Heart failure (HF) accounts for >1 million primary and 3 million secondary admissions each year in the United States alone (1). Robust drug and device development for chronic HF has contributed to significant improvements in length of stay, annual readmissions, and 1-year mortality (2). Unfortunately, post-discharge mortality and readmission rates at 60 to 90 days approach 15% and 30%, respectively (3). Recent penalties by the Centers for Medicare and Medicaid Services for greater than expected 30-day hospital readmission rates for HF patients have reinvigorated a national focus on reducing early rehospitalization risk.

Data from large inpatient HF registries suggest that the use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs) and beta-blockers at the time of discharge was associated with improved mortality or rehospitalization rates at 60 to 90 days follow-up in patients with HF with reduced, but not preserved, ejection fraction (EF) (4–6). Although these therapies can modify medium- and long-term disease course, short-term prognosis may be more related to hemodynamic abnormalities rather than disease progression. Unfortunately, these unacceptably high readmission rates occur despite the frequent use of these guideline-based therapies (7) and adherence to several national performance measures for patients with HF.

There is an urgent call to action (8) to change current clinical practices and to stem the growing rates of early HF readmissions. It may be important to revisit and re-examine the available medical therapies that have the potential to reduce early readmission risk in patients with HF, in particular, digoxin and mineralocorticoid receptor antagonists (MRAs).

**Digoxin**

The landmark National Institutes of Health–sponsored DIG trial (Digitals Investigators Group) demonstrated that digoxin improved all-cause and HF-specific hospitalization rates without adversely influencing survival in patients with chronic HF in sinus rhythm when added to diuretics and ACE inhibitors (9). Furthermore, all of the current drug armamentarium of life-prolonging therapies has been tested, in which the majority of patients were receiving background digitalis therapy. Given its immediate beneficial hemodynamic and neurohormonal effects (Fig. 1), a reduction in HF events may be expected to occur very soon after initiation of therapy. This may be particularly important to achieve a goal of reducing early readmission rates that are related to hemodynamic abnormalities rather than progression of HF. Despite approval by the U.S. Food and Drug Administration in 1998 and tempered support from guideline committees of this time-honored agent, the use of digoxin has precipitously decreased in the past several decades. Digoxin is currently indicated as a Class IIa agent (Level of Evidence: C) for patients with stage C HF with reduced EF based on the most recent iteration of the American College of Cardiology/American Heart Association guidelines (4). The reasons underlying this decline may be related to the lack of established mortality effect, the lack of industry support, and the absence of this.
topic at national and international meetings. Because digoxin has recently been shown to reduce all-cause hospital admission within 30 days of administration, it is plausible that this agent could reduce 30-day all-cause readmission rates in patients hospitalized with HF (10). A phase II study is currently under consideration by the National Heart, Lung, and Blood Institute’s Heart Failure Network to investigate the effects of newly initiated digoxin during HF hospitalization on 60-day combined mortality and HF readmission.

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (NMRA), such as spironolactone and eplerenone, are another class of agents that have a demonstrable readmission risk reduction, but are yet to have widespread uptake in the United States. Less than one third of eligible patients without any specific contraindications received an MRA at discharge in the Get With The Guidelines-HF quality improvement registry of >40,000 patients hospitalized for HF (11). The RALES trial (Randomized Aldactone Evaluation Study) (12) demonstrated robust reduction in mortality and hospitalization rate in 1,663 stable outpatients with New York Heart Association functional class III and IV disease over a 2-year follow-up period. More recently, the EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) (13) extended these benefits to patients with only mild symptoms. The observed effects are likely mediated by promoting reverse cardiac remodeling, attenuating arrhythmogenesis, and reducing myocardial fibrosis (Fig. 1). In a recent large clinical effectiveness study of patients with HF and reduced EF, newly initiated MRAs during hospitalization was associated with a lower risk of first readmission for HF at the expense of a higher risk of readmission related to hyperkalemia and no difference in mortality after discharge (14). Proper patient and dose selection and close clinical monitoring are critical and may avoid untoward side effects. In fact, data from randomized clinical trials suggest that rates of severe hyperkalemia can be relatively low in a setting where there is close follow-up and protocol-driven laboratory monitoring (12,13). Preliminary data from the REMINDER (Impact of Eplerenone on Cardiovascular Outcomes in Patients Post-Myocardial Infarction) trial showed that early in-hospital initiation of eplerenone in patients with acute myocardial infarction was effective in improving natriuretic peptide profiles, without substantially increasing the risk of adverse effects.

Early Drug Effects on Readmission

Interestingly, the absolute risk reductions in admissions observed in trials evaluating digoxin and MRAs are comparable or even surpass those seen with newer and more

Figure 1 Early Physiological Effects of Digoxin and Mineralocorticoid Antagonists on Patients Hospitalized for Heart Failure

Limited data exist evaluating the true hemodynamic and clinical effects of digoxin and mineralocorticoid antagonists in patients hospitalized for heart failure. These theoretical effects are based largely on early human and animal studies. BP = blood pressure; CO = cardiac output; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; PCWP = pulmonary capillary wedge pressure.
expensive agents, such as ivabradine (15). Indeed, although significant heart rate reduction was achieved with ivabradine within the first 2 weeks of therapy, a concomitant impact on early readmissions was not apparent based on inspection of survival curves. Digoxin demonstrated absolute risk reductions in all-cause-, cardiovascular-, and HF-related 30-day admission rates of 2.7%, 3.0%, and 2.5%, respectively, in the DIG trial (10). Event rate reductions may be even more robust in specific high-risk patient subgroups (16). Similarly, eplerenone reduced the risk of 30-day HF hospitalizations by 18% in patients with post-myocardial infarction left ventricular dysfunction in the EPHEBUS trial (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study) (17,18).

**Important considerations.** The DIG trial was performed between 1991 and 1993 in an era when more contemporary therapies (beta-blockers, MRAs, and devices) were not routinely used (9). It is difficult to fully ascertain whether digoxin and MRAs will offer additional benefit over device implantation. However, indirect observational data suggest that there is an incremental benefit of HF medications and device therapy in patients with HF and reduced EF such that added benefit in those who already have a cardiac resynchronization therapy defibrillator device or have one newly placed could be expected (19). Further study of these agents in contemporary patients with cardiac resynchronization therapy defibrillator devices would be desirable. Additionally, ~45% of patients included in the DIG trial were on digoxin therapy before study enrollment, which may explain some, but not all, of the pronounced early effects of digoxin (10). However, the effect of digoxin on the 30-day all-cause hospitalization endpoint was similar in pre-trial digoxin users (hazard ratio [HR]: 0.53, 95% confidence interval [CI]: 0.37 to 0.78) and digoxin-naive patients (HR: 0.82; 95% CI: 0.57 to 1.20; p = 0.107 for interaction) (10). Furthermore, it is noteworthy that other than in the EPHEBUS trial, the data presented here are derived from ambulatory patients with HF (namely, DIG, RALES, and EMPHASIS-HF). However, the immediate post-discharge period may represent a critical period of transition from acute to chronic HF, in which reconciliation and optimization of the patient’s therapeutic regimen are essential and may produce even greater benefits. Regardless, the extrapolation of these data from chronic HF to the inpatient setting should be done with caution, especially with fluctuation renal function and electrolyte imbalances. Careful attention to dose selection and treatment monitoring of digoxin levels is particularly important in this setting. It should be recognized that this paper focuses exclusively on evidence-based pharmacological therapies targeting early hospitalization risk. Several non-pharmacological approaches such as HF disease management programs, educational initiatives, cardiac rehabilitation programs, and other strategies that target adherence to medications may also afford improvements in early readmissions (20–22). In addition to targeted add-on therapy, substantial opportunity may exist to improve implementation and dosing of existing guideline-directed regimens before discharge to reduce early readmission burden (20–22).

As health care costs continue to increase, we must work to improve patient outcomes within the current framework using available therapies. Given recent Centers for Medicare and Medicaid Services penalties, clinicians should consider the use of available therapies that have known benefits on hospitalization risk. Unadjusted 30-day readmission rate may not be the ideal metric (23) in that it inappropriately penalizes health systems that successfully reduce short-term mortality and hospitals that care for the sick and socioeconomically disadvantaged (24). However, focusing attention on the early post-discharge timeframe may help improve specific patient-centered outcomes. At present, most clinicians equate evidence-based with life-prolonging therapies. Unlike other areas of cardiology, the benefits of reducing admission rates and improving quality of life may have been underrecognized in HF. Future clinical trials should give consideration to including early post-discharge events as clinical endpoints to help define early success of therapies. Current national performance measures should be expanded to focus on improving uptake and physician use of other evidence-based therapies in HF aside from ACE inhibitors/ARBs and beta-blockers. Hospitalization for HF remains a major clinical entity in the United States, representing >6.5 million hospital days. Before moving back to the drawing board and drug development engine, efficacious therapies that are affordable, highly cost-effective, and already widely available should be considered (25). Based on available data and unacceptably high readmission rates, digoxin and MRAs should be considered in patients hospitalized for HF and reduced EF unless specifically contraindicated.

**Reprint requests and correspondence:** Dr. Mihai Gheorghiade, Center for Cardiovascular Innovation, Northwestern University, Feinberg School of Medicine, 645 North Michigan Avenue, Suite 1006, Chicago, Illinois 60611. E-mail: m-gheorghiade@northwestern.edu.

**REFERENCES**


