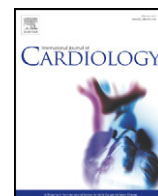


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## International Journal of Cardiology

journal homepage: [www.elsevier.com/locate/ijcard](http://www.elsevier.com/locate/ijcard)Health-related quality of life and anemia in hospitalized patients with heart failure<sup>☆</sup>I.H. Kraai<sup>a,\*</sup>, M.L.A. Luttik<sup>a</sup>, P. Johansson<sup>b</sup>, R.M. De Jong<sup>a</sup>, D.J. Van Veldhuisen<sup>a</sup>, H.L. Hillege<sup>a</sup>, T. Jaarsma<sup>c</sup><sup>a</sup> Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands<sup>b</sup> Department of Cardiology, University Hospital of Linköping, SE-581-85 Linköping, Sweden<sup>c</sup> Department of Social and Welfare Studies, Faculty of Health Sciences, Linköping University, Norrköping, Sweden

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## ABSTRACT

**Background:** Anemia is a serious and highly prevalent co-morbidity in chronic heart failure (HF) patients. Its influence on health-related quality of life (HR-QoL) has rarely been studied, and no data is available regarding the role it plays in hospitalized HF patients.

**Methods:** Baseline data from the COACH study (Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure) were used. HR-QoL was assessed by means of generic and disease-specific questionnaires. Analyses were performed using ANOVA and ANCOVA, with covariates of age, gender, eGFR, diabetes, and NYHA class.

**Results:** In total, 1013 hospitalized patients with a mean age of 71 (SD 11) years were included; 70% of these patients had no anemia (n = 712), 14% had mild anemia (n = 141), and 16% had moderate-to-severe anemia (n = 160). Independent associations were found between anemia and physical functioning (p = 0.019), anemia and role limitations due to physical functioning (p = 0.002), anemia and general health (p = 0.024), and anemia and global well-being (p = 0.003).

**Conclusion:** In addition to the burden of HF itself, anemia is an important factor which influences HR-QoL in hospitalized HF patients, and one that is most pronounced in the domain related to physical functioning and general health.

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## 1. Introduction

Relief of symptoms and improvement in health-related quality of life (HR-QoL) are recognized as important objectives in the treatment of heart failure (HF) in international HF guidelines [1]. However, despite the improvements in medical treatment resulting in prolonged survival and reduction of hospitalizations, HF patients still have an impaired HR-QoL [2]. HR-QoL in HF patients is seriously reduced compared to a normative population in the community [2], as well as compared to patients with other chronic diseases [3]. Health status measurements such as HR-QoL quantify the extent to which a patient is impaired by the disease [4]. A poor health status is a significant predictor of adverse prognosis in patients with chronic HF [5]; therefore, reduction of HF symptoms and improvement in HR-QoL should be an important treatment goal for clinicians and other health-care professionals. In clinical trials, there is also an increasing interest in measuring patient-reported outcomes such as HR-QoL, since this has recently been recommended by the US Food and Drug Administration [6].

Anemia is a serious co-morbidity in patients with chronic HF and is prevalent in more than one-third of these patients [7]. Anemia may cause a wide range of symptoms and impairments which correspond to the symptoms of HF such as dizziness, tachycardia, and dyspnea [1]. The severity of the symptoms depends on the degree of anemia, other co-morbidities, compensatory mechanisms, and the physiological status of the patient. Although the influence that anemia has on HF patients in terms of HR-QoL has rarely been studied, intervention trials to correct anemia have already used HR-QoL as an effect parameter [8–11]. To date, only one study has examined the direct relationship between HR-QoL and anemia in a population of 826 HF-stable outpatients with a mean age of 64 years [12]. To our knowledge, there are no data available regarding the role it plays in hospitalized HF patients. The aim of the present study is to further assess the relationship between HR-QoL and anemia in hospitalized HF patients. The following research questions will be addressed in this study: Is there an independent association between HR-QoL and anemia in hospitalized HF patients? Is this association present in specific aspects of HR-QoL?

## 2. Methods

## 2.1. Participants

Baseline data from the COACH study (Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure) were used for this study. The COACH

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study was a multicenter, randomized controlled trial designed to compare the effects of basic support and intensive support in HF patients, using a control group receiving usual care [13]. Details on the design of the COACH study have been published elsewhere [14]. In short, 1023 patients from seventeen hospitals in the Netherlands were included in the study from October 2002 to February 2005. Patients were included during admission to the hospital with symptoms of HF and NYHA II–IV. The HF diagnosis was made on the basis of a combination of typical signs and symptoms, for which hospitalization was considered necessary, including the need for intravenously administered medication. Other enrolment criteria were 18 years of age or older and having evidence of structural underlying heart disease. Patients with impaired left ventricular ejection fraction (LVEF) and those with preserved LVEF could also be included. Patients were excluded if they were unable to complete data collection forms, had undergone invasive intervention within the last 6 months or had one planned for the ensuing 3 months, or were in ongoing evaluation for heart transplantation. During hospitalization, patients were randomized to one of the following groups: basic support, intensive support, or control group. Our investigation conforms to the principles outlined in the Declaration of Helsinki. The medical ethics committee approved the study protocol, and all the enrolled patients provided their written informed consent. The authors of this manuscript have certified that they are in compliance with the Principles of Ethical Publishing in the *International Journal of Cardiology* [15].

## 2.2. Measurements

### 2.2.1. HR-QoL

HR-QoL was assessed using three instruments: two generic (RAND 36-item Health Survey 1.0 and Cantril's Ladder of Life) and one disease-specific instrument, the Minnesota Living with Heart Failure Questionnaire (MLHFQ). In general, disease-specific questionnaires are used for patients with a specific health condition, while generic instruments are used in patients with various health conditions [16,17]. Generic instruments are not affected in terms of their validity, reliability, and responsiveness if a patient has co-morbidities which manifest similar effects as a primary disease [18]. Generic HR-QoL can be influenced by nonmedical phenomena such as employment and family relationships [16]. Therefore we used a global QoL instrument (Cantril's Ladder of Life) in addition to a generic HR-QoL instrument (RAND 36-item Health Survey 1.0) [19].

The RAND 36-item Health Survey 1.0 consists of eight domains: physical functioning, social functioning, role limitations (physical problems), role limitations (emotional problems), mental health, vitality, bodily pain, and general health perception. For each domain, scores range from 0 (poorest health) to 100 (best health). Higher scores reflect better HR-QoL. The RAND 36-item Health Survey 1.0 includes the same items as those in the SF-36; however, the scoring algorithm is different compared to the SF-36. Therefore the RAND 36-item Health Survey 1.0 does not have component summary scores [20]. Moreover, unlike the SF-36, the RAND 36-item Health Survey 1.0 does not have norm scores available for comparison. It has, however, previously been used in a

Dutch population and was found to have good psychometric properties [21,22]. Generally speaking, a difference of 5 points on the domain scores is considered to be clinically relevant. The Cantril's Ladder of Life assesses a patient's global well-being on a scale between zero, indicating the poorest, and 10, indicating the best well-being, and has been used in HF research before [23,24]. The MLHFQ is a widely used disease-specific questionnaire in HF research [19,25] that has good psychometric properties [25]. The MLHFQ has a total score ranging between zero and a maximum of 105, and consists of two domains, a physical component and an emotional component with, respectively, 40 and 25 as maximum possible scores. Lower scores on the MLHFQ reflect better HR-QoL [26].

### 2.2.2. Clinical measurements

Anemia was defined for adult men and women according to the definition of the World Health Organization (WHO) as a hemoglobin (Hb) level being, either below 8.0 mmol/L or below 7.5 mmol/L, respectively [27]. To examine the association between the severity of the anemia and HR-QoL, subgroups of anemic patients were created. To create suitable groups for comparison in the present study, we combined data from patients with severe anemia and moderate anemia into one group, denoted as the moderate-to-severe anemia group. Mild anemia was defined for male and female patients as an Hb level below 8.0 mmol/L and 7.5 mmol/L, respectively. Moderate-to-severe anemia was defined as an Hb level lower than 7.5 mmol/L in male patients, and an Hb level lower than 6.8 mmol/L in female patients [28].

Demographic and clinical data were collected from patient interviews and from patients' medical charts at baseline, except for LVEF, which was measured close to admission and at a maximum of one year before or after.

## 2.3. Statistical analysis

Patient characteristics and clinical and HR-QoL outcomes were described using means ( $\pm$ SD) for continuous variables and using percentages and numbers for categorical variables. Continuous variables were tested using one-way analysis of variance (ANOVA), and categorical variables using the Chi square test. Welch F tests were performed if the homogeneity of variance was violated according to Levine's test. Analysis of covariance (ANCOVA) was used to assess an independent association between anemia and HR-QoL, along with a correction for variables known to influence Hb levels and HR-QoL such as age [29], gender [27,30], diabetes [2], eGFR [31], and NYHA classification [32]. Severity of anemia (no anemia, mild anemia, and moderate-to-severe anemia) was the factor variable, while HR-QoL was the dependent variable. Comparisons between the different anemia groups were performed using post hoc analyses with correction for multiple comparisons using Bonferroni. A regression analysis was performed to determine the contribution of anemia to the physical functioning domains. Statistical analyses were performed using SPSS version 18.0.3 for Windows.

**Table 1**  
Characteristics of the study population.

Characteristics	All patients (n = 1013)	Non-anemic (n = 712)	Mild-anemic (n = 141)	Moderate-to-severe anemic (n = 160)	p Value
<i>Demographics</i>					
Age yrs	71 ( $\pm$ 11)	70 ( $\pm$ 11)	72 ( $\pm$ 11)	73 ( $\pm$ 11)	0.001
Male % (N)	62% (632)	62% (439)	56% (79)	71% (114)	0.019
<i>Clinical variables</i>					
NYHA % (N)					
II	51% (506)	53% (369)	46% (65)	46% (72)	
III	46% (458)	44% (312)	51% (72)	48% (74)	0.088
IV	3% (34)	3% (21)	2% (3)	6% (10)	
LVEF	34 ( $\pm$ 14)	33 ( $\pm$ 14)	36 ( $\pm$ 15)	36 ( $\pm$ 15)	0.011
eGFR (mL/min/1.73 m <sup>2</sup> )	56 ( $\pm$ 20)	59 ( $\pm$ 19)	50 ( $\pm$ 21)	48 ( $\pm$ 23)	<0.001
Hb (mmol/L)	8.3 ( $\pm$ 1.1)	8.9 ( $\pm$ 0.8)	7.5 ( $\pm$ 0.3)	6.6 ( $\pm$ 0.5)	<0.001
BNP (ng/L)	680 ( $\pm$ 729)	623 ( $\pm$ 675)	734 ( $\pm$ 796)	887 ( $\pm$ 856)	0.001
<i>Discharge medication % (N)</i>					
ACE/ARB	83% (838)	87% (617)	76% (107)	71% (114)	<0.001
$\beta$ -Blockers	66% (670)	67% (479)	68% (96)	59% (95)	0.141
Diuretics	96% (970)	96% (682)	97% (137)	94% (151)	0.487
<i>Medical history % (N)</i>					
Diabetes	28% (285)	25% (175)	31% (44)	41% (66)	<0.001
COPD	26% (267)	25% (176)	29% (41)	31% (50)	0.174
Stroke	10% (105)	8% (60)	11% (15)	19% (30)	0.001
Hypertension	43% (436)	42% (299)	55% (78)	37% (59)	0.003

Note: Characteristics described as means ( $\pm$ SD); p: between anemic groups; Hb: hemoglobin; Non-anemic female: Hb  $\geq$  7.5 mmol/L; Non-anemic male: Hb  $\geq$  8.0 mmol/L; Mild anemic female: 6.8 mmol/L  $\leq$  Hb < 7.5 mmol/L; Mild anemic male: 7.5 mmol/L  $\leq$  Hb < 8.0 mmol/L; Moderate-to-severe anemic female: Hb < 6.8 mmol/L; Moderate-to-severe anemic male: Hb < 7.5 mmol/L; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; ACE/ARB: angiotensin-converting enzyme/angiotensin II inhibitor; COPD: chronic obstructive pulmonary disease.

### 3. Results

#### 3.1. Study population

Patients were included in the current study if baseline levels of Hb were available; as a result of this, 1013 patients were included. Patients had a mean age of 71 ( $\pm 11$ ) years, while 62% of the patients were male. Most patients were classified as NYHA III–IV upon admission; while on discharge most were NYHA class II (51%) or III (46%). Co-morbidities were present: 28% of the patients had diabetes, 26% had chronic obstructive pulmonary disease (COPD), 10% have had a stroke and 43% had hypertension (Table 1). On the basis of the WHO definition, 30% were anemic, 14% had mild anemia, and 16% had moderate-to-severe anemia. Baseline characteristics differed significantly across the anemic groups. The severity of anemia was associated with higher age ( $p=0.001$ ), higher LVEF ( $p=0.011$ ), lower eGFR levels ( $p<0.001$ ), male gender ( $p=0.019$ ), the use of angiotensin-converting enzyme or angiotensin II inhibitor ( $p<0.001$ ), higher prevalence of the co-morbidities of diabetes ( $p<0.001$ ), and stroke ( $p=0.001$ ). A non-significant association was found for NYHA classification and severity of anemia (Table 1).

#### 3.2. Association between HR-QoL and anemia

For the RAND 36-item Health Survey 1.0, univariate analyses (Table 2) indicated significant associations between anemia and the five domains of the survey: physical functioning ( $p<0.001$ ), role limitation physical ( $p<0.001$ ), role limitation emotional ( $p=0.028$ ), bodily pain ( $p=0.038$ ), and general health ( $p=0.002$ ). Three domains remained significant in the multivariate analyses: physical functioning ( $p=0.019$ ), role limitation physical ( $p=0.002$ ), and general health ( $p=0.024$ ). In terms of the contribution of anemia to HR-QoL for the domains physical functioning and role limitation physical, anemia showed for physical functioning the lowest standardized beta coefficient ( $-0.076$ ) when compared to NYHA classification ( $-0.29$ ), gender ( $-0.11$ ), renal function (0.10), age ( $-0.09$ ) and the presence of diabetes ( $-0.09$ ). For role limitation physical these figures were less attenuated; anemia ( $-0.11$ ), NYHA classification ( $-0.17$ ), gender ( $-0.03$ ), renal function (0.001), age (0.04) and the presence of diabetes ( $-0.04$ ). Post hoc analyses (Fig. 1) indicated an independent significant association between non-anemic versus mild anemic patients ( $p=0.019$ ), and between non-anemic versus moderate-to-severe anemic patients ( $p=0.026$ ) in the domain of role limitation

physical. For the domain of general health, significant associations were found between non-anemic versus moderate-to-severe anemic patients ( $p=0.040$ ). A non-significant association between non-anemic versus mild anemic patients for the domain of physical functioning ( $p=0.059$ ) was found.

Using Cantril's Ladder of Life, a significant univariate association was found between anemia and global well-being ( $p=0.003$ ). This association remained significant in the multivariate analyses ( $p=0.003$ ), specifically between non-anemic versus moderate-to-severe anemic patients ( $p=0.002$ ) (Fig. 2).

For MLHFQ, neither the total score, nor the physical and emotional components were associated with anemia.

### 4. Discussion

This is the first study to report on a significant independent association between HR-QoL and anemia in patients hospitalized for HF. The current study provides further support for the relationship between HR-QoL and anemia in HF patients. Although the association between HR-QoL and anemia was reported in other diseases [33,34], in HF patients only one study reported on this direct relationship in a stable outpatient population with a mean age of 64 years, independent of functional class, ejection fraction, gender, and age [12]. The present study adds to this by showing that this independent association is also present in hospitalized HF patients. In these patients, hospitalized because of severe HF symptoms which often result in a severely impaired HR-QoL [2], we still found an independent association between anemia and HR-QoL.

The present study is also the first to use both generic and disease-specific questionnaires to assess the association between HR-QoL and anemia. In using those questionnaires, we considered HR-QoL in patients in terms of its specific relationship to their HF and in terms of a general, broader concept, unrelated to any specific disease. Independent associations were only found between generic HR-QoL and anemia, which would indicate that HF patients with anemia have additional difficulties on top of their HF symptoms; these difficulties cannot be detected by disease-specific questionnaires alone. Another explanation could be that the MLHFQ was not sensitive enough in this population because of the small sample sizes in the anemia groups [35]. Moreover, the MLHFQ is not specifically designed for use in acute HF, though it is very frequently used in HF trials to study patients with chronic HF. The most pronounced associations between HR-QoL and anemia were

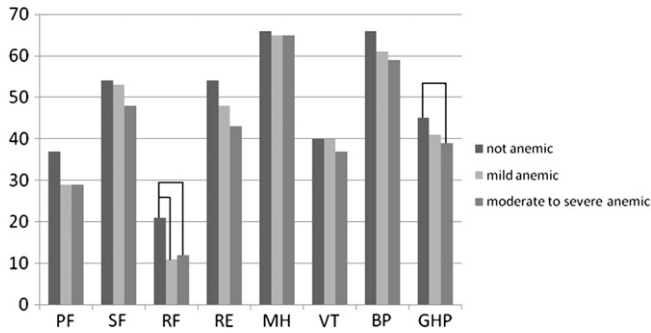
**Table 2**  
Univariate and multivariate analyses of the association between HR-QoL and anemic and non-anemic patients.

Characteristics	Non-anemic (n = 712)	Mild anemic (n = 141)	Moderate-to-severe anemic (n = 160)	*p	**p
<i>RAND 36-item Health Survey</i>					
Physical functioning	37 ( $\pm 27$ )	29 ( $\pm 23$ )	29 ( $\pm 23$ )	<0.001	0.019
Social functioning	54 ( $\pm 31$ )	53 ( $\pm 31$ )	48 ( $\pm 30$ )	0.056	
Role limitation physical	21 ( $\pm 35$ )	11 ( $\pm 27$ )	12 ( $\pm 28$ )	<0.001	0.002
Role limitation emotional	54 ( $\pm 45$ )	48 ( $\pm 45$ )	43 ( $\pm 45$ )	0.028	0.146
Mental health	66 ( $\pm 23$ )	65 ( $\pm 20$ )	65 ( $\pm 24$ )	0.949	
Vitality	40 ( $\pm 23$ )	40 ( $\pm 21$ )	37 ( $\pm 22$ )	0.319	
Bodily pain	66 ( $\pm 33$ )	61 ( $\pm 31$ )	59 ( $\pm 34$ )	0.038	0.142
General health	45 ( $\pm 19$ )	41 ( $\pm 17$ )	39 ( $\pm 18$ )	0.002	0.024
<i>MLHFQ</i>					
Total	43 ( $\pm 22$ )	46 ( $\pm 20$ )	45 ( $\pm 21$ )	0.104	
Physical component	22 ( $\pm 10$ )	24 ( $\pm 9$ )	24 ( $\pm 9$ )	0.138	
Emotional component	7 ( $\pm 6$ )	7 ( $\pm 6$ )	7 ( $\pm 6$ )	0.989	
<i>Ladder of Life</i>					
	6.4 ( $\pm 1.9$ )	6.2 ( $\pm 1.8$ )	5.8 ( $\pm 2.0$ )	0.003	0.003

Note: Characteristics described as mean ( $\pm$ SD); Hb: hemoglobin; Non-anemic female: Hb  $\geq 7.5$  mmol/L; Non-anemic male: Hb  $\geq 8.0$  mmol/L; Mild anemic female: 6.8 mmol/L  $\leq$  Hb  $< 7.5$  mmol/L; Mild anemic male: 7.5 mmol/L  $\leq$  Hb  $< 8.0$  mmol/L; Moderate-to-severe anemic female: Hb  $< 6.8$  mmol/L; Moderate-to-severe anemic male: Hb  $< 7.5$  mmol/L.

\* p univariate association between HR-QoL and anemia severity.

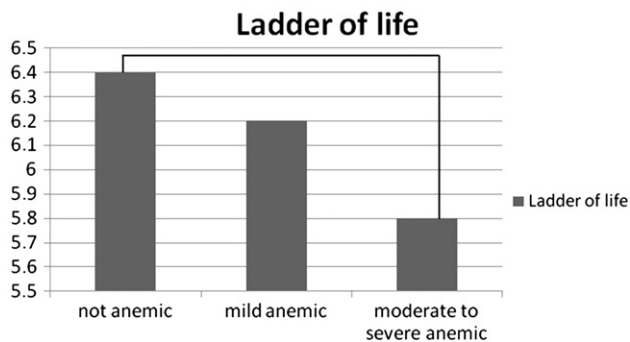
\*\* p multivariate association between HR-QoL and anemia severity with covariates age, gender, NYHA classification, diabetes, and eGFR level.



**Fig. 1.** Post hoc analyses of health-related quality of life measured using the RAND 36-item Health Survey in heart failure patients without anemia, and in those with mild and moderate-to-severe anemia. Lines indicate a significant difference ( $p < 0.05$ ) between the group with correction for age, gender, NYHA classification, diabetes, and eGFR level. (PF = physical functioning; SF = social functioning; RF = role limitations due to physical functioning; RE = role limitations due to emotional functioning; MH = mental health; VT = vitality; BP = bodily pain, GHP = general health perception).

found in the domains of physical functioning and limitations due to physical functioning. Both domains reflect limitations in terms of performing daily activities, such as climbing stairs, bathing or dressing, or carrying groceries, which are due to physical health problems [21,22]. These daily activities are particularly important for older adults in maintaining or increasing their quality of life [36]. Moreover, physical activity in terms of exercise and the performance of daily activities is recommended for HF patients [1,37]; this is an established life-style recommendation [37,38] for improving HR-QoL [37]. Furthermore, independent associations were found for general health and global well-being, which reflects the fact that HF patients with anemia have a lower opinion of their health than do HF patients without anemia. This independent association remains if we correct for other comorbidities such as stroke and hypertension. This is in accord with the literature: HR-QoL declines with any increasing burden of comorbidity in cardiac patients [2,39]. In general, older people with anemia experience a decline in functional status and physical strength as compared to non-anemic elderly [40]. In contrast to the study by Thein and colleagues, in which anemia was associated with depressive symptoms [40], we found no relationship between anemia and the mental aspects of HR-QoL. We also did not find any significant association between anemia and the HR-QoL domain of vitality, which reflects feelings of energy and tiredness [21,22]. Tiredness and lack of energy are symptoms of both anemia and HF, which may explain why no significant association was found for this domain.

In addition to the substantial risk of adverse events and death in anemic HF patients [41], these patients also seem at risk of a decline in their HR-QoL. Although our study had a cross-sectional design



**Fig. 2.** Post hoc analyses of health-related quality of life measured using Cantril's Ladder of Life in heart failure patients without anemia, and in those with mild, moderate, and severe anemia. Line indicates a significant difference ( $p < 0.05$ ) between the group with correction for age, gender, NYHA classification, diabetes, and eGFR level.

which precludes conclusions as to causality, our findings suggest that specific treatment for anemia should be considered because effective treatment may improve HR-QoL in these HF patients. Although the best treatment for anemia in HF patients is still open to debate [42], the first randomized clinical trials suggest that treating anemia improves exercise tolerance, reduces symptoms, and improves HR-QoL [11,41].

One limitation of our study is that we performed post hoc analyses that assessed the association between HR-QoL and anemia using baseline data from the COACH study; this study was originally designed to determine the effectiveness of two interventions (basic support versus intensive support) as compared to "care as usual" in HF patients with the following primary endpoint: the composite of HF hospitalization or death from any cause and the number of unfavorable days. Another limitation is that data from clinical trials are known to present difficulties in terms of generalizability. However, we believe that this is a sample that reasonably represents the clinical sample of HF patients in general [2] in view of the mean age of 71 years and the distribution of male patients in the study population.

## 5. Conclusion

The most important finding of this study is that HR-QoL has been shown to be independently associated with anemia in hospitalized HF patients in terms of global well-being, general health, physical functioning, and limitations due to physical functioning. HR-QoL was found to be particularly lower in patients with severe-to-moderate anemia. The association between HR-QoL and (severe) anemia in HF patients is remarkable, and might serve as a possible mechanism for improving HR-QoL in anemic HF patients. More research into this association is needed.

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