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Frequency and clinical outcome of cardiogenic shock during acute myocardial infarction among patients receiving reteplase or alteplase

Results from GUSTO-III

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Aims Reteplase has been reported to achieve better patency of the infarct artery than alteplase. As infarct artery patency is strongly associated with survival among patients with cardiogenic shock, we postulated that treatment with reteplase would improve outcomes among shock patients.

Methods We compared 30-day mortality rates among patients in GUSTO-III who either presented with shock or developed shock after enrolment; all patients received either front-loaded alteplase or reteplase (two bolus doses of 10 MU, 30 min apart).

Results Shock occurred in 260 (5·3%) of 4921 patients randomized to alteplase and 560 (5·5%) of 10 138 patients randomized to reteplase. Of these patients, 28 (10·8%) and 55 (9·8%) randomized to alteplase and reteplase, respectively, presented with shock. In-hospital, 35% and 37% of shock patients assigned to alteplase or reteplase, respectively, underwent coronary angiography, with similar rates of percutaneous (~11–13%) or surgical (~2–3%) revascularization procedures subsequently performed. Death within 30 days occurred in 169 (65%) and 353 (63%) shock patients randomized to alteplase and reteplase, respectively ($P=0·59$). Of patients presenting with shock, 64% and 58% of patients randomized to alteplase or reteplase died within 30 days ($P=0·59$).

Conclusion Compared with alteplase, reteplase did not improve outcome among patients who presented with shock or developed shock after receiving thrombolytics. The newer-generation thrombolytic agents remain of limited efficacy in the treatment and prevention of shock.
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Key Words: Cardiogenic shock, randomized clinical trial, reteplase, alteplase, thrombolysis.

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Introduction

Patients with cardiogenic shock account for a large proportion of the morbidity and mortality of acute infarction[1–5]. In the Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial, although shock occurred in only 7·2% of patients, this patient group accounted for 58% of mortality in the entire trial[3]. In contrast to the disappointing results that have been attained with thrombolytic therapy[1,3,4,6], preliminary data indicate that mechanical reperfusion, adjunctive pharmacological therapy, and the use of assist devices may improve outcome in this high-risk group[1,3,5,7–14]. However, because thrombolytic therapy remains the most readily available means of achieving reperfusion

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among patients with acute myocardial infarction[15], including shock patients, more effective thrombolytic agents that may also improve outcome among shock patients are being examined.

Recombinant plasminogen activator (reteplase) is a mutant alteplase that lacks the finger, epidermal growth factor, and kringle-1 domains[16,17]. Reteplase has compared favourably with both alteplase and streptokinase in prior trials[18–21]. Indeed, in the International Joint Efficacy of Thrombolytics (INJECT) trial[20], patients randomized to reteplase had a significantly lower rate of cardiogenic shock and heart failure during the first 30 days as compared with those randomized to streptokinase.

Prior trials have indicated that reteplase may achieve better patency of the infarct artery than alteplase[18,19,21]. This was the impetus for the Global Use of Strategies to Open Occluded Coronary Arteries III (GUSTO-III) trial, comparing 30-day outcome of patients randomized to receive either reteplase or alteplase[22]. Although reteplase was not found to be superior to alteplase for the treatment of acute myocardial infarction[22], we postulated that its greater efficacy in achieving early, complete, and sustained reperfusion[18,19,21] and reducing the occurrence of heart failure[20] would selectively result in better outcome in the highest-risk subgroup, patients with cardiogenic shock.

Methods

GUSTO III study population

The GUSTO-III trial has been previously described[22]. In brief, patients of any age who presented after 30 min of continuous symptoms but within 6 h of the onset of symptoms of acute myocardial infarction and who had ST-segment elevation of at least 1 mm in two or more limb leads on 12-lead electrocardiography, or ST-segment elevation of at least 2 mm in the precordial leads, or left bundle-branch block were considered eligible. Patients who met the inclusion criteria were approached for participation. The protocol was approved by the institutional review board at each hospital.

Shock patients in GUSTO III

Patients with cardiogenic shock were a predefined subgroup for analysis. Shock was defined as systolic blood pressure less than 90 mmHg for at least 1 h that was not responsive to fluid administration alone, thought to be secondary to cardiac dysfunction, and associated with signs of hypoperfusion or cardiac index less than $2{\cdot}2\,l\,.\,min^{-1}\,.\,mm^2$ and pulmonary capillary wedge pressure greater than 18 mmHg[3,23]. Patients in whom systolic blood pressure increased to more than 90 mmHg within 1 h after administration of positive inotropic agents, or patients who died within 1 h of hypotension but met other criteria for cardiogenic shock were still classified as having cardiogenic shock. The decision to place a pulmonary artery catheter was made by the attending physician.

Diagnoses of ventricular septal defect, ventricular rupture, and mitral regurgitation were made by the site investigator based on echocardiography, left-heart catheterization, right-heart catheterization, or post-mortem analysis.

Coronary angiography and revascularization

Shock patients underwent coronary angiography and coronary revascularization at the discretion of the attending physician. The use of assist devices such as intra-aortic balloon pumping was also at the discretion of the attending physician.

Among patients who underwent coronary angiography, the attending physician determined the infarct-related artery and the severity of its stenosis. The flow status of the infarct-related artery was also graded as Thrombolysis in Myocardial Infarction (TIMI) flow 0–3 or categorically as either open or closed. In our analysis, the infarct-related artery was considered patent if flow status was reported as TIMI 3 or 'open'.

Drug regimens

Patients were randomly assigned in a 2:1 ratio to receive reteplase (Boehringer Mannheim, Gaithersburg, MD, and Mannheim, Germany) in two bolus doses of 10 MU given 30 min apart, or an accelerated infusion of alteplase (Genentech, South San Francisco, CA, and Boehringer Ingelheim, Ingelheim, Germany) in a bolus dose of 15 mg, followed by the infusion of $0{\cdot}75\,mg\,.\,kg^{-1}$ body $weight^{-1}$ over a 30-min period (not to exceed 50 mg) and the infusion of $0{\cdot}5\,mg\,.\,kg^{-1}$ body $weight^{-1}$ over the next 60 min (up to 35 mg). Aspirin was given at 160 mg upon enrolment and at 160 to 325 mg daily thereafter. Intravenous heparin was also given with a targeted activated partial thromboplastin time of 50 to 70 s. All other drugs were given at the discretion of the attending physician.

Study end-points

As in the GUSTO-III trial[22], the primary end-point of this shock analysis was all-cause mortality at 30 days of follow-up.

Statistical analysis

Continuous data are presented as medians with 25th and 75th percentiles unless otherwise stipulated, and discrete

variables are presented as frequencies and percentages. The chi-square test, the Fisher's exact test, and the Wilcoxon test were used for analysis of differences in categorical variables and adverse events. All tests of significance were two-tailed, and treatments were compared according to the intention-to-treat principle. Logistic regression models were formulated to calculate the effect of treatment on outcome. These models included the following predefined covariates[22]: age, baseline systolic blood pressure, baseline heart rate, location of infarction, time to randomization, and enrolment in the United States as compared with other countries.

Results

Frequency of shock in GUSTO-III

A total of 15 059 patients from 20 countries were enrolled in the GUSTO-III trial between October 1995 and January 1997. Based on the 2:1 randomization design, 4921 patients (32·7%) were randomized to alteplase and 10 138 (67·3%) to reteplase. Cardiogenic shock occurred in 260 patients (5·3%) randomized to alteplase and 560 patients (5·5%) randomized to reteplase; 28 patients (10·8%) randomized to alteplase and 55 patients (9·8%) randomized to reteplase presented with cardiogenic shock. The remaining patients subsequently developed cardiogenic shock. Of the shock patients randomized to alteplase, 244 (94%) received the drug, as compared with 539 patients (96%) randomized to reteplase ($P=0·12$). Among the patients presenting with shock, 26 patients (93%) randomized to alteplase and 54 (98%) randomized to reteplase received the respective drugs ($P=0·26$).

Of the 820 shock patients in GUSTO-III, 271 (33%) were enrolled in the United States. Similar proportions of shock patients in the United States (69%) and in the other countries (68%) were randomized to reteplase.

Baseline characteristics and additional in-hospital treatment

The baseline characteristics of shock patients assigned to the two drugs did not differ significantly (Table 1). Of the 820 patients presenting with cardiogenic shock or developing shock after enrolment, 299 patients (36%) underwent coronary angiography in-hospital: 35% and 37% of patients assigned to alteplase and reteplase, respectively (Table 2). Percutaneous or surgical revascularization procedures were performed in similar proportions of patients assigned to either alteplase or reteplase (Table 2). Shock patients enrolled in the United States underwent coronary angiography more commonly, had more revascularization procedures, and received intra-aortic balloon pumps more frequently (Table 3).

Infarct artery patency

Among the patients who underwent coronary angiography, there was no significant difference in the severity of stenosis between shock patients randomized to receive alteplase or reteplase (Table 4). In addition, there was no significant difference in the patency of the infarct-related artery among shock patients randomized to either treatment.

Outcome

Adverse events during the follow-up period occurred in a similar proportion of patients in both groups (Table 5). By 30 days, 50 of the 83 patients (60%) who presented with shock died, as compared with 472 of 737 patients (64%) who developed shock after enrolment ($P=0·50$). Mortality did not differ significantly in the two treatment arms (Table 5): 169 (65%) and 353 (63%) for alteplase and reteplase, respectively ($P=0·59$). The adjusted and unadjusted odds ratios for 30-day mortality based on treatment strategy were very similar (data not shown). Among the patients who presented with cardiogenic shock, 18 (64%) randomized to alteplase died within 30 days compared with 32 (58%) randomized to reteplase ($P=0·59$). Of the 522 patients with shock who died within 30 days, 236 (45%) died within 24 h of enrolment and 298 (57%) within 48 h. The vast majority of deaths (98%) occurred during the initial hospitalization.

Shock patients enrolled in the United States had better 30-day mortality than other countries (53% vs 66%, $P<0·001$). Adjusting for the predefined covariates, this difference persisted (adjusted odds ratio 0·56, 95% confidence interval 0·41 to 0·77). When the greater use of revascularization procedures and intra-aortic balloon counterpulsation among shock patients in the United States was also accounted for, however, there was no longer any significant difference in outcome (adjusted odds ratio 0·86, 95% confidence interval 0·60 to 1·23).

Discussion

Prior trials have demonstrated that patients with cardiogenic shock complicating acute myocardial infarction and receiving thrombolytic therapy have a dire prognosis[1,3,4,6]. We postulated that treatment with reteplase, which has been reported to result in earlier, more complete, and sustained reperfusion of the infarct-related artery compared with alteplase[18,19,21], would result in better outcome among shock patients, given that the patency of the infarct-related artery is most strongly associated with acute and long-term survival

Table 1 Demographic and clinical characteristics of shock patients assigned to reteplase or alteplase

	Reteplase (n=560)	Alteplase (n=260)
Age (years)	70·8 (60·8, 77·0)	71·0 (61·9, 76·5)
Male gender	344 (61%)	165 (63%)
Weight (kg)	75 (65, 85)	75 (65, 86)
Height (cm)	170 (162, 175)	170 (160, 177)
Time from symptom onset		
to randomization (h)	2·4 (1·6, 3·7)	2·6 (1·6, 3·7)
to treatment (h)	2·8 (1·9, 3·9)	2·8 (2·0, 4·0)
Baseline blood pressure (mmHg)		
Systolic	115 (97, 138)	122 (100, 141)
Diastolic	70 (60, 82)	74 (60, 88)
Baseline heart rate (beats · min^{-1})	82 (66, 100)	82 (65, 100)
Baseline Killip class		
I	307 (56%)	148 (58%)
II	140 (25%)	58 (23%)
III	48 (9%)	19 (8%)
IV	55 (10%)	28 (11%)
Location of infarction		
Anterior	334 (60%)	152 (58%)
Inferior	201 (36%)	100 (38%)
None	0	2 (1%)
Other	25 (5%)	6 (2%)
Right-heart catheter	152 (27%)	67 (26%)
Transvenous pacemaker	92 (16%)	50 (19%)
Intra-aortic balloon pump	117 (21%)	65 (25%)
Hypertension	273 (49%)	123 (47%)
Diabetes mellitus	124 (22%)	70 (27%)
Hypercholesterolaemia	176 (32%)	74 (29%)
Smoking status		
Current smoker	167 (31%)	81 (33%)
Never smoked	181 (33%)	83 (33%)
Former smoker	194 (36%)	84 (34%)
Prior myocardial infarction	172 (31%)	68 (26%)
Prior angina	289 (52%)	133 (51%)
Prior coronary bypass surgery	31 (6%)	9 (3%)
Prior coronary angioplasty	23 (4%)	8 (3%)
Prior heart failure	48 (9%)	16 (6%)
Prior thrombolytic use	33 (6%)	12 (5%)

Table 2 In-hospital referral to coronary angiography and coronary revascularization and use of assist-devices among shock patients assigned to reteplase or alteplase

	Reteplase (n=560)	Alteplase (n=260)
Coronary angiography	207 (37%)	92 (35%)
Percutaneous revascularization	64 (11%)	34 (16%)
Coronary artery bypass surgery	15 (2·7%)	5 (1·9%)
Intra-aortic balloon pumping	92 (16%)	45 (17%)

Table 3 In-hospital referral to coronary angiography and coronary revascularization and use of assist devices among shock patients in the United States and elsewhere

	United States (n=271)	Outside United States (n=549)
Coronary angiography	178 (66%)	121 (22%)
Percutaneous revascularization	62 (23%)	36 (7%)
Coronary artery bypass surgery	13 (5%)	7 (1%)
Intra-aortic balloon pumping	84 (31%)	53 (10%)

among patients with cardiogenic shock[5]. The principal findings of the current study were that compared with alteplase: (1) reteplase did not improve outcome among patients presenting with cardiogenic shock; (2) reteplase did not reduce the proportion of patients who developed cardiogenic shock after enrolment; (3) reteplase did not improve outcome among patients who developed cardiogenic shock after enrolment. These data suggest that the newer generation thrombolytic agents remain of limited efficacy in the treatment of cardiogenic shock and are still associated with high mortality rates when cardiogenic shock develops.

Table 4 Patency rates among shock patients assigned to reteplase or alteplase and undergoing coronary angiography

	Reteplase	Alteplase	*P*
Percent stenosis of infarct-related artery (n=273)*	99 (90, 100)	99 (90, 100)	0·53
Presenting with shock (n=20)†	100 (95, 100)	95 (85, 100)	0·47
Developing shock (n=253)‡	99 (90, 100)	99 (90, 100)	0·39
Flow status (n=219)			
TIMI 0	51 (33·3%)	25 (37·9%)	
TIMI 1	24 (15·7%)	11 (16·7%)	
TIMI 2	28 (18·3%)	5 (7·6%)	
TIMI 3	39 (25·5%)	18 (27·3%)	
Open	6 (3·9%)	5 (7·6%)	
Closed	5 (3·3%)	2 (3·0%)	
TIMI 3, open	45 (29·4%)	23 (34·9%)	0·431
Presenting with shock (n=15)			
TIMI 3, open	3 (25%)	0 (0%)	1·0
Developing shock (n=204)			
TIMI 3, open	42 (29·8%)	23 (26·5%)	0·42

*Available for 186 patients randomized to reteplase and 87 patients randomized to alteplase.
†Available for 14 patients randomized to reteplase and six patients randomized to alteplase.
‡Available for 172 patients randomized to reteplase and 81 patients randomized to alteplase.
TIMI=Thrombolysis in Myocardial Infarction.

Table 5 Occurrence of adverse events among shock patients assigned to reteplase or alteplase

	Reteplase (n=560)	Alteplase (n=260)
Stroke	17 (3%)	9 (3%)
Moderate to severe bleeding	113 (20%)	50 (19%)
Reinfarction	77 (14%)	36 (14%)
Arrhythmias		
2nd degree atrioventricular block	31 (6%)	20 (8%)
3rd degree atrioventricular block	94 (17%)	38 (15%)
Asystole	180 (32%)	101 (39%)
Atrial fibrillation/flutter	125 (22%)	59 (23%)
Sustained ventricular tachycardia	114 (20%)	59 (23%)
Mechanical causes of shock		
Mitral regurgitation	23 (4%)	6 (2%)
Ventricular septal defect	11 (2%)	11 (4%)
Cardiac rupture or tamponade	26 (5%)	13 (5%)
Death		
<24 h after enrolment	155 (28%)	81 (31%)
<48 h after enrolment	199 (36%)	99 (38%)
In-hospital	349 (62%)	161 (62%)
Within 30 days after enrolment	353 (63%)	169 (65%)

Thrombolytic therapy for the treatment of shock

There have been no trials in which patients with acute myocardial infarction who presented with cardiogenic shock have been specifically randomized to thrombolytic therapy or control[24,25]. However, the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico study, comparing streptokinase with control, included patients with cardiogenic shock[26]: 69·9% of the 146 patients who presented with shock and received streptokinase died within 21 days, as compared with 70·1% of the 134 shock patients in the control group. In contrast, a meta-analysis of large trials comparing thrombolytic therapy for acute myocardial infarction with control demonstrated that among patients presenting with a systolic blood pressure <100 mmHg, mortality was reduced from 35·1% in the control group to 28·9% in patients who received thrombolytic therapy[27]. The proportion of patients with hypotension who were in shock was not defined[27]. A retrospective analysis of patients admitted to Duke University Medical Center in the years 1987 through 1988 also demonstrated high mortality rates in shock patients receiving thrombolytic therapy; among 36 patients treated with thrombolytic therapy alone, the in-hospital mortality rate was 58%[5].

Other large trials examining the efficacy of thrombolytic therapy for myocardial infarction have included patients with cardiogenic shock[23,28], but as was true in the GUSTO-III trial, the vast majority of these patients developed shock after enrolment. Thus, there are few firm data demonstrating efficacy of thrombolytic therapy for the treatment of patients presenting with cardiogenic shock.

Among the relatively few patients who presented with cardiogenic shock enrolled in GUSTO-III, we did not observe a better outcome for patients assigned to reteplase; 30-day mortality was similarly high for both groups. The relative advantage of reteplase over alteplase in achieving more rapid and effective reperfusion has been reported primarily in non-shock patients[18,19,21]. In our analysis, albeit limited by the small number of patients, we did not detect better patency rates among shock patients receiving reteplase. Similarly, among the 315 patients who presented with cardiogenic shock in GUSTO-I, Holmes *et al*.[3] demonstrated that treatment with alteplase did not reduce 30-day mortality compared with other treatment arms, despite the better patency rates generally reported with alteplase[29]. These data suggest that the benefit of thrombolytic agents with greater efficacy in achieving patency of the infarct-related artery may be diminished in cardiogenic shock.

The lack of benefit of thrombolytic agents in cardiogenic shock may be attributed to reduced coronary thrombolysis in states of low perfusion pressure[3,30,31]. The use of intra-aortic balloon counterpulsation may enhance the efficacy of coronary thrombolytic agents[30,31]. In GUSTO-III, intra-aortic balloon counterpulsation was under-utilized in high-risk patients with cardiogenic shock, only 21–25% of whom had a balloon pump inserted. However, intra-aortic balloon counterpulsation was used more commonly in the United States. The better outcome among shock patients enrolled in the United States may therefore be attributed, in part, to the greater use of intra-aortic balloon counterpulsation, thus enabling stabilization of the patient until revascularization could be undertaken.

As mentioned above, Holmes *et al*.[3] demonstrated that treatment with alteplase did not reduce 30-day mortality compared with other treatment arms in GUSTO-I. Indeed, a trend in favour of streptokinase was noted. Similar results were reported by the International Study Group[32]. These prior reports led to speculation that agents that are less fibrin specific than alteplase exert a more potent thrombolytic effect in shock patients. Our findings do not support this hypothesis; reteplase is less fibrin specific than alteplase, yet it did not improve outcome in shock patients.

In light of the discouraging results attained with thrombolytic therapy for patients who presented with shock, there is an emerging interest in the use of mechanical revascularization in these patients. Although the reported results with mechanical revascularization seem slightly better than those attained with thrombolytic therapy, there may be a selection bias in clinical practice regarding the use of mechanical revascularization[10,11,14]; the clinical and angiographic profile of patients undergoing angioplasty is often more favourable than that of patients who receive medical therapy alone. Indeed, a recent prospective randomized trial of 55 patients with shock following myocardial infarction compared revascularization (surgical or percutaneous) with medical therapy[33]. The study was stopped prematurely due to low inclusion rates. However, in this small cohort emergency angioplasty did not improve outcome. Thus, there are currently no firm data that thrombolytic therapy alters outcome among patients presenting with shock nor conclusive randomized data that more aggressive approaches improve the outcome of these patients.

Thrombolytic therapy and prevention of shock

Prior studies have demonstrated that the rapid administration of thrombolytic therapy reduces the occurrence of cardiogenic shock as compared with placebo[34,35]. In addition, the GUSTO Angiographic Substudy demonstrated that alteplase resulted in better patency than streptokinase and accordingly resulted in improved left ventricular function[29]. These trials have laid the ground for the widely accepted paradigm that more rapid and complete reperfusion is associated with greater myocardial salvage. Because cardiogenic shock is often the result of extensive myocardial damage[1], better perfusion of the infarct zone would be expected to reduce the occurrence of shock after thrombolytic therapy[5]. Accordingly, in the GUSTO-I trial[3], a smaller proportion of patients assigned to alteplase developed shock (5·5%) as compared with the other treatment arms (6·9%). Likewise, in the INJECT trial[20], patients randomized to reteplase had a significantly lower rate of cardiogenic shock and heart failure during the first 30 days as compared with those randomized to streptokinase.

In GUSTO-III a similar proportion of patients assigned to reteplase and alteplase developed shock after enrolment. A prior study comparing reteplase with front-loaded, accelerated alteplase in patients with acute myocardial infarction demonstrated better patency of the infarct-related artery with reteplase[18]. In our analysis of shock patients who underwent coronary angiography, we did not detect differences in patency rates between the two treatment arms. This may explain the lack of a difference in the rate of ensuing shock. It is worth mentioning, however, that other trials have also shown that the use of therapeutic strategies associated with better patency rates of the infarct-related artery as compared with front-loaded alteplase did not result in an attenuated rate of shock development. In the Global Use of Strategies To Open Occluded Coronary Arteries IIb (GUSTO IIb) Angioplasty Substudy[36], shock was not reduced in the angioplasty arm compared with

front-loaded, accelerated alteplase, despite the better patency achieved with angioplasty. Similarly, the double-bolus administration of alteplase, which reportedly is associated with a higher rate of TIMI 3 flow[37], did not reduce the occurrence of cardiogenic shock[38]. These findings suggest that the incremental increase in the amount of myocardium that can be salvaged by improving the patency of the infarct-related arter relative to alteplase may be small.

Shock developing after thrombolytic therapy

In the present study, the outcome of patients who developed shock after enrolment was poor. Holmes *et al*.[3] reported similar findings in GUSTO-I. These data suggest that patients who develop shock after thrombolytic therapy have a poor outcome, regardless of the thrombolytic agent used. Berger *et al*.[14] recently reported that the adjusted outcome of shock patients (i.e. 89% developed shock after thrombolytic treatment) who received aggressive treatment including revascularization in GUSTO-I was better than those who did not, suggesting that an aggressive approach should be considered for these patients. Our findings in GUSTO-III support this approach; shock patients in the United States received more aggressive treatment, including more revascularization procedures, and accordingly had better outcome at 30 days than shock patients from other countries.

Limitations

This study has limitations germane to subgroup analysis of randomized clinical trials[39]. In addition, angiographic data were available in only a proportion of patients, with variable time intervals between thrombolytic therapy and coronary angiography. Thus, although reteplase has been generally associated with earlier, more complete, and sustained reperfusion of the infarct-related artery as compared with alteplase in animal studies[17,40] and in humans[18,19,21], its effect in this study population remains unascertained.

Conclusion

Despite the generally favourable properties of reteplase in restoring and maintaining patency of the infarct-related artery, outcome of shock patients was not improved in the GUSTO-III trial. These findings underscore the limitations of thrombolytic therapy in the prevention and management of cardiogenic shock. Alternative or complementary therapeutic modalities are thus exigent for this high-risk subgroup.

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