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REVIEW

Midodrine in the management of heart failure with reduced ejection fraction: a systematic review

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midodrine, HFrEF, heart failure, hypotension; guideline-directed medical therapy.

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Abstract

Background: Guideline-directed medical therapy (GDMT) has significantly improved outcomes of patients with heart failure with reduced ejection fraction (HFrEF). However, the presence of hypotension often limits GDMT up-titration. Midodrine is a peripheral vasoconstrictor that may improve blood pressure in select patients with HFrEF and enable the optimisation of medical therapy.
Aims: This systematic review aimed to evaluate the safety and efficacy of midodrine in the treatment of HFrEF.
Method: A systematic review was registered (CRD42024594291) and conducted in accordance with PRISMA guidelines. A search was completed on 29 September 2024 among PubMed, Medline, EMBASE, Cochrane and SCOPUS databases. Primary outcome measures included tolerance of GDMT, left ventricular ejection fraction (LVEF) recovery, heart failure hospitalisations and all-cause mortality.
Results: Five studies were included (12 063 HFrEF patients). A meta-analysis was precluded due to heterogeneity in study design, population and reported outcomes. Two studies suggested that midodrine was associated with an increase in the prevalence of patients prescribed GDMT and improvements in LVEF. Two studies concluded that midodrine use was associated with increased hospitalisations, intensive care visits and mortality. One study suggested midodrine use was safe in patients with cancer and heart failure.
Conclusion: There is a lack of high-quality evidence to support the use of midodrine to facilitate GDMT up-titration in HFrEF. Supporting evidence of improving GDMT tolerance and LVEF stems from observational studies without comparator groups. Randomised trials are urgently needed to determine whether midodrine safely facilitates GDMT in HFrEF patients.

Introduction

Heart failure (HF) is a complex and progressive medical syndrome characterised by the reduced ability of a heart to pump or fill with blood. Estimated to impact 64 million people globally, HF's 5-year mortality of 50% remains comparable to several malignancies.[1–3] HF syndromes exist on a spectrum of cardiac dysfunction; however, HF is often grouped into two main conditions. HF with preserved ejection fraction (HFpEF) describes patients with an ejection fraction (EF) >40%, while HF with reduced EF (HFrEF) describes patients with an EF <40%.[4,5] In recent years, the emergence of guideline-directed medical therapy (GDMT) has led to significant improvements in HFrEF mortality and morbidity.[6] This armamentarium of therapies works synergistically to reduce ventricular remodelling and prevent progressive decline in left

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ventricular (LV) function.[7] Although, due to the blood pressure (BP)-lowering effects of GDMT therapy, concomitant hypotension often limits the up-titration and optimisation of GDMT.[8]

Midodrine is a potent vasoconstrictor that acts on peripheral alpha-1 adrenergic receptors to increase systemic vascular resistance (SVR). It is currently approved for the treatment of symptomatic orthostatic hypotension.[9] However, clinicians have also prescribed midodrine off-label to improve BP and optimise GDMT in select HFrEF patients with persistent hypotension, and to bridge intravenous vasopressors for patients with advanced HF.[10,11] Yet, the potential benefits of midodrine may be outweighed by its tendency to increase cardiac preload and afterload through venous and arterial vasoconstriction.[12] These changes may potentially augment myocardial oxygen demand and precipitate adverse events, particularly among patients with diminished cardiac reserve. Additionally, midodrine has non-cardiac side effects including increased risk of urinary retention, bradycardia and supine hypertension.[13] Consequently, there are no current European Society of Cardiology (ESC) or American College of Cardiology (ACC) recommendations for the utilisation of midodrine in patients with HFrEF.[9]

Despite this, midodrine has been used off-label by clinicians to augment BP in select patients with HFrEF in order to initiate and optimise medical therapy.[10,14] Gautam *et al.* previously summarised the existing literature on the role of midodrine in HF management.[15] However, this review included all HF patients, rather than those specifically with HFrEF. Achieving maximal tolerated doses of GDMT carries a Class 1A recommendation in HFrEF management guidelines, whereas up-titration of mineralocorticoid receptor antagonists (MRAs) and sodium glucose cotransporter-2 inhibitors (SGLT2is) only carries a Class 2B recommendation in the treatment of HFpEF.[16] Thus, our review sought to evaluate the role of midodrine in up-titrating GDMT only in HFrEF patients – those who are most likely to benefit from GDMT up-titration. Moreover, the review by Gautam *et al.* was not conducted systematically and does not incorporate three recent large-scale retrospective cohort studies (12 049 HFrEF patients). These recent cohort studies serve as the highest quality and most up-to-date literature on this topic, warranting an updated synthesis of existing evidence.

Thus, this systematic review aimed to evaluate the safety and efficacy of midodrine in the treatment of HFrEF. In doing so, we aimed to provide clinicians with updated and synthesised evidence on whether midodrine could be used to improve BP in select patients with HFrEF, to safely optimise GDMT and improve HF morbidity and mortality.

Material and methods

This review was registered with PROSPERO (reference number CRD42024594291) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines (see Supplementary Information 1) (Fig. 1).

Search strategy and selection criteria

The PICO (population, intervention, comparison, and outcome) framework was employed to formulate the research question. The population comprised patients with a diagnosis of HFrEF. The intervention was the provision of midodrine. The comparator group included patients who received either standard care (control) or an active comparator drug. Primary outcome measures included tolerance of GDMT, LVEF recovery, HF hospitalisations and all-cause mortality.

A comprehensive search was conducted on 29 September 2024, across PubMed, Medline, EMBASE, Cochrane and SCOPUS. The search terms applied were as follows: '("heart failure" OR HFrEF OR CHF) AND midodrine'. There was no restriction on publication period. Supplementary Information 2 details the search strings for each database. Reference lists of included articles were also screened to identify additional relevant studies.

Studies were included if they evaluated the use of midodrine in the management of HFrEF. We included case reports, case–control studies, cohort studies and randomised controlled trials where available. Exclusion criteria included: (a) studies that included specific HF patient sub-groups such as only intensive care patients or only patients on dialysis, (b) non-original articles, (c) lack of English full-text availability and (d) studies involving participants younger than 18 years.

Data extraction

Two reviewers (SZ and EZ) independently screened titles and abstracts according to the inclusion and exclusion criteria. A third reviewer (NP) resolved disputes. Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to facilitate the screening process. The following data were then extracted from included studies: title and year of publication, study design and duration, number of participants, intervention characteristics and outcome data.

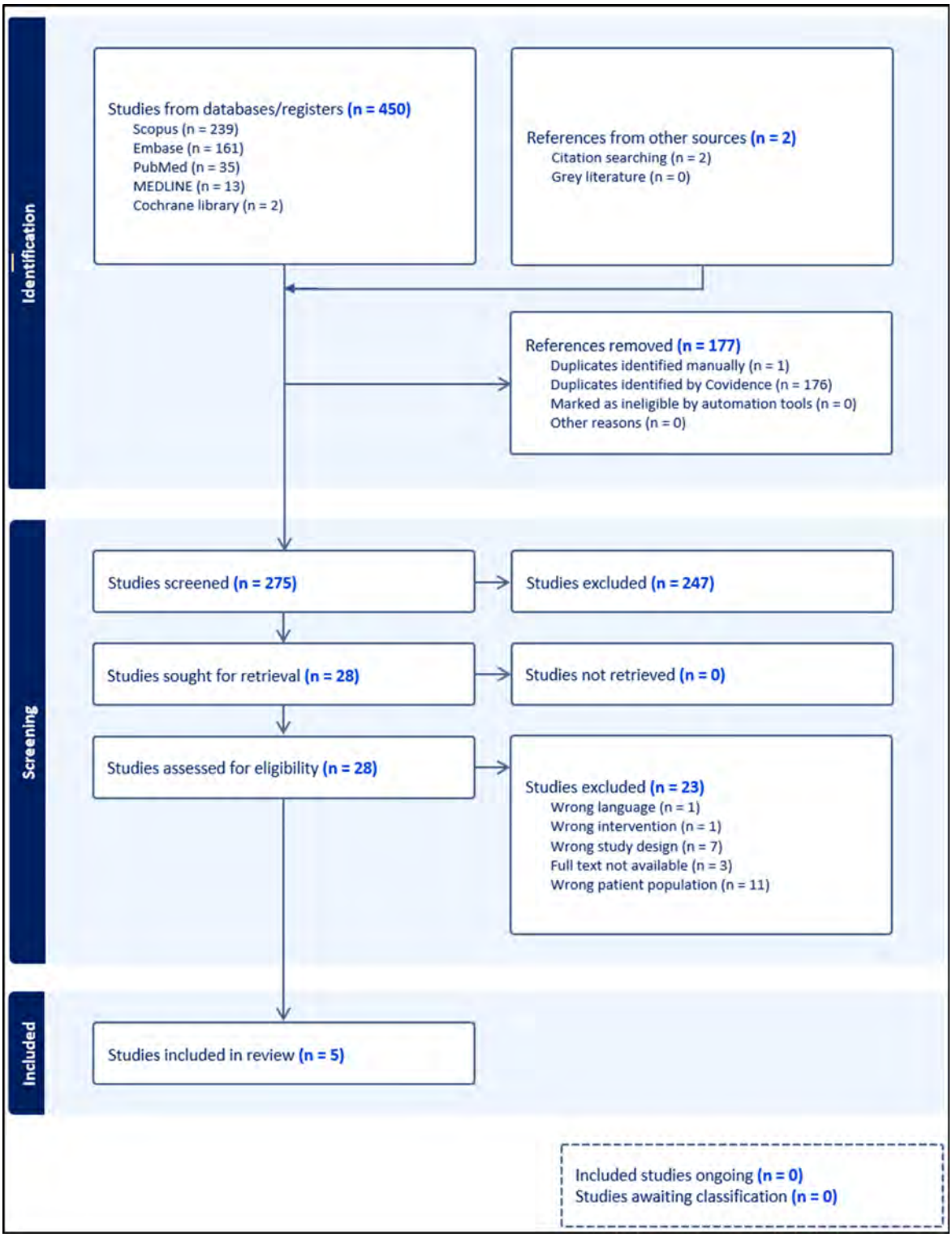

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart illustrating the search strategy and the application of the inclusion and exclusion criteria for articles that evaluated the role of midodrine in heart failure with reduced ejection fraction.

Quality assessment

Methodological quality was independently assessed by two reviewers (SZ and EZ). The Newcastle-Ottawa checklist was used to evaluate risk of bias in observational studies, while the Murad tool was employed to evaluate case reports and case series (see Supplementary Information 3).

Statistical analysis

In this review, we did not perform a meta-analysis or subgroup analysis based on GDMT prescribing patterns, LVEF recovery, all-cause mortality or HF hospitalisations. This was due to heterogeneity in the study design, population and reported outcomes among included studies. Only two studies quantitatively reported echocardiogram findings, while changes in GDMT prescribing patterns and hospitalisations were reported inconsistently among studies. Moreover, HFrEF was inconsistently defined among the included studies, preventing patient data from being accurately amalgamated and synthesised. Thus, quantitative data were synthesised in both tabular and narrative forms, facilitating the assessment of effect sizes.

Ethics

Ethical approval was not required.

Results

Study characteristics

The search among five databases, supplemented by citation searching, yielded 452 publications. After removing 177 duplicates through automated and manual methods, 275 studies were included for title and abstract screening. Of these, 28 studies were eligible for full-text review. Studies were excluded for various reasons, including wrong language ($n = 1$), wrong intervention ($n = 1$), wrong study design ($n = 7$), full text not available ($n = 3$) and wrong patient population ($n = 11$). Additionally, three studies were only published as conference abstracts without full texts, and this was confirmed by all three reviewers (SZ, EZ, NP). In total, five studies met the inclusion criteria for full-text review (see Tables 1 and 2).

Classification of LVEF among the included studies

The American Heart Association (AHA) classifies HF by LVEF and defines HFrEF as an LVEF of ≤40% in their 2022 guidelines. However, the five studies varied significantly in their classification of HFrEF (Table 3). Scoma *et al*. selected patients with an LVEF of <50%, but only included patients with an LVEF of <40% in the primary analysis. Zakir *et al*. included patients with an LVEF of <35%, whereas Wu *et al*. included patients with an LVEF of <50%. Wu *et al*. therefore may have been up-titrating GDMT in patients with a phenotype more consistent with HFpEF, who may have been less likely to respond well to medical management. The variability in LVEF classification among the included studies impacts the comparability of the data among studies and serves as an important limitation in this systematic review.

Studies supporting the use of midodrine in HFrEF management

A prospective study by Zakir *et al*. included 10 patients with HFrEF and symptomatic hypotension limiting GDMT up-titration.[10] The underlying aetiology of HFrEF was not documented. After 6 months of midodrine treatment, a significantly higher proportion of patients were able to tolerate renin-angiotensin-aldosterone system (RAAS) inhibitors (50% to 90%; $P < 0.001$), beta-blockers (80% to 100%; $P < 0.01$) and mineralocorticoid receptor antagonists (70% to 90%; $P < 0.001$). There were associated improvements in echocardiographic parameters, including a significant increase in mean LVEF% (24 ± 9.4% vs 32.2 ± 9.9%; $P < 0.01$) and a decrease in mean LV end-diastolic diameter (6.22 ± 0.75 cm vs 5.9 ± 0.87 cm; $P < 0.04$). Moreover, B-type natriuretic peptide (BNP) levels decreased significantly (1402 ± 1559 vs 706 ± 592; $P < 0.0001$), and systolic BP increased from 79.2 ± 4.6 mmHg to 99 ± 11 mmHg ($P < 0.0004$). These changes were associated with improvements in clinical outcomes, including a significant reduction in average total hospital admissions (32 vs 12; $P = 0.02$) and total hospital days (150 vs 58; $P = 0.02$).

In their case series ($n = 4$), Shiu *et al*. used non-fixed-dose regimens of midodrine as a bridging therapy to facilitate the initiation and up-titration of GDMT for hypotensive HF patients.[14] After gradually titrating midodrine, four patients who were previously unable to tolerate neurohormonal antagonist therapy were started on a beta-blocker and an angiotensin receptor blocker or angiotensin receptor-neprilysin inhibitor. The commencement of HF therapy was associated with improvements in LV function, demonstrated by an increase in LVEF% for each patient. Once GDMT was up-titrated, midodrine was weaned and tapered.

Table 1 Characteristics of studies included in review

First author (year) region	Study design	Dataset characteristics	Dose of midodrine	Comparator group	Follow-up	Primary outcome	Secondary outcome
Zakir (2009)[10] USA	Prospective study	Ten patients with HFrEF (LVEF% <35) and symptomatic hypotension (systolic BP < 85 mmHg with either dizziness or light-headedness) interfering with optimal medical therapy	5 mg orally every 6 h, increased to a maximum of 10 mg every 6 h	No comparator group	6 months	Tolerance of optimal HF medical therapy (proportion of patients prescribed ACEi, ARNI, and aldactone/ eplerenone pre- and post-treatment after midodrine)	BP, BNP levels, LVEDD, LVEF%, number of hospital admissions, total hospital days, NYHA class, adverse effects of midodrine
Shiu (2022)[14] USA	Case series	Case report 1: 56 yo male with pre-treatment LVEF% 35. Case report 2: 58 yo female with pre-treatment LVEF% 18. Case report 3: 61 yo female with pre-treatment LVEF% 30. Case report 4: 57 yo female with pretreatment LVEF% 31	Case report 1: 2.5 mg BID to 10 mg TID. Case report 2: 2.5 mg BID to 5 mg TID. Case report 3: 2.5 mg BID to 5 mg TID. Case report 4: 5 mg BID to TID then daily	No comparator group	Case report 1: 24 months. Case report 2: 2 months. Case report 3: 1 month. Case report 4: 12 month	Tolerance of GDMT (ability to be started on GDMT medication), LVEF% pre- and post-treatment with midodrine	N/A
Scoma (2024)[9] USA	Retrospective cohort study	Hospitalised adults for a primary diagnosis of decompensated systolic HF with LVEF% <50 (only patients with LVEF% <40 were included in the primary analysis). 106 patients receiving midodrine were compared to 294 patients in the control group	Not specified	Control cohort (no midodrine)	6 months	Prevalence of GDMT at 6-month follow-up, prescription pattern and dose adjustments	All-cause mortality, hospitalisations for HF and initiation of advanced therapy (such as an LVAD or OHT)

Table 1 *Continued*

First author (year) region	Study design	Dataset characteristics	Dose of midodrine	Comparator group	Follow-up	Primary outcome	Secondary outcome
Wu (2024)[17] Brazil	Retrospective cohort study	Patients aged >20 years with HF and LVEF% <50 and diagnosed hypotension (ICD-10-CM code I95) or cardiogenic shock (ICD-10-CM code T57.0) or SBP <90 mmHg. 5813 patients in the midodrine group were compared to 5813 patients in the control group	Not specified	Control cohort (no midodrine)	Mean follow-up for the midodrine group: 10.3 months Mean follow-up for the non-midodrine group: 11.5 months	CKD stage 4 or stage 5 diagnoses, episodes of acute pulmonary oedema, respiratory failure, stay in intensive care unit, emergency room visits, all hospitalisation, cardiac arrest, all-cause mortality	N/A
Irazarry-Caro (2024)[18] USA	Retrospective cohort study	85 adult patients with HF and cancer who were treated with midodrine at some point in their disease course. 36 patients had HFmrEF (LVEF 41–49) and 23 had HFrEF (LVEF% <40)	The most frequently used dose was 5 mg TID. The maximum daily dose was 30 mg daily	Patients who had midodrine discontinued at some point during their care	Median follow-up of 38 months	Adverse effects associated with midodrine, including bradycardia, exacerbation of pre-existing arrhythmias, marked elevation of supine BP, pruritus, numbness or tingling and changes in urination	Changes in NYHA class symptoms, cardiac biomarkers, echocardiographic parameters, changes in GDMT, cardiovascular hospitalisations, overall survival

ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; BID, twice daily; BNP, B-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; N/A, not applicable; NYHA, New York Heart Association; OHT, orthotopic heart transplant; TID, three times daily; yo, year-old.

Table 2 Main results from the included studies

First author (year)	Tolerance of GDMT	Echocardiogram results	HF hospitalisations, HF symptomatology and all-cause mortality	Other findings
Zakir (2009)	After 6 months of midodrine therapy, a higher proportion of patients were on optimal HF therapy. ACEi and ARB use increased from 50% to 90% ($P < 0.001$). Beta-blocker use increased from 80% to 100% ($P < 0.01$). Aldactone/eplerenone use increased from 70% to 90% ($P < 0.001$)	With midodrine therapy, LVEDD decreased from 6.22 ± 0.75 cm to 5.9 ± 0.87 cm ($P < 0.04$), while LVEF% increased from 24 ± 9.4 to 32.2 ± 9.9 ($P < 0.01$)	NYHA class decreased from 3.4 at baseline to 2.4 after 6 months of midodrine therapy ($P < 0.001$). Average total hospital admissions decreased from 32 in the 6 months prior to enrolment, to 12 within the 6 months of the study period ($P = 0.02$). Total hospital days also decreased from 150 to 58 ($P = 0.02$)	Mean systolic BP increased from 79.2 ± 4.6 to 99 ± 11 ($P < 0.0004$) with midodrine therapy. BNP levels decreased from 1402 ± 1559 at baseline to 706 ± 592 ($P < 0.0001$) at 6 months
Shiu (2022)	Prior to treatment with midodrine, persistent hypotension prevented each patient from tolerating GDMT. After treatment with midodrine, each patient was able to tolerate carvedilol or metoprolol succinate and losartan or sacubitril-valsartan. Two patients were able to tolerate spironolactone 25 mg daily. Midodrine was successfully tapered and discontinued once GDMT was commenced and up-titrated	All four case reports described an increase in LVEF% (case report 1: 35% to 52%, case report 2: 18% to 53%, case report 3: 30% to 40%, case report 4: 31% to 49%)	Not assessed	Not assessed
Scoma (2024)	Patients in the midodrine cohort were more likely to undergo initiation or up-titration of ACEi/ARB/ARNI (35.8% vs 24.8%, $P = 0.041$), beta-blockers (25.5% vs 15.0%, $P = 0.023$) and SGLT2i (19.8% vs 11.2%, $P = 0.04$) when compared to the control cohort at the 6-month follow-up	Not assessed	Patients prescribed midodrine experienced more frequent hospitalisations for HF (39.6% vs 25.2%, $P = 0.006$) and were more likely to require an LVAD or OHT. Six-month all-cause mortality was higher in the midodrine group when compared to the control group (OR 4.68, 95% CI, 2.03–10.78, $P < 0.001$)	Not assessed
Wu (2024)	Not assessed	Not assessed	Patients prescribed midodrine had fewer emergency room visits than the non-midodrine group ($P < 0.0001$) but more all-cause hospitalisations ($P < 0.0001$) and more ICU visits ($P < 0.0001$). All-cause mortality was higher in the midodrine group ($P = 0.023$)	There was no difference between groups with respect to CKD stage 4 or 5 diagnoses ($P = 0.971$ and $P = 0.149$), episodes of acute pulmonary oedema ($P = 0.532$) or cardiac arrests ($P = 0.455$). Episodes of respiratory failure were higher in the midodrine group ($P < 0.001$)
Irazarry-Caro (2024)	Midodrine use was not associated with a statistically significant up-titration of GDMT medications for patients with HFmrEF and HFrEF	Not reported specifically for HFrEF patients	Not reported specifically for HFrEF patients	Not reported specifically for HFrEF patients

ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; BNP, B-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association; OHT, orthotopic heart transplant.

Table 3 Classification of HFrEF in terms of LVEF% among the included studies

First author (year)	Classification of HFrEF used by the included studies	Alignment of selected study classification with the AHA clinical guidelines definition of HFrEF*
Zakir (2009)	<35	No
Shiu (2022)	Four patients with LVEF% of 35, 18, 30 and 31 respectively	Not applicable
Scoma (2024)	<50 (although only patients with an LVEF% of <40 were included in the primary analysis)	Yes, for primary analysis only
Wu (2024)	<50	No
Irazarry-Caro (2024)	HFmrEF defined as LVEF% of 41–49, HFrEF defined as LVEF% of <40	Yes

*The American Heart Association (AHA) classifies heart failure by left ventricular ejection fraction (LVEF) and defines heart failure with reduced ejection fraction (HFrEF) as an LVEF ≤40% in their 2022 guidelines. HFmrEF, heart failure with mildly reduced ejection fraction.

Studies not supporting the use of midodrine in HFrEF management

Scoma *et al.* conducted a single-centre study on midodrine's effect on GDMT prescription patterns among patients hospitalised for decompensated HFrEF.[9] At 6-month follow-up, patients in the midodrine group ($n = 106$) were more likely to undergo initiation and up-titration of beta-blockers (25.5% vs 15.0%; $P = 0.023$), RAAS or neprilysin inhibitors (35.8% vs 24.8%; $P = 0.041$), and SGLT2is (19.8% vs 11.2%; $P = 0.04$), compared to the control group ($n = 294$). However, the icumidodrine group experienced worse clinical outcomes, with a higher all-cause mortality rate (odds ratio (OR) 4.68, 95% confidence interval (CI) 2.03–10.78; $P < 0.001$) and increased HF hospitalisations (39.6% vs 25.2%; $P = 0.006$). Patients prescribed midodrine were also more likely to require inotropic support (31.6% vs 6.7%; $P < 0.001$) and receive advanced therapies such as left ventricular assist device (6.6% vs 4.4%; $P < 0.001$) or orthotopic heart transplant (OHT) (7.5% vs 2.4%; $P < 0.001$).

A retrospective cohort study by Wu *et al.* compared hypotensive HFrEF patients treated with midodrine ($n = 5813$) with matched controls ($n = 5813$).[17] Patients treated with midodrine had fewer emergency room visits than those in the non-midodrine group ($P < 0.001$) at a mean follow-up time of 10.3 months to 11.15 months respectively. However, this group demonstrated high rates of all-cause hospitalisations (hazard ratio [HR] 1.212; $P < 0.001$), intensive care unit (ICU) admissions (HR 1.141; $P < 0.001$) and all-cause mortality (HR 1.090; $P = 0.023$).

Irizarry-Caro *et al.* conducted a retrospective cohort study evaluating the safety profile of midodrine among patients with both HF and cancer, analysing its association with cardiovascular outcomes and overall survival.[18] Of the 85 adult patients studied, 36 had HF with mildly reduced EF (HFmrEF) (EF 41%–49%) and 23 had HFrEF (EF < 40%). After a median follow-up of 38 months, the authors concluded that midodrine use was not associated with a significant GDMT up-titration among patients with HFmrEF and HFrEF. This study only isolated the group of HFrEF and HFmrEF patients when reporting the tolerance and up-titration of GDMT medications; other outcome measures were not isolated for these subgroups. Midodrine use in patients with cancer and HF (HFpEF, HFmrEF or HFrEF) was not associated with increased mortality, adverse effects or worse cardiovascular outcomes.

Discussion

GDMT optimisation remains the cornerstone of HFrEF management.[6] However, this is frequently limited by symptomatic hypotension. Midodrine has been proposed as a direct pharmacological bolster for cardiogenic hypotension and may yield the added benefit of improving cardiac remodelling through alpha-1A agonism.[19] This systematic review aimed to evaluate the currently available evidence on midodrine's role in managing HFrEF. Although two studies suggest a role for midodrine in improving the tolerability and up-titration of GDMT, these were small in comparison to three studies that demonstrate an increased frequency of adverse outcomes with midodrine use.

Two studies indicated that midodrine facilitated the initiation or up-titration of GDMT.[10,14] Of the two studies that evaluated cardiac function with echocardiography, both found midodrine use to be associated with improvements in LVEF.[10,14] Additionally, Zakir *et al.* found an association between midodrine use and improved clinical outcomes, including reduced total hospital admissions, hospital days, BNP levels and NYHA class symptom scores. One study concluded that midodrine was not associated with changes in GDMT prescribing patterns; however, midodrine use was also not associated with mortality or worse cardiovascular outcomes.[18]

Wu *et al.* found higher rates of all-cause hospitalisations, intensive care visits and mortality among the midodrine group. Similarly, Scoma *et al.* concluded that while patients prescribed midodrine were more likely to undergo up-titration of GDMT, midodrine use was also associated with increased HF hospitalisations, all-cause

mortality and the requirement of advanced HF therapies. These adverse effects may be due to midodrine's potential to create a mismatch between myocardial oxygen supply and demand.[13] Thus, the counterproductive increase in SVR in a failing heart may outweigh the benefits of improved pharmacotherapy.[13] Moreover, excessive midodrine consumption may lead to severe hypertension and reflex bradycardia, which may be even more pronounced in HFrEF patients prescribed beta-blockers.[20] Notably, one study concluded that patients prescribed midodrine had fewer emergency room visits but more hospitalisations.[17] This may also suggest that patients prescribed midodrine were more unwell at baseline and therefore less likely to be discharged from the emergency department and more likely to require hospitalisation. Additionally, many HFrEF patients are known to utilise HF services and therefore may be directly admitted to the ward, explaining the discrepancy between the emergency visit and hospitalisation data. An alternative explanation is that midodrine may mask haemodynamic instability, preventing patients and clinicians from recognising episodes of cardiovascular compromise.[17] This delay in detection and treatment may potentially lead to greater hospitalisations and ICU stays and higher rates of all-cause mortality.

The inconsistencies among studies may be due to low-quality study design, selection bias and heterogeneity in indication, population size, dosage pattern and follow-up times.

Notably, the two studies that did not support the use of midodrine in the treatment of HFrEF may have been impacted by selection bias.[9,17] This is because midodrine may have been prescribed at higher rates among patients with worse prognostic factors. Scoma *et al*., for example, reported higher hospitalisation rates and 6-month mortality in patients prescribed midodrine. However, when compared with the control at baseline, the midodrine group had higher rates of NYHA class IV symptoms, more patients with AHA stage D HF, more severe LV dysfunction and more patients with chronic kidney disease. After adjusting for these baseline differences, the overall 6-month mortality was no longer statistically significant. Therefore, for these studies, it is unclear whether midodrine use was an independent risk factor for mortality or a marker of disease severity.

All three retrospective cohort studies used de-identified data, limiting the control of specific clinical details such as the indication, timing and dosage of midodrine. Additionally, Wu *et al*. included studies that used midodrine to correct haemodynamic instability, rather than to facilitate the up-titration of GDMT. The indication for midodrine use in the other two cohort studies was not recorded.[9,18] It is possible that midodrine may have been used as a reactive clinical decision to treat symptomatic hypotens-ion rather than a strategic manoeuvre to optimise GDMT. Thus, the retrospective studies may have been confounded by indication. It is also unclear at what point midodrine was initiated during a patient's HF journey, and therefore these studies may have inadvertently compared midodrine use in stable outpatients with those experiencing decompensated HF. Thus, the heterogeneity in the timing and indication may explain the inconsistent findings of these respective cohort studies.

The studies not classified as retrospective cohort studies may be considered low quality. The investigcation by Zakir *et al*. was a prospective study without a comparator group and that by Shiu *et al*. was a case series. Both studies had very small sample sizes ($n = 4$ and $n = 10$ respectively) and lacked comparator or control groups.

Further research in the form of randomised controlled trials is necessary to clarify the safety and efficacy of midodrine in managing HFrEF. These trials should include large sample sizes and a placebo control arm. Outcome measures should include the initiation and up-titration of GDMT and their correlation with measures such as NYHA symptom scores and LVEF and HF hospitalisations. Given midodrine's potential role in precipitating ischaemic events, cardiac-specific mortality should be included as an additional outcome measure alongside all-cause mortality. Additional retrospective cohort studies, with propensity-matched covariates to mitigate confounders, may also be beneficial.

This systematic review has several limitations. Although this review aimed to evaluate the role of midodrine in the management of HFrEF specifically, the LVEF used to define HFrEF varied among the included studies. For example, Zakir included patients with LVEF % <35, whereas Wu *et al*. included patients with LVEF% <50. Additionally, non-English texts and studies available only as conference abstracts were excluded.

Conclusion

From the five included studies, there is a lack of high-quality evidence for the role of midodrine in the management of HFrEF. Evidence supporting the use of midodrine is generally limited to case reports, case series and prospective studies with small sample sizes and no comparator groups. Recent retrospective cohort studies suggest that midodrine use may be associated with increased hospitalisations and all-cause mortality, though these findings may be impacted by selection bias. Larger randomised controlled trials are necessary to further clarify midodrine's role in HFrEF management. Clinicians should interpret existing data with caution, weighing midodrine's potential benefits against its risk of adverse cardiac events.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Supplementary Information 2: Search Strings.
Supplementary Information 3: Risk of Bias Assessment.
Table S1: Newcastle - Ottawa Quality Assessment Scale Cohort Studies.
Table S2: Murad Tool for Quality Assessment of Case Reports and Case Series.
Data S1: Supporting Information.