MAYO CLINIC

Alpha-1 and 1 for All

Evaluating the role of midodrine for vasopressor discontinuation

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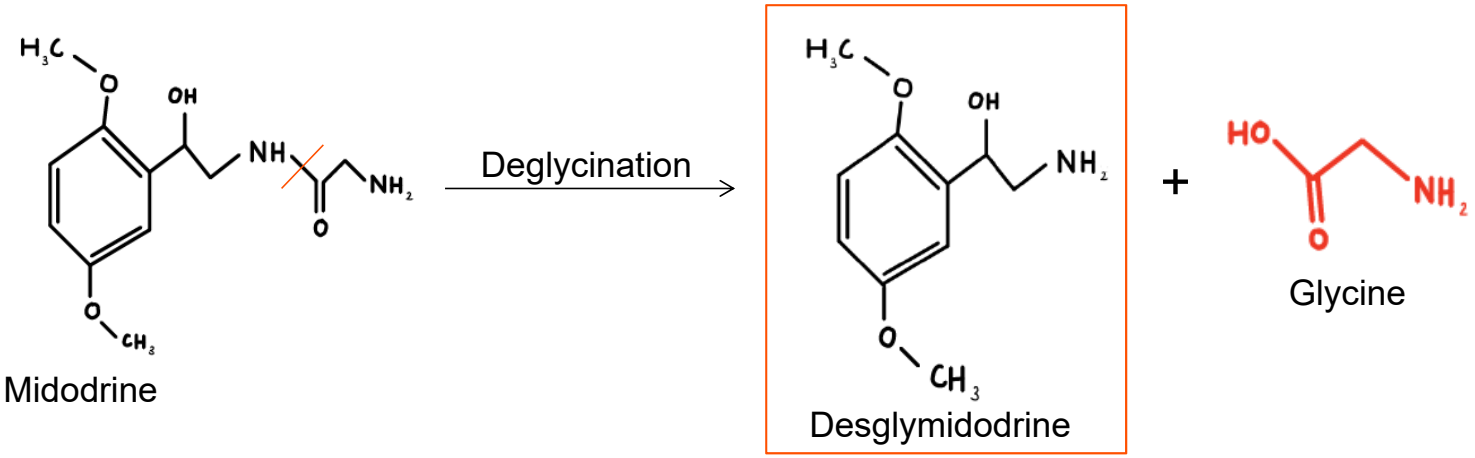
Pharmacy Grand Rounds
October 6, 2020

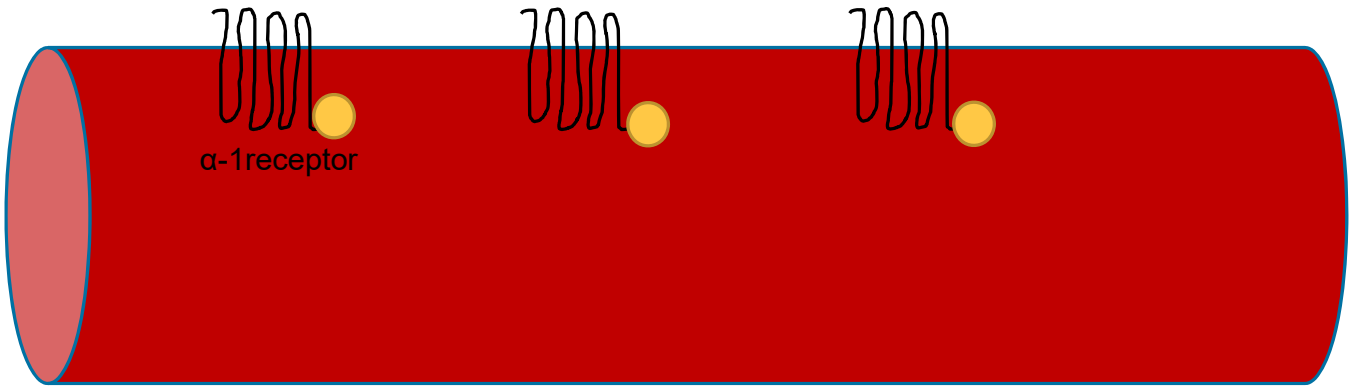
Objectives

- Explain the mechanism of action of midodrine
- Review the current evidence for midodrine and its impact on vasopressor discontinuation
- Identify midodrine's role in therapy for vasopressor discontinuation

Explain the mechanism of action of midodrine

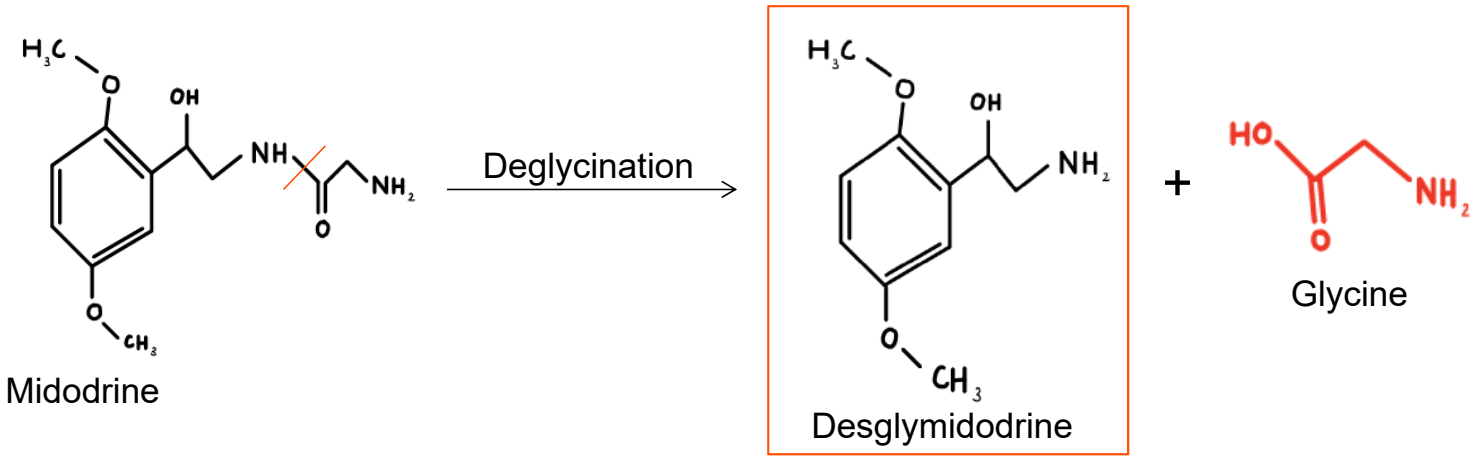
Mechanism of action

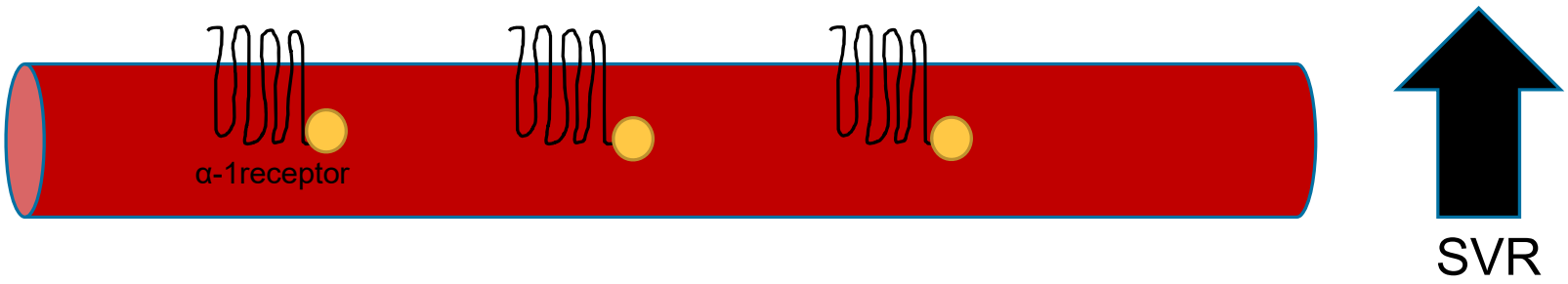




McTavish and Goa. *Drugs* 1989; 38(5):757-777

Mechanism of action





SVR: Systemic vascular resistance

McTavish and Goa. *Drugs* 1989; 38(5):757-777

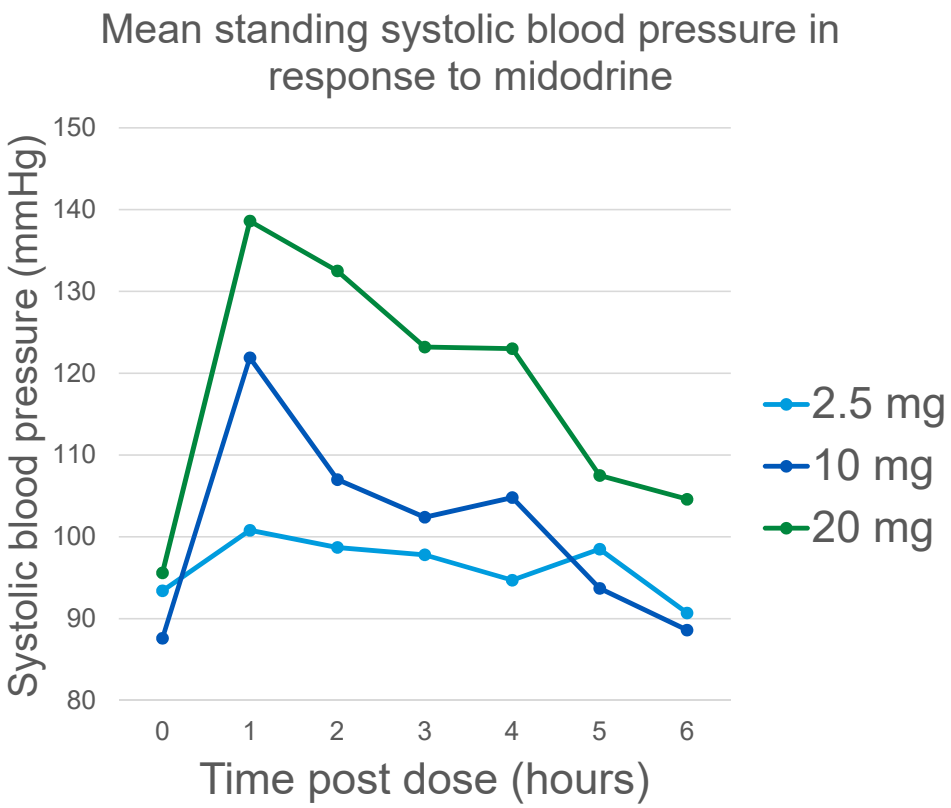
Receptor selectivity

	Alpha-1	Beta-1	Beta-2	DA	V1/V2
Norepinephrine	++++	++			
Epinephrine	+++	+++	++		
Phenylephrine	+++				
Dopamine	+	+++	++	++	
Vasopressin					+++
Midodrine	+++				

DA: dopamine receptor
V1/V2: vasopressin receptor 1 and 2

Hollenberg. *Am J Respir Crit Care Med* 2011; 183(7):847-855

Pharmacokinetics



2.5 mg	10 mg	20 mg
↑ 7 mmHg	↑ 34 mmHg	↑ 43 mmHg

- Peak: 1-2 hours
- Bioavailability: 93%
- Half-life: 3-4 hours

Wright RA et al. Neurology 1998: 51(1): 120-4

Midodrine considerations

Dosing considerations

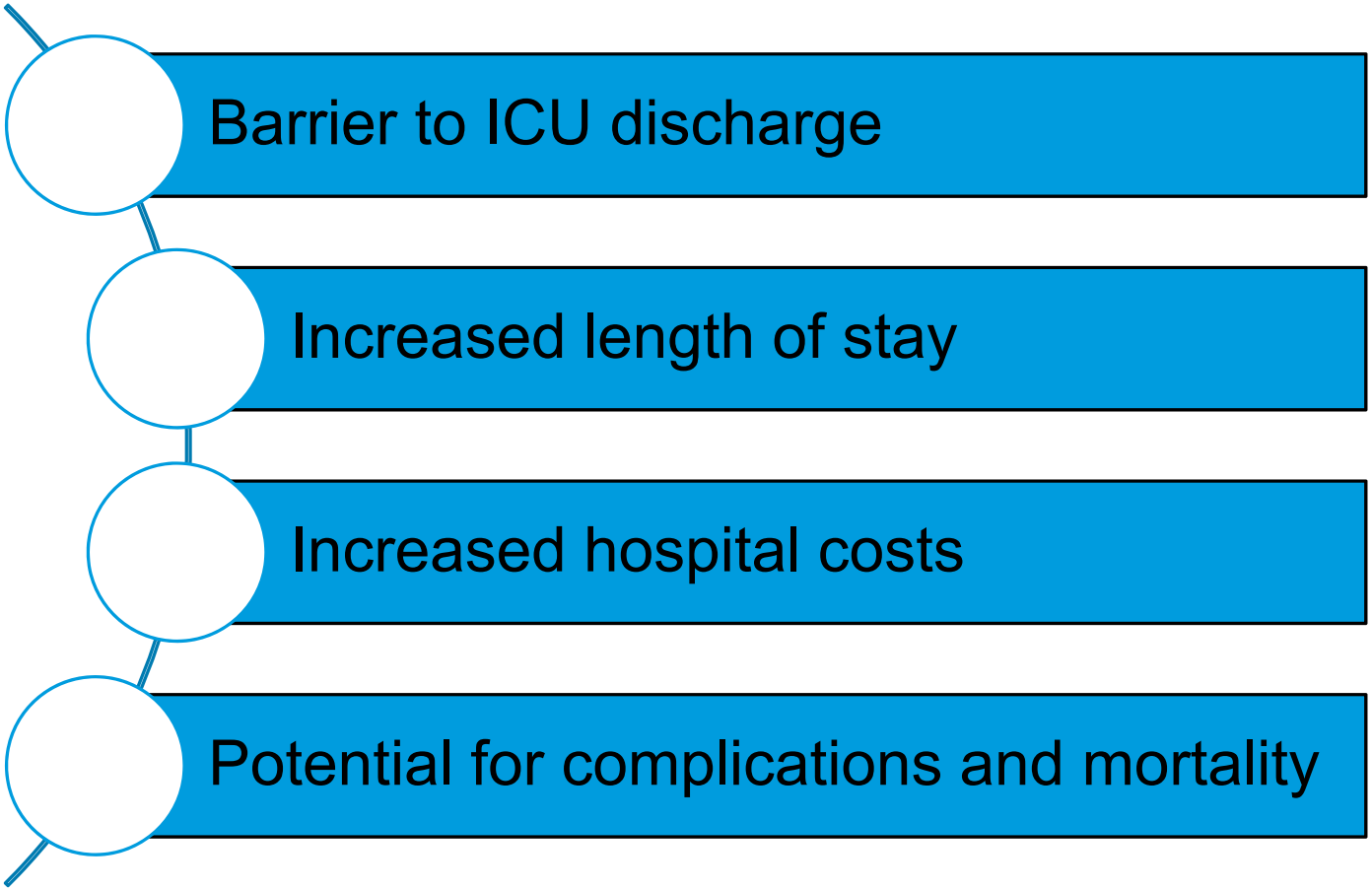
- No clear guidance
- 2.5-20 mg every 6-8 hours
- Max reported 40 mg every 8 hours

Side effects

- Supine hypertension
- Reflex bradycardia
- Dysuria, urinary retention
- Piloerection

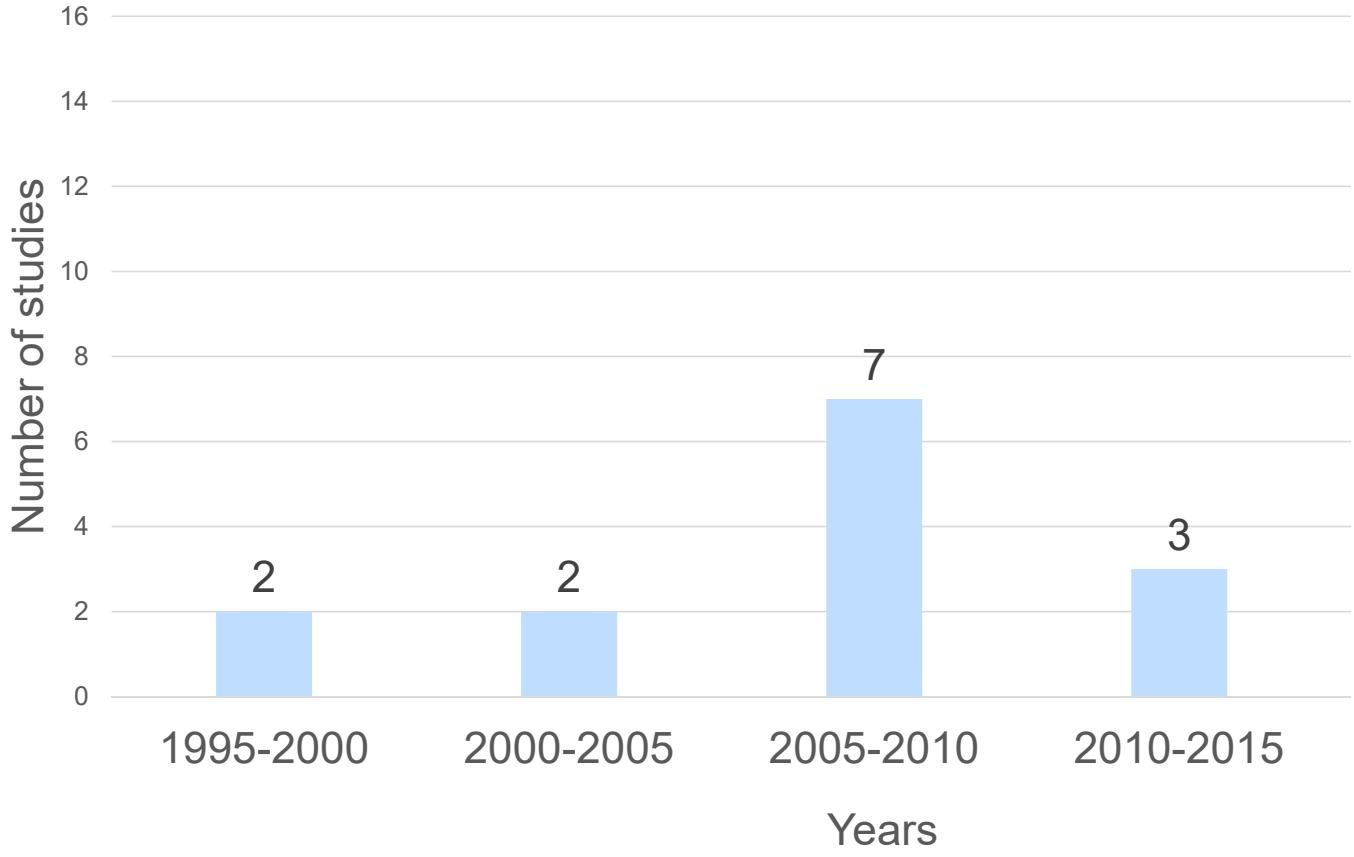
McTavish and Goa. *Drugs* 1989; 38(5):757-777

Potential impacts of prolonged vasopressor use



Levine et al. *J of Crit Care* 2013.28:756-62

Growing body of literature for midodrine for vasopressor discontinuation by year



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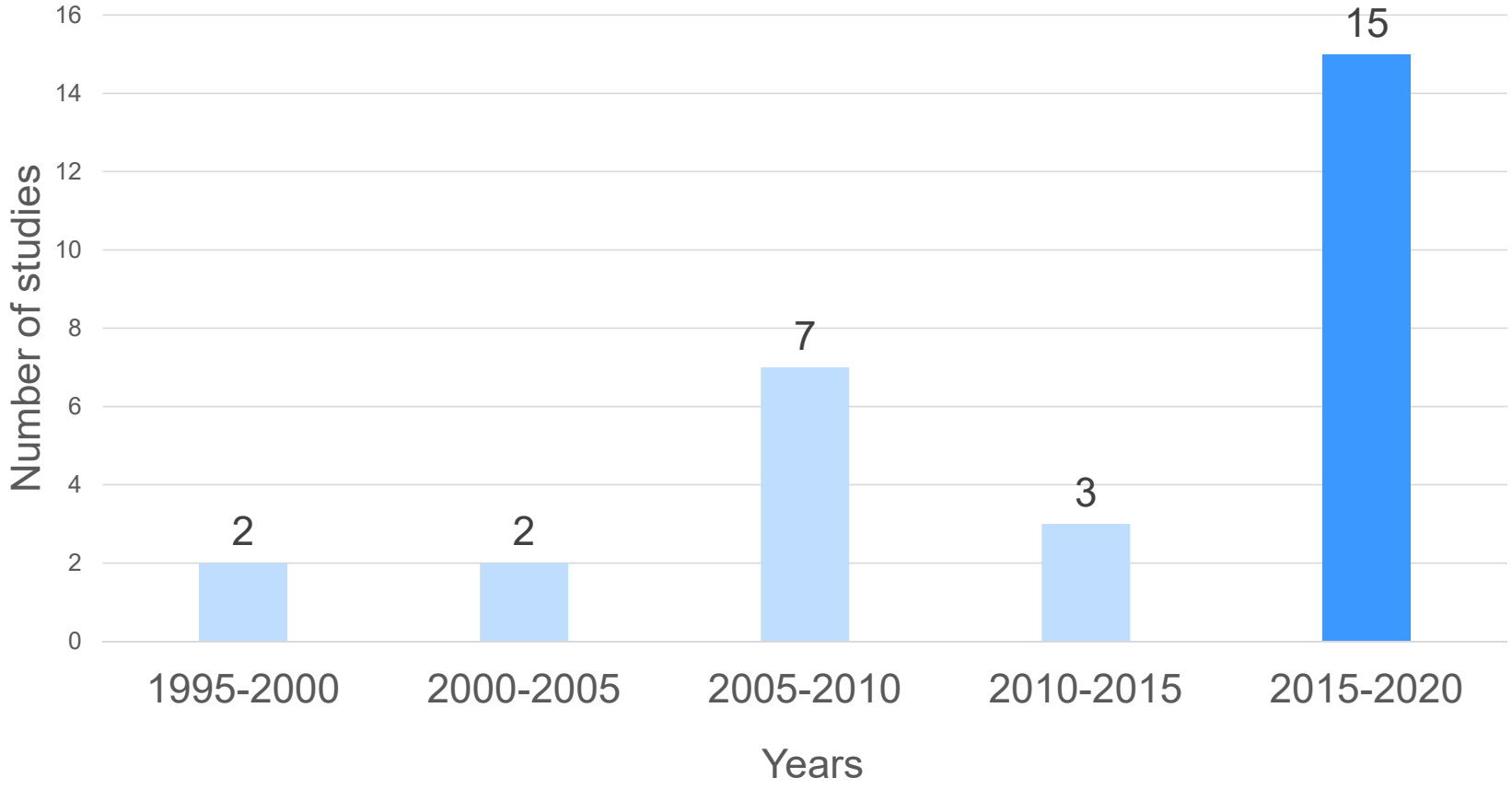
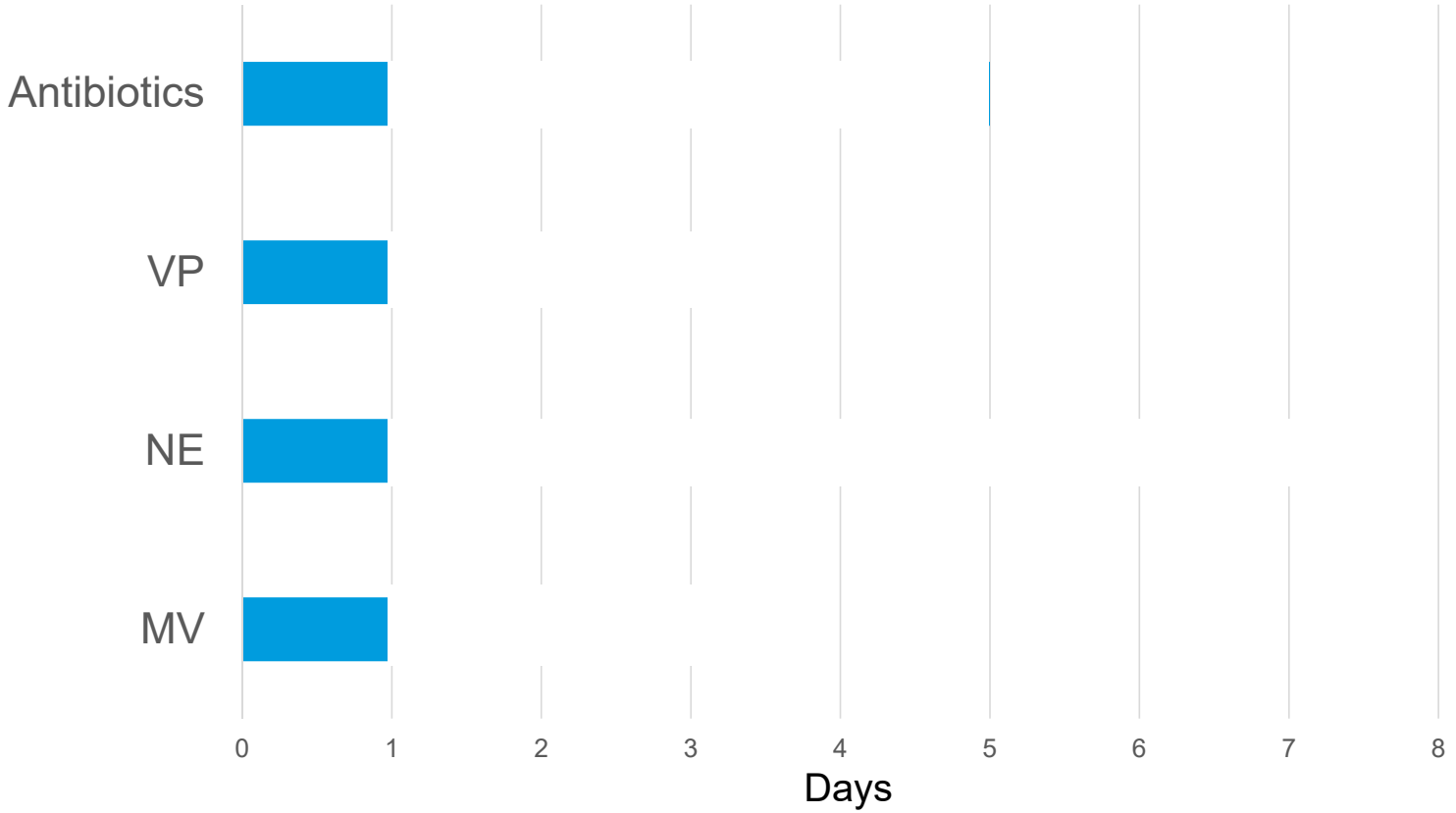


Knowledge check 1

How does midodrine primarily elicit its effect on blood pressure?

A. Midodrine binds to alpha-2 receptors
B. Midodrine binds to alpha-1 receptors
C. Desglymidodrine binds to alpha-1 and beta-1 receptors
D. Desglymidodrine binds to alpha-1 receptors

A 65 y.o female with sepsis secondary to pneumonia



VP: vasopressin, NE: norepinephrine, MV: mechanical ventilation

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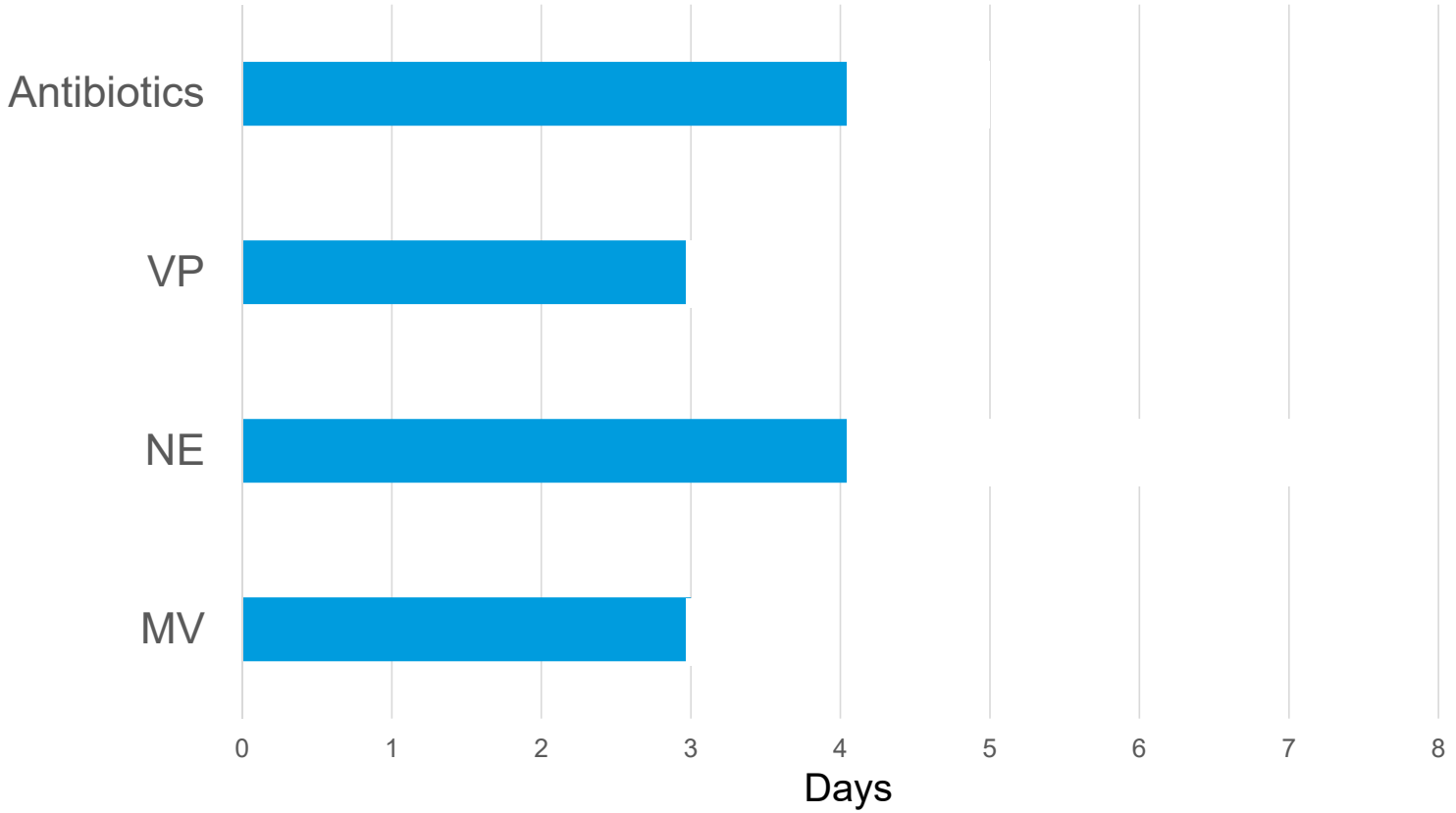

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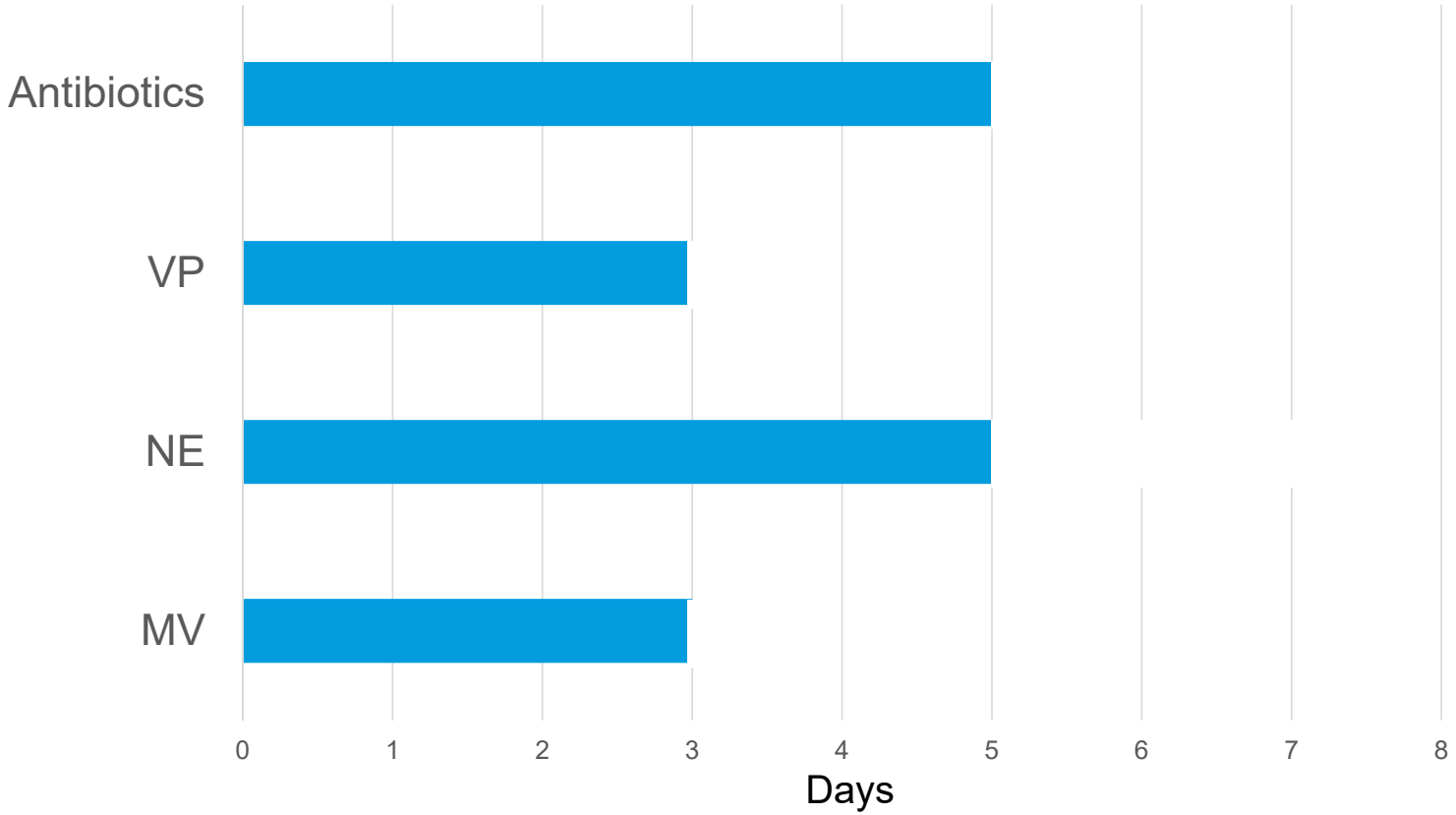

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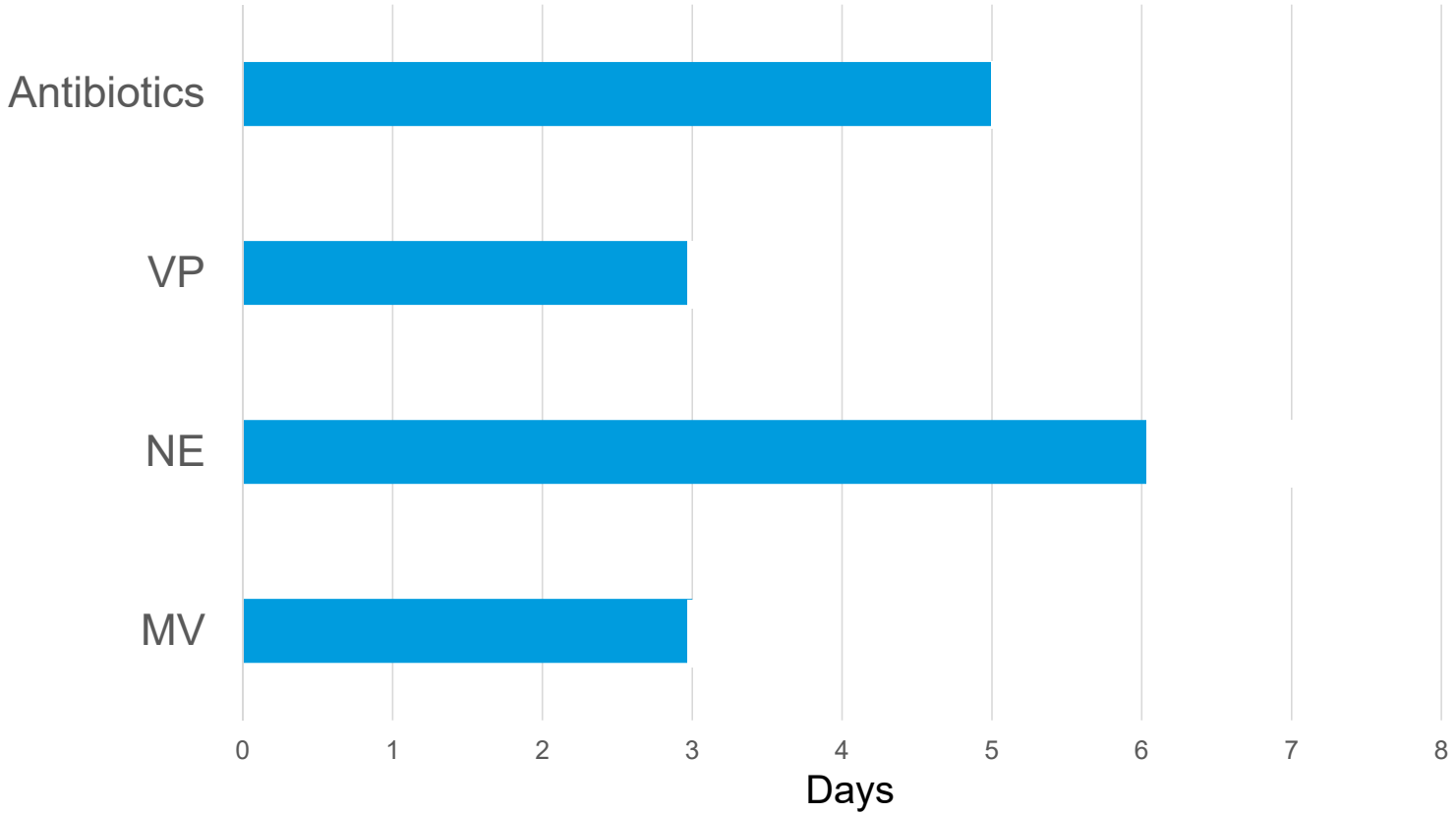

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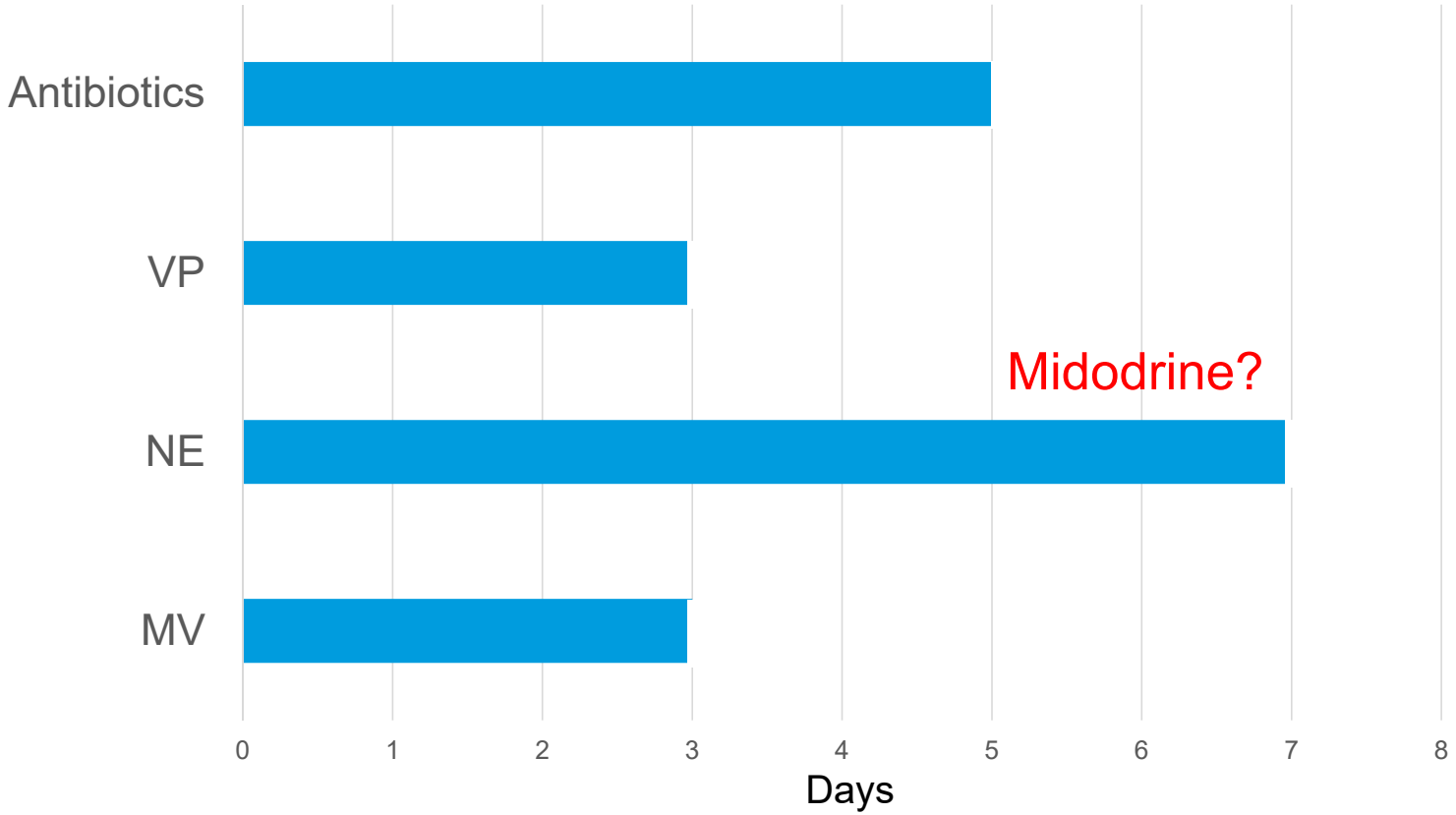


VP: vasopressin, NE: norepinephrine, MV: mechanical ventilation

Review the current evidence for midodrine and its impact on vasopressor discontinuation

Levine et al. (2013)

Design

- Single center, prospective observational study

Population

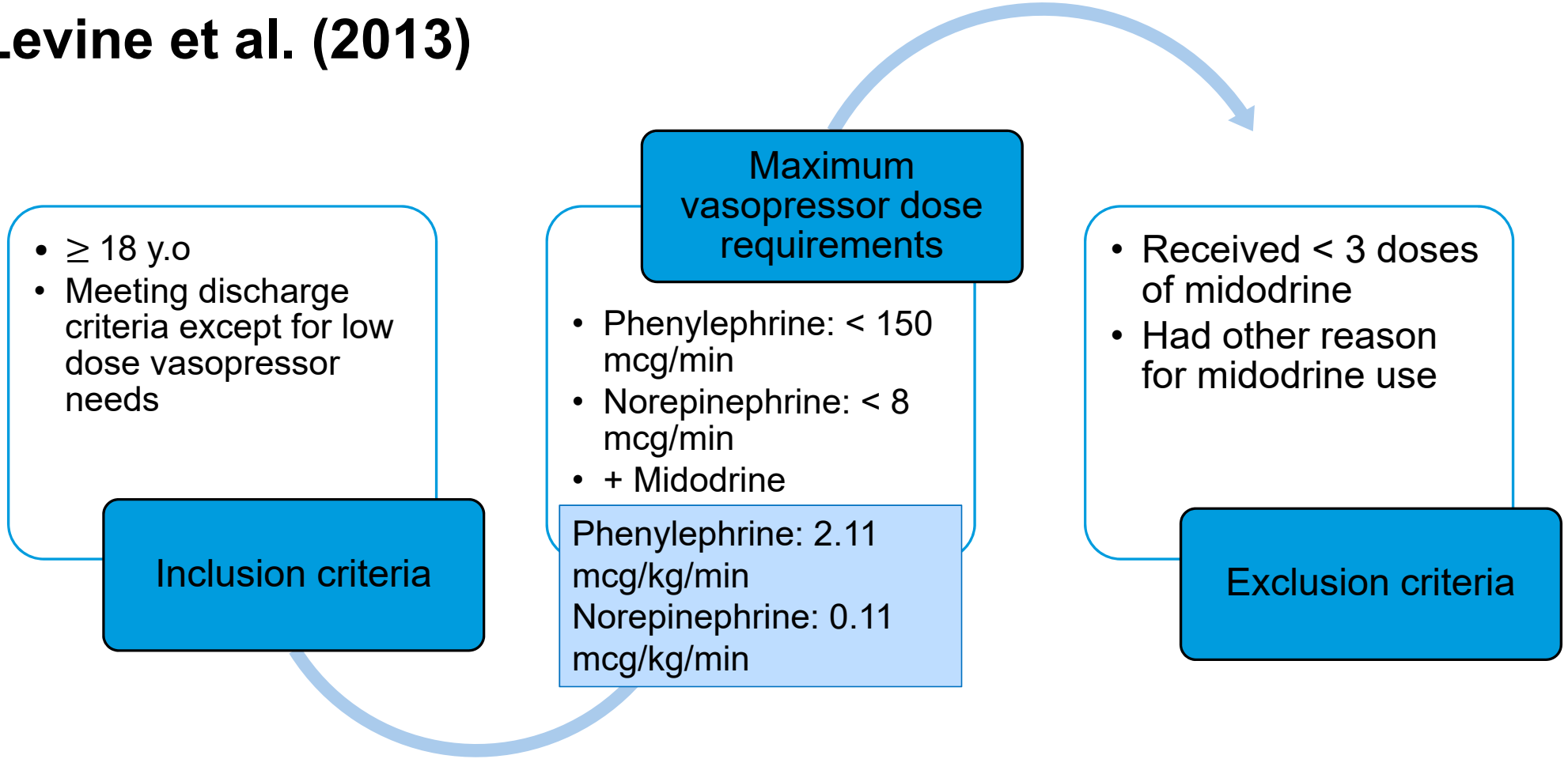
- Surgical ICU patients with persistent vasopressor needs

Study Question

- Does adding midodrine to a patient on IV vasopressors increase the rate of vasopressor decline?

Levine et al. *J of Crit Care* 2013.28:756-62

Levine et al. (2013)



Levine et al. *J of Crit Care* 2013.28:756-62

Demographics

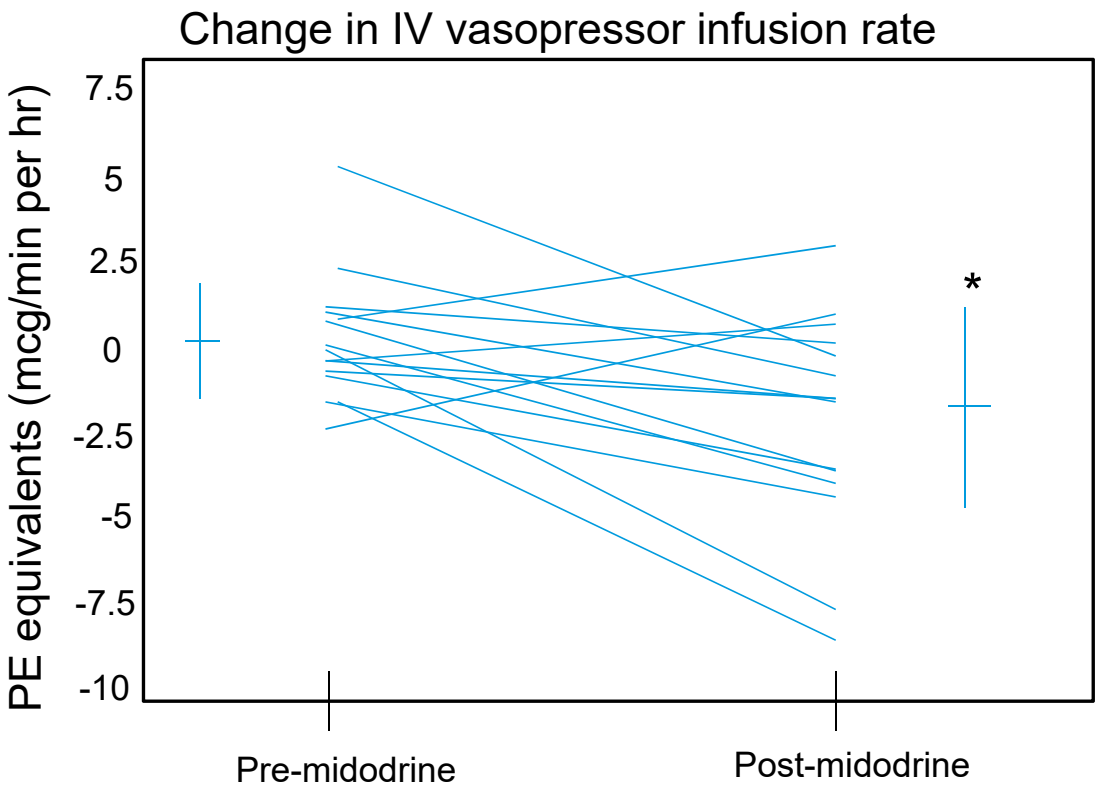
Patient demographics (n = 20)		
Age, years (mean, SD)		65 ± 14
Males, n (%)		9 (45)
APACHE II (mean, SD)		18 ± 6
Vasopressor days before midodrine (median, IQR)		3 (2-6)
PE equivalent rate prior to midodrine, mcg/min (mean, SD)		41 ± 33.4
Admitting surgical service, n (%)	Vascular	4 (20)
	General	3 (15)
	Orthopedic	4 (20)
	Thoracic	8 (40)
	Neurosurgery	1 (5)

SD: standard deviation

Levine et al. *J of Crit Care* 2013.28:756-62

Results

- Most common dose of midodrine: 20 mg three times daily
- At 24 hours, 14 patients (70%) of patients were off IV vasopressors
- Median time from midodrine initiation to vasopressor discontinuation was 17 hours
- Median duration of midodrine: 4 days (IQR 3-7)



Levine et al. *J of Crit Care* 2013.28:756-62

Levine et al. (2013)

Strengths

- Specific population

Weaknesses

- Small sample size
- Observational study design
- TID midodrine dosing
- Primary outcome not clinically relevant

Levine et al. *J of Crit Care* 2013.28:756-62

Whitson et al. (2016)

Design

- Two-arm, single center, retrospective study

Population

- Medical ICU septic shock patients requiring ≥ 24 hours of IV vasopressors and demonstrating clinical stability

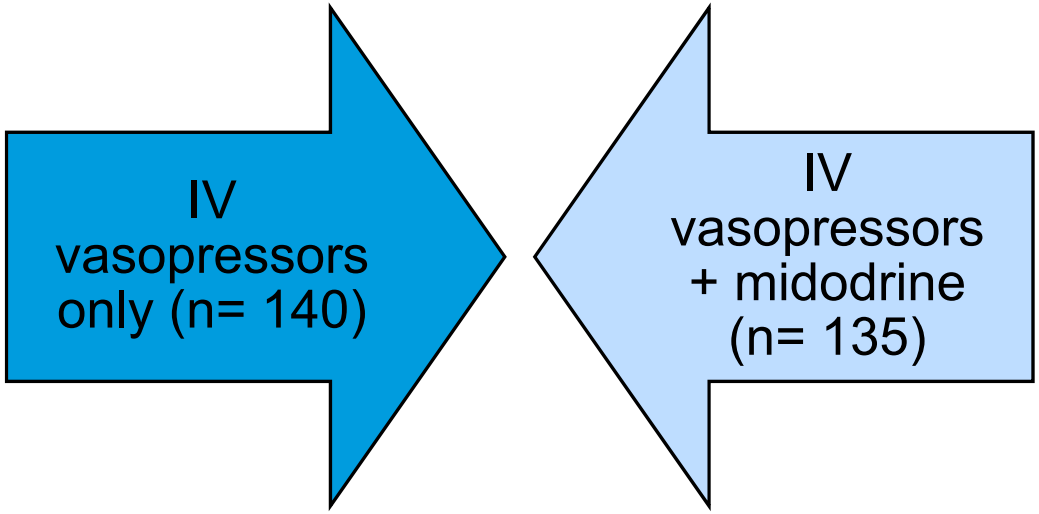
Study Question

- Does adding midodrine reduce the duration of vasopressor use and ICU LOS?

LOS: Length of stay

Whitson et al. *CHEST* 2016: 149:1380-3.

Study Groups



- Starting dose: 10 mg every 8 hours titrated to effect
- Max dose: 40 mg every 8 hours
- Mean dose: 18.7 ± 9.6 mg

Whitson et al. *CHEST* 2016: 149:1380-3.

Demographics

		IV vasopressors only (n = 140)	IV vasopressors + midodrine (n = 135)
Age, years (mean ± SD)		65 ± 19	69.3 ± 16
Males, n (%)		79 (56)	64 (47)
APACHE IV (mean ± SD)		84.3 ± 26.8	82.6 ± 26.4
Mechanical ventilation, n (%)		106 (75.7)	92 (68.1)
Corticosteroid administration, n (%)		40 (28.6)	36 (26)
Source of sepsis	Pulmonary	58 (41.4%)	52 (38.5%)
	Urinary	58 (41.4%)	54 (40%)
	Abdominal	10 (7.1%)	12 (8.9%)
	Skin	6 (4.3%)	8 (5.9%)
	Idiopathic	7 (5%)	9 (6.7%)
	Meningitis	1 (0.7%)	0 (0%)

- No statistically significant differences found between groups

Whitson et al. *CHEST* 2016: 149:1380-3.

Dosing pearls

Vasopressor dosing upon initiation

- NE: 0.09 ± 0.09 mcg/kg/min
- PE: 1.05 ± 0.77 mcg/kg/min

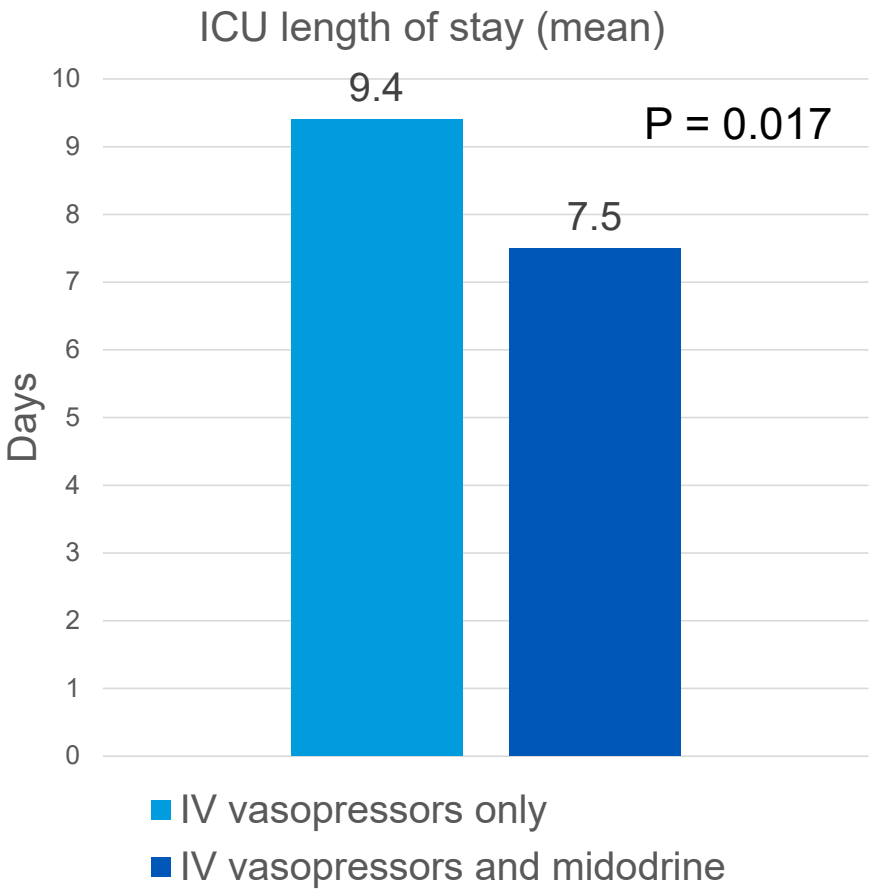
Midodrine dosing

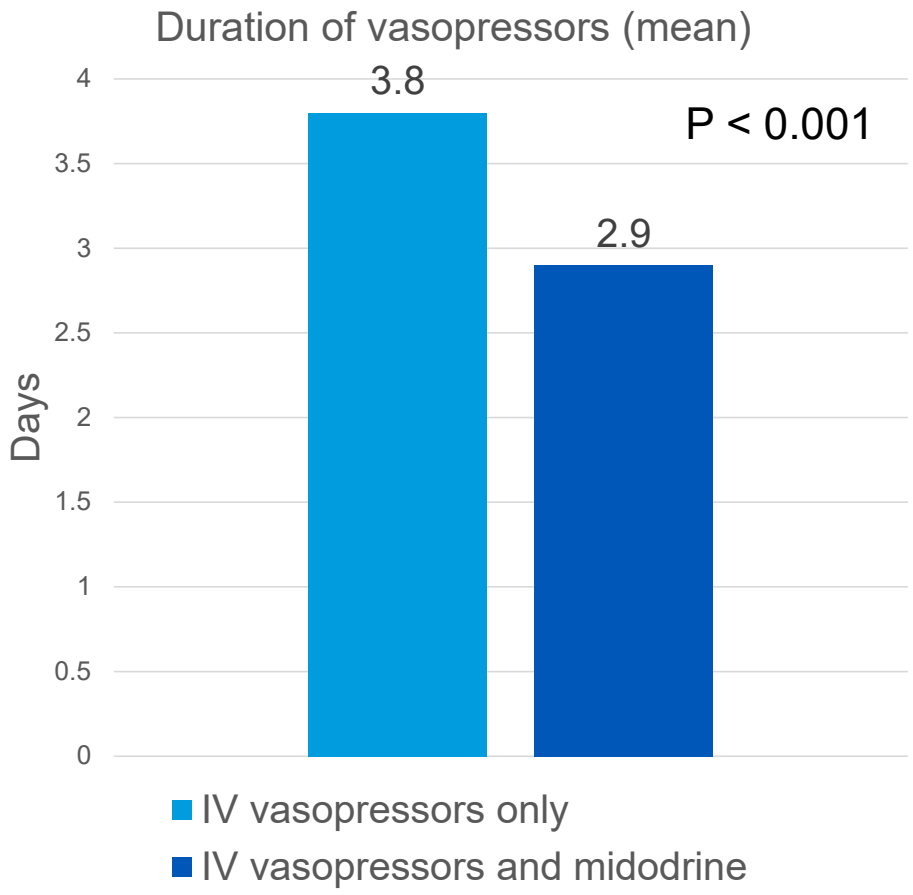
- Average duration: 6.15 days

NE: Norepinephrine
PE: Phenylephrine

Whitson et al. *CHEST* 2016: 149:1380-3.

Results





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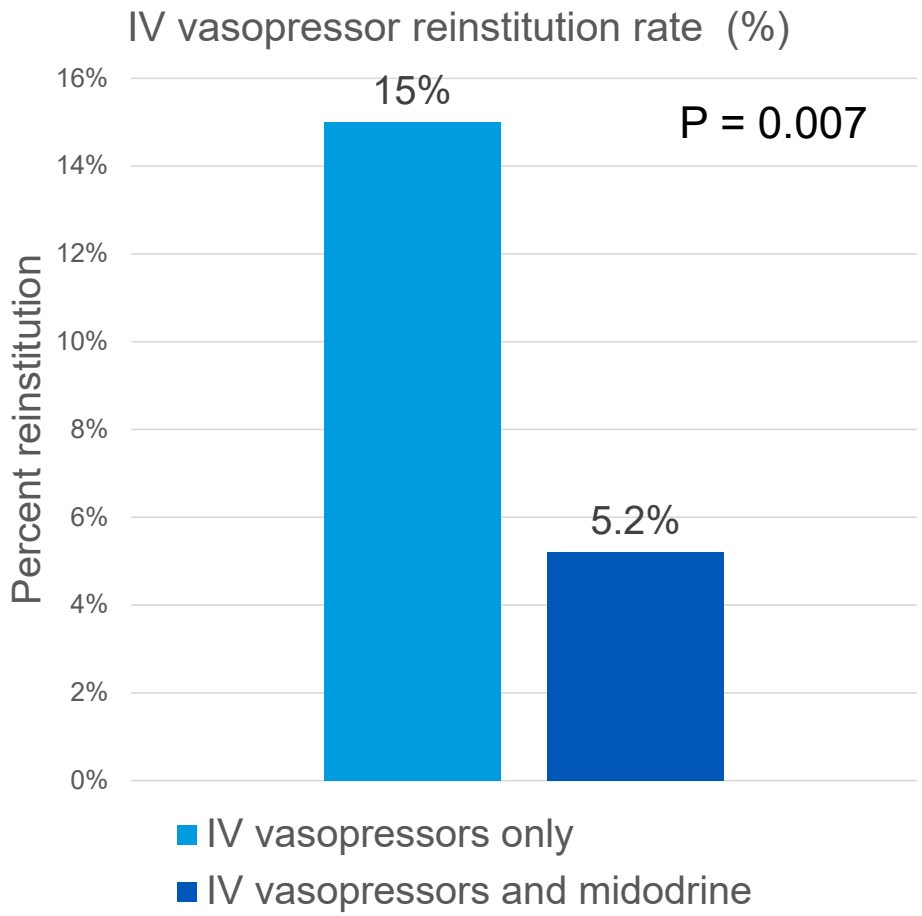

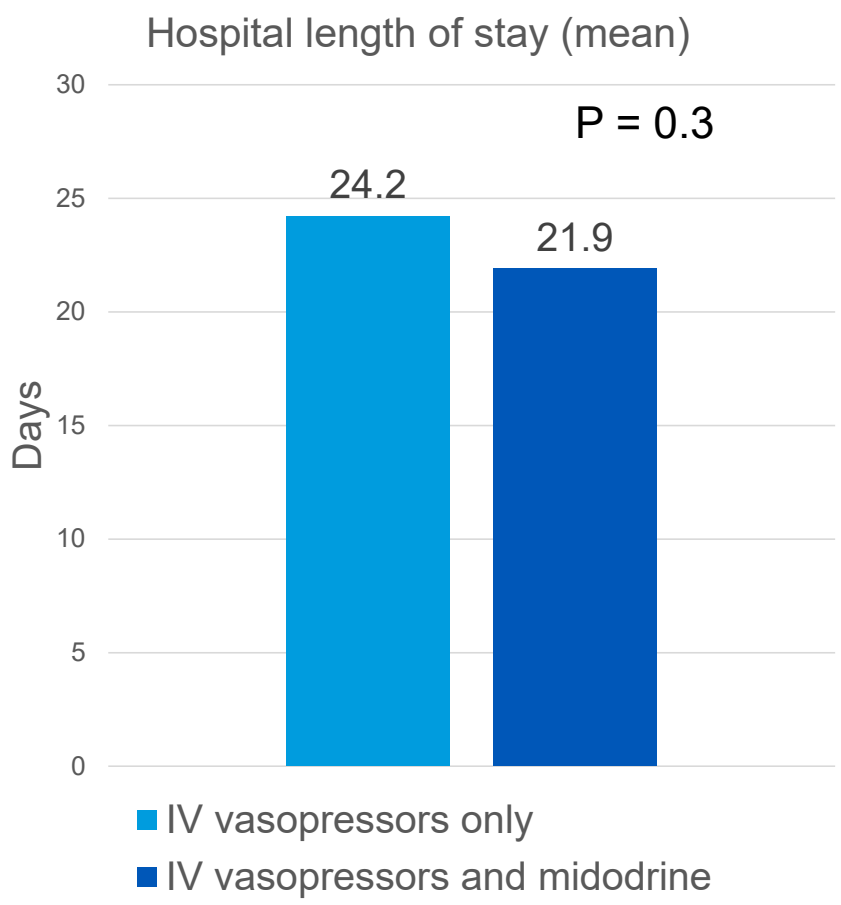

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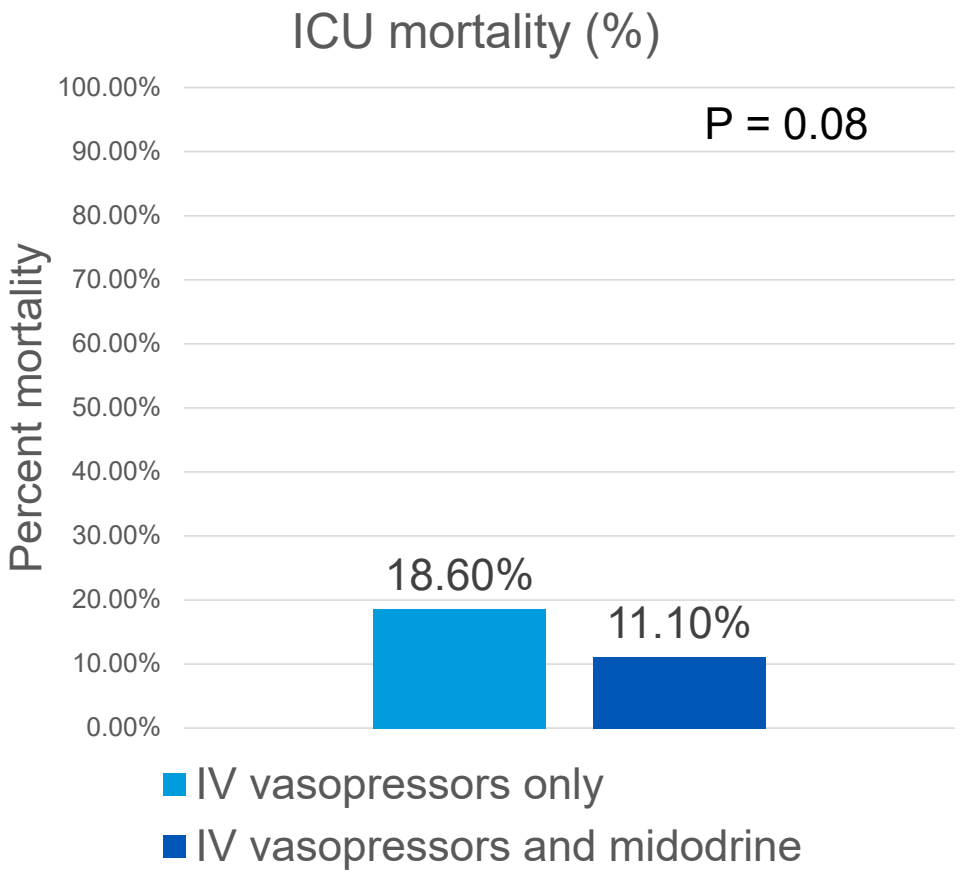
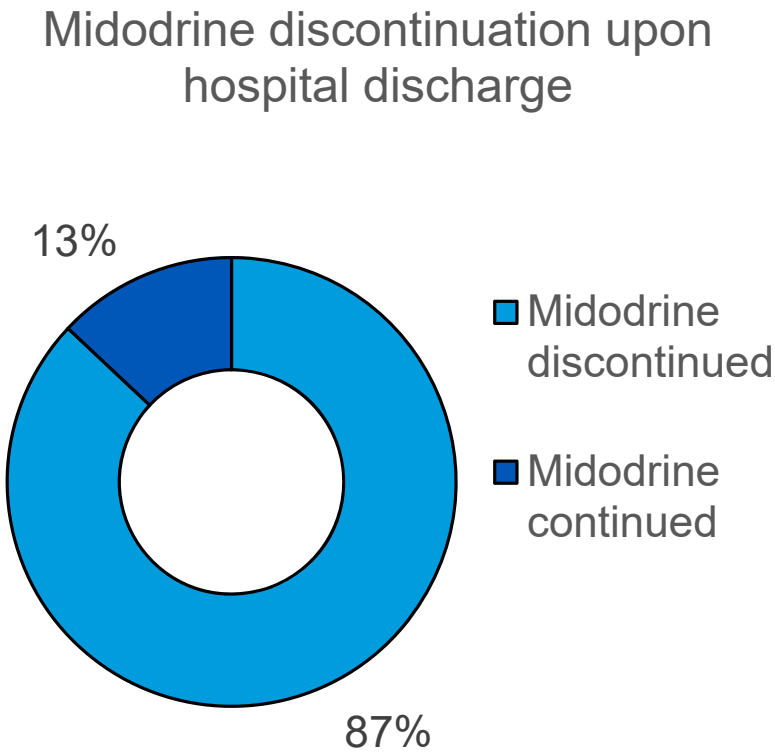




Whitson et al. *CHEST* 2016: 149:1380-3.

Whitson et al. (2016)

Strengths

- Comparison group
- Well matched baseline characteristics
- Largest sample size so far

Weaknesses

- Observational study design
- Concurrent corticosteroid use

Whitson et al. *CHEST* 2016: 149:1380-3.

Poveromo et al. (2016)

Design

- Single center, retrospective observational study

Population

- Adult ICU patients who received midodrine

Primary Outcome

- Time to IV vasopressor discontinuation after midodrine initiation

Secondary outcomes

- ICU length of stay and ICU readmission rates

Poveromo et al. *J of Clin P&T* 2016 .41:260-265

Study population

Inclusion criteria

- Admitted to an ICU
- Received one or more vasopressors*
- Mixed hypotension

IV vasopressors + Midodrine
n= 94

vs.

IV Vasopressors only
n= 94

*Norepinephrine, epinephrine, dopamine, phenylephrine or vasopressin

Poveromo et al. *J of Clin P&T* 2016. 41:260-265

Dosing

Dose range: 2.5-10 mg every 6-8 hours

Most common dose: 10 mg every 8 hours

Mean duration of midodrine: 4.4 days

Poveromo et al. *J of Clin P&T* 2016: 41:260-265

Baseline demographics

		IV vasopressors only (n = 94)	IV vasopressors + midodrine (n = 94)	*P* Value
Age, years (mean ± SD)		65.9 ± 15.5	64.3 ± 15	0.48
Males, n (%)		64 (62.8%)	64 (68.1%)	0.44
APACHE IV, median (IQR)		82 (66-93)	59 (44-83)	0.02
MAP when IV vasopressors initiated (mean ± SD)		65.9 ±13.3	67.7 ± 11.9	0.35
Corticosteroid use, n (%)		38 (40.4)	52 (55.3)	0.04
Number of vasopressors used, n (%)	1	59 (62.8)	38 (40.4)	< 0.01
	2	23 (24.4)	39 (41.5)	< 0.01
	3 or more	12 (12.8)	17 (18.1)	< 0.01

MAP: mean arterial pressure (mmHg)

Poveromo et al. *J of Clin P&T* (2016) 41:260-265

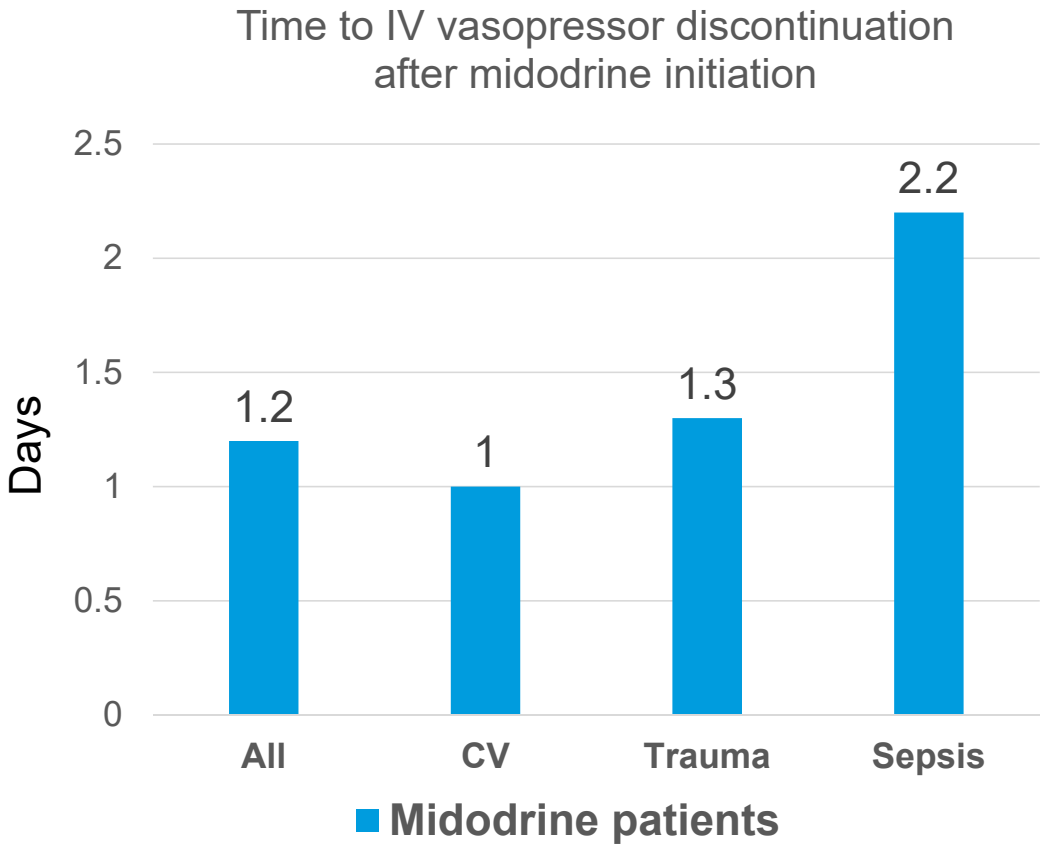
Baseline demographics

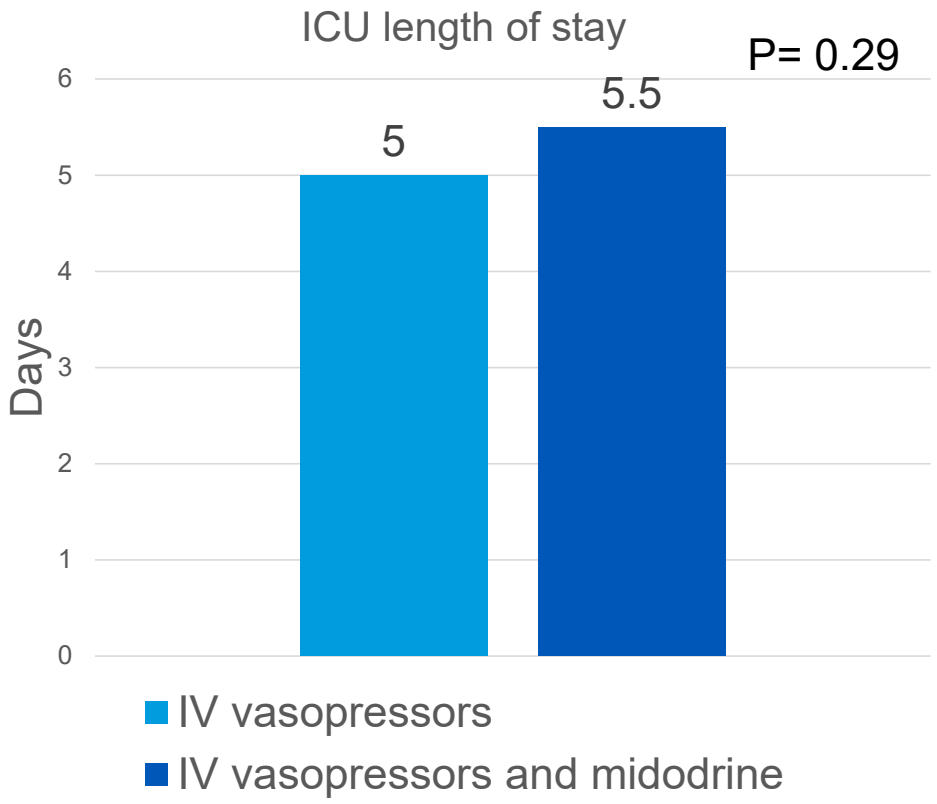
		IV vasopressors only (n = 94)	IV vasopressors + midodrine (n = 94)
Principal diagnosis, n (%)	CV	43 (46)	43 (46)
	Trauma	28 (30)	28 (30)
	Sepsis	23 (24)	23 (24)
Vasopressors choice (%)	PE	59.6	69.1
	NE	36.2	50
	DA	35.1	44.7
	VP	10.6	11.7
	EPI	9.6	8.5
NE equivalent IV vasopressor rate (mcg/kg/min), median (IQR)		0.05 (0.03-0.08)	0.05 (0.03-0.08)

CV: Cardiovascular

Poveromo et al. *J of Clin P&T* (2016) 41:260-265
Khanna et al. N Engl J Med 2017; 377:419-30

Results





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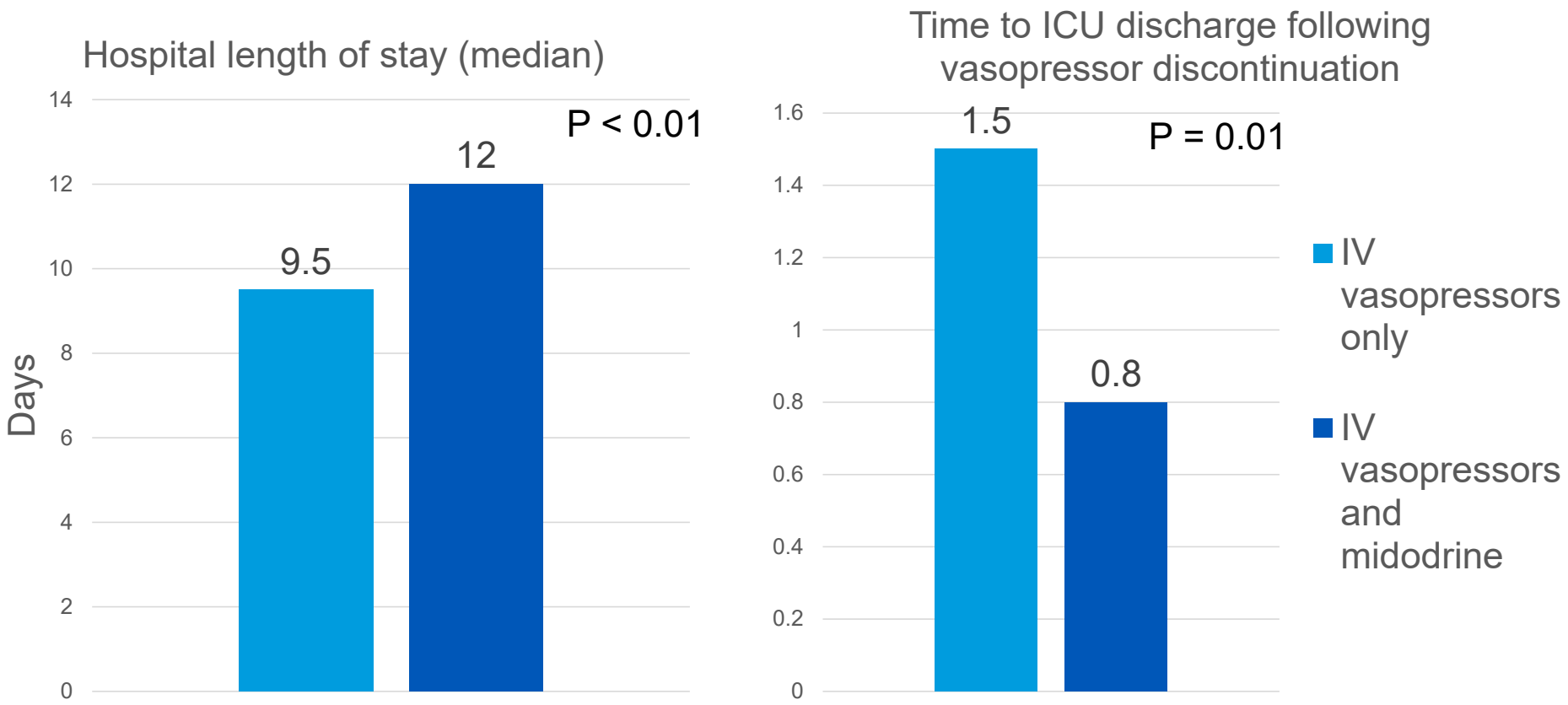


- 12.8% of patients in the midodrine group experienced bradycardia

Poveromo et al. *J of Clin P&T* (2016) 41:260-265

Poveromo et al. (2016)

Strengths

- Comparator group
- Study size

Weaknesses

- Corticosteroid use
- Primary outcome was not compared
- Variation in baseline characteristics

Poveromo et al. *J of Clin P&T* (2016) 41:260-265

Comparison of evidence

Levine et al. (2013)	Whitson et al. (2016)	Poveromo et al. (2016)
Surgical	Septic shock	Mixed
5-20 mg TID	10-40 mg q8hr	2.5-10mg q6-8hr

Levine et al. *J of Crit Care* 2013.28:756-62
Whitson et al. *CHEST* 2016: 149:1380-3
Poveromo et al. *J of Clin P&T* (2016) 41:260-265

Knowledge check 2

Based on the presented research, would you consider recommending midodrine for a patient with persistent vasopressor use?

A. Yes
B. No

Identify midodrine’s role in therapy for vasopressor discontinuation

MIDAS 2020

Design

- Multicenter, randomized, double-blind placebo-controlled trial

Population

- Adult ICU patients requiring single-agent IV vasopressor treatment

Primary outcome

- Time from start of midodrine to vasopressor discontinuation

Secondary outcomes

- Time to ICU discharge readiness, ICU/hospital LOS, and rates of readmission

Santer et al. *Intensive Care Med* 2020. 10.1007

MIDAS 2020

Inclusion Criteria

- Unable to liberate from vasopressors for at least 24 hours
- Requiring single agent vasopressor treatment
- Doses of < 100 mcg/min PE, < 8 mcg/min NE, or < 60 mcg/min metaraminol at randomization

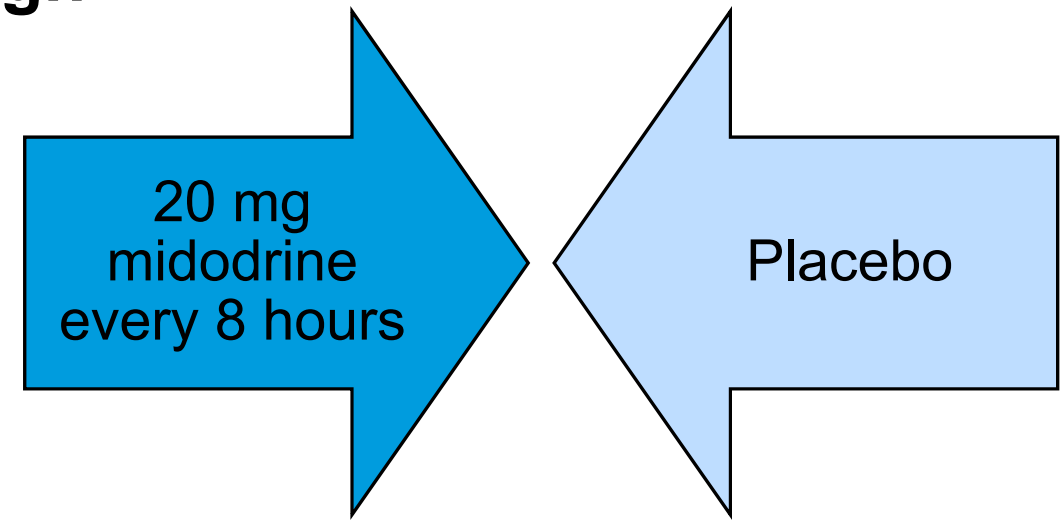
Exclusion Criteria

- Liver failure, chronic renal failure, or severe heart failure (EF < 30)
- Patients that received midodrine prior to enrollment
- Bradycardic (HR <50)

EF: Ejection fraction
HR: Heartrate

Santer et al. *Intensive Care Medicine* 2020

Study design



- Patients were randomized 1:1 to receive either midodrine or placebo in addition to IV vasopressors
- If blood pressure goals were met for at least 24 hours without vasopressors, the study drug could be discontinued
- Protocolized dose titration

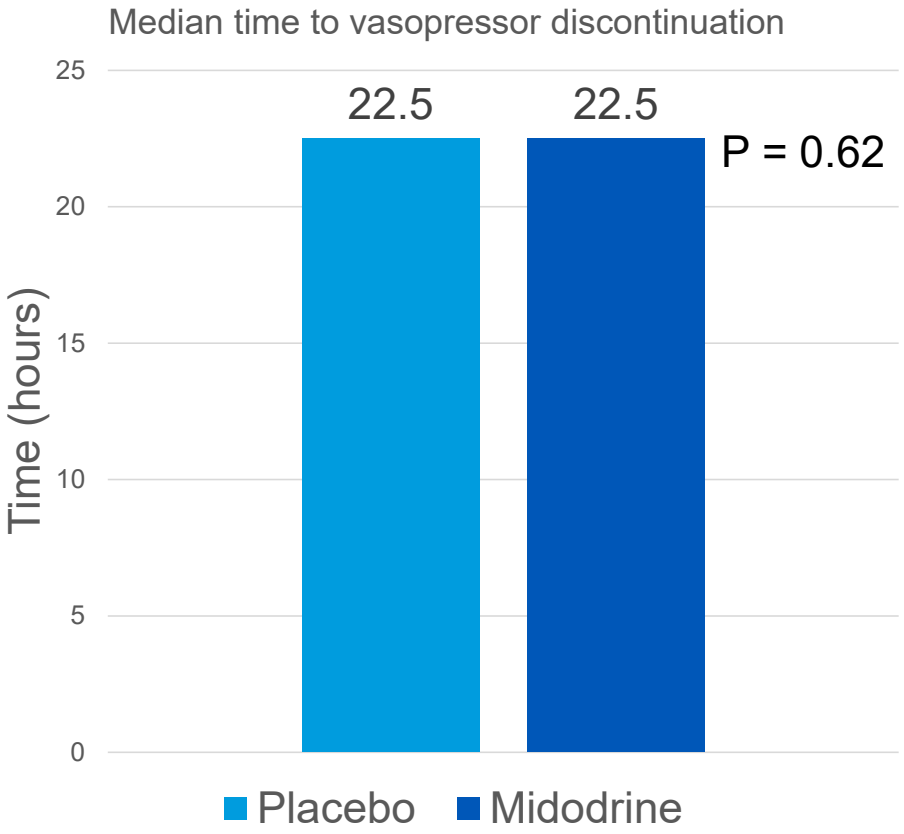
Santer et al. *Intensive Care Medicine* 2020

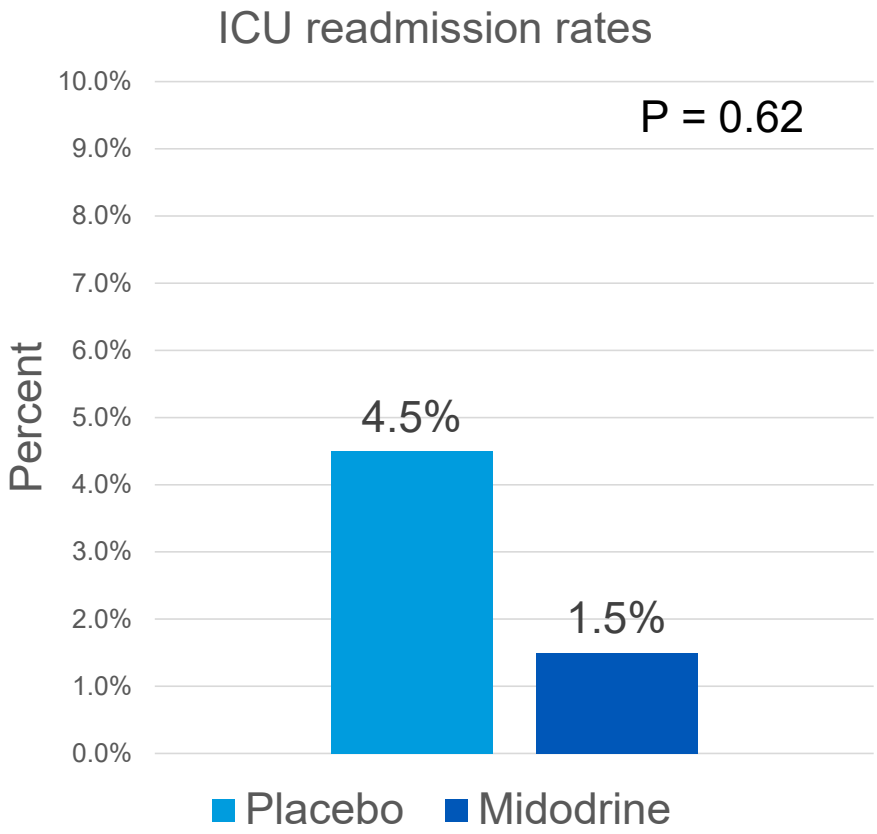
Baseline demographics

		Placebo (n= 66)	Midodrine (n= 66)
Age, mean (SD)		66.7 (14.7)	70 (12.6)
Males, n (%)		32 (48.5)	36 (54.5)
APACHE II, mean (SD)		14.8 (5.9)	14.7 (5.2)
Indication for ICU admission	Post-op/surgical	42 (63.6)	45 (68.2)
	Sepsis	13 (19.7)	13 (19.7)
	Medical/other	11 (16.7)	8 (12.1)
Baseline MAP (mmHg), median (SD)		72.8 (8.2)	75.9 (9.4)
Epidural analgesia, n (%)		13 (19.7)	18 (27.3)
Vasopressor dose at enrollment (mcg/kg/min), mean	NE	0.06	0.06
	PE	0.43	0.61
	Metaraminol	0.61	0.6

Santer et al. *Intensive Care Medicine* 2020

Outcomes





Santer et al. *Intensive Care Medicine* 2020

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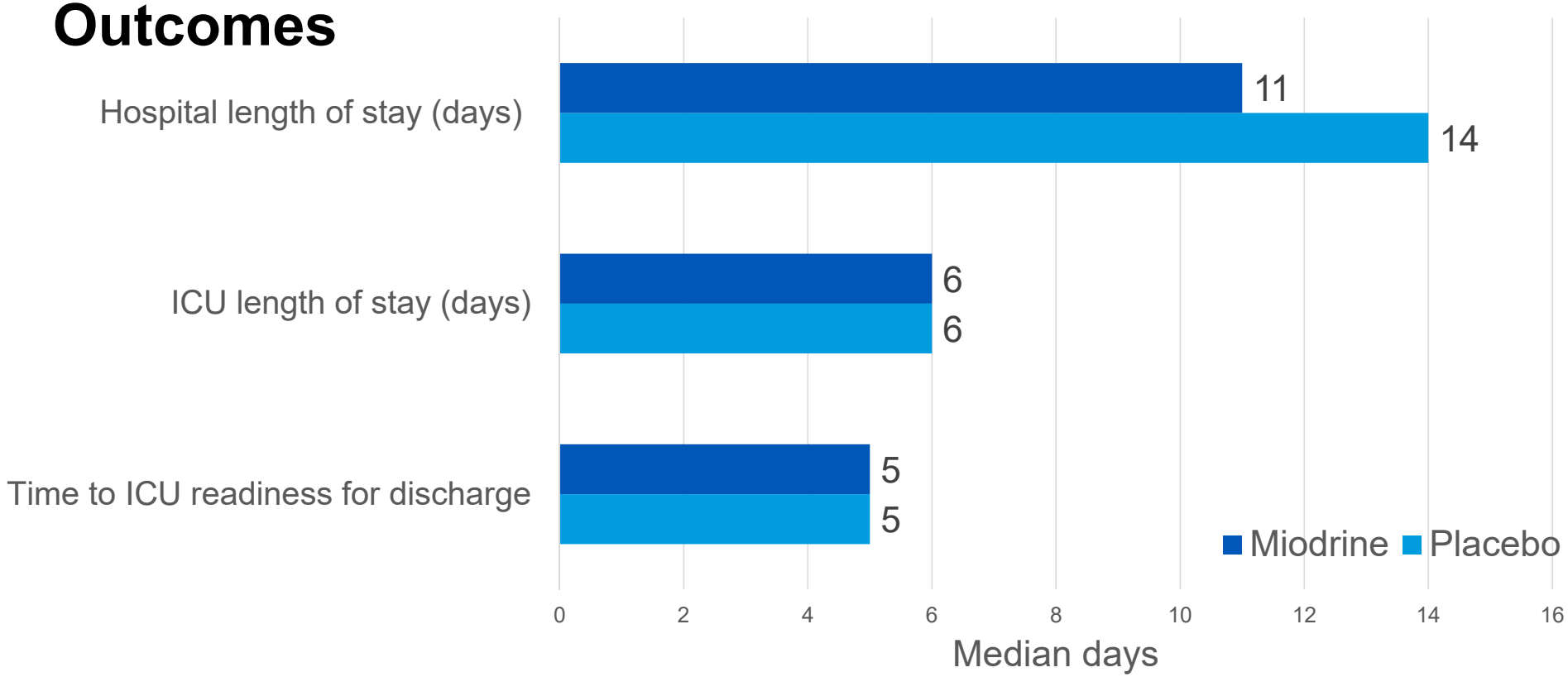


- Post-hoc analysis in patients with epidural analgesia: Midodrine reduced time to vasopressor discontinuation by 18.5 hours compared to placebo (p= 0.045)

Santer et al. *Intensive Care Medicine* 2020

Safety outcomes

Hypertension	Bradycardia	Atrial fibrillation
• Midodrine: 10.7% • Placebo: 3.6% • P = 0.19	• Midodrine: 7.6% • Placebo: 0% • P = 0.02	• Midodrine: 4.6% • Placebo: 1.5% • P = 0.31

Santer et al. *Intensive Care Medicine* 2020

MIDAS 2020

Strengths

- Randomized controlled trial
- Looked at safety outcomes
- Protocolized dosing

Weaknesses

- Slow enrollment
- High baseline MAPs
- Healthier patient population

Santer et al. *Intensive Care Medicine* 2020

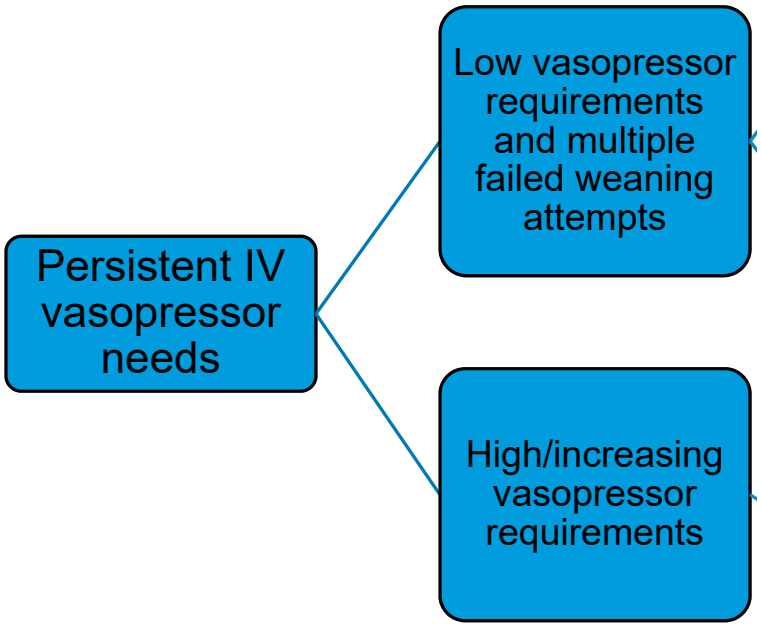
Knowledge check 3

You are the pharmacist covering the MICU today. A 55 yoM admitted for septic shock has been on 0.07 mcg/kg/min NE for three days now. Every time the NE drip is turned off, his MAP drops to 60 mmHg.
Vitals: HR 67, BP 98/70, SpO2 98% on room air

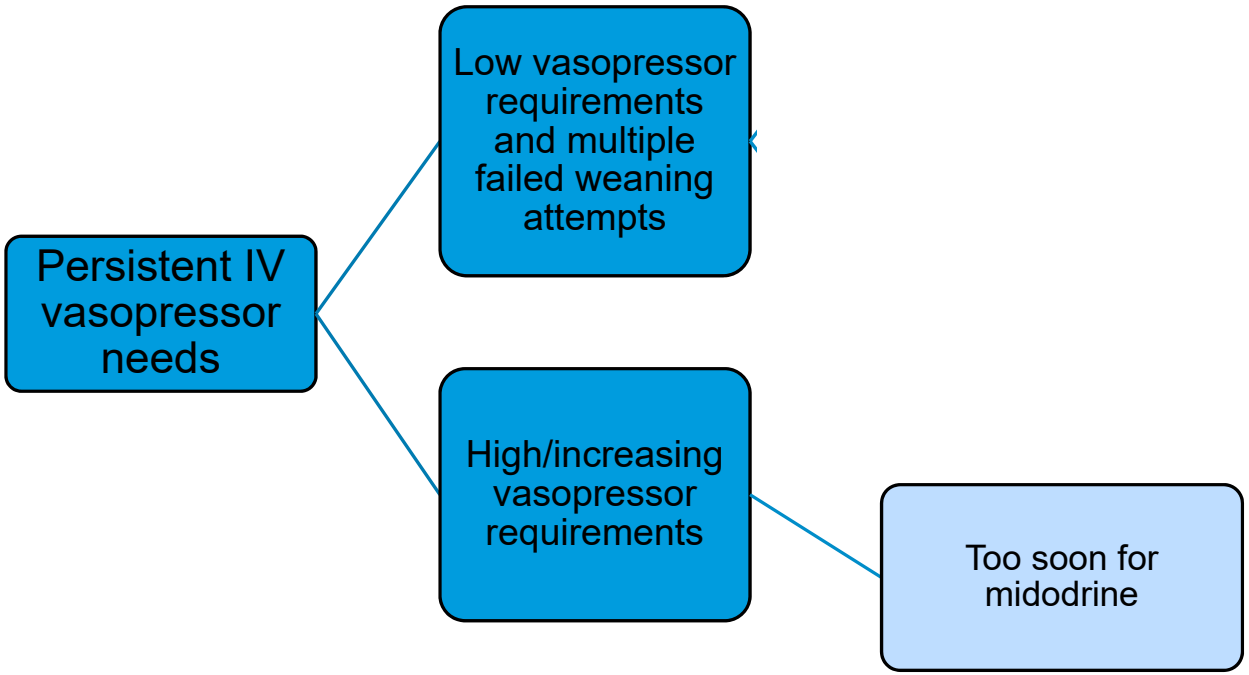
The team asks if you think they should start midodrine. How do you respond?

A. Start midodrine 20 mg three times daily
B. Start midodrine 20 mg q8 hours and monitor for tachycardia
C. Start midodrine 10 mg q8 hours and monitor for bradycardia
D. Do not start midodrine because it is ineffective in shortening time to vasopressor discontinuation

Place in therapy



Place in therapy



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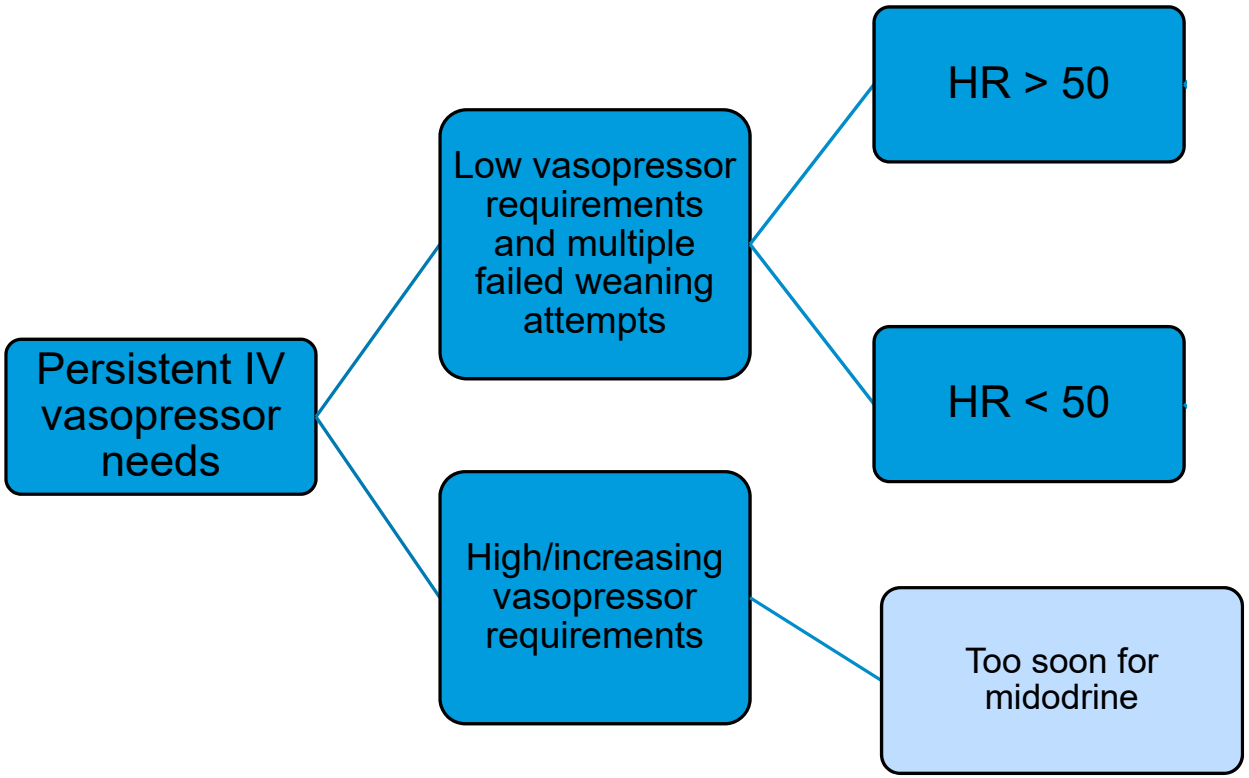

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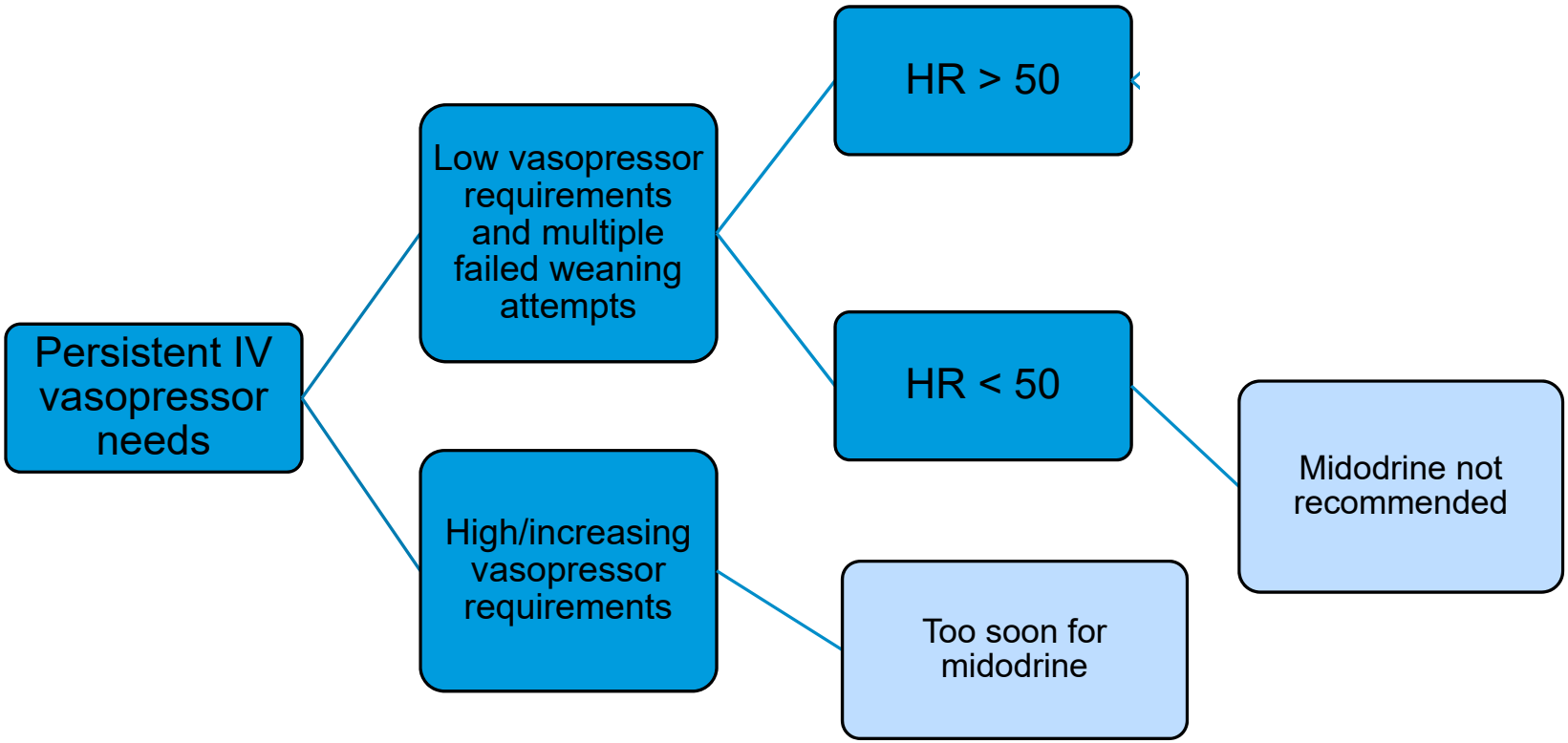

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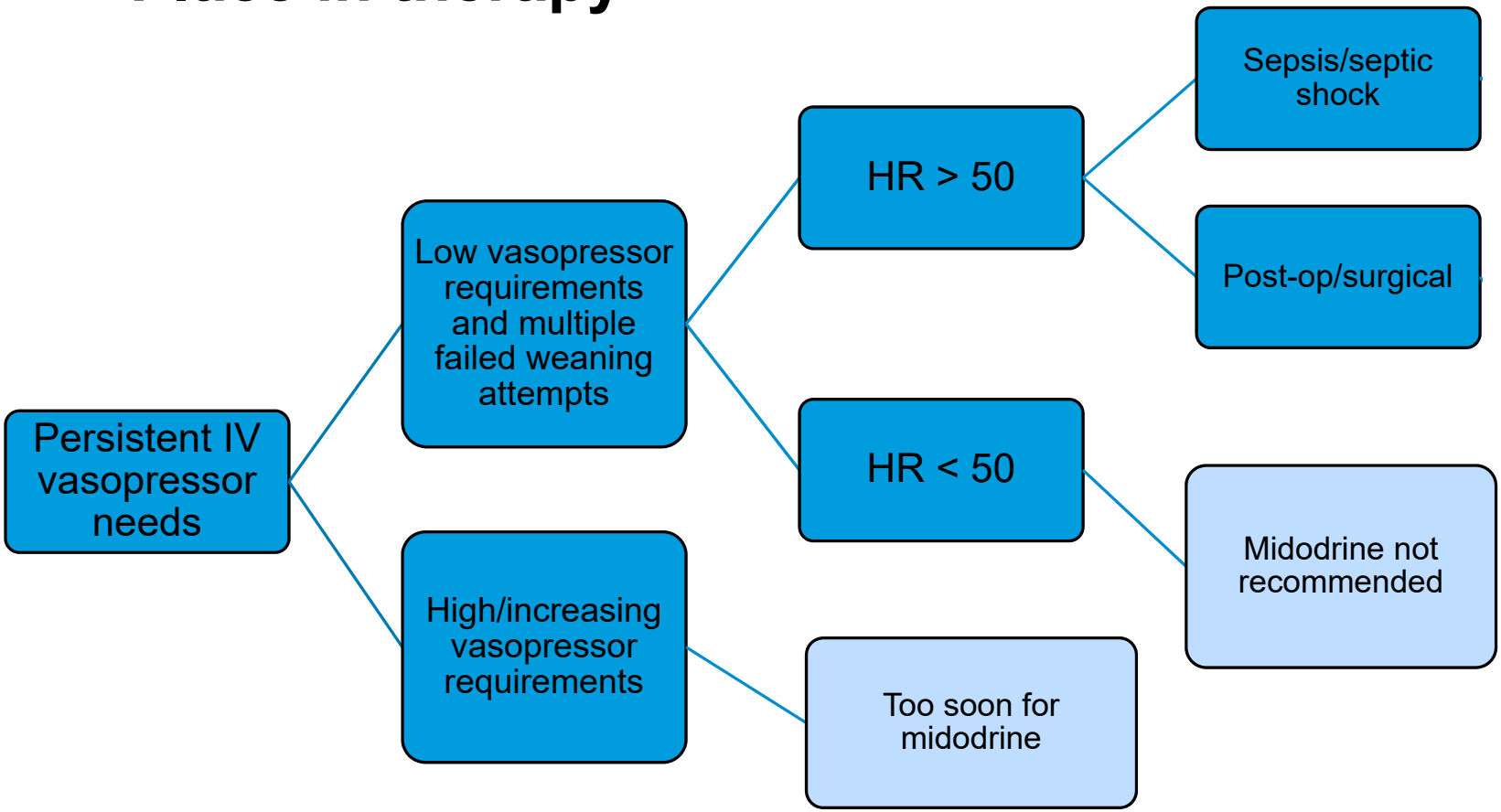

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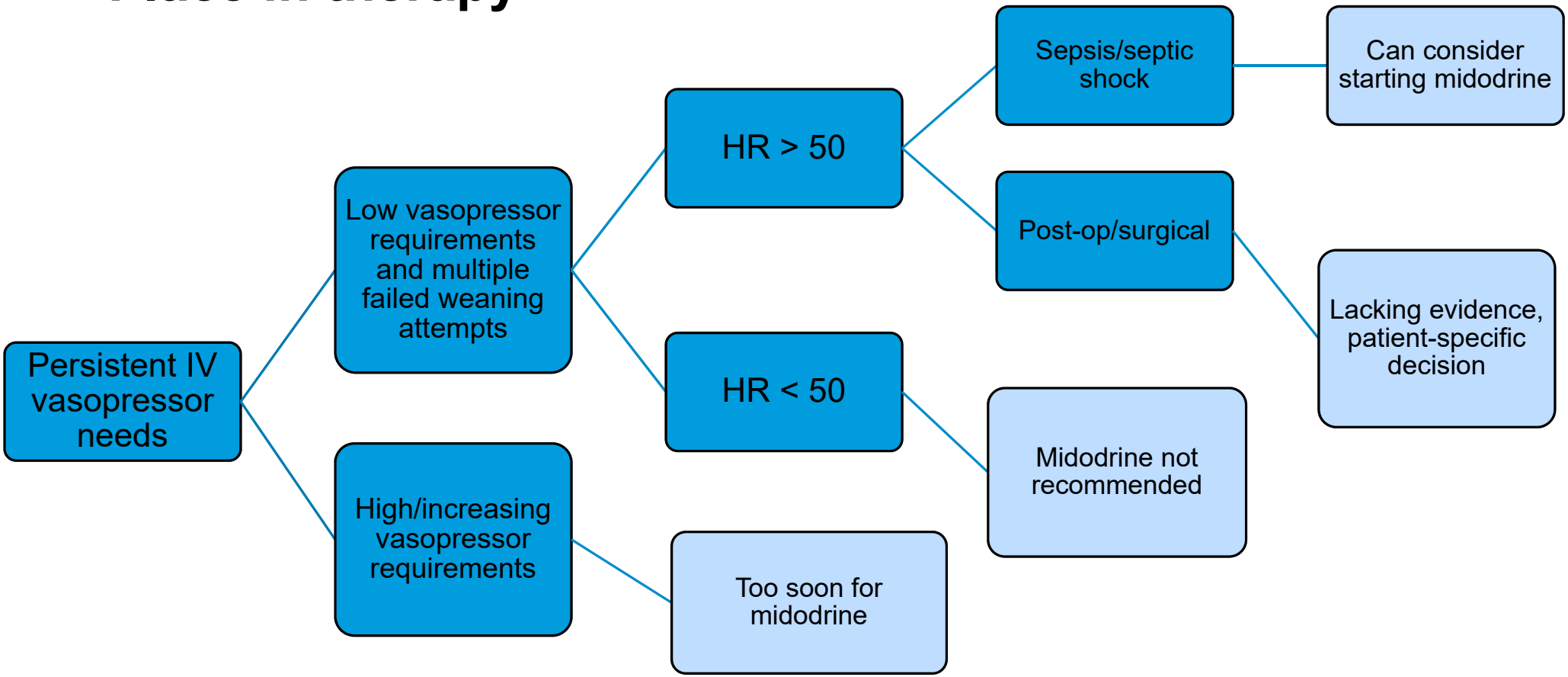
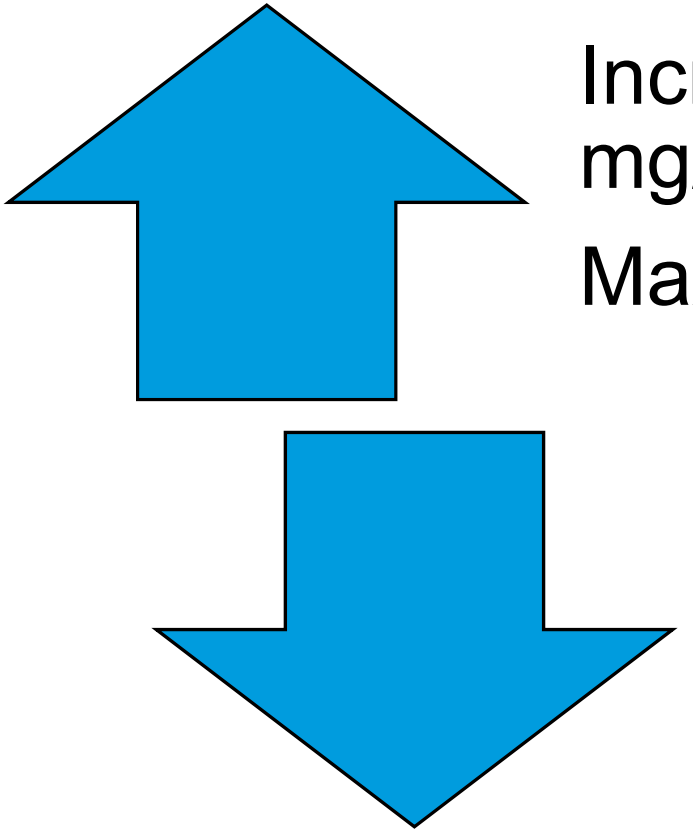


Midodrine pearls

- Check for reversible causes of hypotension
- Avoid if clinically unstable
- Monitor vitals and renal function
- Start at 10-20 mg every 6-8 hours
- Reassess need at hospital discharge
- Remember to titrate up and down

Dose titration



Increase by 10 mg/dose per day

Max: 40 mg q8 hours

Decrease by 5-10 mg/dose per day

Discontinue at 5 mg

Remaining questions

- What is the best frequency of midodrine dosing?
- What is the most appropriate starting dose?
- Is there any benefit in early versus late initiation in septic shock?

QUESTIONS & ANSWERS