Heart Failure Guideline Directed Medical Therapy: Which One and When?

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Over the past several decades, major strides have been made in the management of heart failure with reduced ejection fraction (HFrEF). The 2022 AHA/ACC/HFSA guidelines recommend four drug classes in all patients with symptomatic HFrEF [1]. This guideline directed therapy (GDMT) includes renin angiotensin receptor (RAAS) blockade, preferentially with angiotensin receptor neprilysin inhibitors (ARNI), beta blockers, mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter inhibitors (SGLT2i). An optimal GDMT regimen has been estimated to achieve greater than 70% mortality benefit [2]. Unfortunately, most patients with HFrEF are not taking the appropriate medications or doses. Several clinical challenges and questions arise when attempting to initiate and titrate these medications. Although the guidelines offer several suggestions for this process, each patient’s hemodynamic profile varies markedly, thus making development of a uniform algorithm difficult. As new trials are performed, greater emphasis is being placed on more aggressive titration of GDMT. Most importantly, initiation of GDMT should start during hospitalization and continue with close outpatient follow-up.

When a patient is hospitalized for acute decompensated heart failure, clinicians must take advantage of the opportunity to initiate or optimize current GDMT under close observation. In the decision to initiate GDMT, volume status, blood pressure, heart rate, and kidney function should be considered. Beta blockers (carvedilol, metoprolol succinate, and bisoprolol) and ARNI should be given priority, because of their established mortality benefits [4–7]. Patients with substantial congestion better tolerate ARNI or RAAS blockade, because of afterload reduction and augmented diuresis. Beta blockers should be started when the patient is euvolemic before discharge. However, beta blockers taken prior to admission must not be stopped during acute decompensation, unless concern exists for cardiogenic shock or symptomatic hypotension [7].

In addition to ARNI, SGLT2i augment diuresis through an osmotic effect and can safely be started in hospitalized patients who are euvolemic or hypertone [8]. The SOLOIST-WHF trial enrolled patients with heart failure and diabetes with acute decompensated heart failure before or within 3 days of discharge to receive sotagliflozin. The combined endpoint of cardiovascular death, HF hospitalization, or urgent HF visit decreased by 33% with this treatment [8]. Overall SGLTi are very well tolerated, but special attention must be paid to the few adverse effects, such as soft tissue infections, euglycemic diabetic ketoacidosis, and volume depletion, if combined with overdiuresis.

After addressing volume status, blood pressure is the next parameter dictating inpatient management.
ARNI have profound blood pressure lowering effects and may be poorly tolerated in patients with systolic blood pressure < 100 mmHg [4]. Therefore, for patients with borderline blood pressure, a very low dose ACEi, such as lisinopril 2.5 mg, or a non-selective beta blocker, such as metoprolol succinate, are preferred if the patient is euvoemic.

An elevated heart rate has been established as an independent predictor for mortality in patients with HFrEF [9]. However, in the acute setting, the goal is treating the underlying driver of sinus tachycardia, which is often elevated filling pressure. Sinus tachycardia in this scenario is a compensatory mechanism to maintain cardiac output; therefore, heart rate is discussed primarily in outpatient management.

Renal function is a crucial consideration for multiple GDMT therapies. For RAAS blockade, an initial increase in creatinine of 30% can be expected and should not prompt discontinuation. However, if the creatinine level increases by more than 30%, the medication should be stopped [10]. Volume depletion, cardiorenal syndrome, and concurrent use of nonsteroidal medications should be considered. An eGFR < 30 mL/min/1.73 m² or potassium > 5.0 meq are contraindications to starting MRA. After initiation of MRA, a basic metabolic panel should be repeated at 72 hours, 1 week, 4 weeks, and 6 months. For SGLT2i, cutoffs of eGFR < 20 mL/min/1.73 m² for empagliflozin and < 30 mL/min/1.73 m² for dapagliflozin have been used [11, 12].

After discharge from the hospital, patients should be seen within 7–10 days in a clinic. At that time, they will ideally be taking starting doses of an ARNI and beta blocker. If they are not already taking an MRA and SGLT2i, these medications should be started if the necessary criteria are met. After a patient is taking all four classes of medications, focus should be placed on titration of the beta blocker and ACEi or ARNI.

For patients who are euvoemic, with a heart rate > 70 bpm, the beta blocker should be titrated first. Data suggest that the magnitude of heart rate reduction confers a greater mortality benefit than the beta blocker dose. Therefore, physicians should aim for titrating the beta blocker to a goal heart rate < 70 bpm [5]. However, if at the first clinic visit, a patient is deemed to have continued congestion, or the HR is < 70 bpm, ARNI should be titrated first. Of note, if a patient was started on ACEI initially and the clinician wishes to trial transition to ARNI for added mortality benefit, a 36 hour washout period is required [4]. Medications should be titrated every 1 to 2 weeks until the desired doses are achieved.

For patients with continued heart failure symptoms on the above optimized regimen, additional therapies are recommended. These therapies include hydralazine and nitrates, ivabradine, digoxin, vericiguat, and omega 3 polyunsaturated fatty acids (N-PUFA) [1]. Hydralazine and nitrates have a class I indication for African American patients with NYHA class III–IV HFrEF to provide added mortality benefit [13]. Importantly, initiation of ARNI should not be delayed to start hydralazine and nitrates. Ivabradine, a “funny” sodium channel blocker, has a class IIa recommendation for patients in normal sinus rhythm, with a heart rate > 70 bpm, and taking the maximum tolerated beta blocker dose [14]. Digoxin decreases hospitalization for symptomatic patients with HFrEF taking maximally tolerated GDMT [15]. Vericiguat, a soluble guanylate cyclase stimulator, has also been shown to decreased hospitalization and carries a class IIb recommendation [16]. Finally, N-PUFA decrease inflammation and endothelial dysfunction, and have been associated with diminished hospitalization for cardiac causes [17].

Notably, recent data support a more aggressive strategy to achieve higher doses of GDMT during and immediately after hospitalization. Until recently, data regarding rapid titration strategies included retrospective and small prospective studies with mixed outcomes [18–21]. However, the STRONG-HF trial is the first multinational, prospective randomized trial comparing high intensity care vs usual care for initiation and titration of GDMT in patients admitted with acute decompensated heart failure. The high intensity group involved up-titration of treatment to 50% of the recommended GDMT doses by hospital discharge and to 100% by 2 weeks after discharge. These patients received close clinical and laboratory follow-up for 2 months. The primary outcome was 180-day readmission due to heart failure or all cause death. The study was terminated early, after enrollment of 1078 patients, because of a greater than expected difference between groups. The primary outcome difference was 15.2% vs 23.3% (adjusted risk difference 8.1%; 95% CI 2.9–13.2) in the high intensity and...
usual care groups, respectively. At 90 days, the high intensity group successfully up-titrated to full doses of RAAS blockade (55% vs 2%), beta blockers (49% vs 4%), and MRA (84% vs 46%). At the time of enrollment, SGLT2i were not approved or widely used; therefore, overall prescription throughout the study was low (10% in the high intensity group and 5% in the usual care group). Of note, the diuretic doses were lower at 90 and 180 days in the high intensity group [22].

STRONG-HF emphasizes the importance of diligent titration and close follow-up. Future studies will be crucial in directing this strategy as new therapies emerge, such as SGLT2i. Furthermore, the exclusion criteria of this trial, such as SBP < 100 mmHg, HR < 60 bpm, potassium < 5.0 meq, and eGFR < 30 mL/min/1.73 m², underscores the importance of understanding specific patient factors that predict which GDMT will be tolerated.

The initiation and titration of GDMT can be cumbersome and pose various challenges. Each patient’s hemodynamic profile dictates the titration schemes. A general approach to GDMT titration in hospital and in clinical settings has been outlined by using volume status, blood pressure, heart rate, and kidney function. As new data are being published on the safety and efficacy of GDMT titration, algorithms can be refined to ensure that all patients are receiving maximal benefits from their heart failure medication regimens.

**Conflict of Interest**
The authors declare no conflicts of interest.

**REFERENCES**


