Short communication

Medical therapy for patients with recent-onset heart failure with reduced ejection fraction during the COVID-19 pandemic: Insights from the Veteran’s affairs healthcare system

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ABSTRACT

This study aims to evaluate trends in guideline-directed medical therapy (GDMT) for patients with recent-onset heart failure with reduced ejection fraction (HFrEF) following the onset of the COVID-19 pandemic using an interrupted time series analysis in the Veteran’s Affairs Healthcare System. Among 71,428 patients with recent-onset HF/EF between 1/1/2018 and 2/28/2021, we found the pandemic was not associated with differences in treatment rates for beta-blockers, renin-angiotensin-aldosterone system inhibitors, or mineralocorticoid receptor antagonists; there was a 2.6 % absolute decrease (95% CI: 0.5 %–4.7 %) in ARNI rates in April 2020; which decreased over the pandemic. Despite the changes to healthcare delivery, the COVID-19 pandemic was associated with minimal changes in GDMT rates among patients with recent-onset HFrEF.

1. Introduction

Rapid optimization of heart failure (HF) medical therapy is critical given the condition’s substantial morbidity [1,2]. The coronavirus-19 (COVID-19) pandemic caused a major disruption in outpatient cardiovascular care, leading to both more telemedicine as a substitute for face-to-face visits and fewer overall encounters [3–6]. Within the Veteran’s Health Administration (VA), the largest integrated healthcare system in the United States, we evaluated whether this shift in outpatient care was associated with changes in the use of guideline-recommended medical therapy (GDMT) among patients with recent-onset HF with reduced ejection fraction (HFrEF) between 1/1/2018 and 1/28/2021.

2. Methods

Briefly, we used VA claims and electronic health record (EHR) data sources, including inpatient encounters, outpatient encounters, laboratory values, vital signs, and pharmacy data, to evaluate rates of GDMT eligibility and treatment among a cohort with recently-diagnosed HF. We previously described the methods of evaluating GDMT use among VA patients with HFrEF [7].

We included patients with a recent HF diagnosis at the VA between 1/1/2018 and 2/28/2021 and with left ventricular ejection fraction (LVEF) ≤40 % within 1 year of diagnosis. Index date was the later date between the diagnosis and LVEF documentation. We excluded patients with an earlier HF diagnosis, prior heart transplant or ventricular assist device, and lack of VA medication fills.

We captured patient medical characteristics (including diagnoses, vital, and laboratory values), neighborhood social risk, drive time to VA specialty care, and VA facility COVID prevalence. We classified patients residing in the top quartile of the CDC/ATSDR Social Vulnerability Index (SVI), which ranks census tracts on 15 social risk factors, as high vulnerability [8]. We categorized patients in the top quartile of drive time to specialty care as having long drive times. We also classified the top quartile of facilities as high-COVID based on the number of COVID-19 infections through 11/30/2020, indexed to the number of 2019
Cohort characteristics.

| Demographics | Overall | Pre-pandemic | Post-pandemic | Standardized differences |
|--------------|---------|--------------|---------------|--------------------------|
| N = 71,428   | 71,282  | 47,282       | 24,146        |                          |
| Age          | 71.8    | 71.8         | 72.0          | 0.02                     |
| Sex, women   | 2.6 %   | 2.5 %        | 2.8 %         | 0.12                     |
| Race         | 0.6 %   | 0.5 %        | 0.6 %         | 0.01                     |
| Ethnicity    | 19.5 %  | 19.4 %       | 19.8 %        | 0.01                     |
| Native American/Alaska Native | 1.0 % | 0.9 % | 0.9 % | 0.01 |
| Pacific Islander | 0.9 % | 0.9 % | 1.0 % | 0.01 |
| White        | 71.8 %  | 72.2 %       | 71.1 %        |                          |
| Missing      | 6.1 %   | 6.0 %        | 6.4 %         |                          |
| Vitals       |         |              |               |                          |
| Systolic blood pressure, mmHg | 129.7 | 129.5 | 130.2 | 0.04 |
| Systolic blood pressure available | 99.5 % | 99.7 % | 99.0 % | 0.01 |
| Diastolic blood pressure, mmHg | 75.1 | 74.9 | 75.5 | 0.05 |
| Diastolic blood pressure available | 99.5 % | 99.7 % | 99.0 % | 0.01 |
| Respiratory rate, breaths per minute | 18.1 | 18.1 (2.4) | 18.1 (2.5) | 0.00 |
| Respiratory rate available | 99.0 % | 99.2 % | 98.4 % | 0.01 |
| Heart rate, beats per minute | 79.8 | 79.5 | 80.3 | 0.05 |
| Heart rate available | 99.5 % | 99.7 % | 99.0 % | 0.01 |
| Oxygen saturation, % | 96.2 | 96.2 (2.6) | 96.3 (2.6) | 0.04 |
| Oxygen saturation available | 97.3 % | 97.4 % | 96.9 % | 0.01 |
| Body mass index, kg/m² | 28.7 | 29.7 (6.8) | 29.7 (6.7) | 0.00 |
| Left ventricular ejection fraction (%) | 31.7 | 31.7 (7.7) | 31.6 (7.7) | 0.01 |

Continuous variables listed as mean (standard deviation). Categorical variables listed as percentage (frequency). The standardized differences for continuous and binary variables are Cohen’s $d$; for categorical variables, Cramer’s $V$ was used. For both, an absolute value of the standardized difference of ≤0.20 is often considered small.

patients.

We evaluated GDMT treatment rates based on prescription fills within 6 months of the index date. These included the following: 1) guideline-recommended beta-blockers (BB) 2) any of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI) (ACEI/ARB/ARNI) 3) mineralocorticoid receptor antagonists (MRA); and 4) ARNI. In addition, we analyzed whether patients received ≥50% of the target dose for (5) BB and (6) ACEI/ARB/ARNI therapies [9,10]. We identified medications filled in the VA and non-VA medications entered into the VA EHR. We determined treatment rate based on the proportion of patients who filled a prescription, excluding patients who did not meet guideline-based indications or had concomitant medicines based on allergies, comorbidities, vitals, or laboratory values. Details regarding the cohort design and estimating treatment rates have been
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published previously [7].

We used a “slope and level” interrupted time-series model with mixed-effects logistic regression to evaluate the association between GDMT rates and the pandemic. We included a continuous time variable for the date of recent-onset HFrEF to account for pre-pandemic temporal trends. Seasonal indicators and facility random effects were included. In the main analysis, we classified patients as post-pandemic if their 6-month follow-up extended to March 2020 or later. In a sensitivity analysis, we only classified patients as post-pandemic if their index date was in March 2020 or later. We assumed that the pandemic could be associated with both an acute (level) change and a gradual (slope) change. To compare the frequency of recent-onset HFrEF diagnoses over time, we used a level-change model with Poisson regression.

We reported the level and slope changes as odds ratios (ORs). In addition, we calculated the average marginal effect of the pandemic for patients with an index date in April 2020 (follow-up period of 4/–9/2020); April 2020 marked the maximal reduction in VA in-person cardiology encounters and was early in the pandemic before health systems could fully adapt [6]. The average marginal effect was the estimated rate based on pre-pandemic trends. By performing stratified analyses and comparing the average marginal effects, we evaluated whether the association differed based on the following: (1) neighborhood social risk, (2) specialty drive time, and (3) facility COVID-19 burden. As sensitivity analyses, we adjusted for medical characteristics (Table 2). Hospitals with a high COVID burden had smaller reductions in ARNI uptake (OR 1.01 per month post-pandemic; 95% CI: 0.99–1.03) compared to those with a lower burden. However, there was a small, non-significant increase in the slope of ARNI uptake (OR 0.97 per month post-pandemic; 95% CI: 0.90–1.05).

The pandemic was associated with a 2.6% absolute decrease (95% CI: −5.0% to −0.8%) in the ARNI rate, although this effect was not significant. There was also a small, non-significant increase in the slope of ARNI uptake (OR 1.02 per month post-pandemic; 95% CI: 1.00–1.04). The pandemic was associated with a 2.6% absolute decrease (95% CI: 0.5%–4.7%) in ARNI rates. For the other treatment metrics, including the proportion of ≥50% of the target doses, estimated treatment rates were not significantly different from pre-pandemic trends.

Treatment rates were similar with and without the Medicare Part D data. For ACEI/ARB/ARNI, the difference was 1.8%; for BB, MRA, and ARNI, the differences were <0.8%.

We stratified the analyses based on three patient characteristics: (1) neighborhood social risk, (2) specialty drive time, and (3) facility COVID-19 burden. Overall, our results were similar across the characteristics (Table 2). Hospitals with a high COVID-19 burden had larger reductions in ARNI rates.

3. Results

We identified 71,428 patients with recent-onset HFrEF diagnosed between 1/1/2018 and 2/28/2021 including 43,346 patients pre-pandemic, 9,997 patients with partial pandemic overlap, and 18,185 patients with post-pandemic follow-up. The pandemic was associated with a 21.9% (95% CI: 19.7%–24.0%) decrease in the monthly number of recent-onset HFrEF diagnoses. Medical characteristics were relatively stable over time (Table 1).

Fig. 1 displays the GDMT rates over time with the OR for the level change post-pandemic and the slope change. For BB, ACEI/ARB/ARNI, and MRA therapies, there was no immediate change in the level associated with pandemic onset, although a small increase in the slope was observed.

Incorporating the level and slope changes, the pandemic was associated with a 1.7% absolute increase (95% CI: 0.2%–3.3%) in the ACEI/ARB/ARNI therapy rate for patients with a 6-month window from 4/–2020–9/2020 (Table 2). With ARNI, we found an immediate decrease with pandemic onset (post-pandemic OR 0.84; 95% CI: 0.75–0.94). However, there was a small, non-significant increase in the slope of ARNI uptake (OR 1.01 per month post-pandemic; 95% CI: 1.00–1.02). The pandemic was associated with a 2.6% absolute decrease (95% CI: 0.5%–4.7%) in ARNI rates. For the other treatment metrics, including the proportion of ≥50% of the target doses, estimated treatment rates were not significantly different from pre-pandemic trends.

3.1. Sensitivity analyses

In the sensitivity analyses, we varied our assumptions regarding patients with partial pandemic overlap. The reduction in ARNI rates persisted; however, when reclassifying the group with partial overlap as pre-pandemic or excluding them, the pandemic was no longer associated with a significant change in ACEI/ARB/ARNI rates. The results were also similar for the other GDMT rates. Adjusting for medical characteristics and excluding patients with missing relevant vitals/labs did not affect our findings.

4. Discussion

Among patients in a large integrated healthcare system, we found minimal change in the rates of HF GDMT early in the COVID-19 pandemic when in-person visits were at their nadir. However, ARNI therapy was an exception. While ARNI rates have gradually increased in
We also observed a decrease in the number of new HFrEF diagnoses. This may suggest a delayed diagnosis of incident HFrEF, consistent with the reduction in acute HF hospitalizations [12].

Our analysis focused on patients with a HFrEF diagnosis. The largest pandemic effect for patients with HFrEF may be the likelihood of timely encounters were provided virtually compared with 14% before the pandemic. This limited the ability to establish pre-COVID trends. The pandemic rapidly ushered in a new era of telehealth, which may explain why the HFrEF GDMT rates remained stable. However, beyond solely maintaining the suboptimal status quo, telehealth uptake may represent an opportunity to improve HFrEF disease management and GDMT rates.

### Table 2

Percent change in GDMT rates for patients with recent-onset HFrEF in April 2020 compared with pre-pandemic trends, stratified by key characteristics.

| BB ACEI/ ARNI | ≥50 % | ACE/ ARNI | ≥50 % |
|---------------|-------|-----------|-------|
| BB ARNI      | Target | ARNI Dose | Target |
| -0.6 to 2.5  | 3.3    | to 2.2    | to 1.8 | to 2.1 |
| p-value for difference between subgroups |
| Drive distance from VA specialty care |
| Short drive time | 1.0 | 1.8 | 0.0 | -3.3 | -0.7 | 0.0 |
| (0.1 to (1.8 | -3.8 | to -2.4 | -3.2 | to -2.3 to 1.6) | to 1.6) | 4.3) |
| Long drive time | 0.6 | 1.6 | 2.3 | -1.0 | 1.8 | 0.5 |
| (2.3 | 2.3 | 2.3 | 2.3 | 2.3 | 2.3 |
| p-value for difference between subgroups |
| 0.80 | 0.91 | 0.18 | 0.29 | 0.21 | 0.03 |

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### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

- AS consults for Acumen, LLC. SK reports receiving unrestricted grants from Novartis and personal fees from Bayer and Bristol-Myers Squibb outside the submitted work. MPT reports employment with iRhythm Technologies, Inc., personal fees from Medtronic Inc., personal fees from Abbott, grants from Bristol Myers Squibb, grants from American Heart Association, personal fees from Biotronik, personal fees from Sanofi, personal fees from Pfizer, grants from Apple, grants and personal fees from Bayer, personal fees from Myokardia, personal fees from Johnson & Johnson, personal fees from Milestone Pharmaceuticals, outside the submitted work.

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