Might midodrine be useful in patients with decompensated and worsening chronic heart failure? Author's reply

Dear editor

We thank Fernández–Fernández et al. [1] for their interest in our manuscript [2] and for raising the question about the potential use of midodrine in patients with decompensated and worsening chronic heart failure.

Midodrine, is an oral alpha-1 receptor agonist, approved nearly 30 years ago by the Food and Drug Administration for the treatment of dysautonomia and orthostatic hypotension. Indeed, midodrine acts by activating the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone. A systematic review of published data, however, has revealed only a limited role of midodrine in the treatment of orthostatic hypotension [3].

A non-negligible proportion of patients with decompensated and worsening heart failure (HF) may present with persistent hypotension and/or low cardiac output state. A low cardiac output state, renal vein congestion, or both conditions affect renal perfusion pressure and may contribute to kidney dysfunction and poor diuretic response. In this setting an adequate organ perfusion should be pursued by optimizing mean blood arterial pressure which may improve renal perfusion pressure and thus the glomerular filtration rate. This concept lays the theoretical foundation for the use of a vasoactive agent capable of supporting the circulation in this specific clinical setting. To achieve this goal, HF patients may require often inotropic support and/or vasopressor therapy. While midodrine, for its pharmacologic properties, could be included in the armamentarium of treatments of hypotension, it seems to have a constrained role as a direct pharmacological support for acute hypotensive patients. In fact the limited vasopressor activity of midodrine in acute setting is suggested by the negative results of randomized controlled trials investigating the efficacy of this drug in reducing intravenous vasopressor requirement in acute patients in intensive care unit patients [4,5]. Moreover the safety of this use in ischemic heart disease patients who may have left ventricular dysfunction requires more data [6].

Fernández–Fernández et al. [1], interestingly, draw the attention also on the relieve of hypotension in worsening chronic HF patients, in order to continue or optimize guideline-directed medical therapies (GDMT). Indeed, many HF patients may experience drop in blood pressure while up-titrating GDMT. While there is no strong consensus regarding the definition of severe hypotension, low blood pressure is generally considered relevant only when associated with symptoms. In this regard many patients with HF may tolerate up titration of HF medications despite low BP measurements (<100 mm Hg, but >80 mm Hg), thus it is important to not discontinue medications just for asymptomatic low blood pressure measurements. Importantly some patients may tolerate medications with gradual up-titration than with rapid up-titration. For example in patients with low blood pressure the use of shorter acting angiotensin converting enzyme inhibitors (ACE-i), such as captopril, may allow smaller but more frequent doses for up-titration, than long-acting ACE-i. Moreover, in selected cases, for maintain a beneficial effect on prognosis, a low dose of multiple neurohormonal-blocking agents may be preferred rather than using a high-dose of a single drug. Frequent patient reassessments after discharge is fundamental especially to combining new classes of drugs for HF with reduced ejection fraction (HFrEF) [7] but also for patients with mildly reduced ejection fraction (HFmrEF) [8]. However we agree that hypotension could be the Achilles' heel for up titration of GDMT and differently from the real word practice, most trials have included patients without significant hypotension at baseline. In the last years, some Authors have described, in small case series, the off-label use of Midodrine in hypotensive HFrHF patients [9,10]. However from these small reports the role of Midodrine administration to allow initiation and optimization of GDMT remains unfortunately unproven as well as its safety.

Understanding the mechanism of hypotension in patients who develop low pressure on stable medications, or are not able to tolerate new treatments, is fundamental because hypotension can be the marker of advanced pump failure reflecting the severity of systolic HF. These fragile patients may be sensitive also to small increase in afterload induced by an alpha-1 agonist as the Midodrine, and this may be a cause of concern, especially for the risk of potential worsening of cardiac failure.

Therefore, although the idea to find a way to facilitate the implementation of GDMT in HFrEF is stimulating, we feel that the available data and the theoretical basis for Midodrine use in HFrHF do not fully support the effort of initiating a dedicated study.

Declaration of Competing Interest

None.

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