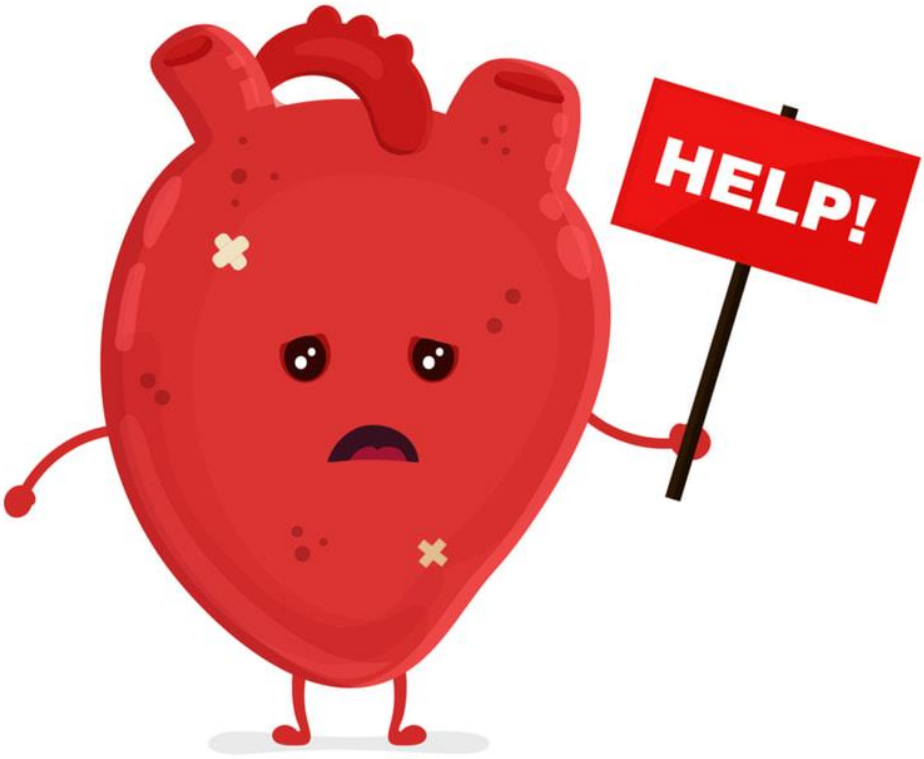
The More the Merrier: Midodrine as a Bridge to GDMT in Hypotensive Heart Failure Patients



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Harneal Diocee, PharmD

PGY-2 Pharmacotherapy Resident

Controversies in Clinical Therapeutics

University of the Incarnate Word Feik School of Pharmacy

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Learning Objectives for Pharmacists

1. Discuss current guideline directed medical therapy for heart failure with reduced ejection fraction and their effects on blood pressure.
2. Explain the mechanism of action of midodrine.
3. Evaluate the risk versus benefit of using midodrine to provide blood pressure support in hypotensive patients.
4. Assess a patient with HFrEF and symptomatic hypotension and determine if the use of midodrine is appropriate.

Learning objectives for Technicians

1. List current GDMT for HFrEF.
2. Recognize the risks versus benefits of using midodrine to assist with blood pressure support in hypotensive patients with HFrEF.
3. List midodrine dosing for symptomatic hypotension in heart failure.

Abbreviations

ACEi – angiotensin converting enzyme inhibitor

ARB – angiotensin receptor blocker

ARNI – angiotensin receptor neprilysin inhibitor

BP – blood pressure

CO – cardiac output

D/C – discontinue

GDMT – guideline directed medical therapy

HF – heart failure

HFpEF – heart failure with preserved ejection fraction

HFrEF – heart failure with reduced ejection fraction

HR – heart rate

LV – left ventricle

MAP – mean arterial pressure

MRA – mineralocorticoid receptor antagonist

RAAS – renin angiotensin-aldosterone system

SGLT2i – sodium glucose cotransporter 2 inhibitor

SVR – systemic vascular resistance

Background

- Epidemiology[2, 3]
  - 6 million Americans have known heart failure
  - Hospitalizations increasing since 2012
    - Increased from 1467 to 1689 per 100,000 patients
  - Prevalence of 4.3% in those aged 65-70
    - Expected to reach 8.5% by 2030
  - 30-day mortality increased from 7.2% to 8.6% from 2006 through 2014
- Cost burden of HFrEF and HFpEF[4]
  - Median annual medical costs: $24,383 per patient
  - 30-day post discharge costs: $6283 per patient
  - Mean hospitalization costs of HFrEF vs. HFpEF ($16,679 v $15,301)

Pathophysiology and Compensatory Mechanisms[5]

- Normal blood pressure in patient without heart failure ~110/70mmHg (MAP ~ 83 mmHg)

$$BP = CO \times SVR$$

$$CO = HR \times SV$$

- Frank Starling Mechanism
  - Ability for the heart to change contractility
  - Depending on sarcomere length-tension relationship
  - In HF this relationship changes, and can plateau

Figure 1 – Heart failure effects on MAP[5]

$$BP = SV \times HR \times SVR$$

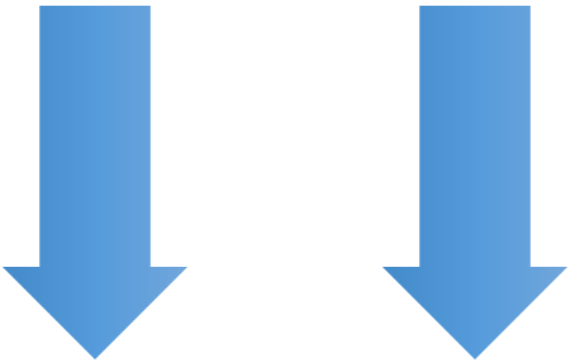


Figure 2 – Heart Failure Compensatory Mechanisms[5]

Figure 3 – Activation of neurohormonal system (i.e., RAAS)[5]

- Upregulation of RAAS
- Overtime cardiac function further deteriorates

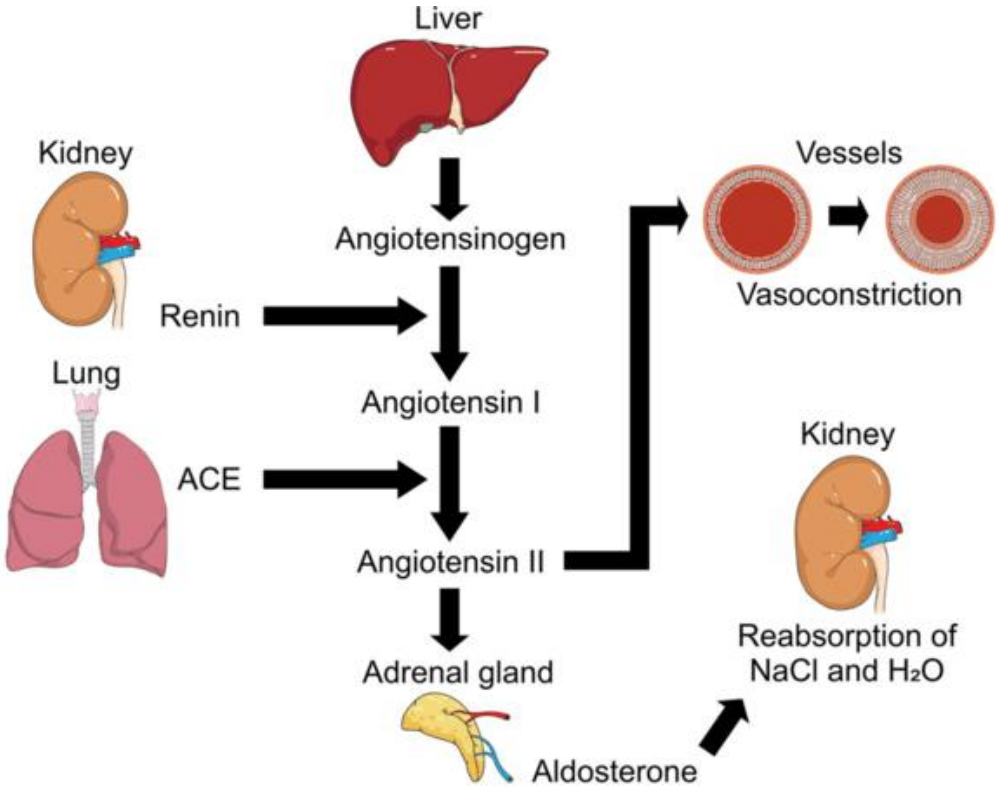
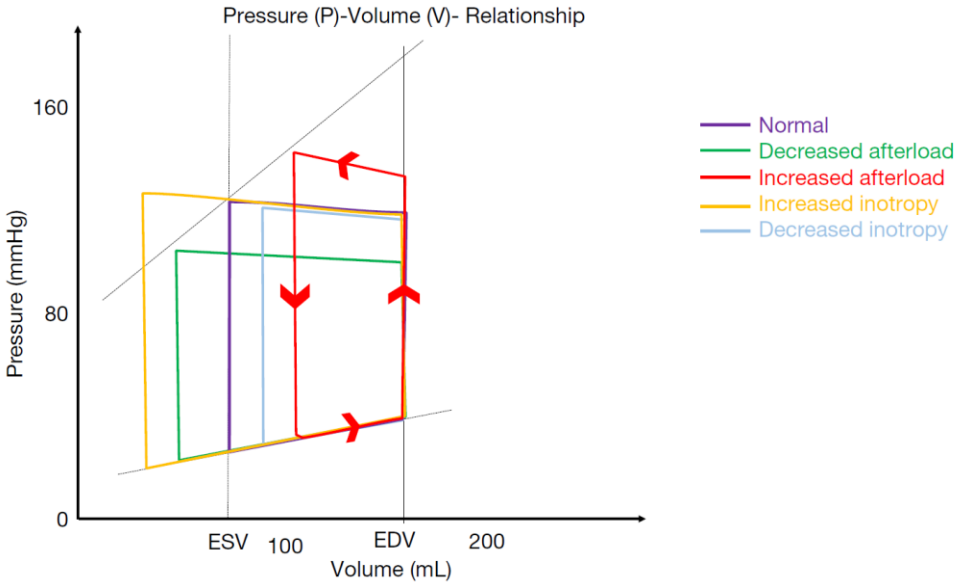


Figure 4 – Pressure-volume relationship[5]

- LV function dependent on contractility, preload, and afterload



Effect of inotropy and afterload on pressure-volume relationship

- Baroreceptor stimulation
  - Impaired contractility
  - RAAS system and release of natriuretic peptides stimulated
    - Increased preload – antidiuretic hormone
    - Increased afterload – vasoconstriction of kidney and vasculature
  - Positive inotropic effect through beta-1 stimulation and chronotropic effects
  - Peripheral vasoconstriction through alpha-1

Figure 5– Neuroendocrine Activation in Heart Failure[5]

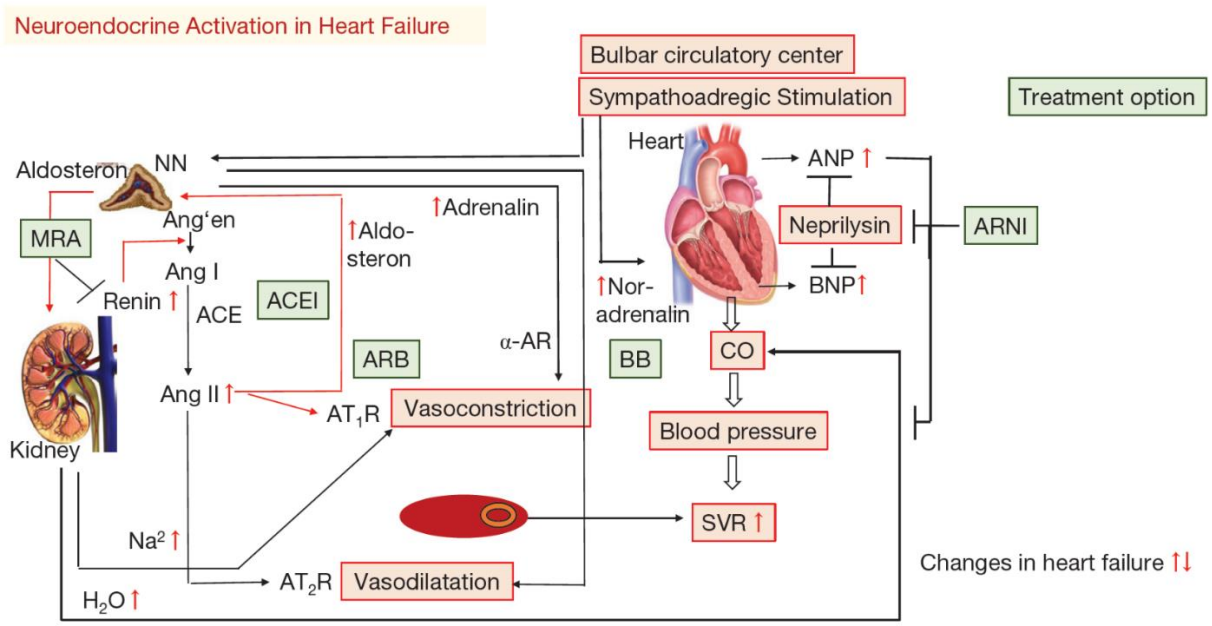


Table 1 – 2022 AHA/ACC Guideline for the Management of Heart Failure Guideline Directed Medical Therapy[6]

Drug	Initial Dosing	Target Dosing	Morbidity	Mortality
ACEi				
Captopril	6.25mg TID	50mg TID	↓	↓
Enalapril	2.5mg BID	10-20mg BID	↓	↓
Lisinopril	2.5-5mg daily	20-40mg daily	↓	↓
Ramipril	1.25-2.5mg daily	10mg daily	↓	↓
ARB				
Candesartan	4-8mg daily	32mg daily	↓	↓
Losartan	25-50mg daily	50-150mg daily	↓	↓
Valsartan	20-40mg daily	160mg BID	↓	↓
ANRI				
Sacubitril-valsartan	24mg/26mg BID	97mg/103mg BID	↓	↓
Beta blockers				
Bisoprolol	1.25mg daily	10mg daily	↓	↓
Carvedilol	3.125mg BID	25mg BID (Wt <80kg) 50mg BID (Wt >80kg)	↓	↓
Metoprolol succinate	12.5-25mg daily	200mg daily	↓	↓
MRAs				
Spironolactone	12.5-25mg daily	25-50mg daily	↓	↓
Eplerenone	25mg daily	50mg daily	↓	↓
SGLT2i				
Dapagliflozin	10mg daily	10mg daily	---	↓
Empagliflozin	10mg daily	10mg daily	---	↓

Table 2 – GDMT Effects on MAP[5]

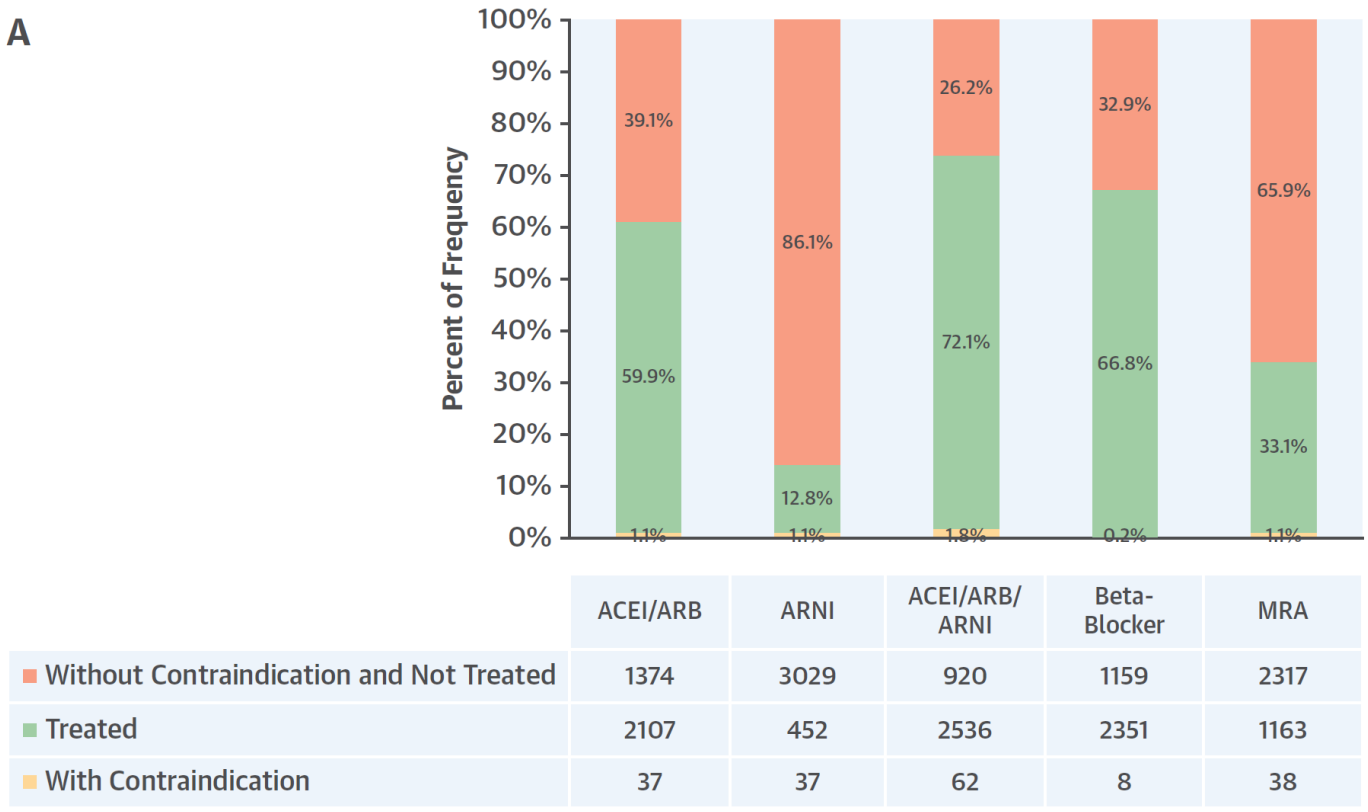
GDMT Effects on MAP	
Beta blockers	↓ HR, SVR*
ACE/ARB/ARNI	↓ afterload and remodeling
MRA	↓ remodeling
SGLT2i	↓ preload, otherwise idiopathic mechanism

- Current guidelines recommend initiation and titration be individualized and optimized without delay[6,17]
    - Symptoms, vital signs, functional status, and tolerance are some factors that can affect initiation and titration of GDMT
    - Conventional sequence
        - ACE/ARB/ARNI + beta blocker → MRA → SGLT2i
        - Titrate to target dosing, then initiate the next GDMT
    - Newer sequencing
        - Initiation of multiple GDMT agents at a time and titrating as hemodynamics allow
        - Key difference is to have all agents on, then titrate doses

Table 3 – CHAMP-AF Registry[7]

Population	Cohorts	Observations	Conclusions
3518 HFrEF patients from 150 US primary and cardiology practices **Mainly white males** **Mean age: 65 yo** **Mean LVEF: 29%**	Contraindicated vs. Treated vs. Not treated without contraindication	RAAS inhibitor: 73.4% BB: 67% MRA: 33.4% RAAS, BB, and MRA: 22.1%	There are significant gaps in GDMT use for HFrEF

Figure 6 – CHAMP-AF Registry[7]



	ACEI/ARB	ARNI	ACEI/ARB/ ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38

- Bottom line
  - Only about 2% of patients had a documented contraindication to a specific medication class
  - 22% of patients were on all parts of GDMT that were not contraindicated
  - Missing elements of HFrEF GDMT can increase morbidity and mortality
  - Limitation: SGLT2i were not included as they were not GDMT at the time of the study (2015-2017)

Table 4 – GDMT and Their Effects on Systolic Blood Pressure[8-16, 18]

Drug Class	Drug	Trial	SBP Reduction	Increased Risk of Hypotension?
Beta blocker	Carvedilol Metoprolol succinate Bisoprolol	COMET (2003) MERIT HF (1999) CIBIS II (1999)	-3.0 mmHg -2.1 mmHg Not reported	No
ACE	Enalapril	CONSENSUS (1987) CONSENSUS II (1992)	-20 mmHg -8 mmHg	Yes
ARB	Valsartan	Val-HeFT (2001)	-5.2±16.0 mmHg at 1 year	Yes
ARNI	Sacubitril-valsartan	PARADIGM-HF (2014)	-3.2±0.4 mmHg lower than enalapril at 8 months	Yes
SGLT2i	Empagliflozin Dapagliflozin	EMPEROR-Reduced (2020) DAPA-HF (2019)	-2.4±0.4 mmHg at 1 year -1.92±14.92 mmHg at 18 months	Yes
MRA	Spironolactone Eplerenone	MRA, BP, and Outcomes in HFrEF (2019) EPHESUS (2003)	-1.2±17.9 mmHg +5 mmHg at 1 year	No

Table 5 – Midodrine[19]

Mechanism of Action	FDA Indications	General Dosing	ADRs
Alpha-1 agonist - Increases SVR and BP	Diuretic resistance or hypotension in cirrhosis	Initial: 2.5-5mg PO TID Max: 40mg PO TID	Piloerection, pruritis (mainly on scalp), dysuria, paresthesia
	Hemodialysis induced hypotension		
	Vasovagal syncope		
	Vasopressor sparing agent		

Table 6 – Midodrine as a Bridge for GDMT in Hypotensive HF Patients?

Pros	Cons
Well tolerated	Frequency of dosing
Allow for quicker initiation of all GDMT	Opposing HF GDMT mechanisms
	Potentially increased mortality if not closely monitored

Table 7 – Rizvi and colleagues[20]

<table>
<tr><th colspan="3">Continuation of Newly Initiated Midodrine Therapy After ICU and Hospital Discharge</th></tr>
<tr><th colspan="3">Background</th></tr>
<tr><td>Objective</td><td colspan="2">- Identify incidence of continuation of newly initiated midodrine upon ICU and hospital discharge and identify risk factors associated with its occurrence</td></tr>
<tr><th colspan="3">Methods</th></tr>
<tr><td>Study Design</td><td colspan="2">- Single center, retrospective case series from January 2011 to October 2016 at the Mayo Clinic, Rochester, MN</td></tr>
<tr><td>Patient Selection</td><td>Inclusion Criteria
- Age > 18 years
- Use of midodrine in any ICU</td><td>Exclusion Criteria
- Patients on midodrine prior to hospital admission
- Death prior to ICU discharge
- Denial of medical records review for research</td></tr>
<tr><td>Intervention</td><td colspan="2">- Midodrine use in ICU patient
o Patients discharged from ICU on midodrine
o Patients discharged from hospital on midodrine
- Dosing: 5-40mg PO q8-12h
- Primary purposes of midodrine: early acute phase as a vasopressor sparing agent or for de-resuscitation to wean IV medications</td></tr>
<tr><td>Outcomes</td><td colspan="2">- Primary Outcome
o Incidence of midodrine continuation at ICU discharge (defined as any midodrine exposure in 24 hours after transfer from ICU to hospital ward)
- Secondary Outcomes
o Incidence of discharge from hospital on midodrine
o Concurrent use of antihypertensive drugs among patients continued midodrine therapy at ICU transfer and hospital discharge
o ICU length of stay
o In hospital mortality
- Safety Outcomes
o One year mortality (between patients continued and those not continued)</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">- Univariate arms were compared using Pearson chi-square test or Fisher exact test for categorical variables
- Student t test or Wilcoxon rank sum test for continuous data</td></tr>
<tr><th colspan="3">Results</th></tr>
<tr><td>Baseline characteristics</td><td colspan="2"><table>
<tr><th>Characteristic</th><th>Midodrine Discontinued at ICU Discharge (n=338)</th><th>Midodrine Continued at ICU Discharge (n=672)</th></tr>
<tr><td>Age, years, mean (SD)</td><td>62.7 (15.4)</td><td>64.1 (14.4)</td></tr>
<tr><td>Male, n (%)</td><td>195 (57.7)</td><td>385 (57.3)</td></tr>
<tr><td>Congestive heart failure, n (%)</td><td>96 (28.4)</td><td>199 (29.6)</td></tr>
<tr><td>CV ICU as admitting, n (%)</td><td>92 (27.2)</td><td>299 (44.5)</td></tr>
</table></td></tr>
<tr><td>Efficacy</td><td colspan="2">1 year mortality after hospital discharge
<table>
<tr><th>Endpoint</th><th>HR (95% CI)</th><th>P-value</th></tr>
<tr><td>Male</td><td>1.17 (95% CI 0.91-1.09)</td><td>0.23</td></tr>
<tr><td>CV ICU</td><td>0.29 (95% CI 0.21-0.40)</td><td><0.001</td></tr>
<tr><td>Continued on midodrine at hospital discharge</td><td>34%</td><td><0.001</td></tr>
<tr><td>Risk of in hospital mortality, adjusted HR</td><td>0.45 (95% CI 0.30-0.68)</td><td><0.001</td></tr>
</table></td></tr>
</table>

	ICU length of stay, days, mean (SD)	8.5 (10.7)	<0.001
	Hospitalization is a readmission, days, mean (SD)	111 (11.0)	0.98

- ICU LOS (midodrine v without): 7.5 ± 8.9 vs. 10.6 ± 13.4 days
- Among the 909 that survived hospital discharge (81%), 53% (484/909) of those patients received midodrine in the 24 hours before discharge and 34% (311/909) had midodrine on the hospital discharge summary
- Congestive heart failure was a key predictor in continuing midodrine at hospital discharge

Safety

Endpoint	HR (95% CI)
Death at 1 year (midodrine vs. without)	45% vs. 31%; HR 1.56 (95%CI 1.23-1.99); p<0.001

- Of those discharged on ICU and hospital on midodrine, 50% were on anti-hypertensives. 19 and 24% on BB, 0 and 1% on ACE/ARB, 11 and 33% on diuretics

Author's Conclusions

Author's Conclusions

- High prevalence of midodrine continuation at ICU and hospital discharge, and careful planning and medication reconciliations need to take place prior to hospital discharge.

My Discussion and Conclusion

Strengths

- Noted that congestive heart failure was a key predictor in continuing midodrine at hospital discharge
- 1 year mortality
- Included insight that if midodrine was continued following hospital discharge it could potentially increase mortality

Limitations

- Since this article is not focusing on heart failure patients specifically, it decreases the external validity to whether midodrine is specifically helpful in a heart failure population, since this study included a wide range of disease states
- No insight on whether midodrine assisted with HF GDMT
- HF GDMT was different at the time of study (2011-2016), ARNIs and SGLT2i's were not GDMT at that time
- Over 50% on vasopressors (not the HF population traditionally), inclusion of multiple ICUs without subgroup analysis, retrospective, single center, BP not assessed following discharge

My Bottom Line

- Midodrine use following discharge needs to be carefully monitored as continuation following an ICU stay can increase mortality
- Benefits for bridging HF GDMT are unknown from this piece of literature
- Midodrine can potentially decrease ICU LOS

Table 8 – Zakir and colleagues[21]

<table>
<tr><th colspan="3">The Use of Midodrine in Patients with Advanced HF</th></tr>
<tr><th colspan="3">Background</th></tr>
<tr><td>Background</td><td colspan="2">- ADHERE Registry found that only 47% of hospitalized patients w/ previous diagnosis of HF due to systolic blood pressure
- OPTIMIZE HF found that use of ACEi and BB were both 83% (50,000 hospitalized patients with HF)</td></tr>
<tr><td>Objective</td><td colspan="2">- Exploring midodrine as a way of supporting BP in patients who do not tolerate ACEi/ARB, BB, and/or MRA due to symptomatic hypotension</td></tr>
<tr><th colspan="3">Methods</th></tr>
<tr><td>Study Design</td><td colspan="2">- Observational, prospective study</td></tr>
<tr><td>Patient Selection</td><td>Inclusion Criteria
- LVEF ≤35%
- Symptomatic hypotension (<85mmHg w/ dizziness or lightheadedness) interfering w/ optimal medical therapy</td><td>Exclusion Criteria
- Severe valvular dysfunction
- HR <40bpm
- Liver failure
- Undergoing hemodialysis</td></tr>
<tr><td>Intervention</td><td colspan="2">- Midodrine 5mg PO q6h increased to a maximum dose of 10mg PO q6h
- No comparator group</td></tr>
<tr><td>Outcomes</td><td colspan="2">- Outcomes (baseline and 6m) – thoughts below
o Comparison of BP, NYHA class, BNP, ACE/ARB/BB/MRA use (and use of optimal dose), LVEF
- Safety Outcomes (baseline and 6m) – thoughts below
o Hospital admissions (6m prior to enrollment, then w/in 6m of study period), total hospital days</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">- P value <0.05 – statistically significant
- All variables: student t-test</td></tr>
<tr><th colspan="3">Results</th></tr>
<tr><td>Baseline characteristics</td><td colspan="2">
<table>
<tr><th>Characteristic</th><th>Midodrine (n=10)</th></tr>
<tr><td>Male, n (%)</td><td>8 (80)</td></tr>
<tr><td>Age (years), mean (SD)</td><td>63.3 (18)</td></tr>
<tr><td>Weight (#), mean (SD)</td><td>179 (56)</td></tr>
<tr><td>CAD, n (%)</td><td>5 (50)</td></tr>
<tr><td>CKD (eGFR <60mL/min*), n (%)</td><td>9 (90)</td></tr>
<tr><td>Diabetes mellitus, n (%)</td><td>9 (90)</td></tr>
<tr><td>Previous HTN, n (%)</td><td>3 (30)</td></tr>
<tr><td>LVEF <40%, n (%)</td><td>10 (100)</td></tr>
<tr><td>RV failure (Bi-ventricular), n (%)</td><td>5 (50)</td></tr>
</table>
*eGFR calculated with MDRD equation
</td></tr>
</table>

Efficacy

Endpoint	Baseline	6 months	p-value
Midodrine	100%	90%	---
SBP, mean (SD)	79.2 (4.6)	99.0 (11)	<0.004
DBP, mean (SD)	49.1 (4.2)	58.8 (4.9)	<0.002
NYHA class, mean	3.4 (5 class IV, 4 class III, 1 class II, 0 class I)	2.4 (1 class IV, 4 class III, 3 class II, 2 class I)	<0.001
ACE/ARB use	50%	90%	<0.001
ACE/ARB mg % of optimal dose*	20%	57.5%	<0.001
BB use	80%	100%	<0.01
BB mg % of optimal dose*	37.5%	75%	<0.001
MRA use	70%	90%	<0.001
MRA mg % of optimal dose*	43.7%	95%	<0.001
LVEF %, mean (SD)	24 (9.4)	32.2 (9.9)	<0.001
Total hospital admissions	32 (6m prior to enrollment)	12 (w/in 6m of study period)	0.02

*See target dosing in Table 2

Safety

- No adverse effects reported

Author's Conclusions

Author's Conclusions

- The use of midodrine was well tolerated in this small cohort and its use allowed for up titration of other agents

My Discussion and Conclusion

Strengths

- Overall, a general HF population, low EF, population mimics South Texas area
- Inclusion of bi-ventricular heart failure
- Outcomes are relevant to what are generally studied w/ HF studies
- Population and hypothesis align with the controversial question

Limitations

- Midodrine dosing frequency was higher than normal
- Unclear if symptomatic hypotension regardless of SBP could be included, small sample size, no comparator
- Unable to determine what BP improvement was due to enhanced GDMT vs. midodrine use, , unknown final dose of midodrine, unknown duration of midodrine, unknown benefit after 6 months,
- ARNI and SGLT2 is part of HF GDMT now (however SGLT2i do not significantly lower BP), unknown titration schedule of GDMT

My Bottom Line

- Midodrine can safely and effectively be used to support blood pressure to initiate GDMT in patients with HFrEF
- Optimal duration of midodrine is unknown
- ARNI is now first line

Table 9 – Shiu and colleagues[22]

Patient Details	HF Details	Interval Events	Midodrine Course	Conclusions
56-year-old Caucasian male **PMH: HTN, hypothyroidism, HLD, HFrEF**	LVEF: 35% HR: 45 bpm (sinus bradycardia) SBP: 90mmHg GDMT: ramipril 2.5mg daily, carvedilol 3.125mg BID	GDMT improved LVEF to 40% 3 years later: symptomatic hypotension (70/52mmHg) → all GDMT D/C	Initial: 2.5mg TID Titrated by 2.5mg to max of 10mg TID to sustain SBP no greater than 100mmHg Carvedilol 6.25mg BID and losartan 25mg daily reintroduced Midodrine taper: 5mg TID → 5 mg BID → 5 mg daily → D/C	Midodrine duration: 24 months LVEF improved from 35% to 58%
58-year-old African American female **PMH: HTN** **Episode of ventricular fibrillation and subsequent cardiac catheterization with no significant CAD**	LVEF: 18% AICD placed GDMT: furosemide, carvedilol, losartan (doses unknown)	2 weeks later: hospitalized for hypotension → carvedilol and losartan D/C	Initial: 2.5mg TID Titrated to 5mg TID Carvedilol and losartan restarted and titrated (doses unknown) Midodrine D/C without taper	Midodrine duration: 2 months 2 years later: sacubitril/valsartan 49/51mg bid, carvedilol 25mg BID, furosemide 40mg PRN LVEF improved from 18% to 53%
61-year-old Caucasian female **PMH: HTN** **Referred to cardiology due to left bundle branch block on screening EKG.** **LVEF 48%** **Nuclear scan with no evidence of MI**	8 years later: sub-massive, multiple pulmonary emboli, and extensive DVT, AF with left bundle block LVEF: 30% GDMT: None	Initiated on amiodarone Imaging demonstrated CHF associated with hypotension requiring IV pressors (unknown drug/dose) Midodrine was initiated to wean pressor requirements Carvedilol was initiated, but patient unable to tolerate	Initial: 2.5mg BID Titrated to 2.5 mg TID → 5mg TID Discharged on losartan 25mg daily, metoprolol succinate 25mg daily, spironolactone 25mg daily 1 week later: losartan changed to sacubitril/valsartan 24/26mg BID 1 month later: midodrine D/C	Midodrine duration: 1 month LVEF improved from 30% to 40%

57-year-old Hispanic female **PMH: HFrEF, T2DM, HTN, DLP, tobacco use** **NSTEMI** **Cardiac catheterization: severe CAD and aneurysm of ascending and abdominal aorta, and moderate to severe aortic regurgitation → underwent CABG, aortic root replacement, aortic valve replacement, replacement of coronary buttons, and dual chamber pacemaker**	LVEF: 31% In the next 2 years: multiple HF hospitalizations GDMT: unknown	Continually hypotensive, and patient was not tolerating GDMT	Initial: 5mg BID Titrated to 5mg TID Carvedilol 6.25mg BID, sacubitril/valsartan 24/26mg BID, and spironolactone 25mg daily initiated Midodrine tapered from TID to BID → daily → D/C	Midodrine duration: 12 months LVEF improved from 31% to 49% Patient had no further admissions to hospital for heart failure in last 6 months

Final Recommendations

Literature Considerations

- Midodrine use following hospital discharge needs to be carefully monitored
- Midodrine can safely & effectively be used to support blood pressure to initiate GDMT
- Optimal duration is unknown
- GDMT is different compared to early trials

Population Considerations

- Patients with symptomatic hypotension
- Patients unable to tolerate any or minimal GDMT
- Patients with reliable adherence
- Patients with reliable follow up

My Recommendations

- Midodrine can be a reasonable option to allow GDMT initiation and titration
  - Initial: 2.5mg PO TID
  - Max: 40mg PO TID
- Monitoring
  - Blood Pressure
  - Prostatism (BPH)
  - Duration of midodrine
  - Initiation of GDMT

References

1. https://stock.adobe.com/search?k=heart+disease+cartoon
2. Roger VL. Epidemiology of Heart Failure: A Contemporary Perspective. *Circ Res*. 2021;128(10):1421-1434.
3. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. *Circ Heart Fail*. 2018;11(12):e004873.
4. Urbich M, Globe G, Pantiri K, et al. A Systematic Review of Medical Costs Associated with Heart Failure in the USA (2014-2020). *Pharmacoeconomics*. 2020;38(11):1219-1236.
5. Schwinger RHG. Pathophysiology of heart failure. *Cardiovasc Diagn Ther*. 2021;11(1):263-276.
6. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2022 May 3;145(18):e1033] [published correction appears in Circulation. 2022 Sep 27;146(13):e185]. *Circulation*. 2022;145(18):e895-e103.
7. Greene SJ, Butler J, Albert NM, et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. *J Am Coll Cardiol*. 2018;72(4):351-366.
8. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003;362(9377):7-13.
9. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001-2007.
10. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353(9146):9-13.
11. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316(23):1429-1435.
12. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-1675.
13. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.
14. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020;383(15):1413-1424.
15. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995-2008.
16. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709-717.
17. McMurray JJV, Packer M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. *Circulation*. 2021;143(9):875-877.
18. Swedberg K, Held P, Kjekshus J, Rasmussen K, Rydén L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med*. 1992;327(10):678-684.
19. Midodrine [Package insert]. Online: Shire US Inc; 2017. Midodrine [Package insert]
20. Rizvi MS, Nei AM, Gajic O, Mara KC, Barreto EF. Continuation of Newly Initiated Midodrine Therapy After Intensive Care and Hospital Discharge: A Single-Center Retrospective Study. *Crit Care Med*. 2019;47(8):e648-e653.
21. Zakir RM, Folefack A, Saric M, Berkowitz RL. The use of midodrine in patients with advanced heart failure. *Congest Heart Fail*. 2009;15(3):108-111.
22. Shiu P, Grewal GS, Kozik TM. Midodrine to optimize heart failure therapy in patients with concurrent hypotension. *SAGE Open Med Case Rep*. 2022;10:2050313X221100400.