

# Vasopressin Stewardship

## Less or More?

Seth Bauer, PharmD

Gretchen Sacha, PharmD

Department of Pharmacy  
Cleveland Clinic



@SethRBauer



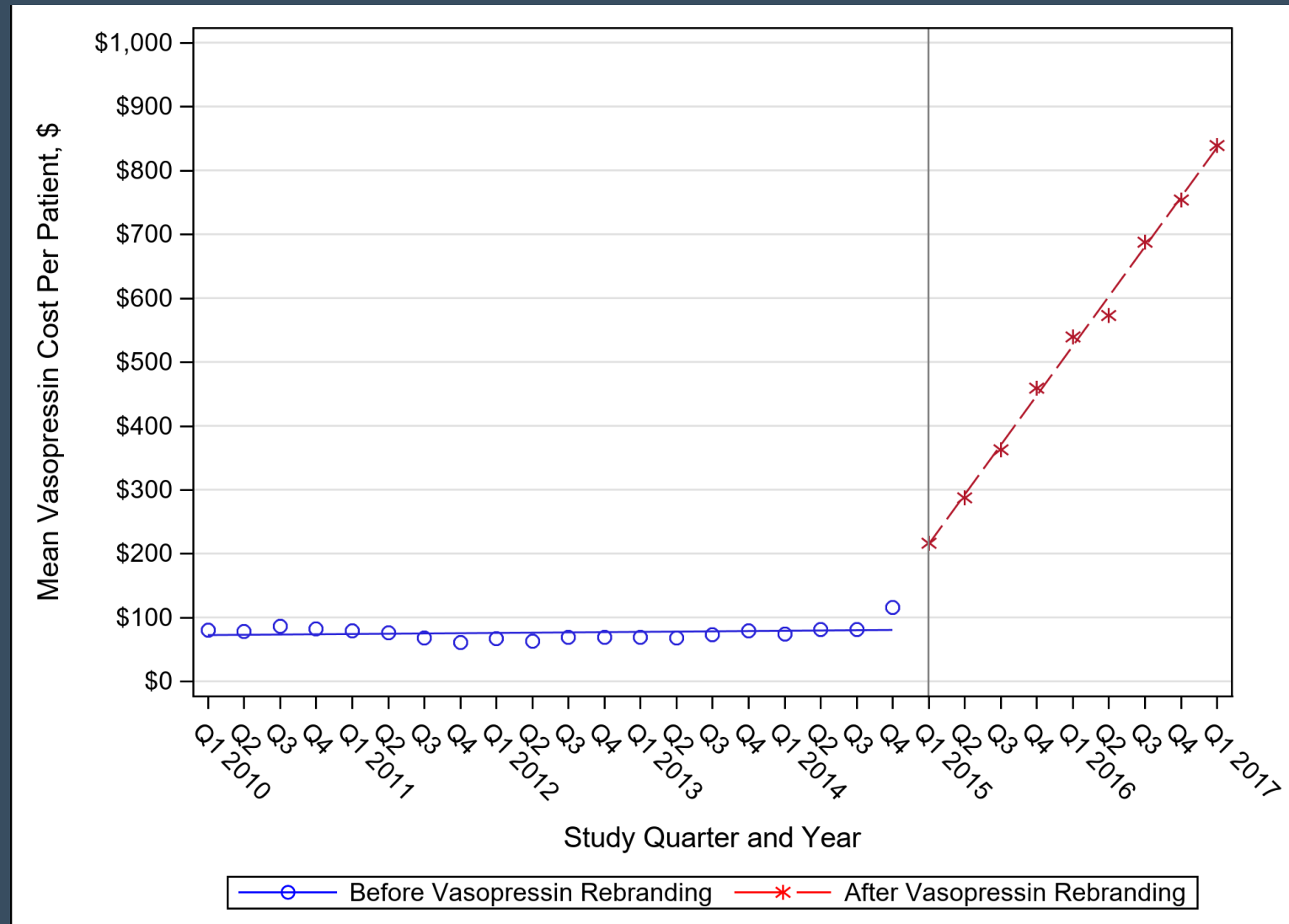
@gretchensacha



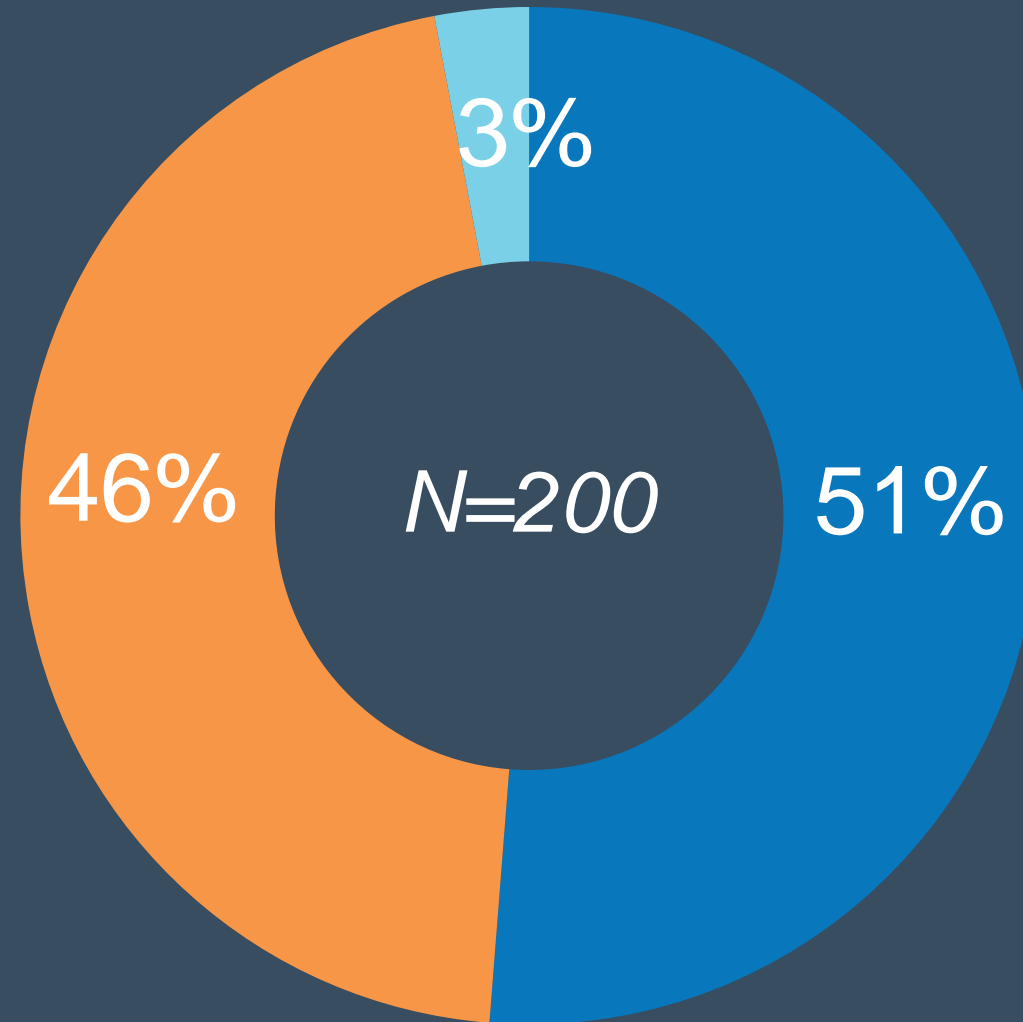
# Initiation of Vasopressin



# Vasopressin Cost Over Time



# Pharmacist-Recommended AVP Initiation



- NE  $\leq$  30 mcg/min (or  $\leq$  0.3 mcg/kg/min)
- NE  $>$  30 mcg/min (or  $>$  0.3 mcg/kg/min)
- Other

# Cleveland Clinic MICU Guideline



## Vasoactive medication titration in SEPTIC SHOCK

### Initiation

#### Norepinephrine (NE, "Levo") 1st

- Start if MAP not at goal
- Start at 5 mcg/min, titrate to goal MAP
- Usual max 80 mcg/min

#### Vasopressin (AVP, "Vaso") 2nd

- Request order if MAP not at goal on NE  $\geq 50$  mcg/min
- Start at ordered dose (usual dose 0.03 units/min without titration)
- If MAP goal not reached after starting AVP continue titrating NE to goal MAP

#### Phenylephrine (PE, "Neo")

- In patients who develop a tachyarrhythmia on NE, request order for PE and titrate off NE
- Start at ordered dose, titrate to goal MAP
- Usual max 500 mcg/min

Version: December 1, 2016

### Discontinuation

Epinephrine (Epi) 1st  
Wean off Epi first

Norepinephrine (NE, "Levo")

#### Vasopressin (AVP, "Vaso") 2nd

- Once NE has been titrated down to  $< 50$  mcg/min, do not request additional bags of AVP
- Continue titrating NE down
- Once AVP bag finished contact LIP to discontinue order

If MAP not at goal after stopping AVP and NE increased to  $> 50$  mcg/min, contact LIP to consider resuming AVP

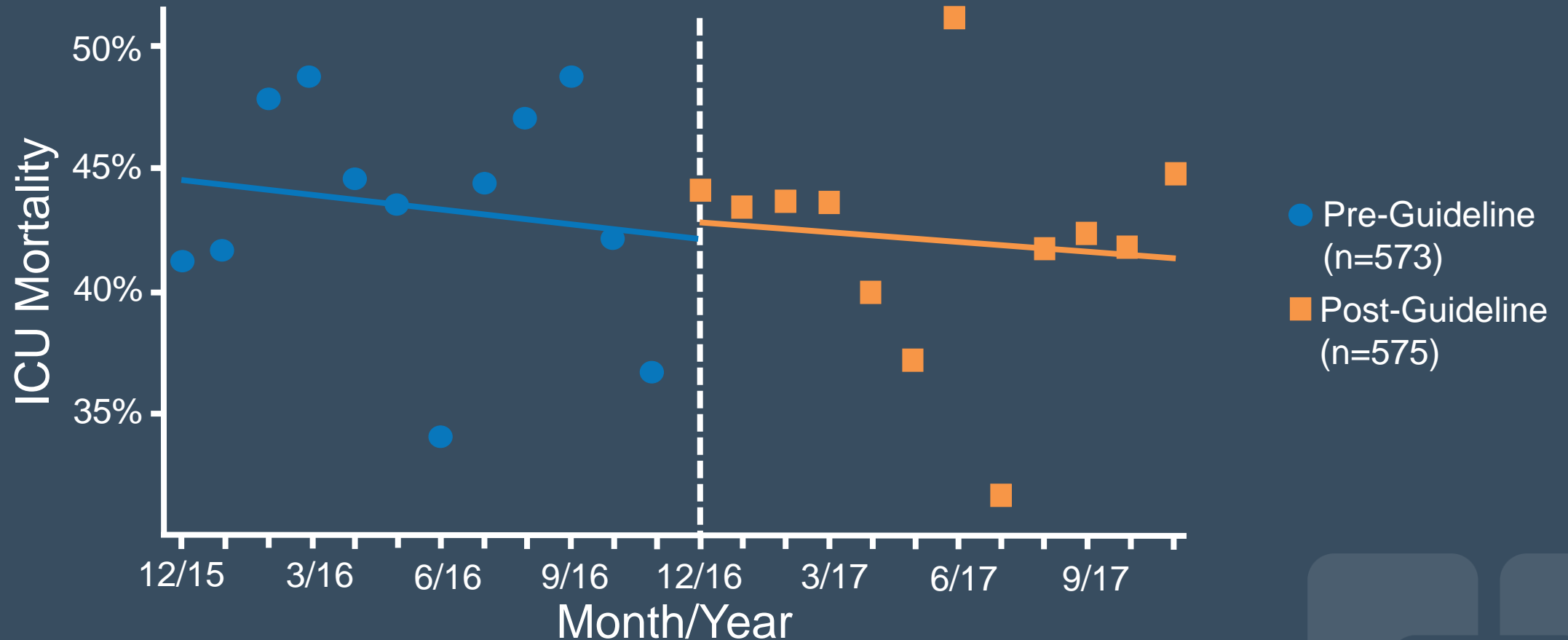
# Processes of Care

	Pre-Guideline (n=573)	Post-Guideline (n=575)	ARD, MD, or HR (95% CI)
Started on AVP	305 (53.2)	217 (37.7)	-15.5% (-21.2% to -9.8%)
AVP start NE mcg/min	28.8 ± 20.6	39.7 ± 23.7	MD 10.8 (6.9 to 14.7)
AVP start NE mcg/kg/min	0.37 ± 0.30	0.54 ± 0.33	MD 0.16 (0.11 to 0.22)
Hours to MAP ≥65 mmHg	0.25 (0.25-0.33)	0.25 (0.25-0.32)	HR 0.96 (0.86-1.08)
Additional catecholamine	216 (37.7)	209 (36.4)	-1.3% (-7.0% to 4.2%)
Corticosteroid exposure	244 (42.6)	238 (41.4)	-1.2% (-6.9% to 4.5%)

Data presented as n (%), mean ± SD, or median (95% CI)

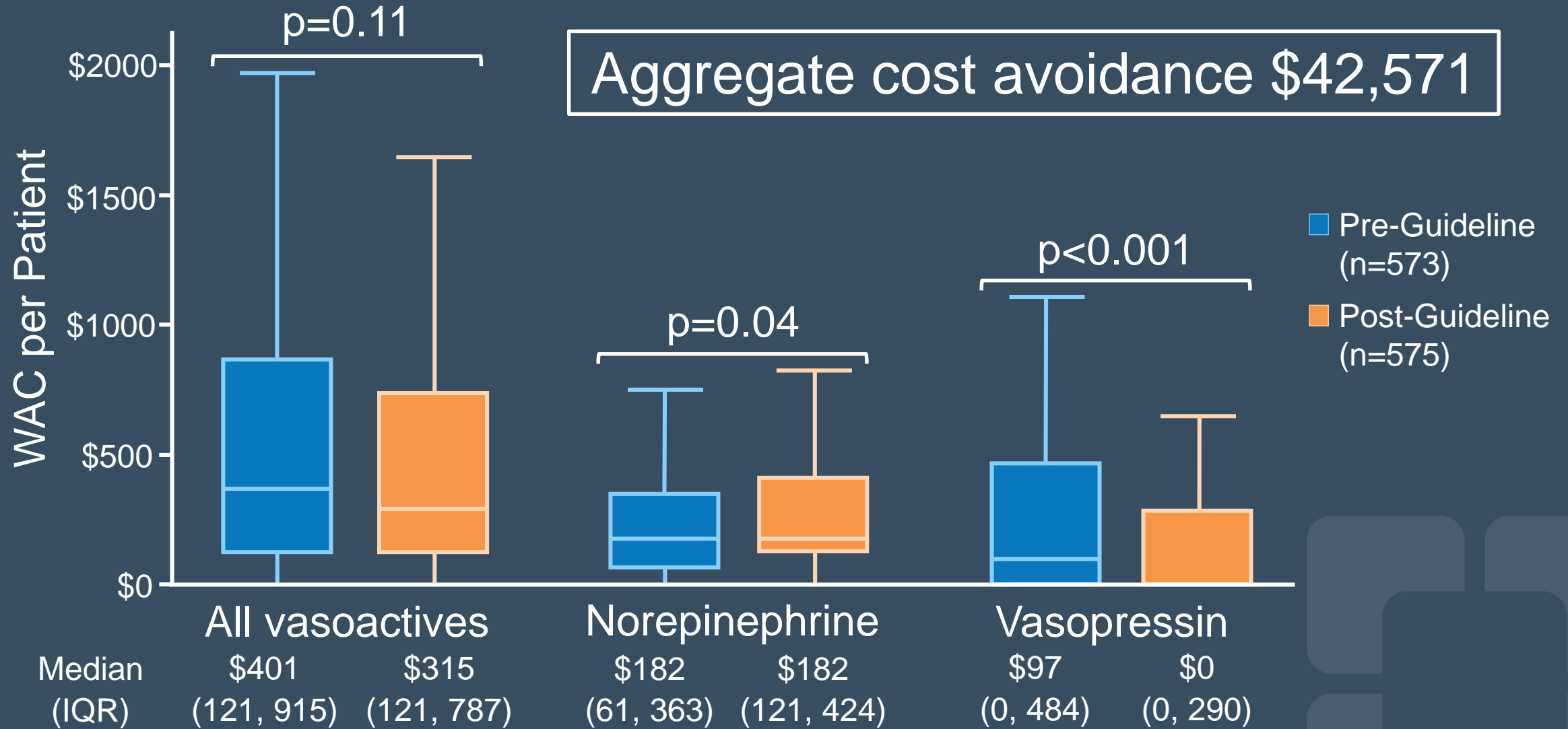
ARD = absolute risk difference, MD = mean difference, HR = hazard ratio

# ICU Mortality Over Time



- No evidence for a difference in monthly mortality trend pre-guideline vs. post-guideline ( $\Delta\beta$  0.07%; 95% CI -0.8% to 1.0%)

# Vasoactive Cost per Patient





# AVP Guideline Follow-up Questions

- Why was a mortality difference not detected?
- Why was an individual patient total vasoactive cost savings not observed?



# AVP Guideline Follow-up Questions

- Why was a mortality difference not detected?
- Why was an individual patient total vasoactive cost savings not observed?



# Processes of Care

	Pre-Guideline (n=573)	Post-Guideline (n=575)	ARD or MD (95% CI)
Started on AVP	305 (53.2)	217 (37.7)	-15.5% (-21.2% to -9.8%)
AVP start NE mcg/min	28.8 ± 20.6	39.7 ± 23.7	MD 10.8 (6.9 to 14.7)
AVP start NE mcg/kg/min	0.37 ± 0.30	0.54 ± 0.33	MD 0.16 (0.11 to 0.22)

Data presented as n (%) or mean ± SD

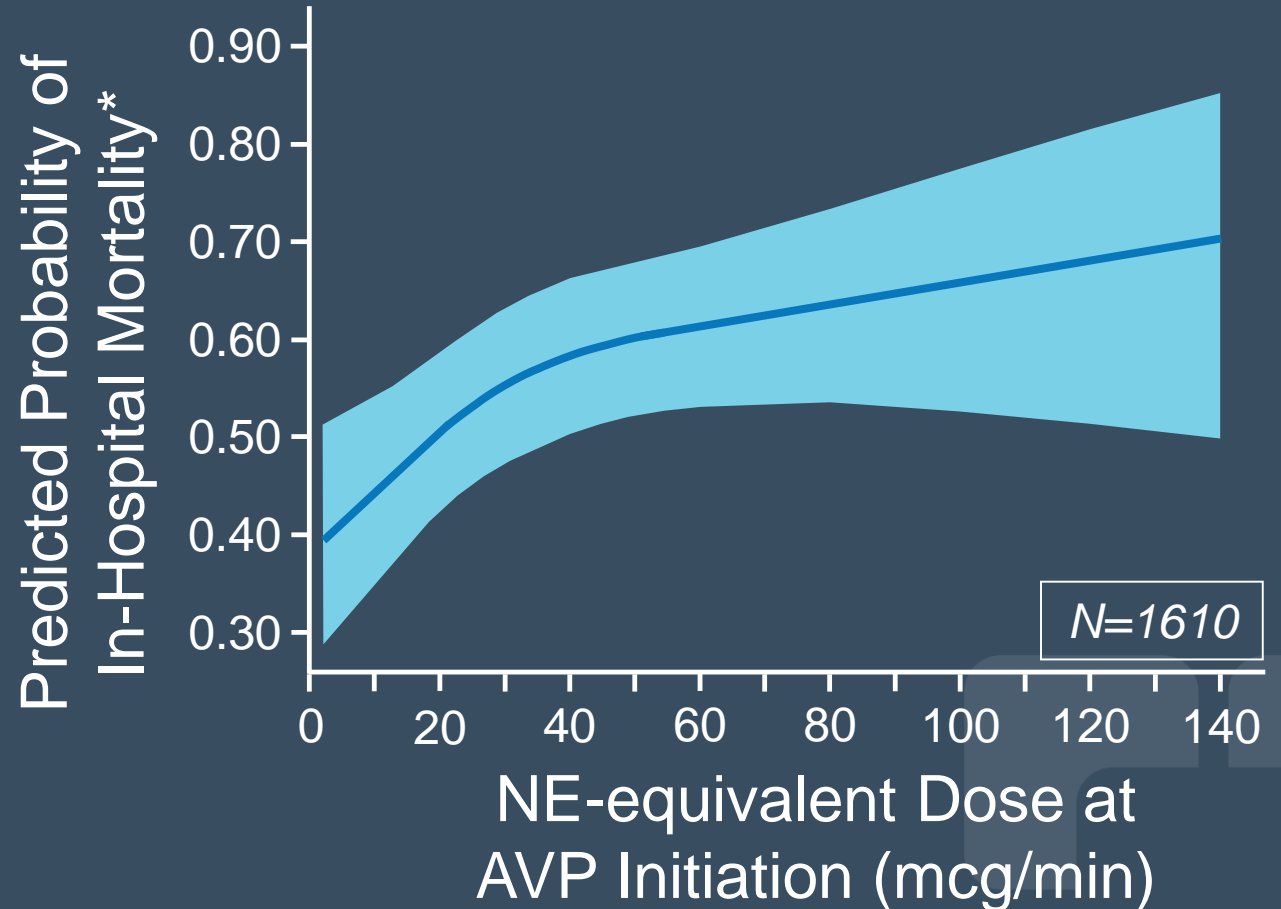
ARD = absolute risk difference, MD = mean difference

# NE Dose at AVP Start and Mortality

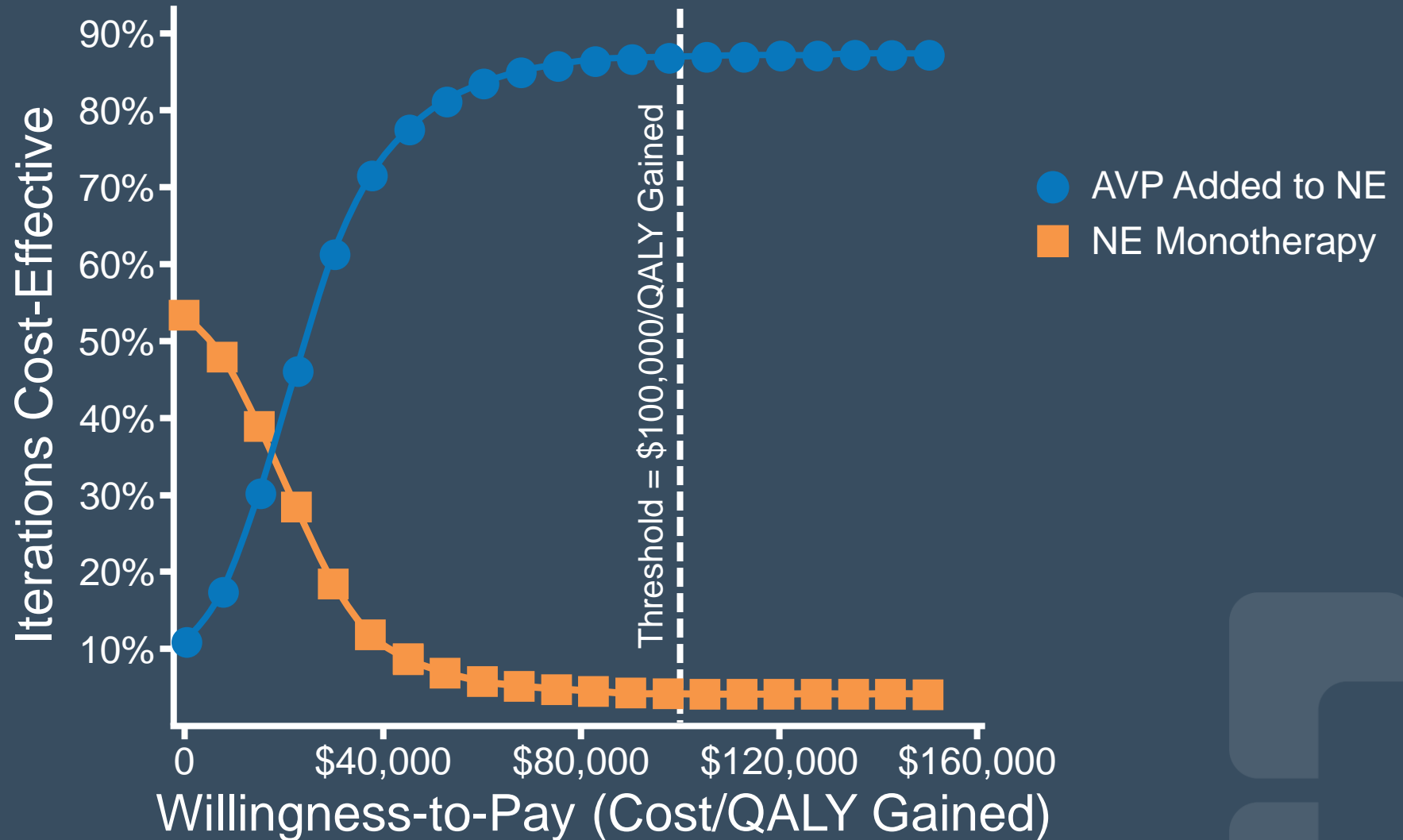
NE Dose	Mortality Adjusted OR (95% CI)*
NE 25 mcg/min <sup>†</sup>	1.33 (1.14-1.54)
NE 60 mcg/min <sup>†</sup>	2.57 (1.55-4.25)

\*Adjusted for age, gender, race, weight, lactate, SOFA, APACHE III, ICU type, mechanical ventilation, immunosuppression, AKI, fluid balance, fluid bolus volume, hours after NE start, and antibiotic receipt

<sup>†</sup>Reference NE 10 mcg/min



# Vasoactive Cost-Effectiveness



# Conclusions

- Need to understand local AVP use practices
- Initiate AVP at “lower” NE dose
- Vasopressin is a cost-effective therapy



# Discontinuation of Vasopressin

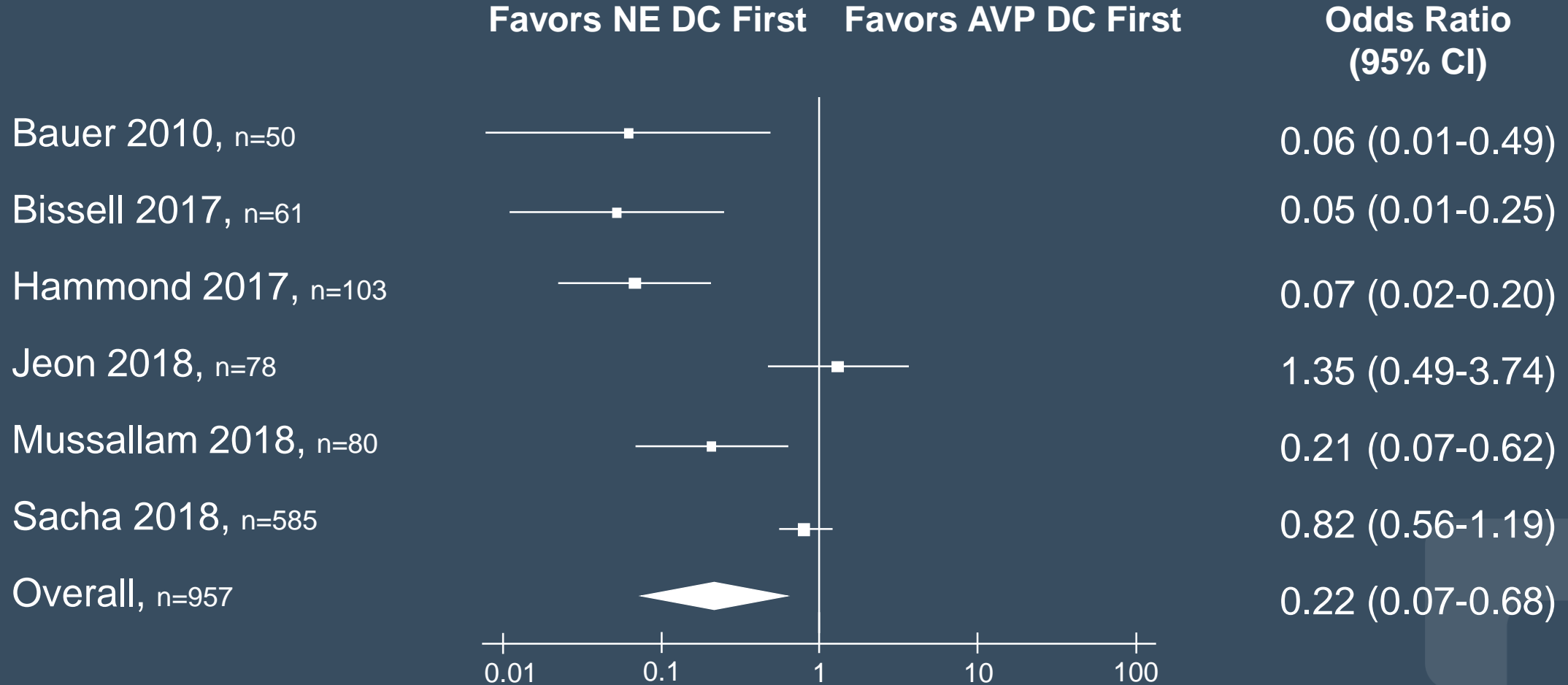


# Discontinuation Trials

	Study Design	N	Intervention	Hypotension Definition
2018 Jeon et al.	Single Center Double-blind RCT	78	NE and AVP tapered off per protocol	Sustained MAP <65 mmHg despite fluids Evaluated in the first hour after tapering the first vasopressor
2018 Sacha et al.	Single Center Retrospective	585	NE and AVP titrated per clinician	MAP <60 or 65 mmHg with intervention: 1. Increase in the dose of the remaining agent 2. Reinstitution of the discontinued agent 3. Administration of a fluid bolus
2018 Musallam et al.	Single Center Retrospective	80	NE and AVP titrated per clinician	
2017 Hammond et al.	Single Center Retrospective	154	NE and AVP titrated per clinician	
2017 Bissell et al.	Single Center Retrospective	61	NE and AVP titrated per clinician	Evaluated within the first 24 hours after the discontinuation of the first vasoactive agent
2010 Bauer et al.	Single Center Retrospective	50	NE and AVP titrated per clinician	



# NE and AVP Discontinuation Order: Clinically Significant Hypotension



# What Drives Hypotension?

2018 Sacha et al.	AVP D/C First N=155	NE D/C First N=430	P Value
Hypotension, n (%)	85 (54.8)	214 (49.8)	0.28
MAP <60 & Intervention, n (%) <sup>*</sup>			
Fluid Bolus	34 (21.9)	86 (20.0)	0.61
Restarted Vasopressor	27 (17.4)	183 (42.6)	<0.01
Increased Vasopressor	68 (43.9)	10 (2.3)	<0.01

\*Subcategories are not mutually exclusive.

**Hypotension:** MAP <60 mm Hg with one or more subsequent interventions including increased dose of the remaining agent by at least 25%, reinstatement of the discontinued agent, or administration of a fluid challenge of at least 1 L of crystalloid (or equivalent volume of colloid). Evaluated in first 24 hours

# What Drives Hypotension?

2019 Meta Analysis	AVP D/C First N=336	NE D/C First N=621
Hypotension, n (%)	204 (60.7)	269 (43.3)
MAP <60 & Intervention, n (%)*		
Fluid Bolus	34 (21.9)	86 (20.0)
Restarted Vasopressor	27 (17.4)	183 (42.6)
Increased Vasopressor	68 (43.9)	10 (2.3)

\*Subcategories are not mutually exclusive.

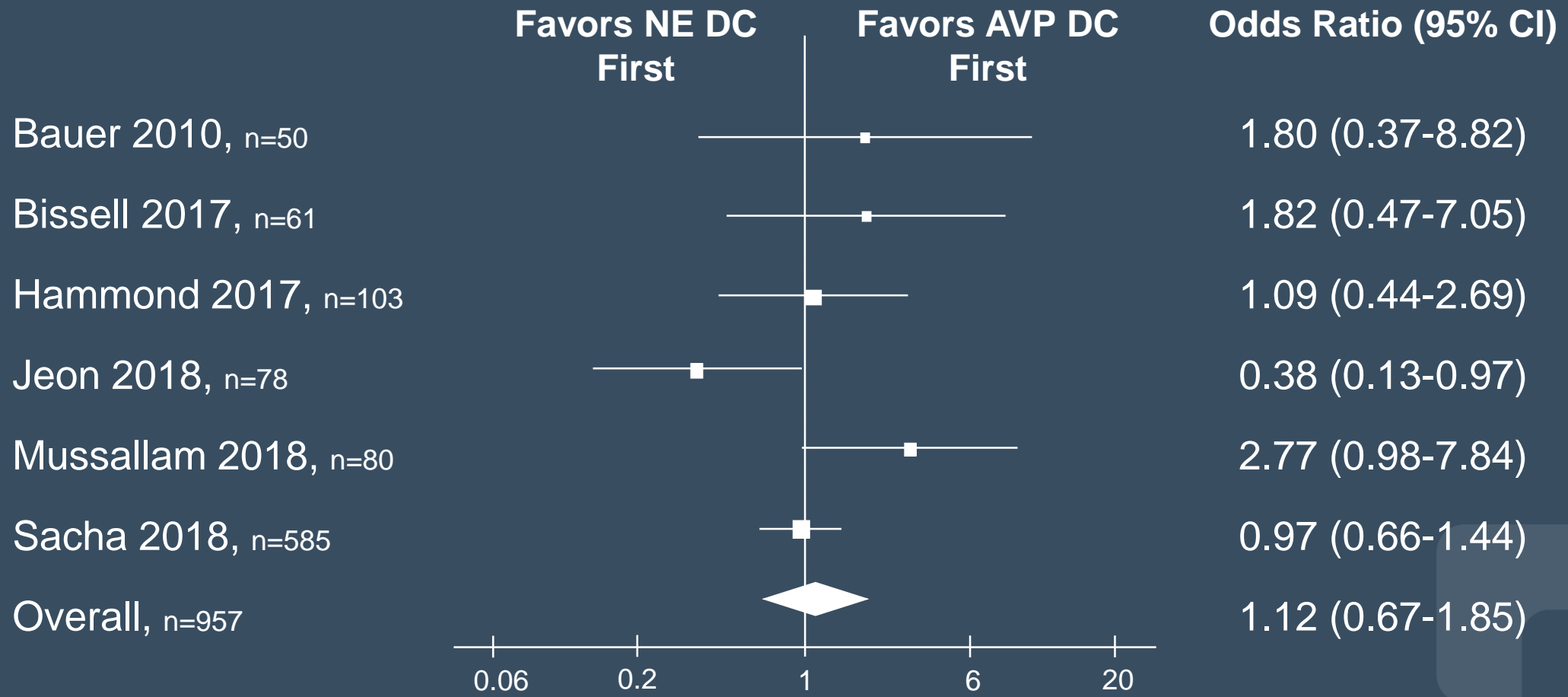
**Hypotension:** definitions slightly varied but all consisted around having MAP < 60-65 mmHg requiring intervention (including increasing dose of remaining vasopressor agent, restarting discontinued agent, administering fluid bolus/challenge)

# Were Clinical Outcomes Impacted?

<b>2018 Sacha et al.</b>	<b>Total N=585</b>	<b>AVP D/C First N=155</b>	<b>NE D/C First N=430</b>	<b>P Value</b>
Hypotension	299 (51.1)	85 (54.8)	214 (49.8)	0.28
In-Hospital Mortality	279 (47.7)	75 (48.4)	204 (47.4)	0.84
ICU Mortality	242 (41.4)	70 (45.2)	172 (40.0)	0.26
MV Duration, days	9.0±10.5	9.9±11.4	8.6±10.2	0.24

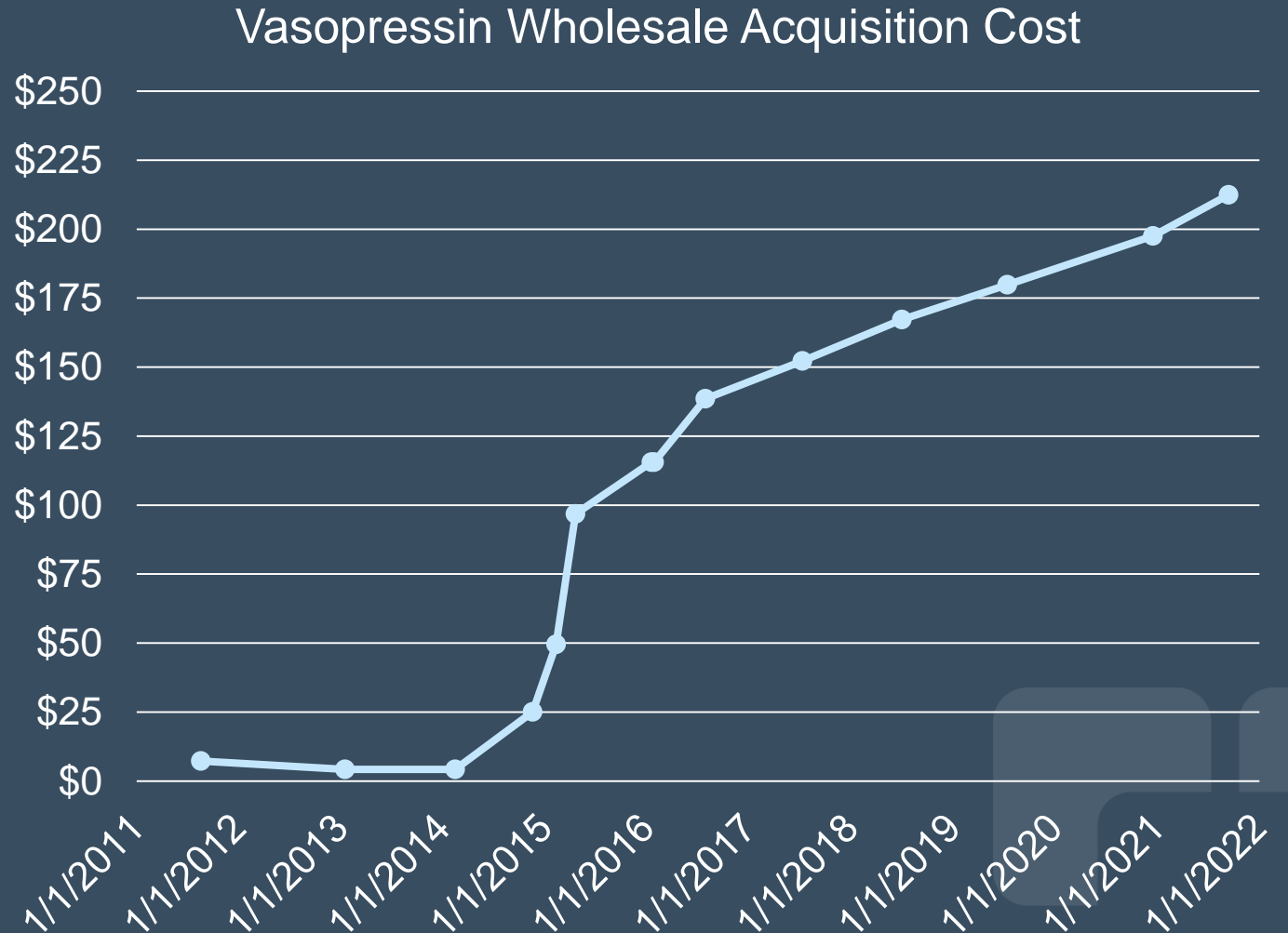
Data presented as number (%) or mean ± standard deviation

# NE and AVP Discontinuation Order: Short Term Mortality



# Cost Implications

- ~30% of patients with septic shock receive vasopressin
- Current WAC= **\$212.38** per 20 unit vial



# Cost Implications

Meta Analysis Data	AVP D/C First N=336	NE D/C First N=621
Vasopressin Duration, days	1.1 (0.5-2.0)	1.9 (1.1-3.1)

- Vasopressin duration of 0.8 days = 19.2 hours
- Vasopressin 20 units in 100 mL
  - 0.03 units/min = 9 mL/hr = 11 hours per bag
  - 0.04 units/min = 12 mL/hr = 8 hours per bag
- Estimate can save at least 1-3 bags of vasopressin per patient

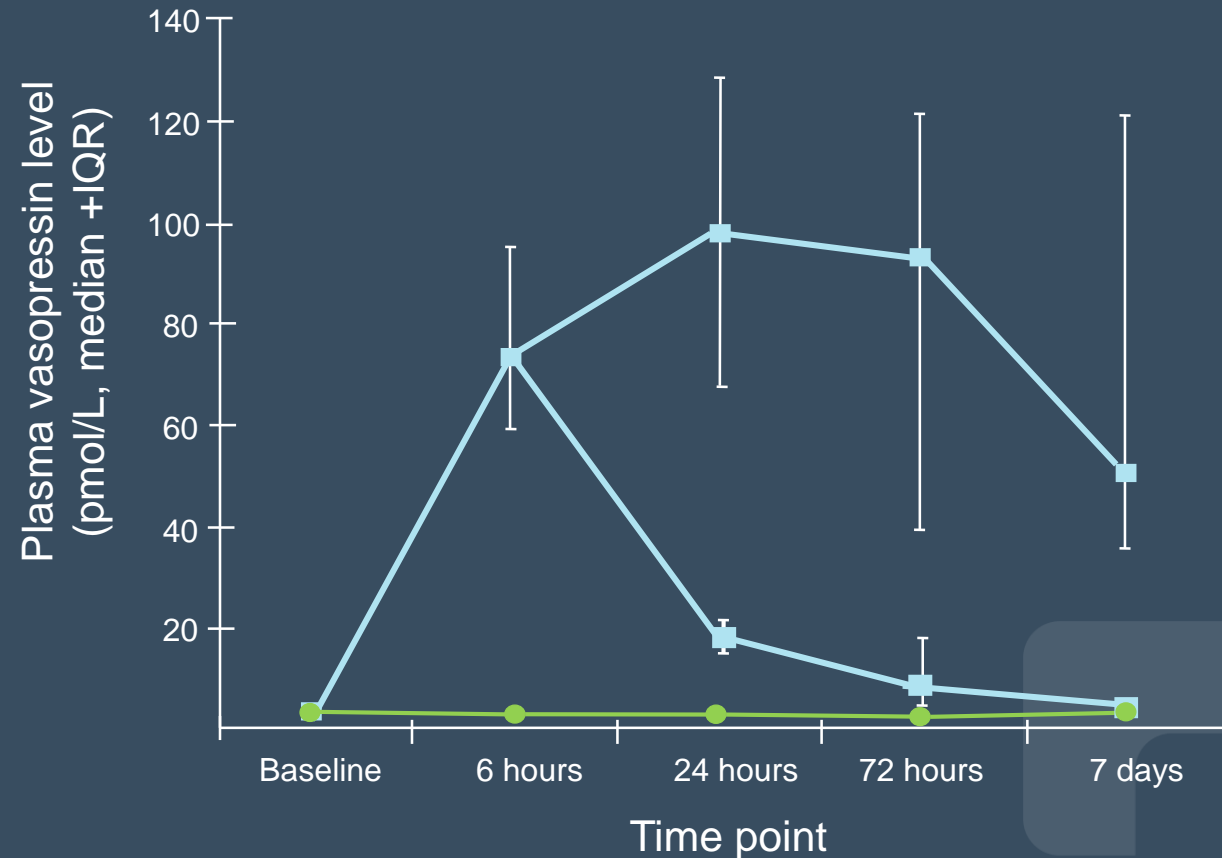
# When to Discontinue Second Agent?

2018 Jeon RCT N=78	2018 Sacha N=585	2018 Mussallam N=80	2017 Hammond N=154	2017 Bissell N=61	2010 Bauer N=50
0.3 mcg/kg/min (21-30 mcg/min) *Tapered AVP	8 mcg/min	7.2 mcg/min	11.5 mcg/min	0.06 mcg/kg/min (4.2-6 mcg/min)	10.5 mcg/min
Less hypotension but increased hospital mortality	No difference in hypotension or mortality	More hypotension but no difference in mortality	More hypotension but no difference in mortality	More hypotension but no difference in mortality	More hypotension but no difference in mortality



# When to Discontinue Second Agent?

- What phase of septic shock?
  - Recovery phase?
- Recovery of vasopressin deficient state?



# Conclusions

- Discontinue vasopressin before norepinephrine
- May need to increase norepinephrine dose to compensate
- Discontinue once in recovery phase





**Every life deserves world class care.**