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Short communication

Impact of sustained adherence to guideline-directed medical therapy on clinical outcomes in older adults with new-onset heart failure with reduced ejection fraction[☆]

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1. Introduction

Advanced age is a major risk factor for heart failure (HF), with a four-fold higher prevalence in patients over the age of 65 [1]. The 2022 AHA/ACC/HFSA guideline recommends initiation of four classes of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF)—beta blockers (BB), angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i) [2]. This recommendation is supported by multiple randomized control trials (RCTs) demonstrating improved outcomes with GDMT [2]. However, patients ≥ 70 years are underrepresented in these trials [3].

Caring for older patients involves balancing their medical complexities and polypharmacy with various social, behavioral, and environmental challenges. While existing observational studies suggest benefits of single or dual GDMT with BB and ACEi/ARB/ARNi in older adults, they focus on prescriptions at discharge rather than sustained use [4]. Therefore, we investigated the effect of sustained adherence to multi-drug GDMT in older patients with new HFrEF on all-cause mortality

compared to younger counterparts.

2. Methods

2.1. Study design

We conducted a retrospective cohort study using available de-identified and aggregated electronic health record (EHR) data from Stanford Health Care (SHC). The study period was January 1, 2010 to December 4, 2023. The study was exempt from informed consent by the Institutional Review Board due to de-identified nature of the data accessed.

2.2. Study population

Eligible patients included adults 18 to 90 years with incident HFrEF, defined as the presence of International Classification of Diseases (ICD) codes for systolic heart failure or at least two ejection fraction measures $< 40\%$. Eligible patients initiated GDMT including BB, ACEi/ARB/ARNi, and MRA. SGLT2i was not included as a requirement. The index date was defined as the date of being on full GDMT (BB, ACEi/ARB/ARNi,

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and MRA) concurrently. To avoid potential survivorship bias, patients were required to survive ≥ 12 months after the index date and have ≥ 1 prescription filled between 6 and 12 months. The cohort was further subdivided into younger (age 18–69 years) and older (age ≥ 70 years) groups. The fully-adherent GDMT group maintained all three GDMT prescriptions continuously for ≥ 12 months, a time frame selected to reflect sustained adherence, while the comparator group (partially-adherent GDMT group) discontinued one or more components of GDMT within 12 months.

2.3. Outcomes

The primary outcome was all-cause mortality at 24 months after the index date. We also evaluated secondary outcomes including major adverse cardiac events (MACE), defined as a composite of nonfatal myocardial infarction, nonfatal stroke, and any coronary revascularization in the study period, using ICD or CPT codes. Other secondary outcomes included any hospitalization, ICU admission, and HF hospitalization. An effect modification analysis of the primary outcome was performed by stratifying all patients in each age cohort based on their Charlson Comorbidity Index (CCI) and finding the best split point to generate quartiles with approximately equal numbers of patients [6].

2.4. Statistical methods

Baseline characteristics were compared between groups using chi-square tests for categorical variables and *t*-tests for continuous variables. We estimated the hazard ratio (HR) for the odds of the outcome in

the fully-adherent GDMT vs. partially-adherent groups using Cox proportional hazard regression. To address confounding, we performed 1:1 propensity score (PS) matching based on high-dimensional propensity scores derived from lasso regression on candidate covariates, with 5-fold cross validation [5]. Covariates included demographics (age, sex, race, ethnicity), clinical data (diagnoses, procedures, and comorbidities), and healthcare utilization (counts of prescription and healthcare encounters). Comorbidities were defined using CCI [6]. Kaplan-Meier curve for the primary outcome was generated by censoring patients who were lost to follow-up or when there was no more available data after a certain time point. Analysis was conducted by Atropos Health using R, version 4.2.

3. Results

We identified a total of 4559 patients with incident HFReF who met inclusion criteria. Patients were further divided into ages 18–69 years ($N = 2846$) and ages ≥ 70 years ($N = 1713$). After propensity score matching the fully-adherent GDMT group with the partially-adherent group in each age category, there were a total of 1970 patients in the younger cohort and 1160 patients in the older cohort (Table 1). The fully-adherent and partially-adherent groups within each age cohort had similar baseline characteristics; however, the fully-adherent group in both age cohorts had a lower mean serum creatinine at baseline compared to the control group. This difference in baseline renal function persisted when estimated glomerular filtration rate (eGFR) was calculated and considered. In addition, eGFR was lower in the age ≥ 70 years group compared to the younger group (Table 1). Other significant

Table 1

Baseline characteristics of propensity score-matched study cohorts stratified by GDMT adherence and age.

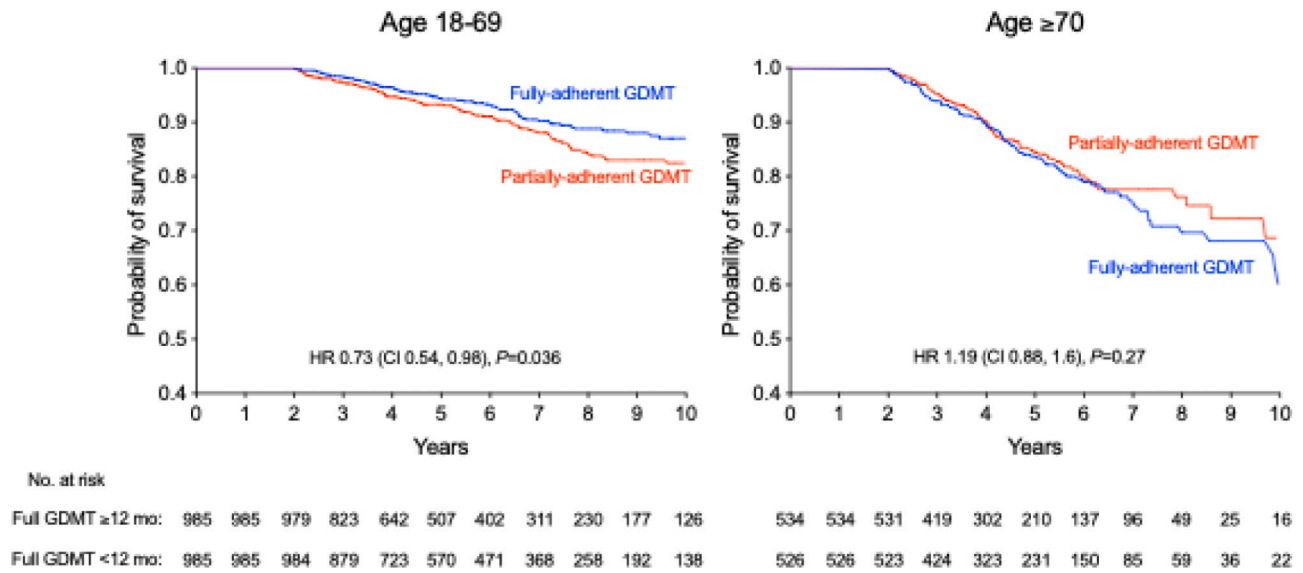
	Full GDMT LESS than 12 M PSmatched 18–69 yrs	Full GDMT MORE than 12 M PSmatched 18–69 yrs	P-value	Full GDMT LESS than 12 M PSmatched ≥ 70 yrs	Full GDMT MORE than 12 M PSmatched ≥ 70 yrs	P-value
N	985	985		580	580	
Female (%)	303 (30.8 %)	309 (31.4 %)	0.76	229 (39.5 %)	239 (41.2 %)	0.56
Mean age (sd)	55.1 (11.6)	54.8 (11.9)	0.57	77.3 (5.2)	77.5 (5.1)	0.51
Race			0.62			0.34
White (%)	525 (53.3 %)	529 (53.7 %)		359 (61.9 %)	381 (65.7 %)	
Other (%)	186 (18.9 %)	181 (18.4 %)		104 (17.9 %)	78 (13.4 %)	
Asian (%)	137 (13.9 %)	156 (15.8 %)		71 (12.2 %)	72 (12.4 %)	
Black (%)	137 (13.9 %)	119 (12.1 %)		46 (7.9 %)	49 (8.4 %)	
Hispanic (%)	141 (14.3 %)	145 (14.7 %)		55 (9.5 %)	53 (9.1 %)	
Index year			0.84			0.48
2010–2014 (%)	212 (21.5 %)	219 (22.2 %)		80 (13.8 %)	69 (11.9 %)	
2015–2019 (%)	492 (49.9 %)	479 (48.6 %)		330 (56.9 %)	326 (56.2 %)	
2020–present (%)	281 (28.5 %)	287 (29.1 %)		170 (29.3 %)	185 (31.9 %)	
Mean follow-up days (sd)	2701.2 (2095.8)	2907.4 (2292.9)	0.0037	1840.6 (826.3)	1915.3 (853.1)	0.13
Number of encounters (sd)	3.7 (3.4)	3.8 (3.7)	0.53	4.4 (3.7)	4.3 (3.6)	0.64
Baseline smoking (%)	94 (9.54 %)	108 (10.96 %)	0.20	29 (5 %)	30 (5.17 %)	1
Baseline BNP (sd)	3483.8 (4331.7)	3332.1 (4335.3)	0.44	3877.9 (4507.2)	3568 (4200.4)	0.23
Baseline BMI (sd)	30.3 (7.7)	30.3 (7.4)	1	28 (5.8)	28.1 (5.9)	0.77
Baseline Cr (sd)	1.2 (0.5)	1.1 (0.4)	<0.001	1.2 (0.4)	1.1 (0.3)	<0.001
Baseline eGFR (sd)	71.7 (24.6)	81.7 (22.0)	<0.001	61.4 (19.7)	66.3 (17.9)	<0.001
Baseline EF (sd)	33.9 (14.3)	32.6 (12.2)	0.0030	38.6 (14)	35.8 (12.4)	<0.001
Baseline HR (sd)	82.7 (17.3)	84.4 (20.9)	0.049	77.8 (16.5)	77.9 (16.9)	0.92
Baseline SBP (sd)	123.7 (22.8)	126 (22.3)	0.024	127.3 (21.1)	130.3 (22.1)	0.018
Baseline Na (sd)	137.7 (3.8)	138.1 (3.5)	0.015	138.2 (3.6)	138.5 (3.9)	0.17
Comorbidity score (sd)	4.5 (2.6)	4.7 (2.9)	0.11	7.7 (2.8)	7.7 (3)	1
Malignancy (%)	76 (7.72 %)	117 (11.88 %)	<0.001	118 (20.34 %)	133 (22.93 %)	0.21
Diabetes (%)	328 (33.3 %)	314 (31.88 %)	0.47	195 (33.62 %)	204 (35.17 %)	0.57
MI (%)	305 (30.96 %)	332 (33.71 %)	0.15	191 (32.93 %)	217 (37.41 %)	0.080
Renal disease (%)	318 (32.28 %)	264 (26.8 %)	0.0020	253 (43.62 %)	208 (35.86 %)	0.0040
Duration ACEi/ARB/ ARNI (sd)	428.6 (57.4)	1501.2 (1137.9)	<0.001	634.9 (796.8)	1555 (1110.4)	<0.001
Duration BB (sd)	457.2 (578.7)	1529 (1097.5)	<0.001	708.2 (852.7)	1586.2 (1095.3)	<0.001
Duration MRA (sd)	243.6 (317.2)	1262 (942.5)	<0.001	275 (390.3)	1094.1 (780.3)	<0.001
Duration full GDMT (sd)	154.5 (75.3)	1156.8 (869)	<0.001	152.1 (75)	944.8 (592.1)	<0.001

Duration of individual and full GDMT prescription during study period is included for the GDMT-adherent and control group of each age cohort.

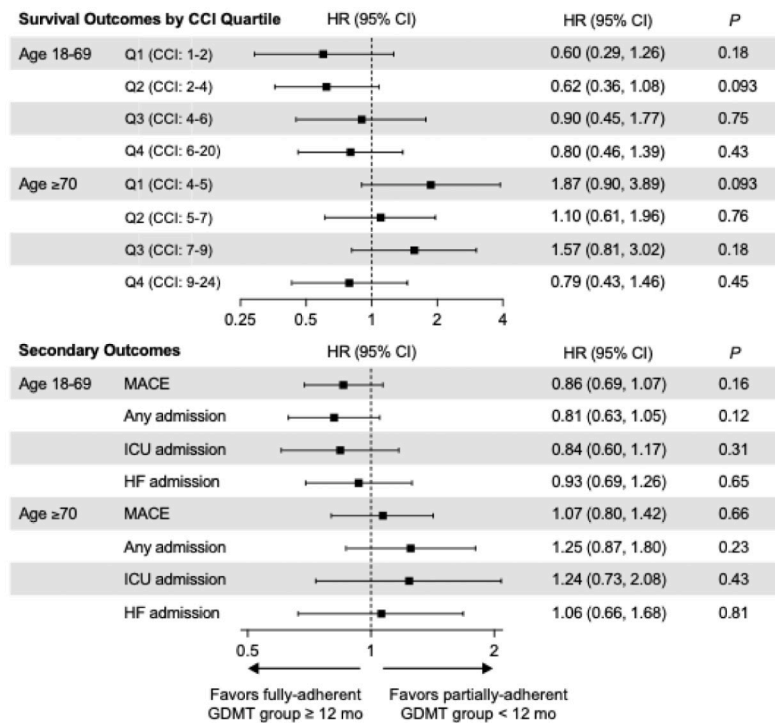
baseline differences included left ventricular ejection fraction, which was lower in sustained adherence GDMT group in both age cohorts. Systolic blood pressure and serum sodium were also higher in the sustained adherence GDMT groups in both age cohorts (Table 1).

As expected, the total duration of continuous exposure to full GDMT was significantly longer in the fully-adherent GDMT group compared to

the control group in both age groups (age 18–69 years: mean 154.5 days, SD 75.3 days vs. mean 1156.8 days, SD 869 days, $P < 0.001$; age ≥ 70 years: mean 152.1 days, SD 75 days vs mean 944.8 days, SD 592.1 days, $P < 0.001$). Additionally, the mean duration of treatment with individual GDMT medications was significantly higher in the fully-adherent GDMT group (Table 1).



(a)



(b)

Fig. 1. (a) Kaplan-Meier curves for survival stratified by age and adherence (b) Forest plot of effect modification analysis of the primary outcome stratified by CCI and secondary outcomes.

The primary outcome of all-cause mortality at 24 months occurred in 81 patients in the fully-adherent GDMT group and 99 patients in the control group in the matched younger cohort (HR 0.73, 95 % CI 0.54–0.98, $P = 0.036$). In contrast, there was no significant difference in all-cause mortality among those in the matched age ≥ 70 years cohort, with 76 events in the partially-adherent group and 96 events in the fully-adherent group (HR 1.19, 95 % CI 0.88–1.6, $P = 0.27$). Kaplan-Meier survival curves showed that this difference extends beyond the study period (Fig. 1a). In an effect modification analysis of the primary outcome stratified by CCI, there is no significant difference based on CCI in either age cohort (Fig. 1b). None of the secondary outcomes were significantly different between the fully-adherent GDMT and partially-adherent groups; however, there was a trend toward improved secondary outcomes in the younger cohort. This trend was not observed in older patients (Fig. 1b).

4. Discussion

The pillars of GDMT have revolutionized the care of patients with HFrEF [2]. While there is a paucity of evidence in older patients, observational studies have linked individual GDMT prescriptions post-discharge to improved outcomes [4]. Our findings suggest sustained adherence to multi-drug GDMT may *not* confer a survival benefit in older adults (≥ 70 years) with incident HFrEF. Notably, younger patients with HFrEF who had sustained adherence to full GDMT had a 27 % lower risk of all-cause mortality compared to controls, as well as a trend toward improved secondary outcomes. This discrepancy in clinical benefit is likely related to a greater burden of comorbidities in older patients that may attenuate the benefit of GDMT.

Our study has several limitations. As a retrospective observational study, it is subject to residual confounding from unmeasured variables. Selection bias may exist due to our inclusion criteria and our required survival period, resulting in a healthier than typical HFrEF patient population. This strategy may have led to exclusion of patients who were less likely to be started on multiple medications. Limited EHR data prevents stringent verification of adherence, and pharmacy prescription dispensing records were utilized as a proxy. Data regarding GDMT dosage and cause of death is unavailable in our dataset. Additionally, we excluded SGLT2i from this analysis due to insufficient data given that recent guideline updates recommending inclusion of SGLT2i as a standard part of GDMT were released in 2022, only 1 year before the conclusion of our study period.

Polypharmacy is highly prevalent at the time of discharge in older patients with heart failure and is well-documented to be associated with an increase in mortality [7,8]. Thus, caring for this population requires meticulously balancing initiating evidence-based therapy and the potential harm from polypharmacy. While contemporary care for patients with HFrEF emphasizes intensive medication regimens, our study challenges the universal applicability of this approach in older adults. Our analysis highlights the challenge of balancing therapeutic benefit and risks of polypharmacy in older patient populations with HFrEF. The observations of this analysis also underscore the need for RCTs targeting

older adults with HFrEF and a more nuanced, patient-centered approach that prioritizes individualized risk-benefit assessments in this population.

CRedit authorship contribution statement

Xichong Liu: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization. **Chan Hee J. Choi:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation. **C. William Pike:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Gavin Hui:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Jananee Muralidharan:** Writing – review & editing, Investigation. **Shriram Nallamshetty:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Ethical statement

The authors declare that all procedures were performed in compliance with relevant laws and institutional guidelines. The data utilized in the manuscript is from a de-identified database and human subjects cannot be identified. According to the local Institutional Review Board, such research is exempt from review.

Declaration of competing interest

The authors 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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