	0.69

Categorical data are presented as *n* (%) and continuous data as median (inter-quartile range), unless stated otherwise. *Variables selected to enter in the multivariate analysis. ADL: activities of daily living; CIRS-G: cumulative illness rating scale for geriatrics; GRACE score: Global Registry of Acute Coronary Events score; LV: left ventricular.

4 Discussion

To our knowledge, this is the first prospective study investigating the determinants of IS in elderly patients with NSTEMI. Our study showed that elderly patients with NSTEMI treated with an IS were younger, had fewer comorbidities, and had a lower heart rate at presentation.

4.1 Determinants of invasive strategy

Advanced age was an independent negative determinant of IS. Many observational studies have shown that invasive strategy is underused in older patients with NSTEMI compared to younger patients.[14] However, our results suggest that even among a population of elderly patients, age itself remains an independent limiting factor for an IS. Surprisingly, advanced age alone was very little reported by the physicians as a reason for avoiding IS, though ethical con-

siderations might have dissuaded physicians to report older age as a limiting factor.[15]

The CIRS-G number of comorbidities score reflects the individuals' multi-morbidity. It was a strong independent negative determinant of IS in this study, and the most commonly-cited reason for denying IS. In contrast to previous studies emphasizing the underutilization of IS in patients with specific comorbidities,[16,17] our results suggest that physicians rather base their decision on multi-morbidity. Conceivably, physicians assess older patients' multi-morbidity in order to determine the risk-to-benefit ratio of IS. Nevertheless, there is no rational basis justifying such clinical practice.[18] In univariate analysis, we identified lower Cockroft eGFR and dementia as being associated with a lower rate of IS. Adequate hydration, a lower dose and choice of contrast media help prevent most of contrast-induced nephropathies,[19] yet many patients with moderate

kidney dysfunction are excluded from IS.[20] Similarly, numerous studies have shown that dementia is a barrier to receiving IS in myocardial infarction, in particular because of the perception of the marginal benefit of IS in patients with dementia.[21] Yet, Tehrani *et al.*,[22] found that within patients with dementia and myocardial infarction, those who underwent an IS had 43% to 64% lower odds of in-hospital mortality than individuals undergoing CS. These results suggest that IS should not be denied on the sole basis of dementia.

As shown in a general population,[23] our study found increased heart rate to be a negative determinant of IS. Heart rate reflects hemodynamic functions. Thus, tachycardia is a strong predictor of hemodynamic instability.[24] Likewise, hemodynamic instability was often reported by the physicians as a reason for avoiding IS. These results confirm that older patients presenting a clinically unstable condition are less likely to undergo an IS.[23]

4.2 Risk-treatment paradox

If recent guidelines suggest that patients at high risk of future cardiovascular events benefit most from IS,[5] high-risk older patients are more commonly managed conservatively.[23] Our results confirmed this risk-treatment paradox and brought up some explanations: (1) older patients tend to exhibit atypical symptoms (e.g., no chest pain),[5] which accordingly leads to a late presentation and a reduced likelihood of receiving an IS.[25] (2) Clinicians' reluctance to use an IS increases with age, due to the fear of adverse outcomes, especially major bleeding events.[23] Interestingly, although bleeding concern was indeed often cited as a reason for avoiding IS, the bleeding risk prediction (CRUSADE) score was not significantly different between the two groups. Likewise, patients who were denied IS because of the perception that they were at low risk of cardiovascular events had actually a very high GRACE score. Our results confirm that inaccurate subjective risk-stratification occurs more frequently with elderly patients, leading to an unjustified denial of IS.[26] This supports the use of validated risk models such as the GRACE and CRUSADE scores to guide clinical decision making. (3) Elderly patients represent a subgroup known to have an intrinsic risk linked to underlying comorbidities. As this risk cannot be modified by an IS, comorbidities can be perceived as a limitation to undertake IS due to a hypothetical lack of benefit.[4]

4.3 Impact of invasive strategy

Because of the under-representation of elderly patients with comorbidities in clinical trials, little data are available regarding this population,[27] and somewhat difficult to compare. Recently, two randomized controlled trials showed that IS did not modify long-term mortality in elderly patients with comorbidities with NSTEMI.[2,4] Similarly, in our study, 6-month all-cause mortality did not depend on the assigned treatment strategy. These results could suggest that long-term prognostic impact of comorbidities outweighs any potential benefit of IS. However, in the After Eighty Study, a significant long-term benefit of IS was documented in terms of myocardial infarction and urgent revascularization, which is consistent with other studies.[28] In order to clearly define the risks and benefits of IS versus CS in older patients, additional endpoints of particular relevance to the elderly, such as quality of life and autonomy, should be included in trial design. Doing so will help identify patients most likely to derive benefit from aggressive intervention. Indeed, even if IS in the elderly may provide no significant reduction in long-term mortality, its use could be justified on the basis of patient comfort or healthcare cost reduction.

4.4 Strengths/limitations

No previous study has determined multivariate factors that lead the cardiologist to opt for an IS in elderly patients with multiple comorbidities presenting with NSTEMI. Only a few studies have examined the risk-treatment paradox encountered in this population. No previous study has included all consecutive elderly patients presenting with a NSTEMI, regardless of their age, comorbidities, life expectancy or initial severity. Thus, its population strongly resembles a "real-life" elderly community. Very few studies have focused on comorbidities in NSTEMI, and none of them have used multiple valid comorbidity scores to assess the disease burden of elderly patients with NSTEMI. The main limitation of this study could be its lack of power, due to the modest size of the population. Thus, this study is hypothesis generating only and its findings will require confirmation in more robust prospective studies before they can be incorporated into clinical algorithms. Nevertheless, the sample size remains statistically relevant since multivariate analyses found several predictive factors for the main criterion.

4.5 Conclusions

In a real-world cohort of elderly patients with NSTEMI, younger patients with fewer comorbidities and who were more clinically stable profited more often from an IS. However, IS did not modify 6-month all-cause mortality. Future RCTs assessing the impact of IS in elderly individuals with comorbidities with NSTEMI are needed. Outcomes of particular relevance to the elderly, such as quality of life and

autonomy, should be included in trial design. Doing so will help determine the profile of elderly patients who would most benefit from an IS.

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