

## Natural History and Patterns of Current Practice in Heart Failure

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FOR THE STUDIES OF LEFT VENTRICULAR DYSFUNCTION (SOLVD) INVESTIGATORS#

A total of 6,273 consecutive relatively unselected patients with heart failure or left ventricular dysfunction, or both (mean age  $62 \pm 12$  years, mean ejection fraction  $31 \pm 9\%$ ), were enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) Registry over a period of 14 months. All patients were followed up for vital status and hospital admissions at 1 year. Ischemic heart disease was the underlying cause of failure or dysfunction in  $\approx 70\%$  of patients, whereas hypertensive heart disease was considered to be primarily involved in only 7%. There were striking differences in the etiology of heart failure among blacks and whites: 73% of whites had an ischemic etiology of failure versus only 36% of blacks; 32% of blacks had a hypertensive condition versus only 4% of whites. The total 1-year mortality rate was 18%; 19% of patients had hospital admissions for heart failure and 27% either died or had a hospital admission for congestive heart failure during the 1st year of follow-up. Factors related to 1-year

mortality or hospital admission for congestive heart failure included age, ejection fraction, diabetes mellitus, atrial fibrillation and female gender. There was no difference in mortality associated with congestive heart failure among blacks and whites, but hospital admissions for heart failure were more frequent in blacks. Digitalis and diuretic agents were the drugs most often used in these patients, who were often taking many medications in relation to severity of congestive heart failure symptoms and ejection fraction. Surprisingly, angiotensin-converting enzyme inhibitors were taken by only 30% of patients, and a substantial number were treated by drugs controversial in the presence of left ventricular dysfunction and heart failure, such as calcium channel antagonists and antiarrhythmic or beta-adrenergic blocking agents.

(*J Am Coll Cardiol* 1993;22[Supplement A]:14A-9A)

Congestive heart failure is a leading cause of morbidity and mortality in industrialized nations. It is estimated that  $>2.5$  million North Americans are afflicted and that 400,000 new related events occur each year (1,2). Congestive heart failure is also a growing public health problem, mainly because of aging of the population and the increase in the incidence and prevalence of heart failure in the elderly. Age is also a major determinant of the high morbidity and mortality rates of congestive heart failure (3). Important data about the natural history of heart failure were derived from the Framingham Heart Study (4,5), but both the spectrum of underlying disease and its management may have changed since then.

The Studies of Left Ventricular Dysfunction (SOLVD) Registry (6) allows the characterization of the natural course of consecutive relatively unselected patients with heart

failure treated in several centers in the United States, Canada and Belgium according to standards of clinical practice that were widely accepted before the results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and SOLVD trials (7-9). The purpose of this report is to review recent SOLVD Registry data, assessing the influence of clinical features on subsequent early morbidity and mortality, the relation between clinical findings and ejection fraction and the patterns of drug use in patients with congestive heart failure.

### Methods

**Study group.** The rationale, design and methods of the SOLVD Registry have been described previously (6). Briefly, from January 1, 1988 to February 28, 1989, a total of 6,273 patients were recruited from 18 of the 23 clinical sites participating in the SOLVD trials.

Patients entered the SOLVD Registry if they had an ejection fraction of  $\leq 45\%$  measured by radionuclide, cardiac catheterization or echocardiographic methods or after a hospital discharge diagnosis of congestive heart failure confirmed by radiologic evidence of pulmonary venous congestion (one or more of the following: pulmonary venous redistribution, basal or perihilar vascular blurring, Kerley B

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Manuscript received September 13, 1992; revised manuscript received February 12, 1993, accepted February 18, 1993.

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lines, alveolar or pulmonary edema and pleural effusions judged secondary to congestive heart failure). Most patients (n = 4,951, 79%) were eligible on the basis of ejection fraction only, 864 (14%) on the basis of a hospital discharge diagnosis of heart failure and 458 (7%) on both.

Eligible patients fulfilling any of the following conditions were excluded: 1) nonvalvular congenital heart disease; 2) acute myocardial infarction or revascularization within 7 days; 3) noncardiac life-threatening diseases likely to significantly shorten survival; 4) lack of reliable means of contact for follow-up; and 5) inability to give informed consent. All patients had to be  $\geq 21$  years of age; there was no upper age limit.

Baseline demographic, clinical and laboratory data were obtained from the patients' medical records. Vital status and hospital admissions at 1 year were obtained by mail or telephone contact. At 1 year, vital status was available for 99% of patients and information on hospital admissions for 96%.

**Statistical analysis.** The significance of differences in total mortality, congestive heart failure-related hospital admissions and death or congestive heart failure-related hospital admissions was assessed for selected categorized variables using the log-rank chi-square statistic. The relative significance of potential risk factors was obtained from multivariate logistic regression models.

## Results

**Patient characteristics (Table 1).** Of the total group of 6,273 patients in the SOLVD Registry, whites accounted for 85.6% (5,368 patients) of the total study group and blacks for 11.1% (695 patients). Roughly 3% (210 patients) belonged to other racial groups and were excluded from this analysis. Overall, 74% were men and 26% women.

Mean age was  $62 \pm 12$  years and 59% of patients were  $\geq 60$  years of age. Women were older than men, among both whites and blacks ( $66.5 \pm 12.7$  vs.  $61.5 \pm 11.1$  years and  $60.5 \pm 13.8$  vs.  $56.1 \pm 13.0$  years, respectively; both  $p = 0.0001$ ). Blacks were younger than whites ( $57.9 \pm 13.5$  vs.  $62.7 \pm 11.7$  years,  $p = 0.0001$ ) and the proportion of women was higher among blacks than among whites (42% vs. 24%,  $p = 0.0001$ ). Mean ejection fraction was  $30.9 \pm 9.2\%$  for all groups. Ejection fraction was lower in blacks than in whites ( $28.6 \pm 9.1$  vs.  $31.2 \pm 9.2\%$ ,  $p = 0.0001$ ). Ischemic heart disease was the underlying etiology of heart failure in approximately 70% of patients, whereas hypertensive heart disease was considered to be primarily involved in only 7%. However, a history of hypertension was present in 43% of patients. Idiopathic dilated cardiomyopathy was responsible for 13% of cases and other etiologies such as valvular heart disease and secondary cardiomyopathy for 11%. There were striking differences in the etiology of heart failure among blacks and whites. Roughly 73% of whites had an ischemic origin of heart failure versus only 36% of blacks ( $p = 0.0001$ ). Only 4% of whites had an hypertensive condition versus 32%

Table 1. SOLVD Registry: Patient Characteristics

Age (yr)	62.2 $\pm$ 12.0	
Ejection fraction (%)	20.9 $\pm$ 9.2	
Gender		
Male	4,468	(73.7)
Female	1,595	(26.3)
Race		
White	5,368	(85.6)
Black	695	(11.5)
Etiology of heart failure		
Ischemic	4,160	(68.5)
Hypertensive	439	(7.2)
Idiopathic	789	(12.9)
Other	682	(11.3)
History of angina	3,516	(60.0)
Prior myocardial infarction	3,756	(63.4)
History of hypertension	2,552	(43.4)
Diabetes mellitus	1,378	(23.4)
Atrial fibrillation	731	(13.8)
Regular alcohol use	1,814	(38.3)
Current smoking	1,264	(33.5)

Data are presented as mean value  $\pm$  SD or number (%) of patients. SOLVD = Studies on Left Ventricular Dysfunction.

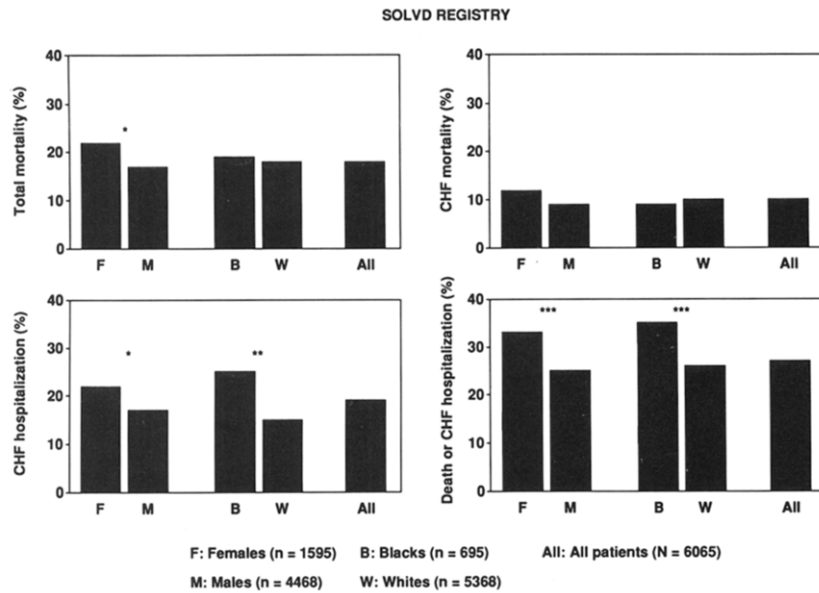
of blacks ( $p = 0.001$ ). Other etiologies were equally distributed.

Approximately 80% of patients in the SOLVD Registry were in New York Heart Association functional class I or II and 20% were in class III or IV. At physical examination, 32% had pulmonary rales, 26% had edema and 20% an elevated jugular venous pressure. A third sound gallop and mitral regurgitation were reported in 17% and 15% of patients, respectively, and atrial fibrillation was observed in 14%.

**Follow-up events at 1 year.** The total mortality rate at 1 year was 18%. Roughly 80% of deaths were of cardiovascular origin. Slightly  $>50\%$  of these patients died of progressive congestive heart failure. In the SOLVD Registry, 19% of patients had one or more hospital admissions for heart failure and 27% either had died or were admitted to the hospital for congestive heart failure during the 1st year of follow-up (Fig. 1).

Age markedly influenced all follow-up events including total mortality, mortality related to heart failure and hospital admissions for congestive heart failure or both (Fig. 2). This was true in both racial groups (Fig. 3A). For all these end points, the rate of events was relatively low in patients  $<55$  years of age and increased steadily thereafter (Fig. 2).

Women had higher rates of all these events at 1 year than did men: 22% versus 17% total mortality ( $p = 0.05$ ), 12% versus 9% congestive heart failure-related mortality ( $p = 0.05$ ), 22% versus 17% hospital admissions for congestive heart failure ( $p = 0.05$ ) and 33% versus 25% death or hospital admissions for congestive heart failure ( $p = 0.0001$ ) (Fig. 1). These differences were observed in whites only. Black men and women had comparable incidence rates of death or



**Figure 1.** Influence of gender and race on follow-up events at 1 year in the total study group of 6,065 patients in the Studies on Left Ventricular Dysfunction (SOLVD) Registry. Women (F) had significantly higher rates of total mortality, mortality or hospital admissions related to congestive heart failure (CHF) and combined mortality and congestive heart failure-related hospital admissions at 1 year than did men (M). Blacks (B) and whites (W) had similar total and congestive heart failure-related mortality rates at 1 year. However, hospital admissions for heart failure were twice as frequent in blacks as in whites and combined death and hospital admissions for heart failure were higher. \*p = 0.05, \*\*p = 0.01, \*\*\*p < 0.005.

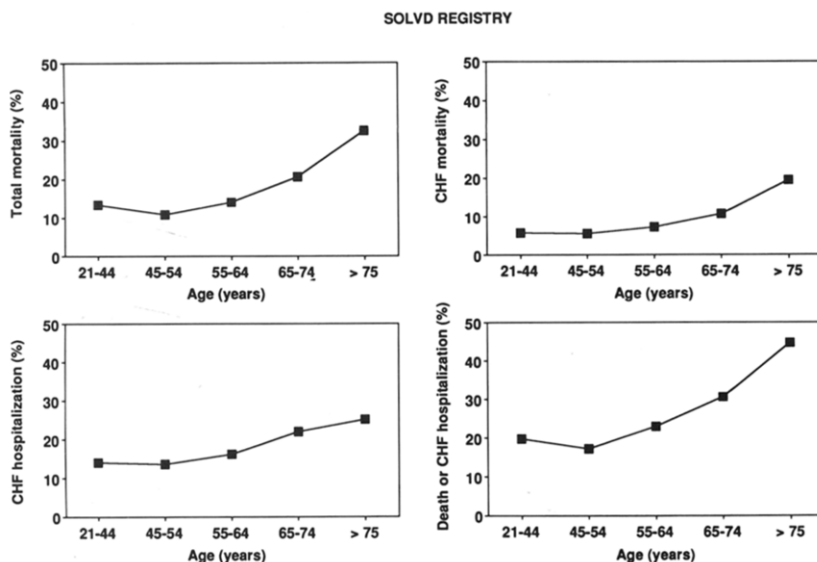
hospital admission for congestive heart failure at 1 year (Fig. 3B).

There was no difference among blacks and whites in total mortality (19% vs. 18%), cardiovascular mortality (13% vs. 15%) and mortality associated with progressive congestive heart failure (9% vs. 10%) (Fig. 1). However, blacks were admitted to the hospital for progressive heart failure significantly more often than were whites during the same time period (25% vs. 17%, p = 0.018) and when the end points of death or hospital admission for congestive heart failure were combined, blacks had a higher incidence of these events than did whites: 35% versus 26% (p = 0.005). This was true at all ages (Fig. 3A).

Total mortality rates and the incidence of deaths or hospital admissions for congestive heart failure at 1 year increased markedly but similarly with decreasing ejection fraction in both racial groups (Fig. 3C). Total mortality rates

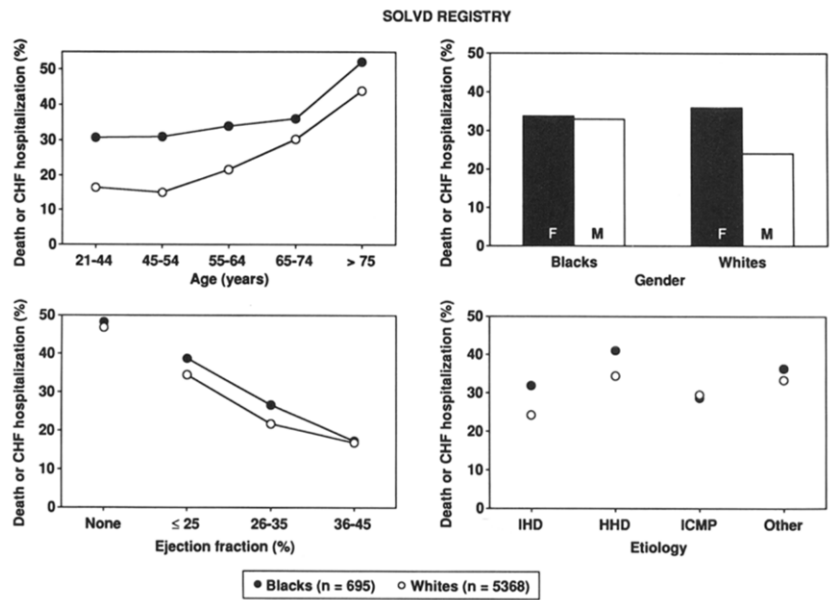
did not appear to be influenced by the origin of heart failure, but the incidence of death or hospital admissions for congestive heart failure was higher in patients with hypertensive and valvular heart disease than in those with ischemic heart disease in both racial groups (Fig. 3D).

**Relation between baseline characteristics and outcome (Table 2).** Factors related to 1-year mortality or hospital admission for congestive heart failure included, in order of importance, advancing age, decreasing ejection fraction, diabetes mellitus, chronic atrial fibrillation, female gender, etiology of heart failure (the odds of having an event increased from ischemic to hypertensive heart disease), cardi thoracic ratio (significant only for hospital admission for congestive heart failure), absence of prior myocardial infarction, history of hypertension, race (significant only for hospital admission and not for mortality) and history of angina (borderline significant only for risk of hospital admission). Age and



**Figure 2.** Age markedly influenced all follow-up events, including total mortality, mortality or hospital admissions related to congestive heart failure (CHF) and combined mortality and congestive heart failure-related hospital admissions at 1 year. SOLVD = Studies on Left Ventricular Dysfunction.

**Figure 3.** Influence of age, gender, ejection fraction and etiology of congestive heart failure (CHF) on death or congestive heart failure-related hospital admissions at 1 year. HHD = hypertensive heart disease; ICMP = idiopathic cardiomyopathy; IHD = ischemic heart disease; Other = other etiologies; other abbreviations as in Figure 1.



ejection fraction had the highest ranking order and the greatest odds ratios among these factors.

In the multivariate analysis, age, ejection fraction, female gender, diabetes mellitus and atrial fibrillation were independently related to mortality, hospital admission for congestive heart failure and mortality plus hospital admission for congestive heart failure at 1 year in patients with ischemic heart disease (roughly 70% of the SOLVD Registry population).

**Patterns of medication use in patients with congestive heart failure.** Diuretic agents were the drugs most often used: they were taken by 62% of patients. Digitalis, long-acting nitrates and antiplatelet agents were taken with a similar frequency (45%, 40% and 40% of patients, respectively). One-third of patients were taking calcium channel blockers

and slightly >30% were taking angiotensin-converting enzyme inhibitors. Overall, 27% were treated with antiarrhythmic agents and 16% with beta-adrenergic blocking agents. Anticoagulant therapy was given to 15% of patients.

As one might expect, patients with a lower ejection fraction and more congestive heart failure symptoms received more diuretic drugs, digitalis and angiotensin-converting enzyme inhibitors: among patients with an ejection fraction <20%, 90% were taking diuretic drugs, 65% digitalis and 55% an angiotensin-converting enzyme inhibitor; among patients with an ejection fraction of 36% to 45%, 45% were taking diuretic drugs, 30% digitalis and 20% an angiotensin-converting enzyme inhibitor. Similarly, as the number of symptoms of heart failure increased, the proportion of patients treated with diuretic drugs, digitalis and

**Table 2.** Log-Rank Tests of Differences in Survival Curves and Odds Ratio for Selected Variables in the SOLVD Registry

Variable	Death		CHF Hospital Admission		Death or CHF Hospital Admission	
	Odds Ratio	p Value	Odds Ratio	p Value	Odds Ratio	p Value
Age	1.48	< 0.0001	1.31	< 0.0001	1.44	< 0.0001
Gender (M/F)	0.70	< 0.0001	0.75	< 0.001	0.67	< 0.0001
Race (W/B)	0.91	NS	1.33	< 0.0001	1.09	< 0.0001
Ejection fraction	1.56	< 0.0001	1.64	< 0.0001	1.66	< 0.0001
Atrial fibrillation (Y/N)	1.81	< 0.0001	1.39	< 0.001	1.76	< 0.0001
Cardiothoracic ratio	—	NS	—	< 0.0001	—	< 0.0001
Diabetes mellitus (Y/N)	1.37	< 0.0001	1.78	< 0.0001	1.63	< 0.0001
Etiology of CHF (ischemic/others)	1.11	< 0.05	1.14	< 0.0001	1.14	< 0.0001
Myocardial infarction (Y/N)	0.79	< 0.05	0.73	< 0.0001	0.72	< 0.0001
Hypertension (Y/N)	1.14	NS	1.27	< 0.01	1.24	< 0.001
Angina (Y/N)	0.88	NS	0.85	< 0.05	0.83	< 0.05
Alcohol (Y/N)	0.86	< 0.05	0.94	NS	0.89	NS
Smoker (Y/N)	0.76	NS	0.97	NS	0.82	NS

For continuous variables, the following dichotomization was used for the calculation of odds ratios: age ≥65 vs. <65 years; ejection fraction <35% vs. ≥35%; cardiothoracic ratio ≥50 vs. <50. B = black; CHF = congestive heart failure; F = female; M = male; N = no; SOLVD = Studies in Left Ventricular Dysfunction; W = white; Y = yes.

angiotensin-converting enzyme inhibitors increased. The presence and severity of heart failure did not influence administration of nitrates and antiarrhythmic agents but showed an inverse relation to the use of beta-blockers and calcium channel blockers.

Fewer patients with ischemic heart disease used diuretic drugs, digitalis and angiotensin-converting enzyme inhibitors compared with patients with heart failure of other etiologies. Conversely, more patients with ischemic heart disease were treated with long-acting nitrates, beta-blockers and especially calcium channel blockers. Antiarrhythmic drug use had a similar frequency in all groups.

### Discussion

**Prognostic factors.** In the SOLVD Registry, the occurrence of left ventricular dysfunction or congestive heart failure, or both, increased steadily with age. The mean age of the patients was 62 years; 59% were  $\geq 60$  years of age, and age clearly influenced all follow-up events, particularly mortality and hospital admissions due to congestive heart failure. The Framingham Heart Study (4,5) showed that heart failure increases progressively with age, from a prevalence of  $\approx 1\%$  in those aged 50 to 59 years to a prevalence of  $\approx 10\%$  in persons 80 to 89 years. The incidence of new onset of heart failure also increased dramatically with advancing age. Heart failure is thus a growing problem in our population because age is increasing. However, it is not clear whether advancing age is a primary determinant of prognosis or whether it reflects greater impairment of left ventricular function because major risk factors of left ventricular dysfunction, such as hypertension, coronary artery disease and diabetes mellitus, are closely related to age.

In multivariate analysis, age, ejection fraction, female gender, diabetes mellitus and atrial fibrillation are independently related to mortality, and hospital admission or death related to congestive heart failure, at least in patients with ischemic heart disease, which is the preponderant etiology of congestive heart failure in whites. Thus, patients with these risk factors represent subgroups that require earlier detection and more aggressive treatment.

In The Framingham Heart Study (4,5), hypertension was the most frequent cause of congestive heart failure. In the SOLVD Registry, an average of 40% of patients had a history of arterial hypertension, but only 7% had cardiomyopathy secondary to hypertension alone. Coronary heart disease now represents the principal cause of congestive heart failure (70% of patients), perhaps because of better treatment of hypertension and the reduction of mortality from acute myocardial infarction and coronary artery disease (3), leading to an increased prevalence of impaired left ventricular function. This appears to be true for whites only. In blacks, coronary heart disease is involved in only one third of cases and hypertensive heart disease is found in another third. Heart failure or left ventricular dysfunction, or both, also occurs earlier in blacks than in

whites: at a mean age of 58 years in blacks versus 63 years in whites.

Our data also show that total mortality and deaths associated with progressive congestive heart failure are similar among blacks and whites, in contrast to data from the National Center for Health Statistics in the United States (3) between 1970 and 1985 that age-adjusted morbidity and mortality rates from heart failure are higher in blacks than in whites. It is possible that this shift between 1980 and now is the result of better hypertension control and a greater impact of therapy in blacks. For example, between 1970 and 1978, the mortality from heart failure decreased by  $\approx 16\%$  in blacks, whereas no such trend was seen in whites (3). However, in the SOLVD Registry, blacks still have an increased incidence of hospital admissions for heart failure: blacks were admitted to the hospital twice as frequently as whites. That may be due in part to the greater incidence of hypertensive heart disease in blacks, which was associated with a greater rate of hospital admission than for ischemic heart disease. However, if one compares only patients with hypertensive heart disease, blacks still have an increased incidence of hospital admission for heart failure. Another explanation may be the lower left ventricular ejection fraction that has been associated with higher rates of hospital admission.

An increase in all event rates was demonstrated at 1 year in white but not in black women. This included increased total mortality and heart failure-related mortality and hospital admission rates in comparison with men. The reasons for the higher morbidity and mortality rates in white women than in white men are unknown.

**Drug therapy.** Diuretic and digitalis therapy are the mainstay in heart failure treatment. Multidrug therapy is common and a substantial number of patients are maintained on drug therapy that is controversial in the presence of left ventricular dysfunction and heart failure (calcium channel blockers, antiarrhythmic agents and beta-blockers). Digitalis, which was very widely used, may also be questionable in the presence of symptomless ventricular dysfunction or in patients without atrial fibrillation. Only 30% of patients in the SOLVD Registry received an angiotensin-converting enzyme inhibitor. With the recognition that these drugs prevent heart failure and prolong survival (7,b), they will undoubtedly be used more frequently in these patients in the future.

**Conclusions.** The SOLVD Registry has identified several factors that are related to 1-year mortality or hospital admission for congestive heart failure—mainly age, ejection fraction, diabetes mellitus, atrial fibrillation and female gender. Because heart failure is an end stage of heart disease that ensues after the organism has exhausted all its compensatory mechanisms and because, once overtly manifest, remains an extremely lethal condition (9), early detection and more aggressive treatment will probably help to improve the prognosis of these patients.

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