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SHORT COMMUNICATION

Alteration of medical therapy in patients with heart failure relative to change in symptom severity

Nasrien E. Ibrahim[1]*, Yang Song[2], Christopher P. Cannon[3], Gheorghe Doros[2,4], Patricia Russo[5], Angelo Ponirakis[6], Claire Alexanian[6] and James L. Januzzi Jr[1,2]

[1]*Cardiology Division, Massachusetts General Hospital, 55 Fruit Street, GRB-800, Boston, MA 02114, USA;* [2]*Baim Institute for Clinical Research, Brookline, MA, USA;* [3]*Cardiology Division, Brigham and Women's Hospital, Boston, MA, USA;* [4]*Boston University, Boston, MA, USA;* [5]*Novartis, Boston, MA, USA;* [6]*American College of Cardiology, Washington, DC, USA*

Abstract

In this observational analysis from the Practice Innovation and Clinical Excellence Registry®, we examined changes in guideline-directed medical therapies relative to changes in symptom severity in ambulatory patients with heart failure with reduced ejection fraction, finding change in medication more often occurring when patients were changing their New York Heart Association symptom severity, rather than during periods of stable symptoms. Additionally, despite being available for a year during the time of our analysis, the use of sacubitril/valsartan was extremely low, and most often added in the context of worsening symptoms, not how this drug was studied and not how the guidelines articulate its use.

Keywords Heart failure; Therapy; Medications; Guidelines

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**Correspondence to: Nasrien E. Ibrahim, Cardiology Division, Massachusetts General Hospital, 55 Fruit Street, GRB-800, Boston, MA 02114, USA. Tel: +1 617 726 9554; Fax: +1 617 726 4105. Email: neibrahim@mgh.harvard.edu*

The optimal use of guideline-directed medical therapies (GDMT) in patients with heart failure with reduced ejection fraction (HFrEF; EF $\leq$ 40%) reduces rates of morbidity and mortality.[1] Despite this evidence, patients with HFrEF are often undertreated. Based on several prospective clinical trials, it is believed that HFrEF therapies are most beneficial when titrated to maximally tolerated doses compared with up-titration when the patient has become clinically unstable.[2–4] Additionally, optimal GDMT is thought to reduce events, compared with a lower dose of medical therapy.[3,4] Factors determining timing of changes in therapy for HFrEF outside of clinical trials remain poorly understood. Accordingly, we examined medication trends amongst patients with HFrEF in the PINNACLE Registry® as a function of HF symptom severity. We hypothesized clinicians would be more likely to add or remove GDMT for HF in a reaction to worsening HF symptom severity, rather than making such changes proactively in the context of stability.

We examined data from the PINNACLE Registry® gathered between 1 May 2008 and 30 June 2016. HFrEF patients with a baseline encounter and a 12 month (±3 month window) follow-up encounter were included in our analysis. Modification of GDMT was defined as addition or removal of GDMT relative to parallel change in New York Heart Association (NYHA) class severity. Change in NYHA class was defined as an increase or decrease in NYHA by at least one class from the index to the 12 month follow-up encounter.

From a sample of 1 824 964 patients with a diagnosis of HF, 721 578 were excluded because of age $<$18 years, missing EF, missing sex, or not having at least a year of follow-up. Out of the 1 103 386 remaining patients, 36.1% (*N* = 398 228) had HFrEF; of these, a total of 30 161 patients had medication information and NYHA class documented at the two time points. At index encounter, study participants had an EF of 29.6 ± 8.4% with a median NYHA symptom severity of Class II. A total of 72.9% of patients were prescribed a beta-blocker, and 61.7% were prescribed an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB). Only a small percentage of patients (1.4%) were prescribed an angiotensin receptor/neprilysin inhibitor (ARNI) at baseline. A total of 50.8% were prescribed a loop and/or thiazide diuretic, and only 4.3% were prescribed digoxin. Data on aldosterone antagonists were not collected in the PINNACLE Registry®.

At the 12 month time point, 79.2% (*N* = 23 867) of patients had no change in NYHA symptom severity, and these patients had the least modification of GDMT. Very few patients were switched to an ARNI likely due to Food and Drug Administration approval not occurring until 2015 and inclusion in the updated clinical practice guidelines not occurring until 2016.[5,6] Notably, consistent with our hypothesis, patients with worsening symptoms [10.5% (*N* = 3174)] had more changes in their medication regimens, including discontinuation of beta-blockers and/or ACEI/ARB and addition of diuretic and/or ARNI compared with those with unchanged or improved NYHA class. It is important to note that reasons for medication adjustments are not available in the PINNACLE registry and as such makes it difficult to ascertain why such changes were made. Those with improvement in symptoms [10.3% (*N* = 3111)] more often received ACEI/ARB and were taken off diuretics compared with those with worsened or unchanged NYHA class (*Table 1*).

Although consistent with our central hypothesis that clinicians are more likely to make change in GDMT at the time of change in symptom severity, our data have limitations. The PINNACLE Registry® has a high rate of missing medication doses. Detailed medication prescribing information is not presently available, and therefore, the reason for medication addition or removal is unknown. In addition, data regarding the prescription practices of mineralocorticoid receptors, a cornerstone of HF management, are missing, and low prescription rates of ARNI are most likely due to the incorporation of ARNI into the guidelines the same year our registry analysis ended. Lastly, in this analysis, we assessed change in NYHA class simultaneously as medication change. We did not assess NYHA following medication modifications landmarked on alterations in symptoms nor did we examine serial change in patient characteristics or impact of incident hospitalization. While the latter approaches might provide more certainty regarding potential cause–effect relationships between symptoms, clinical status, and GDMT change, data are lacking in this regard.

In summary, in this contemporary dataset, despite guideline recommendations, most patients did not have addition of GDMT over the course of 12 months, and significantly fewer proactive alterations were made in GDMT in HFrEF patients with stable symptoms. Our findings suggest opportunities exist to increase prescribing of GDMT as articulated in guidelines and expert consensus documents[7] in order to improve patient outcomes.

Conflict of interest

N.E.I. has received speaker fees from Novartis. C.P.C. has received grant support from Amgen, Arisaph, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck, and Takeda and consulting income from Alnylam, Amgen, Arisaph, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Kowa, Lipimedix*, Merck, Pfizer, Regeneron*, Sanofi*, and Takeda. P.R. is an employee of Novartis Pharmaceuticals. J.L.J.J. has received grant support from Siemens, Singulex, and Prevencio and consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Philips, and Novartis and participates in clinical endpoint committees/data safety monitoring boards for Novartis, Amgen, Janssen, and Boehringer Ingelheim. The remaining authors have nothing to disclose.

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Table 1 Changes in GDMT in those with worsened, unchanged, and improved NYHA class

Medication changes (%)	All patients (*N* = 30 161)	Worsened NYHA class (*N* = 3174)	Unchanged NYHA class (*N* = 23 876)	Improved NYHA class (*N* = 3111)	*P*
Beta-blocker					
Added	8.7	9.9	8.4	9.8	0.001
Removed	5.3	6.3	5.2	5.5	0.02
ACEI/ARB					
Added	9.6	10.2	9.2	11.6	<0.001
Removed	8.3	10.1	8.0	8.5	<0.001
Sacubitril/valsartan					
Added	2.1	4.1	1.7	3.2	<0.001
Removed	0.2	0.3	0.2	0.2	0.44
Diuretic					
Added	9.8	13.0	9.2	10.9	<0.001
Removed	5.5	5.7	5.4	5.9	0.41

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; GDMT, guideline-directed medical therapies; NYHA, New York Heart Association.

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