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RESEARCH LETTER

Polypill Eligibility for Patients with Heart Failure With Reduced Ejection Fraction in South India: A Secondary Analysis of a Prospective, Interrupted Time Series Study

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The vanguard heart failure (HF) registry in India demonstrated significantly lower 5-year mortality rates for patients with HF with reduced ejection fraction (HFrEF) discharged on guideline-directed medical therapy (GDMT), revealing an important target for intervention to improve clinical outcomes.[1] Hospital-based quality improvement initiatives to increase rates of GDMT at hospital discharge have had limited effect, suggesting additional strategies are needed to improve GDMT rates in patients with HFrEF.[2] Polypills for HFrEF have been proposed as an implementation strategy to simplify the current treatment paradigm for undertreated patients with HFrEF.[3] However, the potential effect of HFrEF polypills on increasing GDMT rates in target populations is unknown. The objective of this secondary analysis of a prospective, interrupted times series study is to describe eligibility for a potential HFrEF polypill in the context of GDMT prescription rates for patients with HFrEF who were discharged from 8 hospitals in South India.

The HF QUIK (Heart Failure Quality Improvement in Kerala) study was a prospective, interrupted time series study using longitudinal data from February 2018 to August 2018 that evaluated the effect of a quality improvement intervention on process of care measures and clinical outcomes in patients hospitalized with acute HF in 8 hospitals in South India.[4] Patients were eligible for inclusion if they were (1) adults aged ≥18 years, and (2) met at least 2 criteria for diagnosis of HF as defined by the European Society of Cardiology (clinical symptoms and signs of HF, natriuretic peptide elevation, or echocardiographic evidence of left ventricular systolic or diastolic dysfunction). The HF QUIK quality improvement intervention consisted of checklists, audit and feedback reports with site-specific performance measures, and patient education materials. The control period consisted of usual care according to local hospital practice. Participants were allocated to the control (February 2018 to May 2018) or intervention period (May 2018 to August 2018) based on hospital admission date. The study protocol was reviewed by and received ethics board approval from Duke University (Durham, NC), Centre for Chronic Disease Control (New Delhi, Delhi, India), Cardiological Society of India-Kerala Chapter (Kochi, Kerala, India), and Indian Health Ministry Screening Committee (New Delhi, Delhi, India) in November 2017. Because data were used at the local hospitals for the purpose of quality improvement, sites were granted a waiver of informed consent under the Common Rule. The data

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that support the findings of this study are available from the corresponding author upon reasonable request.

Participants with HFrEF with left ventricular ejection fraction <40% were included in this secondary analysis. The primary outcome was prescription of GDMT defined as an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or angiotensin receptor neprilysin inhibitor, along with a beta blocker and aldosterone antagonist, measured separately and as a combined outcome. Additional outcomes included prescription of loop and thiazide diuretic. Participants were eligible for a HFrEF polypill containing GDMT including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or angiotensin receptor neprilysin inhibitor, beta blocker, and aldosterone antagonist at hospital discharge if left ventricular ejection fraction <40%, heart rate ≥50 beats/min, serum creatinine ≤2.5 mg/dL in men and ≤2 mg/dL in women, and serum potassium <5 mEq/L. Creatinine thresholds were based on guideline-recommended thresholds for aldosterone antagonists. Categorical variables were reported as counts with percentages, and we performed a complete case analysis due to low rate of missing data. The difference in proportions between medication at admission and discharge for control and intervention periods was calculated using chi-square test. We used R software (version 4.0.3, R Foundation, Vienna, Austria) for statistical analyses.

We included 937 participants with HFrEF (n=494 control period, n=443 intervention period). The Table illustrates prescription of medications for HF at admission (reflecting medications participants were on before admission) and at hospital discharge by control and intervention periods. Prescription rates of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or angiotensin receptor neprilysin inhibitor, beta blocker, and aldosterone antagonists were low on hospital admission and increased at hospital discharge. The rate of loop diuretic prescription increased at discharge. The prescription of GDMT increased from 5.5% to 28.8% in the control period and from 4.5% to 42.3% in the intervention period. More than 80% of participants were eligible for a HFrEF polypill at hospital discharge during both control (n/N=364/494) and intervention (n/N=336/443) periods, with similar rates among female and male participants.

In the HF QUIK study population, more than 80% of patients were eligible for a HFrEF polypill at discharge. Although the HF QUIK quality improvement intervention increased rates of GDMT at hospital

Table. Medication Prescription and HFrEF Polypill Eligibility of HF QUIK Participants by Control and Intervention Periods

	Control period* N=494			Intervention period* N=443		
	Admission* N=494	Discharge* N=441	*P* value	Admission* N=443	Discharge* N=404	*P* value
Medication prescription						
ACE-I or ARB or ARNi	123 (24.9%)	208 (47.2%)	<0.01	104 (23.5%)	211 (52.2%)	<0.01
Beta-blocker	152 (30.8%)	333 (75.5%)	<0.01	159 (35.9%)	332 (82.2%)	<0.01
Aldosterone antagonist	94 (19.0%)	286 (64.9%)	<0.01	61 (13.8%)	305 (75.5%)	<0.01
Loop diuretic	197 (39.9%)	409 (92.7%)	<0.01	177 (40.0%)	396 (98.0%)	<0.01
Thiazide diuretic	8 (1.6%)	9 (2.0%)	0.63	6 (1.4%)	8 (2.0%)	0.48
GDMT†	27 (5.5%)	127 (28.8%)	<0.01	20 (4.5%)	171 (42.3%)	<0.01
HFrEF polypill eligibility at discharge‡						
	Control period: discharge N=441 (F: 164, M: 277)			Intervention period: discharge N=404 (F: 127, M: 277)		
Total§	364 (82.5%)			336 (83.2%)		0.81#
Female‖	133 (81.1%)		0.54**	100 (78.7%)		0.11**
Male‖	231 (83.4%)			236 (85.2%)		

ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; GMDT, guideline-directed medical therapy; and HFrEF, heart failure with reduced ejection fraction.

*Among participants with LVEF <40%.

†Defined as ACE-I or ARB or ARNi+beta-blocker+aldosterone antagonist.

‡Eligible participants meet the following criteria: LVEF <40%, heart rate ≥50 beats/min, serum creatinine ≤2.5 mg/dL in men and ≤2 mg/dL in women, serum potassium <5 mEq/L.

§Percentages indicate proportion out of total discharged participants in control (n=441) and intervention (n=404) periods.

‖Percentages indicate proportion of females and males participants eligible for a HFrEF polypill among total females and males participants at hospital discharge in the control and intervention periods.

#*P*-value indicates difference between HFrEF polypill eligibility during control period and intervention periods.

***P*-value indicates difference between female and male participants eligible for a HFrEF polypill at hospital discharge in the control and intervention periods.

discharge from 28.8% in the control period to 42.3% in the intervention period, routine administration of a HFrEF polypill could increase this rate and improve adherence by 44% (95% CI, 26%–65%) in a population that remains undertreated despite targeted quality improvement interventions.[4,5] Availability of multiple HFrEF polypill doses could prioritize safety and tolerability with low-dose initiation and subsequent titration to higher-dose polypills. An important limitation of this analysis is that laboratory values used to determine polypill eligibility at discharge were obtained at time of hospital admission, although renal function frequently changes during hospitalization in many patients with HF. Efficacy, safety, and effectiveness of HFrEF polypills initiated at discharge and titrated in outpatient settings will need to be established in rigorous randomized trials.[3] This analysis demonstrates high potential rates of HFrEF polypill eligibility and suggests a simplified polypill-based management strategy could be transformative for closing the treatment gap in HFrEF inequities in India and globally.

ARTICLE INFORMATION

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REFERENCES

1. Harikrishnan S, Jeemon P, Ganapathi S, Agarwal A, Viswanathan S, Sreedharan M, Vijayaraghavan G, Bahuleyan CG, Biju R, Nair T, et al. Five-year mortality and readmission rates in patients with heart failure in India: results from the Trivandrum heart failure registry. *Int J Cardiol*. 2021;326:139–143. doi: 10.1016/j.ijcard.2020.10.012
2. Agarwal A, Bahiru E, Yoo SGK, Berendsen MA, Harikrishnan S, Hernandez AF, Prabhakaran D, Huffman MD. Hospital-based quality improvement interventions for patients with heart failure: a systematic review. *Heart*. 2019;105:431–438. doi: 10.1136/heartjnl-2018-314129
3. Agarwal A, Yancy CW, Huffman MD. Improving care for heart failure with reduced ejection fraction—a potential polypill-based strategy. *JAMA*. 2020;324:2259–2260. doi: 10.1001/jama.2020.21395
4. Agarwal A, Mohanan PP, Kondal D, Baldridge A, Davies D, Devarajan R, Unni G, Abdullakutty J, Natesan S, Joseph J, et al. Effect of a quality improvement intervention for acute heart failure in south India: an interrupted time series study. *Int J Cardiol*. 2021;329:123–129. doi: 10.1016/j.ijcard.2020.12.048
5. Bahiru E, de Cates AN, Farr MR, Jarvis MC, Palla M, Rees K, Ebrahim S, Huffman MD. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases. *Cochrane Database Syst Rev*. 2017;3:CD009868. doi: 10.1002/14651858.CD009868.pub3