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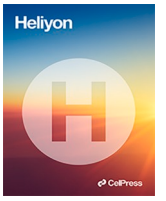

Research article

Association of multimorbidity with guideline-directed medical therapy intensification in heart failure: Findings from the EPIC-HF trial

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A B S T R A C T

A potential contributor to the suboptimal rates of guideline directed medical therapy (GDMT) prescribing for heart failure with reduced ejection fraction (HFrEF) is the burden of multimorbidity in patients with HFrEF. We examined the effect of multimorbidity on GDMT prescription in the EPIC-HF trial, finding that multimorbidity was associated with decreased likelihood of GDMT intensification. Further study is needed to guide treatment in high-risk, multimorbid patients with HFrEF.

1. Introduction

Despite proven benefits of guideline directed medical therapy (GDMT) for patients with heart failure with reduced ejection fraction (HFrEF), multiple studies have shown that rates of GDMT prescribing are suboptimal worldwide [1,2]. A potential contributor to suboptimal GDMT prescribing may be the high burden of multimorbidity in the heart failure population. Estimates consistently show that over 50 % of patients with heart failure have five or more co-occurring chronic conditions [3]. This complexity is associated with adverse outcomes including increased mortality and hospital admission [4]. Registries examining GDMT prescribing demonstrate associations between individual comorbidities and GDMT [1,2], but data are lacking on the cumulative effect of total burden of multimorbidity has at the point of care in the outpatient setting, where most GDMT titration takes place. Using data from the recently completed EPIC-HF trial [5], we examined the association of multimorbidity with the prescription and intensification of GDMT.

2. Methods

The EPIC-HF trial tested the effectiveness of a patient activation tool on GDMT prescribing at 1 month after a visit with an outpatient cardiology clinician. The electronically delivered tool consisted of a 3-min video and a 1-page medication checklist [5]. The

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animated video was delivered to patients as a weblink that explained the benefits of GDMT prescribing and intensification and rationale for patients engaging in discussions about their medications. The 1-page medication checklist was a list of drug classes, each with associated medication names and target doses for each medication (www.patientdecisionaid.org/heart_medications/).

The following comorbidities were manually captured: chronic obstructive pulmonary disease (COPD), liver disease, diabetes, cancer (excluding non-melanoma skin cancer), psychiatric disease, atrial fibrillation or flutter (AF), hypertension, chronic kidney disease (CKD, defined as estimated glomerular filtration rate $\leq$60 mL/min), and obesity (defined as body mass index $\geq$30 kg/m^2). Multimorbidity was defined as the presence of 2 or more comorbidities. Burden of multimorbidity was determined by the cumulative number of a patient's individual non-HFrEF comorbidities. Baseline GDMT prescription prior to the study visit included: evidence-based beta-blockers (EVBB), angiotensin-converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNI), and mineralocorticoid receptor agonists (MRA). The study was performed before FDA approval and widespread use of sodium-glucose transport protein 2 inhibitors for patients with HFrEF and use of this medication was not collected. GDMT intensification was defined as initiationing a GDMT medication, switching from ACE/ARB to ARNI, or dose intensifying GDMT medications by 1 month follow up [5]. The study complies with all ethics regulations and was reviewed and approved by the Colorado Multiple Institutional Review Board (COMIRB) #17–1249. All participants provided written informed consent to participate in the study.

3. Results

Of 306 patients enrolled in EPIC-HF, 292 had 1-month follow up data and were included in the present analysis. Overall, median patient age was 65 years, 71 % were male, and median LVEF was 32.5 %. Multimorbidity was common in the study population: 91.1 % had at least 1 non-HFrEF comorbidity, and 35.6 % of patients had 3 or more non-HFrEF comorbidities. The most common comorbidities were hypertension (51.7 %), obesity (41.4 %), CKD (32.9 %), AF (28.1 %) and diabetes (25.0 %). Increasing burden of multimorbidity was not associated with any significant differences in baseline prescription of ACE/ARB, ARNI, or MRA. An association was seen with increasing baseline doses of EVBB and greater burden of multimorbidity (Fig. 1A). In a multivariate model controlling for age, LVEF, BNP, gender, race/ethnicity, insurance status, and study arm in the original EPIC-HF trial, the presence of three or more non-HFrEF comorbidities, but not one or two, was associated with decreased likelihood of GDMT intensification (Fig. 1B). Individual comorbidities associated with decreased likelihood of GDMT intensification were diabetes (p = 0.02), hypertension (p = 0.003), and CKD (p = 0.047).

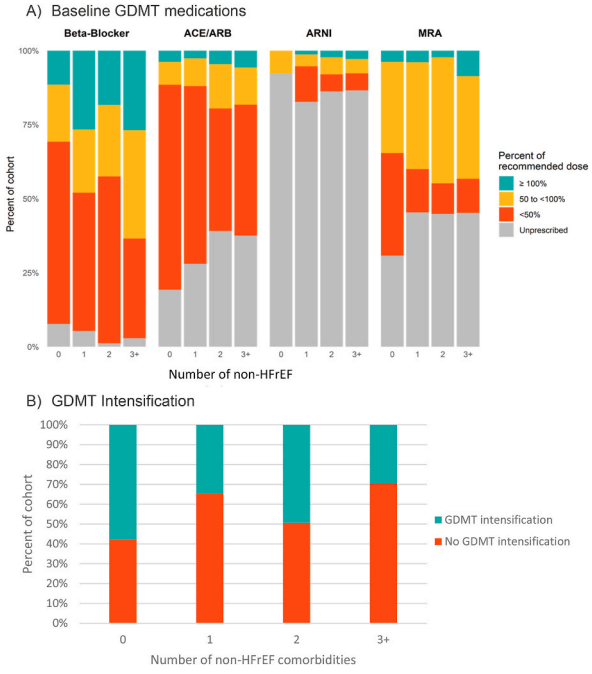

Fig. 1. Association of multimorbidity with baseline GDMT and GDMT intensification **A)** Baseline GDMT use shown as percent of guideline recommended dose by burden of multimorbidity. Increasing multimorbidity was associated with increased doses of beta blockers but not with other GDMT medication types. **B)** GDMT intensification by burden of multimorbidity. Adjusted relative risk from a multivariable model for each additional non-HFrEF comorbidity was 0.64 (0.40–1.02) for 1 non-HFrEF comorbidity, 1.0 (0.67–1.5) for 2 non-HFrEF co-morbidities, and 0.61 (0.39–0.95) for 3 or more non-HFrEF comorbidities. ACE/ARB indicates angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; MRA, mineralocorticoid receptor agonists; HFrEF, heart failure with reduced ejection fraction; GDMT, guideline-directed medical therapy.

4. Discussion

Multimorbidity was common in the study population and 3 or more comorbidities was associated with decreased likelihood of GDMT intensification. Current data is mostly limited to associations of individual comorbidities with GDMT prescribing and intensification. For example, the CHAMP-HF registry reported several such associations. Some are expected from clinical experience, such as the association of CKD with lower doses of ACE/ARB and MRA, but others are more unexpected such as an associations of atrial fibrillation with lower doses of EVBB and obesity and diabetes with higher doses [1]. The predictors and reasons for suboptimal GDMT prescribing remain incompletely understood. Assessment of total burden of multimorbidity, in addition to specific individual comorbidities, may be valuable information for clinicians prescribing GDMT and warrants further investigation.

Limitations of this analysis include inherent limitations of assessment of multimorbidity by disease counts, though these are widely used and are associated with important patient outcomes, limited non-cardiac medication data to assess polypharmacy, and relatively small sample size with lower rates of comorbidities in the trial population.

In summary, multimorbidity was common and 3 or more comorbidities was associated with decreased GDMT intensification. Further study is needed to characterize the relationship between multimorbidity and GDMT prescribing with the goal of improving outcomes in high-risk, multimorbid patients with HFrEF.

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Data availability statement

Data are available from the authors upon reasonable request.

Ethics declarations

The study complies with all ethics regulations.

- This study was reviewed and approved by the Colorado Multiple Institutional Review Board (COMIRB), with the approval number, with the approval number 17–1249.
- All participants provided written informed consent to participate in the study.

CRediT authorship contribution statement

Jonathan Lipsey: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Larry A. Allen:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Robert L. Page:** Writing – review & editing, Investigation. **Laura J. Helmkamp:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Grace Venechuk:** Writing – review & editing, Investigation. **Katy E. Trinkley:** Writing – review & editing, Investigation. **Daniel D. Matlock:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Colleen K. McIlvennan:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Larry Allen reports financial support was provided by American Heart Association. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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