Abstract

Background: Depression is a common comorbidity in heart failure (HF). Many antidepressants inhibit CYP2D6, the enzyme metabolizing beta-blockers metoprolol and carvedilol. This drug-drug interaction (DDI) can significantly increase beta-blocker plasma concentrations, potentially leading to the appearance of suboptimal dosing or adverse effects.

Objective: To investigate the clinical impact of concurrent CYP2D6 substrate beta-blockers and CYP2D6 inhibitor antidepressants on readmissions, adverse events (hypotension, bradycardia, syncope, falls, fractures), and beta-blocker dosing patterns in patients with HF and depression.

Methods: This retrospective cohort study (January 2017–July 2024) analyzed adult patients with HF and depression co-prescribed a CYP2D6 substrate beta blocker and antidepressant. Patients were stratified into an Inhibitor group (strong/moderate CYP2D6 inhibitors) and a Comparator group (weak CYP2D6 inhibitors/non-interacting agents). Outcomes were assessed over a 365-day period. The primary outcome was all-cause rehospitalization. Secondary outcomes included HF readmissions, adverse events (hypotension, bradycardia, syncope, falls, fractures), and assessment of maximum daily beta-blocker dose achieved.

Results: The analysis included 88 patients (Inhibitor n=49, Comparator n=39). All-cause rehospitalization rates were similar between groups (55.1% vs 51.3%; p=0.72). The Inhibitor group had fewer HF-specific readmissions (24.5% vs 43.6%; p=0.06). The inhibitor group experienced a higher incidence of falls with admissions (8.2% vs 5.1%; p=0.57) and falls without admission (20.4% vs 15.4%; p=0.55). There were no significant differences between groups in other secondary outcomes. Patients in both the Inhibitor and Comparator groups experienced lower maximum CYP2D6 beta-blocker dosing per day. 79.4% of the Inhibitor group, and 79.3% of the Comparator group were on a metoprolol dose of ≤ 75 mg/day (p=0.992). 80% of the Inhibitor group and 90% of the Comparator group were on carvedilol doses of ≤ 25 mg/day (p=0.513).

Conclusion: There were no significant differences between the Inhibitor and Comparator groups on all-cause rehospitalizations. Both groups experienced low total CY2D6 beta-blocker daily doses. Although there were no significant differences in maximum daily dosing among groups, the Inhibitor group had numerically fewer heart failure readmissions. Future research is warranted to guide clinicians in appropriate CYP2D6 beta-blocker dosing when prescribed an interacting antidepressant.