Response to Ryan and Parwani: Heart Failure Patients With Low Blood Pressure: How Should We Manage Neurohormonal Blocking Drugs?

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Symptomatic hypotension, though rare, is the Achilles’ heel of heart failure (HF) management. It can be a sign of advanced pump failure, making it challenging to up titrate guideline-directed medical therapy (GDMT), and it can also be a side effect of the HF treatment. A question that frequently arises is, among patients with low blood pressure (BP) at baseline, which medication should be initiated first. A question that frequently arises is, among patients with low blood pressure (BP) at baseline, which medication should be initiated first.

Treating the Patient, Not Necessarily the BP Measurement, Is Important

Most patients with HF tolerate GDMT despite low BP measurements. Furthermore, it is not uncommon for patients to experience a transient drop in BP, especially within 2 to 4 hours of dosing. These symptoms resolve as HF improves. If a patient is able to tolerate without functionally limiting dizziness, lightheadedness or other significant side effects, it is beneficial to up titrate HF medications to target doses. This is achievable even if the systolic BP (SBP) is <100 mm Hg, but >80 mm Hg. However, in patients with baseline SBP <80 mm Hg, initiation of GDMT with angiotensin converting enzyme inhibitors (ACEI) and/or β-blockers usually are not feasible. If because of reversible causes, GDMT may be initiated after resolution and treatment of hypotension. If the patient has bradycardia along with hypotension, β-blockers need to be avoided until bradycardia is evaluated and treated. Hypotension can be a sign of advanced HF and is associated with worse prognosis.

Once HF is manifest, lower BP is associated with a worse prognosis, more commonly so in patients with systolic HF. Because cardiac output is a major determinant of BP, BP declines with advanced pump failure, reflecting severity of systolic HF. It should be kept in mind that other than advanced pump failure, hypotension can be caused by other conditions such as overdiuresis or dehydration, acute coronary syndrome, ischemia, arrhythmia, autonomic dysfunction, gastrointestinal bleeding, or infection. These conditions need to be treated before adjustment of HF medications.

Hypotension as Side Effect of HF Treatment

In most clinical trials with neurohormonal blockade in HF, patients with baseline hypotension were excluded. Still, hypotension was noted as a side effect in ≈6% to 8% of patients, but was rare (in ≈1% to 3%) as a serious adverse event leading to study drug withdrawal. In real-world patients with chronic HF, the prevalence of hypotension seems to be in the range of 5% to 10%. Similarly, ≈3% to 10% of hospitalized patients with HF have SBP<100 mm Hg on admission.

Balance of Medical Therapy in the Symptomatic Hypotensive Patient With HF

Which Agent Should Be Initiated First?

Historical evidence of benefit with ACEI preceded evidence from β-blockers trials in HF; thus ACEI are accepted as background therapy and should be started before initiation of β-blockers. Recent data, however, suggest that it may be safe to initiate β-blockers before ACEI. With this in mind, therapy may be individualized in challenging patients with low BP. In patients with active ischemia, recent acute coronary syndrome, tachyarrhythmias, or certain cardiomyopathies, initiation of β-blockers may precede initiation of ACEI. Furthermore, attention to BP profile of each medication would help avoid hypotension. As such, β-blockers with vasodilatory or α-blocking properties, such as carvedilol, may have slightly more BP lowering effect than metoprolol. In patients with borderline baseline SBP, β-blockers without vasodilatory properties, such as metoprolol succinate, may be easier to use. However, in clinical trials, the BP lowering effects of β-blockers were modest, if at all, and usually less than placebo. More importantly, the benefit of β-blocker treatment was more if the baseline SBP was lower. Similarly, shorter acting ACEI, such as captopril may allow smaller, but more frequent doses for up-titration, than long-acting ACEI in patients with low BP. Other additional agents, such as aldosterone-antagonists, angiotensin receptor blockers, or hydralazine-isosorbide can be considered cautiously in certain patients. The hypotension side effect with angiotensin receptor blockers are not less common than with ACEI, thus angiotensin receptor blockers should not be routinely initiated in patients with HF intolerant to ACEI because of hypotension.

Should the Dose of an Agent Be Increased to a Target Dose Before Initiating Another?

In patients with HF, a careful balance needs to be made between therapies that might lower BP but improve survival and symptoms, while preserving BP to avoid hypoperfusion. Titrating to target doses provides more benefit than very low doses. However, by the same token, the difference in efficacy between intermediate and high doses may be small. If the target doses of an ACEI cannot be achieved, intermediate doses can be used. Thus, it would not be unreasonable to start β-blockers after intermediate doses of ACEI are achieved, or vice versa. Furthermore, individual responses may differ. For example, advanced HF patients with renal insufficiency or hyperkalemia may not tolerate high doses of ACEI, and patients with low cardiac output and hypotension may be sensitive to initial negative inotropic or bradycardic effects of β-blockers. In such patients, cautious initiation and slow up-titration is the key, which may allow better tolerance. Another important strategy is to administer medications apart from each other to reduce risk of hypotension. As such, most patients with low BP tolerate ACEI and β-blockers if given separately or apart from diuretics. Another important strategy is cardiac resynchronization therapy which may result in an increase in SBP and may reduce the incidence of hypotension in HF.
If a Patient Develops Hypotension on Multi-Drug HF Therapy, Which Drug Should be Decreased?

First and foremost, medications for indications other than HF should be closely examined for side effects of hypotension, and should be adjusted or discontinued if possible for hypotension. These may include, but are not limited to calcium-channel blockers, α-blockers, nitrates, centrally acting agents for psychiatric disorders or Parkinson’s disease, and phosphodiesterase-5 inhibitors such as sildenafil. (Table). The second strategy is to change dosing time of medications. If spaced apart from each other and from HF medications, HF medications may be better tolerated. Another common scenario is appropriately high doses of diuretics leading to volume contraction. Slight adjustment or lowering of diuretics may allow optimization of GDMT. In patients with hypotension with end-organ damage or shock, GDMT including ACEI, β-blockers may need to be temporarily reduced or discontinued. It should, however, be kept in mind that abrupt withdrawal of ACEI or β-blocker can lead to clinical deterioration, and shouldn’t be done without a compelling indication. Asymptomatic hypotension should not constitute a reason for reduction or discontinuation of ACEI or β-blockers therapy in stable patients with HF.

Finally, in the setting of symptomatic hypotension if a patient is on several other HF medications in addition to ACEI and β-blockers, such as angiotensin receptor blockers, aldosterone-antagonists, hydralazine and isosorbide, these may need to be reduced or discontinued before considering any changes in ACEI or β-blockers.

In summary, hypotension is a rare but challenging problem in HF management. It is usually transient and can resolve spontaneously, or after adjustment of other medications and/or management of comorbidities.

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