Impact of CYP2D6-Inhibiting Antidepressants on Beta-Blocker Dosing and Safety Outcomes in Heart Failure

David Novak, PharmD Candidate[1,2]; Erica Stevens, PharmD, BCGP[2]; Matthew Pike, PharmD[2]
[1]Southern Illinois University Edwardsville School of Pharmacy, Edwardsville, IL
[2]Carle Foundation Hospital, Urbana, IL

SCHOOL OF PHARMACY

BACKGROUND

- Heart Failure (HF) affects an estimated 6 million adults in the United States[1] with depression occurring in approximately 1-4 adults[2].
- Guidelines recommend the use of beta-blockers due to their benefits in reducing mortality and hospitalization risk[3].
- Multiple studies show that patients do not reach guideline-directed target doses which is often complicated by factors affecting patient adherence and barriers in provider prescribing.
- Select antidepressants inhibit CYP2D6, the primary enzyme responsible for metabolizing the beta-blockers metoprolol and carvedilol. This drug–drug interaction (DDI) can significantly increase beta-blocker plasma concentrations, potentially contributing to adverse effects or imparting desired therapeutic effect at lower than anticipated dosing thresholds.
- Studies have demonstrated that strong CYP2D6 inhibitors can increase metoprolol plasma concentrations by 180–500%[4] (≥ 5-fold AUC increase) which may lead to adverse cardiovascular outcomes such as bradycardia, hypotension, syncope, and falls.

OBJECTIVES

- To investigate the clinical impact of concurrent CYP2D6 substrate beta-blockers and CYP2D6 inhibitor antidepressants on readmissions, adverse events and beta-blocker dosing patterns in patients with HF and depression.

METHODS/RESULTS

Design
- Retrospective cohort study at a 489-bed vertically integrated community teaching hospital
- Chart review from electronic medical record (EMR)

Inclusion
- Adults ≥18 years old
- Patients with a depression-associated ICD-10 diagnoses
- On a baseline CYP2D6 inhibiting antidepressant and newly co-prescribed a CY2D6 substrate beta-blocker (metoprolol tartrate, metoprolol succinate or carvedilol) within 14 days after discharge of a heart failure diagnosis.
- Outcomes were assessed over a 365-day period starting from the prescription date of the CYP2D6 substrate beta-blocker.

Exclusion
- Actively taking metoprolol tartrate, metoprolol succinate or carvedilol 3 months prior to the index heart failure admission.
- Not actively taking an antidepressant or taking any other antidepressant that was not included in the study.

Group Stratification[5]

Cohort	Inhibitory Strength	Antidepressants Included
Inhibitor group	Strong CYP2D6 Inhibitor	bupropion, fluoxetine, paroxetine
	Moderate CYP2D6 Inhibitor	duloxetine
Comparator group	Weak CYP2D6 Inhibitor	citalopram, escitalopram, sertraline, venlafaxine
	Non-Interacting Agent[6]	mirtazapine, trazodone, vilazodone, fluvoxamine, desvenlafaxine, vortioxetine

Primary Outcome
- Incidence of all-cause hospital readmission

Secondary Outcomes
- Readmission for HF exacerbation
- Plausible adverse events related to DDI (hypotension, bradycardia, syncope, falls, fractures, pacemaker placement) with admission
- Reported falls without admission
- Assessment of maximum daily beta-blocker dose achieved

Figure 1: Patient Inclusion/Exclusion

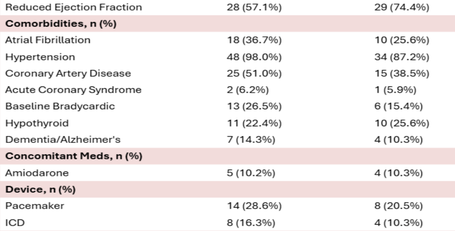

Table 2 – Baseline Characteristics

	Inhibitor Group (n=49)	Comparator Group (n=39)
Age (Years), n (%)		
50-69	20 (40.8%)	17 (43.6%)
70-79	18 (36.7%)	10 (25.6%)
≥80	11 (22.4%)	12 (30.8%)
Sex, n (%)		
Male	20 (40.8%)	16 (41.0%)
Female	29 (59.2%)	23 (59.0%)
Race/Ethnicity, n (%)		
White	42 (85.7%)	37 (94.9%)
African American	4 (8.2%)	2 (5.1%)
Other	2 (4.1%)	0 (0.0%)
Weight (kg), n (%)		
≤85 kg	34 (69.4%)	26 (66.7%)
≥86 kg	15 (30.6%)	13 (33.3%)
HF Classification, n (%)		
Preserved Ejection Fraction	7 (14.3%)	2 (5.1%)
Improved Ejection Fraction	3 (6.1%)	0 (0.0%)
Mildly Reduced Ejection Fraction	11 (22.4%)	8 (20.5%)
Reduced Ejection Fraction	28 (57.1%)	29 (74.4%)
Comorbidities, n (%)		
Atrial Fibrillation	18 (36.7%)	10 (25.6%)
Hypertension	48 (98.0%)	34 (87.2%)
Coronary Artery Disease	25 (51.0%)	15 (38.5%)
Acute Coronary Syndrome	2 (6.2%)	1 (5.9%)
Baseline Bradycardic	13 (26.5%)	6 (15.4%)
Hypothyroid	11 (22.4%)	10 (25.6%)
Dementia/Alzheimer's	7 (14.3%)	4 (10.3%)
Concomitant Meds, n (%)		
Amiodarone	5 (10.2%)	4 (10.3%)
Device, n (%)		
Pacemaker	14 (28.6%)	8 (20.5%)
ICD	8 (16.3%)	4 (10.3%)

Table 3 – Results

	Inhibitor Group (n=49)	Comparator Group (n=39)	p-value
Primary Endpoint			
All Cause Hospital Readmissions	27 (55.1%)	20 (51.3%)	0.72
1 Hospital Readmission	10 (20.4%)	5 (12.8%)	
≥2 Hospital Readmissions	17 (34.7%)	15 (38.5%)	
Secondary Outcomes:			
HF Readmissions	12 (24.5%)	17 (43.6%)	0.06
1 Readmission	6 (12.2%)	9 (23.1%)	
≥2 Readmissions	6 (12.2%)	8 (20.5%)	
Fall Admissions	4 (8.2%)	2 (5.1%)	0.57
1 Admission	3 (6.1%)	2 (5.1%)	
≥2 Admissions	1 (2.0%)	0 (0.0%)	
Fracture Admission	2 (4.1%)	1 (2.6%)	0.70
Bradycardia Admission	0 (0.0%)	0 (0.0%)	-
Syncope Admission	1 (2.0%)	1 (2.6%)	0.86
Hypotension Admission	2 (4.1%)	1 (2.6%)	0.70
Reported Falls w/o Admission	10 (20.4%)	6 (15.4%)	0.55
1 Fall	4 (8.2%)	6 (15.4%)	
≥2 Falls	6 (12.2)	0 (0.0%)	
Other Secondary Outcomes			
Pacemaker Placed	4 (8.2%)	3 (7.7%)	0.93
Beta-Blocker Transition	2 (4.1%)	3 (7.7%)	0.47
Reason for Beta-Bocker Transition			
Indication (Reduced EF)	1 (2.0%)	2 (5.1%)	
Hypotension	0 (0.0%)	1 (2.6%)	
Hypertension	1 (2.0%)	0 (0.0%)	

Table 4 – Maximum Daily CYP2D6 Beta-Blocker Dose Achieved

	Inhibitor Group (n=49)	Comparator Group (n=39)	p-value
Medication			
Metoprolol (succinate/tartrate)	34	29	
≤75 mg/day (%)	27 (79.4%)	23 (79.3%)	0.992
Carvedilol	15	10	
≤25 mg/day (%)	12 (80.0%)	9 (90.0%)	0.513

CONCLUSION

- Although not statistically significant, there was an increased incidence of readmission in the inhibitor group to all-cause diagnoses, falls, fractures, and hypotension. There were also increased falls without readmission and pacemaker placement suggesting a potential increased rate of adverse events.
- Conversely, the Inhibitor Group had a lower rate of HF readmissions compared to the Comparator Group (24.5% vs 43.6%, p=0.06)
- Doses of metoprolol and carvedilol significantly less than guideline-directed recommendations were common in both cohorts.
- While there may be many contributing factors to decreased daily doses of CYP2D6 substrate beta-blockers, our study suggests a strong/moderate CYP2D6 inhibitor antidepressant may have a clinical effect on clinical outcomes.

LIMITATIONS/FURTHER STUDY

Limitations
- ICD-10 codes limited diagnoses to specific codes provided at admission
- Data collection was limited to Carle EPIC system. Admissions, adverse events, or deaths at outside facilities were not analyzed.
- Did not assess for adherence for any medications on the patients chart
- Adverse events without admission were subject to self-reporting
- Pharmacogenomic testing was not assessed
- HF readmissions were not stratified by the beta-blocker type

Further Study
- Future research should investigate if the CYP2D6 interaction should address lower beta-blocker target dosing in heart failure patients to allow for safe yet effective outcomes.

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DISCLOSURES

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

David Novak: Nothing to Disclose
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Matthew Pike: Nothing to Disclose
Contact: dnovak@siue.edu