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LETTER TO THE EDITOR

Determinants of improvement in six-minute walk distance from admission to discharge in acute systolic heart failure: Analysis from the ESCAPE trial

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The 6-minute walk test (6MWT) is a simple, feasible test reflective of daily life activity in patients with chronic heart failure (HF) and has been used as a measure of functional status [1]. The 6MWT is also valuable to assess response to therapeutic intervention in patients with moderate to severe HF [2]. Prior studies demonstrated that the change in the 6-minute walk distance (6MWD) from admission-to-discharge was an independent predictor of survival [3] and worsening HF requiring rehospitalizaiton [4]. The prognostic effect of 6MWT in HF was the basis for its use as a primary endpoint in clinical trials. The aim of this study is to identify determinants of improvement in 6MWD from admission to discharge, and to determine whether the degree of decongesting patients with acute systolic HF with diuretics was a predictor of improvement in walking distance.

The ESCAPE trial randomized 433 patients with acute HF with ejection fraction (EF) ≤ 30% to either clinical assessment alone versus clinical assessment guided by pulmonary artery catheterization (PAC). The study showed that the PAC did not improve or worsen HF outcomes [5, 6]. 6MWD was measured in feet, and assessed at multiple time points including admission and discharge. The degree of decongestion was examined through clinical, laboratory, echocardiographic and PAC variables (Table 1). Continuous variables were expressed as median and interquartile range, and were reported as counts and percentages and compared using Mann-Whitney test and categorical variables were compared using χ^2. Longitudinal comparison of the 6MWD on admission and discharge was performed using paired sample T-test. The association between the improvement in 6MWD and a selection of variables was examined using Spearman's correlation. A multivariable regression model was performed to identify independent predictors of improvement in 6MWD.

Two hundred twenty two patients (mean age 55 years, 78% men) had recorded measurements for 6MWD on admission and discharge. After 7.9 ± 5.6 days, the distance walked increased from 601 ± 375 feet to 806 ± 390 feet ($p < 0.001$). The average improvement in 6MWD from admission-to-discharge was 205 feet (median: 160 feet; 49 m). 110 patients had an improvement in 6MWD > 160 feet and 112 experienced an improvement in 6MWD ≤ 160 feet. Compared with patients with improvement in 6MWD ≤ 160 feet, those with improvement in 6MWD > 160 feet were younger ($p = 0.009$), with a lower 6MWD on admission ($p < 0.001$), lower frequency of atrial fibrillation ($p = 0.036$), lower frequency of aortic stenosis ($p = 0.007$) and a trend towards lower frequency of angina pectoris ($p = 0.088$). No difference was found between the groups with regard to the degree of decongestion or improvement in cardiac output from admission-to-discharge (Table 1). There were also no significant differences between the groups in baseline left and right ventricular EF.

Correlation analysis in the whole cohort (222 cases) showed that the improvement in 6MWD was inversely correlated with patients' age ($n = 222$, $r = –0.179$, $p = 0.008$) and baseline 6MWD

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Table 1. Comparison of clinical, echocardiographic and hemodynamic characteristics of ESCAPE trial patients according to whether improvement in 6-minute walk distance (6MWD) from admission-to--discharge was > or ≤ 160 feet (49 m).

	6MWD improvement > 160 feet (n = 110)	6MWD improvement ≤ 160 feet (n = 112)	P
Baseline demographics			
Age [years], median (IQR]	53.5 (42, 61.5)	58 (48, 68)	0.009
Male sex	79.1% (87/110)	76.8% (86/112)	0.679
White race	50.9% (56/110)	65.2% (73/112)	0.031
Black race	29.1% (32/110)	19.6% (22/112)	0.101
Baseline 6MWD [feet], median (IQR)	487 (245, 681)	706 (369, 993)	< 0.001
Baseline 6MWD [m], median (IQR)	148 (75, 208)	215 (112, 303)	< 0.001
Comorbidities			
Ischemic etiology of HF	41.8% (46/110)	52.3% (58/111)	0.120
Atrial fibrillation	20% (22/110)	32.4% (36/111)	0.036
Angina pectoris	25.5% (28/110)	36% (40/111)	0.088
Coronary artery bypass graft	26.4% (29/110)	30.6% (34/111)	0.482
Chronic obstructive pulmonary disease	15.5% (17/110)	16.2% (18/111)	0.877
Mitral regurge	9.1% (10/110)	12.6% (14/111)	0.400
Aortic stenosis	0% (0/110)	6.3% (7/111)	0.007
Stroke	8.2% (9/110)	8.1% (9/111)	0.984
Malignancy	3.6% (4/110)	7.2% (8/111)	0.241
Depression	19.1% (21/110)	13.5% (15/111)	0.262
Clinical variables of decongestion			
Reduction in 6MWD [feet], median (IQR)	356 (254, 574)	35 (–80, 105)	–
Weight loss [kg], median (IQR)	2.5 (0.91, 4.99)	2.5 (0.9, 5.54)	0.633
Resolution of JVD on discharge	62% (62/100)	64.7% (66/102)	0.204
Resolution of orthopnea on discharge	57.1% (60/105)	49.5% (49/99)	0.274
Resolution of HJR on discharge	70.1% (61/87)	57.6% (57/99)	0.076
Laboratory variables of decongestion			
BNP reduction [pg/mL], median (IQR)	63 (–51, 327)	163 (27, 520)	0.058
PAC variables of decongestion			
RAP change [mm Hg], median (IQR)	–3 (–8, 0)	–2 (–5.5, 2)	0.408
PCWP change [mm Hg], median (IQR)	–7 (–15, –3)	–6 (–13, –1)	0.347
PASP change [mm Hg], median (IQR)	–11.5 (–21.5, 0)	–9 (–18.8, –2.25)	0.792
PADP change [mm Hg], median (IQR)	–7 (–13, –1.75)	–5.5 (–13, 0)	0.665
CI change [L/min/m^2], median (IQR)	0.4 (–0.08, 0.7)	0.38 (–0.09, 0.79)	0.962
CO change [L/min], median (IQR)	0.7(–0.2, 1.4)	0.8 (–0.19, 1.28)	0.964
Echocardiographic variables of decongestion			
IVC inspiration change [cm], median (IQR)	–0.41 (–0.79, 0.12)	–0.21 (–0.77, 0.19)	0.366
IVC expiration change [cm], median (IQR)	–0.4 (–0.88, 0.09)	–0.18 (–0.45, 0.21)	0.126
IVC collapsibility index change [cm], median (IQR)	3.91 (–3.98, 19.86)	1.85 (–8.87, 16.54)	0.574
Left ventricular EF [%], median (IQR)*	19.4 (11, 26.7)	17.6 (12.6, 23.3)	0.777
Right ventricular EF [%], median (IQR)*	22 (12.7, 30.8)	24.3 (18.1, 29.1)	0.823

These echocardiographic variables were recorded at baseline; HF — heart failure; JVD — jugular venous distension; HJR — hepatojugular reflux, BNP — B-type natriuretic peptide; PAC — pulmonary artery catherization; RAP — right atrial pressure; PCWP — pulmonary capillary wedge pressure; PASP — pulmonary artery systolic pressure; PADP — pulmonary artery diastolic pressure; CI — cardiac index; CO — cardiac output; IVC — inferior vena cava; EF — ejection fraction; IQR — interquartile range

(n = 222, r = –0.358, p < 0.001). Nonetheless, no association was found between admission-to-discharge improvement in 6MWD and admission-to-discharge weight loss (p = 0.701), admission-to-discharge reduction in right atrial pressure (p = 0.502), admission-to-discharge reduction in pulmonary capillary wedge pressure (p = 0.370), admission-to-discharge reduction in inferior vena cava diameter during inspiration (p = 0.807) and expiration (p = 0.386), and admission-to-discharge reduction in B-type natriuretic peptide (BNP; p = 0.081) (Fig. 1). Multivariable lin-

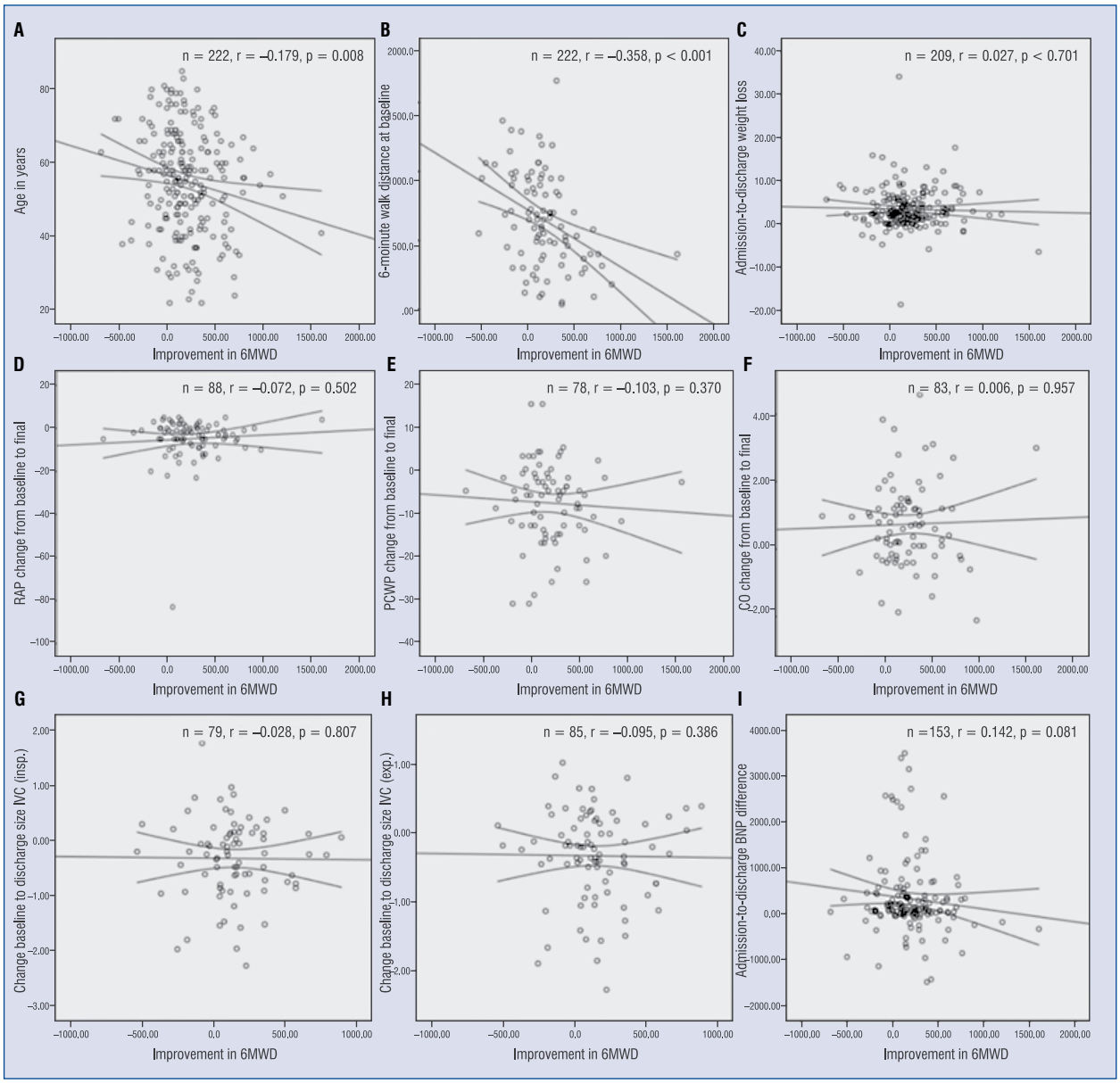

Figure 1. **A–I**. Scatter plots illustrating the association between various variables and improvement in 6-minute walk distance (6MWD) from admission to discharge in patients with acute heart failure enrolled in the ESCAPE trial; BNP — B-type natriretic peptide; CO — cardiac output; IVC — inferior vena cava; PCWP — pulmonary capillary wedge pressure; RAP — right atrial pressure.

ear regression analysis revealed that patients age (standardized β = –0.239, p = 0.022) and 6MWD on admission (standardized β = –0.529, p < 0.001) were independent predictors of improvement in 6MWD after adjusting for EF (standardized β = 0.016, p = 0.869), body mass index (standardized β = 0.146, p = 0.150) and reduction in BNP from admission-to-discharge (standardized β = 0.061, p = 0.529).

It was shown in this analysis that younger age and lower 6MWD on admission determined the improvement in walking distance from admission-to-discharge in patients with acute HF and EF ≤ 30%. These results remained unaltered on multivariate analysis. These finding are in-line with prior work by Passantino et al. [3] who found that age and 6MWD at baseline were inversely related to the increase in distance walked. We found no association between the degree of decongestion and the improvement in walking distance from admission to discharge. The degree of decongestion was thoroughly evaluated in our study through various clinical, laboratory, echocardiographic, and central hemodynamic variables of decongestion via the PAC. The present

findings suggest that diuresis is not the main determinant for the improvement in the functional status of HF patients. Prior studies show that the 6MWD was sensitive to short-term changes in drug therapy [7]; for example, angiotensin converting enzyme inhibitors and beta-blockers were found to significantly improve submaximal exercise tolerance, as assessed by the 6MWD [8–10]. Unfortunately the lack of sufficient data on medication in the limited access dataset, prevented the assessment of the effect of various medications on the improvement in 6MWD.

There are several hypotheses to explain the lack of association between decongestion and improvement in walking distance. For example, a patient with predominantly left-sided failure will initially have symptoms of pulmonary congestion, but after small volume diuresis, symptoms will improve: in this scenario, one would expect a significant improvement in 6MWD despite only modest diuresis. Another scenario is a patient with hypertensive pulmonary edema who may experience relief of dyspnea with intravenous nitroglycerin causing venodilation without change in his volume status. Also, the functional capacity of HF patients is related not only to central "i.e. cardiac" factors, but also to "peripheral factor" like endothelial dysfunction, muscle performance, ventilatory inefficiency, which is less sensitive to improvements in the hemodynamic profile. Furthermore, the intensive diuretic therapy could lead to electrolytes abnormalities causing paradoxical worsening of fatigue and functional capacity. More importantly, the observation that patients with > 160 feet (49 m) improvement in walking distance had lower admission 6MWD best exemplifies that the phenomenon of "regression to the mean" — which describes the tendency of an extreme measurement on a first occasion to become less extreme when checked again — may have been responsible for masking the effect of decongestion on improvement in 6MWD. In this study, it was easier for a patient to have a larger improvement in 6MWD if the initial walking distance was too low. This statistical phenomenon happens in studies when repeated measurements are made for the same patient. Regression to the mean is concerning if the examined variable exhibits significant within-subject variability on repeated measurements and this typically occurs if there is a high threshold for trial enrollment, making the entry measurements away from the patients' true mean. This represents a limitation to our study and therefore our results have to be interpreted with caution. Futher studies are needed to confirm our findings.

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