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ORIGINAL RESEARCH

EMERGING TECHNOLOGIES AND INNOVATIONS

A Computable Algorithm for Medication Optimization in Heart Failure With Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Guideline-directed medical therapy (GDMT) optimization can improve outcomes in heart failure with reduced ejection fraction.

OBJECTIVES The objective of this study was to determine if a novel computable algorithm appropriately recommended GDMT.

METHODS Clinical trial data from the GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure) and HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trials were evaluated with a computable medication optimization algorithm that outputs GDMT recommendations and a medication optimization score (MOS). Algorithm-based recommendations were compared to medication changes. A Cox proportional-hazards model was used to estimate the associations between MOS and the composite primary end point for both trials.

RESULTS The algorithm recommended initiation of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blockers, and mineralocorticoid receptor antagonists in 52.8%, 34.9%, and 68.1% of GUIDE-IT visits, respectively, when not prescribed the drug. Initiation only occurred in 20.8%, 56.9%, and 15.8% of subsequent visits. The algorithm also identified dose titration in 48.8% of visits for angiotensin-converting enzyme inhibitor/angiotensin receptor blockers and 39.4% of visits for beta-blockers. Those increases only occurred in 24.3% and 36.8% of subsequent visits. A higher baseline MOS was associated with a lower risk of cardiovascular death or heart failure hospitalization (HR: 0.41; 95% CI: 0.21-0.80; $P = 0.009$) in GUIDE-IT and all-cause death and hospitalization (HR: 0.61; 95% CI: 0.44-0.84; $P = 0.003$) in HF-ACTION.

CONCLUSIONS The algorithm accurately identified patients for GDMT optimization. Even in a clinical trial with robust protocols, GDMT could have been further optimized in a meaningful number of visits. The algorithm-generated MOS was associated with a lower risk of clinical outcomes. Implementation into clinical care may identify and address suboptimal GDMT in patients with heart failure with reduced ejection fraction. (JACC Adv 2023;2:100289) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

API = Application Programming Interface

ARB = angiotensin receptor blocker

CDSS = clinical decision support systems

CV = cardiovascular

EHR = electronic health record

FDR = false discovery rate

GDMT = guideline-directed medical therapy

HF = heart failure

HFrEF = heart failure with a reduced ejection fraction

MOS = medication optimization score

MRA = mineralocorticoid receptor antagonist

SBP = systolic blood pressure

In heart failure with a reduced ejection fraction (HFrEF), clinical trials have established the benefit of medications[1-9] and as national guidelines[10-12] that recommend those therapies, but it has been well documented that this knowledge can take years to be broadly implemented into practice.[13] The registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting prospective cohort study recently demonstrated low use of guideline-directed medical therapy (GDMT) in U.S. patients with HFrEF.[14] Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs) were only used in 79.6% of patients, beta-blockers were only used in 86% of patients, and mineralocorticoid receptor antagonists (MRAs) were only used in 36.1% of patients. More recently, the Change the Management of Patients with Heart Failure registry has also demonstrated the need for further GDMT optimization.[15]

To address these issues, the American College of Cardiology published an expert consensus decision pathway for optimizing heart failure (HF) treatment that recommended the use of electronic health records (EHRs) to reduce errors, improve decision support, and facilitate guideline adherence.[16] This led our research group to create an Application Programming Interface (API) using the American College of Cardiology/American Heart Association HFrEF guidelines. The objective of this study was to validate that the API appropriately recommended GDMT from clinical trial data and to determine if the API-generated information about medication optimization was associated with clinical outcomes.

METHODS

This study retrospectively validated a computable medication optimization algorithm created for HFrEF using the GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure)[17] and HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) clinical trial data acquired from the NHLBI BioLINCC (National Heart Lung and Blood Institute, Biological Specimen and Data Repository Information Coordinating Center) repository. The study was approved and determined to be not regulated by the University of Michigan Institutional Review Board.

PATIENT POPULATIONS. The GUIDE-IT trial was an 894-patient randomized controlled trial that studied the effects of a natriuretic peptide-guided management strategy compared to the standard of care in patients with HFrEF with an emphasis on titrating medical therapy, including GDMT.[17] The GUIDE-IT trial was an ideal data set to validate this algorithm because of the extensive medication data collected and the purpose of the study was to optimize GDMT over time. Blood pressure, heart rate, potassium, serum creatinine, and medications (drug and daily doses) were documented at baseline, 2 weeks, 6 weeks, 3 months, and every 3 months thereafter until month 24 of the study, a potential 11 visits per patient. The primary outcome for the GUIDE-IT trial was the composite of cardiovascular (CV) death or HF hospitalization.

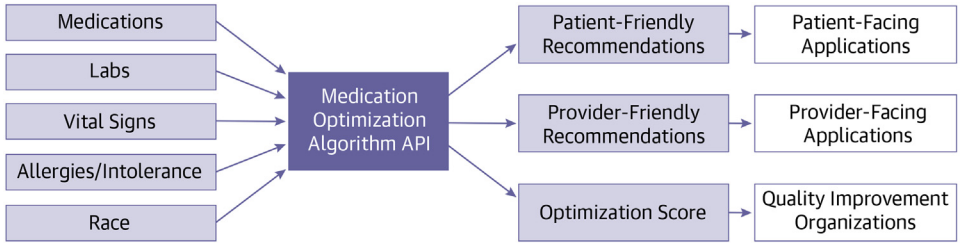
HF-ACTION was a 2,331-patient randomized controlled trial that studied the effects of aerobic exercise training in ambulatory patients with HF and an ejection fraction of <35%.[18] Values for the algorithm variables were available at baseline. Subsequent time points were not included because the input data needed for the algorithm were not collected. The primary outcome for the HF-ACTION trial was the composite all-cause death or hospitalization.

The 2 data sets, GUIDE-IT and HF-ACTION, complement each other well to evaluate the computable medication optimization algorithm. GUIDE-IT provides rich, longitudinal data for patients enrolled at hospital discharge that includes all variables needed to assess medication optimization at each time point. HF-ACTION provides a large data set of patients with HFrEF enrolled in the ambulatory setting with all variables needed to assess medication optimization at baseline.

COMPUTABLE MEDICATION OPTIMIZATION ALGORITHM. The HFrEF medication optimization algorithm creation began with the narrative guideline,[11] then led to structured decision trees developed for each drug class (ACEI/ARB/angiotensin receptor/neprilysin inhibitor (ARNI), beta-blocker, MRA, and hydralazine/nitrate). The algorithm was validated by HF physicians and cardiology pharmacists and was coded in an executable computer format. The executable format allowed for more large-scale validation of the algorithm with synthetically generated patient data. The next step in testing the algorithm was this study.

The HFrEF medication optimization algorithm was created as a REpresentational State Transfer API, so inputs, generated from an outside source, could be computed by the algorithm to provide recommendations for the medications to optimize on an individual

CENTRAL ILLUSTRATION **Overview of the Medication Optimization Algorithm**



	ACEI/ARB		Beta-blocker		MRA
	Initiation	Titration	Initiation	Titration	Initiation
Algorithm identified instances for medication optimization	53%	49%	35%	39%	68%
Instances where the medication was prescribed	21%	24%	57%	37%	16%
Opportunities for medication optimization	79%	76%	43%	63%	84%

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The **left top side of the figure** shows the inputs of the algorithm. The **right top side** shows the outputs of the algorithm and the potential future applications for each output. The **bottom table** shows opportunities for GDMT medication optimization in GUIDE-IT visits.
ACEI = angiotensin-converting enzyme inhibitor; API = Application Programming Interface; ARB = angiotensin receptor blocker; GDMT = guideline directed medical therapy; GUIDE-IT = Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure; MRA = mineralocorticoid receptor antagonist.

patient. The current version of the algorithm (version 0.487) is designed for the inputs of medications (name and daily dose), New York Heart Association classification, systolic blood pressure (SBP), heart rate (HR), serum creatinine, potassium, allergies/intolerance, and race from one patient at a time. The Central Illustration demonstrates a visual for the inputs and outputs of the algorithm.

The algorithm identifies specific HFrEF GDMT medications approved by the Food and Drug Administration. The algorithm outputs medication optimization recommendations for each GDMT drug class. The algorithm also provides a medication optimization score (MOS). The MOS is a percent between 0 (least optimized) and 100 (most optimized) which represents the extent of medication optimization that

TABLE 1 **Examples of Medications, the Algorithm Recommendations, and the Medication Optimization Score Value**

Example	Medications	Recommendations	MOS
Patient 1	Metoprolol succinate 25 mg daily, lisinopril 2.5 mg daily	• Increase the patient's current beta blocker. • Increase the patient's current ACE inhibitor. • Start a mineralocorticoid receptor antagonist.	22%
Patient 2	Carvedilol 25 mg twice daily, lisinopril 20 mg daily	• Switch to sacubitril/valsartan. • Start a mineralocorticoid receptor antagonist.	56%
Patient 3	Metoprolol succinate 200 mg daily, enalapril 40 mg daily, spironolactone 25 mg daily	• Switch to sacubitril/valsartan.	89%

The table provides examples of the algorithm recommendations and MOS when a patient is NYHA functional class II and has normal potassium, serum creatine, systolic blood pressure, and heart rate.
ACE = angiotensin-converting enzyme.

needs to be performed. As the patient is prescribed more GDMT and at higher doses, the score is closer to 100%. **Table 1** provides examples of the algorithm recommendations and the MOS value. To test the inputs and results for the algorithm, visit https://decisionalgorithm.shinyapps.io/heartfailure/.

STATISTICAL ANALYSIS. Patients were excluded from the analysis if the data needed for the algorithm were unavailable at the time point for the analysis. For baseline demographics and outcomes, categorical variables were described with frequencies and percentages, and continuous variables were described with mean ± SD or median (IQR) where appropriate. Continuous variables were compared using a *t*-test when normally distributed and a Wilcoxon rank test when the variable is not normally distributed. Categorical variables were analyzed using a chi-square test or Fisher exact test where appropriate.

Using the GUIDE-IT trial data, the recommendations generated in the algorithm were compared to the medications documented at each visit. We compared the important clinical parameters between those visits that a patient would receive and not receive a recommendation for that drug class from the medication optimization algorithm. The important clinical parameters for the ACEI/ARB class were SBP, serum creatinine, and potassium. The important clinical parameters for the beta-blocker class were SBP and HR. The important clinical parameters for the MRA class were serum creatinine and potassium. The change in medications from a visit to visit was also compared to those recommended by the algorithm.

A Cox proportional-hazards model was used to estimate the associations between MOS (independent variable) with clinical outcomes. The composite primary outcome for the GUIDE-IT trial was the first CV death or HF hospitalization (dependent variable). The MOS was also treated as a time-dependent covariate where the MOS immediately preceding an event or censoring timepoint was used as the independent variable. The composite primary outcome for the HF-ACTION trial was first all-cause death or hospitalization (dependent variable). Additional analysis was performed to control for the HF-ACTION risk score[19] as a covariate because none of these variables are used as inputs for the medication optimization algorithm. A sensitivity analysis was also performed using the lowest dose for all ARBs, which is the base analysis, and the highest dose for all ARBs because ARB dosing was not available in HF-ACTION. A cut point analysis was performed using the HF-ACTION data to find the ideal cut point where the MOS percentage predicts the primary outcome. The findcut Statistical Analysis System macro created by the Mayo Clinic was used to perform this analysis.[20-22] The MOS was the continuous measure and the first all-cause death or hospitalization was the time-to-event outcome in the macro. A combination of the Cox model Wald *P*-values and false discovery rate (FDR) *P* values from the macro were used to identify cut points for the MOS. The FDR *P* values, also known as q values, are corrected to adjust for multiple comparisons. For all statistical tests, differences were considered statistically significant at a *P* value of <0.05. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc).

RESULTS

In the GUIDE-IT data, 841 patients had appropriate data at baseline visit to be included. At baseline, 80.9% (n = 681) of patients were taking an ACEI/ARB, 96.4% (n = 811) of patients were taking a beta-blocker, and 50.7% (n = 426) of patients were taking an MRA. The algorithm identified the need for GDMT optimization in 69.4% (n = 584) of patients.

In the HF-ACTION data, 2,130 patients had appropriate data at the HF-ACTION baseline visit to be included. At baseline, 94.4% (n = 2,011) of patients were taking an ACEI/ARB, 94.5% (n = 2,012) of patients were taking a beta-blocker, and 45.2% (n = 962) of patients were taking an MRA. The algorithm identified the need for GDMT optimization in 72.8% (n = 1,552) of patients. **Table 2** demonstrates the demographics of the patients from the baseline visit.

In the GUIDE-IT data, 883 patients had enough data at any follow-up time to be included in the analysis, with a median of 6 follow-up time points and a total of 5,733 visits. Over the 5,733 visits, 79.7% (n = 4,567), 96.6% (n = 5,535), and 56.5% (n = 3,218) visits demonstrated patients were taking an ACEI/ARB, beta-blocker, and MRA, respectively. For all visits, the MOS was a median of 76% (IQR: 50%-100%). At baseline, the median MOS was 61% (IQR: 40%-100%). In those patients that the algorithm identified needing medication optimization (MOS <100%), the median MOS was 50% (IQR: 34%-64%). **Figure 1** shows a Sankey diagram for the flow of patients between different MOS categories throughout the study.

At baseline in HF-ACTION, the median MOS was 57% (IQR: 44%-100%). In HF-ACTION patients that the algorithm identified needing medication optimization (MOS <100%), the median MOS was 50% (IQR: 40%-61%). See the supplemental figures, Supplemental Figures 1 and 2, representing the histogram of the MOS in each data set.

TABLE 2 Baseline Demographics

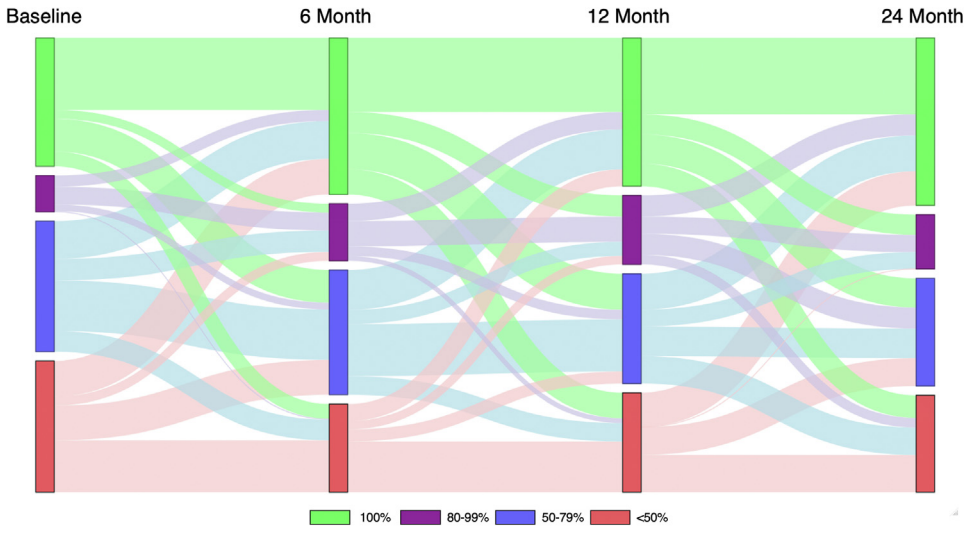
	GUIDE-IT			HF-ACTION		
	Total (n = 841)	MOS <100% (n = 584)	MOS 100% (n = 257)	Total (n = 2,130)	MOS <100% (n = 1,552)	MOS 100% (n = 578)
Age, y	61.3 ± 14	61.3 ± 14	61.1 ± 15	58.6 ± 13	58.9 ± 12	57.7 ± 12
Women	262 (31.2)	188 (32.2)	74 (28.8)	599 (28.1)	437 (28.2)	162 (28)
Race						
White	471 (56)	302 (51.7)	169 (65.7)	1,322 (62.1)	953 (61.4)	369 (63.8)
Black	299 (35.6)	235 (40.2)	64 (24.9)	669 (31.4)	501 (32.3)	168 (29.1)
Other	71 (8.4)	47 (8)	24 (9.3)	139 (6.5)	98 (6.3)	41 (7.1)
Ischemic HF etiology	421 (50)	280 (48)	141 (54.9)	1,096 (51.5)	796 (51.29)	300 (51.9)
Diabetes mellitus	388 (46.1)	252 (48.3)	106 (41.3)	678 (31.8)	499 (32.2)	179 (31)
Chronic kidney disease[a]	309 (36.7)	225 (38.5)	84 (32.7)	742 (34.8)	508 (32.7)	234 (40.5)
Systolic BP, mm Hg	115.8 ± 20	122 ± 18	101.7 ± 15	113.8 ± 18	119.1 ± 17	99.5 ± 13
Heart Rate, beats/min	77 ± 15	75 ± 14	78 ± 15	70 ± 11	71 ± 12	70 ± 11
Potassium, mmol/L	4.4 ± 0.6	4.3 ± 0.5	4.5 ± 0.7	4.3 ± 0.8	4.3 ± 0.5	4.5 ± 0.6
Creatinine, mg/dL	1.45 ± 0.6	1.4 ± 0.5	1.56 ± 0.8	1.33 ± 0.8	1.26 ± 0.5	1.51 ± 1.3
HF-ACTION risk score	-	-	-	53 ± 12	52.7 ± 12	53.8 ± 12
ACEI/ARB	681 (81)	465 (79.6)	216 (84.1)	2011 (94.4)	1,456 (93.8)	555 (96)
Beta-blocker	811 (96)	565 (96.8)	246 (95.7)	2012 (94.5)	1,466 (94.5)	546 (94.5)
MRA	426 (50.7)	221 (37.8)	205 (79.8)	962 (45.2)	459 (29.6)	503 (87)

Values are mean ± SD or n (%). [a]In GUIDE-IT, a chronic kidney disease diagnosis was collected at baseline and HF-ACTION chronic kidney disease was defined as a baseline eGFR category of 3 or greater.

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BP = blood pressure; GUIDE-IT = Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure; HF = heart failure; HF-ACTION = Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training.

GUIDE-IT MEDICATION ADJUSTMENTS AND THE ALGORITHM. Over the course of the GUIDE-IT trial, there were 1,166 (20.3%) visits where patients were not on an ACEI/ARB. Of those not on ACEI/ARB, the algorithm recommended initiating ACEI/ARB in 589 (50.5%) patient visits, leaving 577 (49.5%) visits where the algorithm would not recommend initiation of ACEI/ARB. Patient visits where ACEI/ARBs were not recommended by the algorithm had significantly lower SBP (109 ± 20 mm Hg vs 127.9 ± 14 mm Hg;

FIGURE 1 Sankey Plot of Patients Transferring Between Different Medication Optimization Score Categories Over Time



Node height represents the proportion of patients in each category at the given times of baseline, 6 months, 12 months, and 24 months. Links represent the proportion of patients moving from their node of origin to their respective category at the next timepoint.

TABLE 3 Opportunities for Guideline-Directed Medication Therapy Optimization in GUIDE-IT Visits

	ACEI/ARB		Beta-Blocker		MRA
	Initiation	Titration	Initiation	Titration	Initiation
Algorithm identified visits for GDMT optimization	53% (480/908)	49% (1,475/3,025)	35% (51/146)	39% (1,158/2,942)	68% (1,421/2088)
Medication prescribed at the next visit	21% (100/480)	24% (358/1,475)	57% (29/51)	37% (426/1,158)	16% (224/1,421)
Opportunities for GDMT optimization	79% (380/480)	76% (1,117/1,475)	43% (22/51)	63% (732/1,158)	84% (1,197/1,421)

Values are % (n/N). The table summarizes the opportunities for GDMT optimization identified by the algorithm.

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; GDMT = guideline-directed medical therapy; MRA = mineralocorticoid receptor antagonist.

$P < 0.0001$), higher serum creatinine (2.1 ± 1.0 mg/dL vs 1.6 ± 0.6 mg/dL; $P < 0.0001$), and higher potassium levels (4.3 ± 0.7 vs 4.2 ± 0.5; $P = 0.003$). The algorithm did not recommend initiating an ACEI/ARB on 4,472 (97.9%) visits where it correctly identified the patient as already receiving an ACEI/ARB. The 95 (2.1%) instances where the patient was on an ACEI/ARB and the algorithm recommended it were due to the patient being on an "other" ACEI/ARB in the GUIDE-IT data. Of the total visits in which an ACEI/ARB was not prescribed, there were 908 visits where initiation of an ACEI/ARB was able to be assessed at the next visit. The algorithm recommended the initiation of an ACEI/ARB for 480 of the 908 visits (52.9%). An ACEI/ARB was only initiated on 100 out of the 480 visits (20.8%).

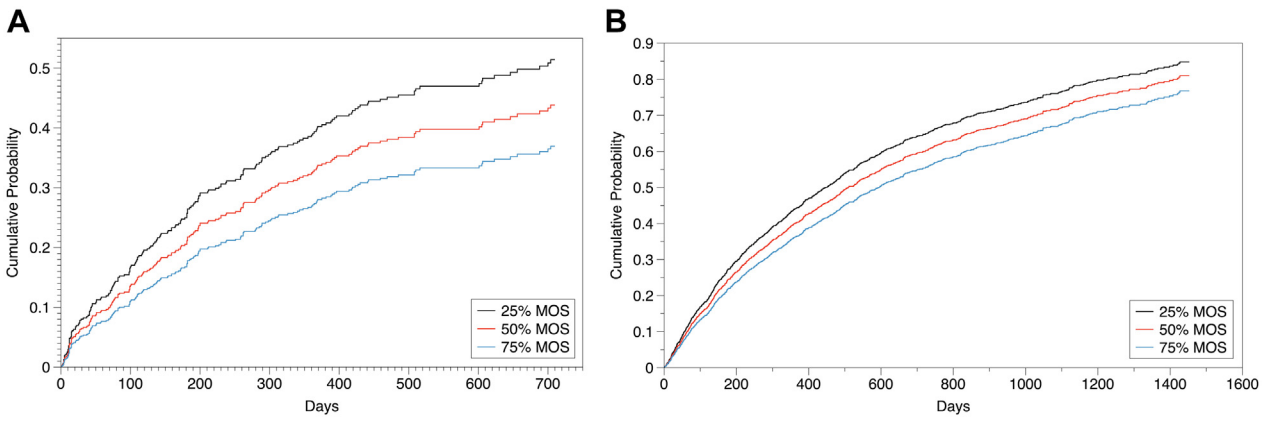
For the GUIDE-IT visits where the patient was already prescribed an ACEI/ARB, there were 3,494 (76.5%) visits where the patient was receiving less than the target ACEI/ARB dose. The algorithm identified 1,689 (48.3%) visits where the ACEI/ARB could be up-titrated. The titration recommendations consisted of increasing the ACEI/ARB dose (79%), switching to ARNI (16%), or initiating an ACEI/ARB (the trial documentation collected "other" as the ACEI/ARB) (5%). The patients where the algorithm recommended titration had significantly higher SBP (127.1 ± 15 vs 103.3 ± 16 mm Hg; $P < 0.0001$), lower serum creatinine (1.3 ± 0.4 vs 1.5 ± 0.7 mg/dL; $P < 0.0001$), and lower potassium levels (4.2 ± 0.4 vs 4.5 ± 0.6 mEq/L; $P < 0.0001$) compared to the visits where the algorithm did not recommend a dose titration. There were 1,073 (23.5%) visits where the patient was at or above the target dose for the ACEI/ARB. The algorithm identified 555 visits where an ARNI could be initiated. There were 3,025 visits where the up-titration of an ACEI/ARB was able to be evaluated at the next visit. The algorithm recommended up-titration in 1,475 visits (48.7%), while the medications were only up-titrated at 358 (24.2%) of those visits.

Beta-blocker prescribing in the GUIDE-IT trial was higher compared to ACEI/ARB with only 197 (3.4%) visits where a beta-blocker was not prescribed. The algorithm identified 64 (32.5%) visits where a beta-blocker was recommended to be initiated, leaving 133 (67.5%) visits where the algorithm did not recommend initiating a beta-blocker. The visits where the algorithm recommended beta-blocker initiation had significantly higher SBP (124.3 ± 15 vs 107.8 ± 16 mm Hg; $P < 0.0001$) and higher HR (86 ± 13 vs 77 ± 20 beats/min; $P < 0.0001$) compared to the visits where a beta-blocker was not recommended. The algorithm recommended the initiation of a beta-blocker in 40 (0.7%) patient visits due to the patient being on a non-HF beta-blocker (9 atenolol and 31 "other" beta-blockers). Of the total visits in which a beta-blocker was not prescribed, there were 146 visits where initiation of a beta-blocker could be assessed at the next visit. The algorithm recommended initiating a beta-blocker at 51 visits (34.9%), but a beta-blocker was only initiated at 29 (56.9%) of those visits.

Of the patients that were prescribed a beta-blocker, there were 3,437 (62.1%) visits where the beta-blocker dose was less than the target dose. The algorithm identified 1,345 (39.1%) visits where the beta-blocker could be up-titrated. The patients in these visits had a significantly higher SBP (127.8 ± 15 vs 109.1 ± 19 mm Hg; $P < 0.0001$) and HR (84 ± 11 vs 70 ± 13 beats/min; $P < 0.0001$) compared to the patients where the algorithm did not recommend titration. There were 2,942 visits where the up-titration of a beta-blocker could be assessed at the next patient visit. The algorithm recommended an increase at 1,158 (39.4%) visits, but the dose was only increased at 426 (36.8%) of those visits.

Patients were not prescribed an MRA in 2,492 (43.5%) visits. The algorithm identified 1,668 (66.9%) visits where an MRA was recommended to be initiated, leaving 824 (33.1%) visits where the algorithm did not recommend initiating an MRA. The patients that were recommended to initiate an MRA had significantly lower serum creatinine (1.4 ± 0.5 vs 2.0 ± 1.2 mg/dL; $P < 0.0001$) and potassium levels (4.2 ± 0.5 vs 4.6 ± 0.7 mEq/L; $P < 0.0001$) compared to the patients that the algorithm did not recommend

FIGURE 2 The Cumulative Probability for the Primary End Point for a Medication Optimization Score of 25%, 50%, and 75%



(A) The cumulative probability estimated by the Cox model is for the composite end point of cardiovascular death or heart failure hospitalization, the GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure) trial's primary outcome. **(B)** The cumulative probability estimated by the Cox model is for the composite end point of all-cause death or hospitalizations, the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial's primary outcome, adjusted by the HF-ACTION risk score. MOS = medication optimization score.

initiating an MRA. The algorithm correctly identified 3,218 (99.3%) visits where the patient was already on an MRA. There were 22 (0.7%) visits where the algorithm did not recognize the patient was on an MRA since the patient was documented as being on an "other" MRA in the GUIDE-IT data. Of the total visits in which an MRA was not prescribed, there were 2,088 patient visits where MRA status could be assessed at the next visit. The algorithm recommended the initiation of an MRA in 1,421 (68.1%) visits. Initiation of an MRA only occurred in 224 (15.8%) of those patient visits. **Table 3** summarizes the opportunities for GDMT optimization identified by the algorithm.

CLINICAL OUTCOMES AND THE MOS IN GUIDE-IT AND HF-ACTION. In GUIDE-IT, 69.4% (n = 584) of patients were identified by the algorithm as needing medication optimization at baseline. A higher MOS was associated with a reduced risk of CV death or HF hospitalizations (HR: 0.41; 95% CI: 0.21-0.80; $P = 0.009$). Due to the protocol-defined changes in medications over time in the GUIDE-IT trial and clinical variables changing, the MOS was analyzed as a time-dependent covariate. As a time-dependent covariate, a higher MOS score was associated with a reduced risk of CV death or HF hospitalizations (HR: 0.38; 95% CI: 0.21-0.66; $P < 0.001$).

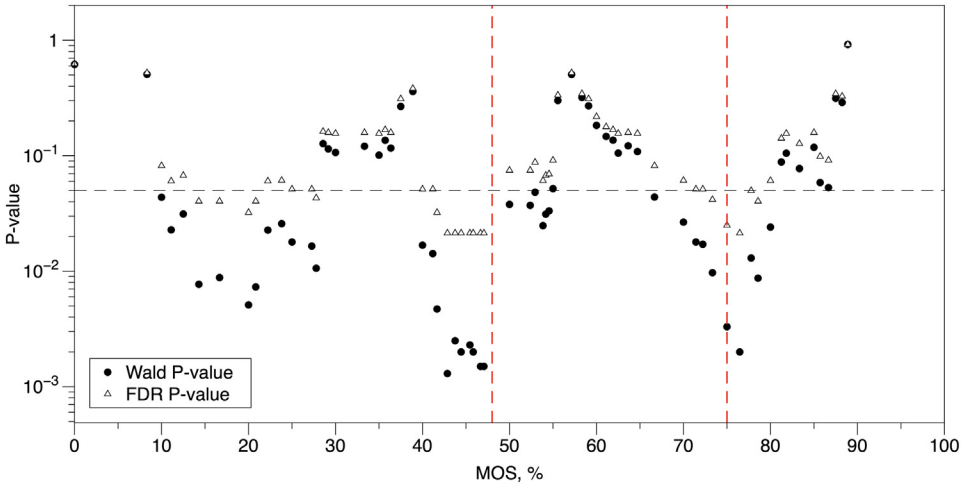
In HF-ACTION, 72.9% (n = 1,552) of patients were identified by the algorithm as needing medication optimization at baseline. A higher MOS was associated with a reduced risk of all-cause death or hospitalizations (HR: 0.60; 95% CI: 0.44-0.84; $P = 0.002$). When controlling for the HF-ACTION risk score, the adjusted HR was similar to the unadjusted HR (adjusted HR: 0.60; 95% CI: 0.43-0.83; $P = 0.002$). **Figure 2** demonstrates the cumulative probability of the composite endpoint for a MOS value of 25%, 50%, and 75% in patients needing optimization for both trials. In a sensitivity analysis, assigning all patients taking ARBs to the highest dose did not significantly change the association of the MOS with the primary outcome in HF-ACTION (HR: 0.60; 95% CI: 0.43-0.83; $P = 0.002$).

A cut point analysis was performed to classify MOS percent ranges that could be used to identify patients who benefit from medication optimization using the algorithm. Using the Wald and FDR P values for interpretation, MOS of 47% and 75% were identified as cut points to use to identify patients that would benefit from medication optimization. **Figure 3** demonstrates the Wald and FDR P values for each MOS value to determine the cut point. See the supplement for a table, Supplemental Table 1, that includes the P values for each cut level.

DISCUSSION

In this study, our guideline-based computable algorithm accurately selected patients with HFrEF who were eligible for GDMT initiation or up-titration. Even

FIGURE 3 Wald and False Discovery Rate *P* Values for Each Medication Optimization Score Value



The *P* values were generated from the cut point analysis in HF-ACTION. The horizontal dotted line represents a *P* value of 0.05. The vertical dotted line represents the statistical cut points. Solid dots represent the Cox model's Wald *P* values, and open triangles represent the false discovery rate *P* values. FDR = false discovery rate; MOS = medication optimization score.

in the GUIDE-IT trial, which specifically focused on GDMT optimization, the algorithm identified numerous opportunities to improve medical therapy; these findings were replicated in HF-ACTION. In both data sets, the MOS generated by the algorithm was prognostically relevant.

Using the GUIDE-IT data, our guideline-based computable algorithm accurately identified patients with HFrEF who were eligible for GDMT initiation or up-titration based on the available inputs. When medication optimization was able to be assessed at the next visit, there was significant room for GDMT improvement. Our analysis identified missed opportunities for optimal GDMT in 79.2%, 43.1%, and 84.2% of patient visits when the algorithm recommended initiation of ACEI/ARB, beta-blockers, or MRAs, respectively, when the medications were not prescribed. Additionally, when the algorithm identified appropriate up-titration, increasing the dose of an ACEI/ARB only occurred at 24.3% of patient visits and 36.8% of patient visits for beta-blockers. Finally, the MOS generated by the algorithm also demonstrated an association with composite primary end points adjudicated in 2 HFrEF clinical trials, GUIDE-IT, and HF-ACTION.

Optimizing heart failure medication confers significant morbidity and mortality benefit. Specifically, GDMT has been shown to reduce mortality by 17%, 34%, and 30% for ACEI/ARBs, beta-blockers, and MRAs, respectively.[23] Furthermore, outcomes have also been shown to correlate with increasing doses of ACE inhibitors and beta-blockers. The ATLAS (Assessment of Treatment with Lisinopril and Survival) trial compared the effect of low-dose lisinopril (2.5-5 mg daily) to high-dose lisinopril (32.5-35 mg daily) on all-cause mortality and CV hospitalizations. While the high dose lisinopril did not improve all-cause mortality compared to low dose lisinopril, the high dose lisinopril did significantly reduce all-cause hospitalizations by 13% ($P = 0.021$) and heart failure hospitalizations by 24% ($P = 0.002$).[9] If all other medications were optimized, the MOS from this algorithm is 78% for a patient on lisinopril 2.5 mg daily and 89% for a patient on lisinopril 40 mg daily. Based on our analysis, this 11% change in MOS would lead to about a 9% lower risk of CV death or HF hospitalization.

Beta-blockers have also been shown to have a dose-related effect on heart failure outcomes. The HF-ACTION study revealed a 13% relative risk lower risk of all-cause death or all-cause rehospitalization when comparing high dose beta-blockers (≥25 mg daily carvedilol equivalents) vs low dose beta-blockers when adjusting for various factors.[24] If all other medications were optimized, the MOS from this algorithm is 78% for a patient on carvedilol 12.5 mg

twice daily and 89% for a patient on carvedilol 25 mg twice daily. Based on our analysis, this 11% change in MOS would lead to about a 9% lower risk of CV death or HF hospitalization.

With the absence of optimal GDMT in a significant portion of the HF population and the increase in complexity of HFrEF GDMT with the addition of newer drug classes, clinical decision support systems (CDSS) have the potential to improve therapeutic regimens for a larger portion of patients with HFrEF. Prior attempts at CDSS in the HF population have shown poor results,[25,26] but failed to include all 4 features shown to predict improved clinical practice when using CDSS.[27] Embedding this HF medication optimization algorithm into CDSS within or outside the EHR may allow for clinicians to improve morbidity and mortality outcomes in patients by fully optimizing HF regimens. The MOS score could be presented in an EHR clinical dashboard for providers to prioritize the patients that need optimization. The recommendations generated from the algorithm could be shown to patients before a clinic visit to facilitate patient-provider communication about GDMT optimization, like in the EPIC-HF (Electronically delivered, Patient-activation tool for Intensification of Chronic medications for Heart Failure with reduced ejection fraction) trial,[28] or in an EHR alert, like in the PROMPT-HF (Pragmatic Trial Of Messaging to Providers Trials Heart Failure) trial.[29] This algorithm could be the basis for many tools used for GDMT optimization.

STUDY LIMITATIONS. There are some limitations to our analysis. First, the data for this analysis was from large clinical trials and cannot be extrapolated to electronic medical record data at this time. In addition, ARNI evaluation is included in our algorithm, but ARNIs were not available to use during the GUIDE-IT or HF-ACTION trials. Additionally, not all patients had follow-up visits to assess the change in GDMT in GUIDE-IT. We were only able to analyze the change in GDMT in patients that had appropriate follow-up visits.

The version of the algorithm used in this analysis also does not include an evaluation of certain drugs (sodium-glucose cotransporter 2 inhibitors and ivabradine) that are more prominent in the recent version of the guidelines or other clinical parameters that may influence a provider's decision to optimize GDMT.[12] The next version of the algorithm includes these medication classes, and will be validated in health system data and, when available, clinical trial data sets.

CONCLUSIONS

The algorithm accurately identified patients with HFrEF that have a potential opportunity for GDMT initiation and titration. Even in a clinical trial with robust protocols, GDMT could have been further optimized in a meaningful number of visits. The algorithm-generated MOS was associated with a lower risk of clinical outcomes. Implementation into clinical care may identify and address suboptimal GDMT in patients with HFrEF.

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PERSPECTIVES

COMPETENCYIN PATIENT CARE AND PROCEDURAL SKILLS: Computable algorithms can accurately identify patients that have a potential opportunity for GDMT initiation and titration. This was shown even in a setting where protocols were in place to optimize GDMT.

TRANSLATIONAL OUTLOOK: Further implementation of this algorithm into clinical care should be studied to determine if the algorithm can assist with GDMT optimization in patients with HFrEF.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.