

# Evaluation of Intravenous Milrinone in the Treatment of Vasospasm following an

## Aneurysmal Subarachnoid Hemorrhage (aSAH)

Rebecca VanDerwall, PharmD, BCPS, Laura Aykroyd, PharmD, BCPS, Ranjeet Singh, MD



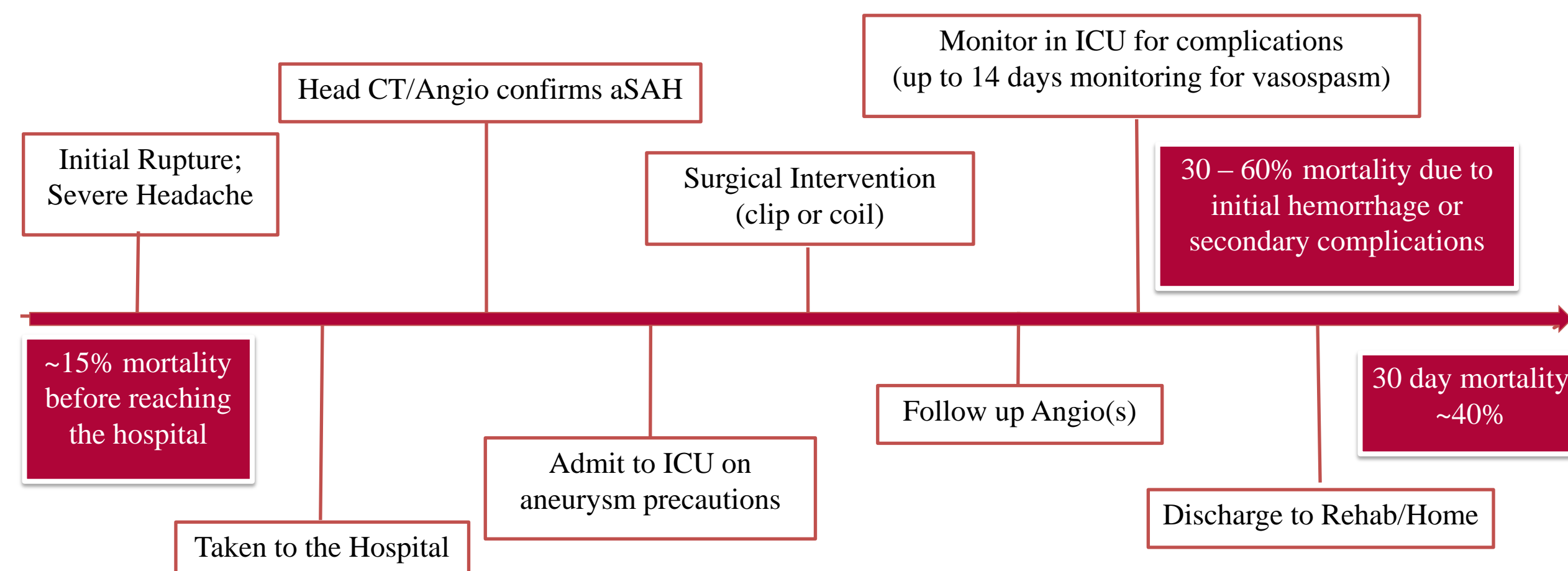
Indiana University Health



Indiana University Health

### Background

- Delayed cerebral ischemia due to cerebral vasospasm is a damaging complication in patients with aSAH<sup>1-3</sup>
- Current use of hyperdynamic therapy is the best available treatment option for cerebral vasospasm<sup>1-3</sup>
- Besides angioplasty and hyperdynamic therapy, multiple intravenous (IV), intra-arterial (IA), and intrathecal vasodilating agents have been used to treat cerebral vasospasm<sup>2</sup>
  - Milrinone has inotropic and vasodilatory effects thought to help prevent vasospasm<sup>4-7</sup>
- Lannes et. al. studied 88 patients in Montreal, Canada, who received continuous with bolus infusions of IV milrinone as first line treatment for cerebral vasospasm
  - 83 survivors – 48.9% at neurologic baseline and 75% good functional outcome (modified Rankin score (mRS)  $\leq 2$ )<sup>7</sup>



**Figure 1. Patient journey from initial presentation of aSAH through discharge.** Due to the non-specific nature of an aSAH presentation, morbidity and mortality remains undesirably high.<sup>1-3</sup>

### Study Outcomes

- Primary Outcome:** Median cerebral blood flow velocity as measure by transcranial Doppler (TDC)
- Secondary Outcomes:**
  - Duration of milrinone infusion
  - Average 24 hour infusion rate of milrinone
  - Functional outcomes (mRS)

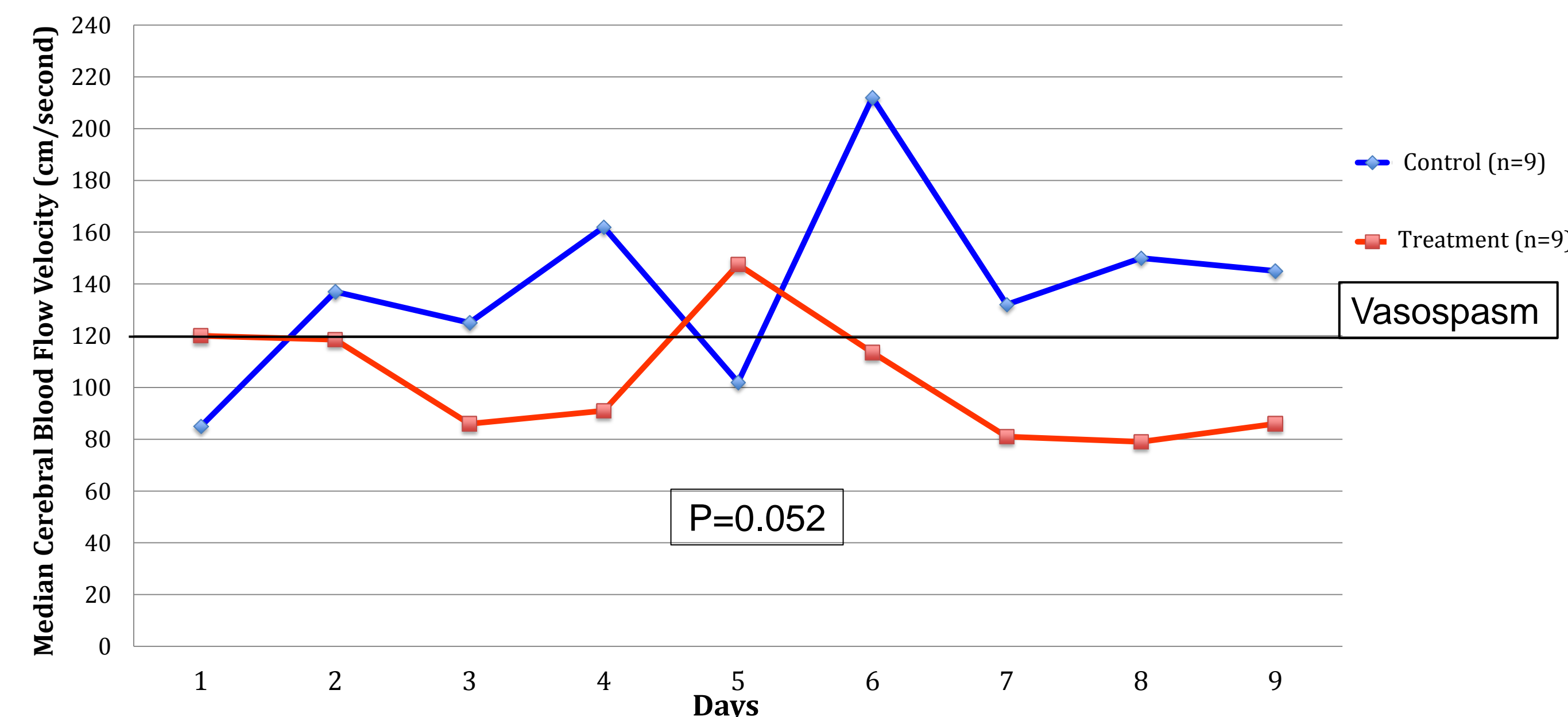
### Interventions and Methods

- Retrospective chart review of patients admitted with aSAH from July 1, 2009 through June 30, 2014
  - Received IA verapamil or papaverine followed by hyperdynamic therapy plus IV milrinone
  - Control patients received IA verapamil or papaverine followed by hyperdynamic therapy without IV milrinone
- Patients matched based on age, gender, presenting Glasgow Coma Scale, and Fisher Grade on admission

### Results

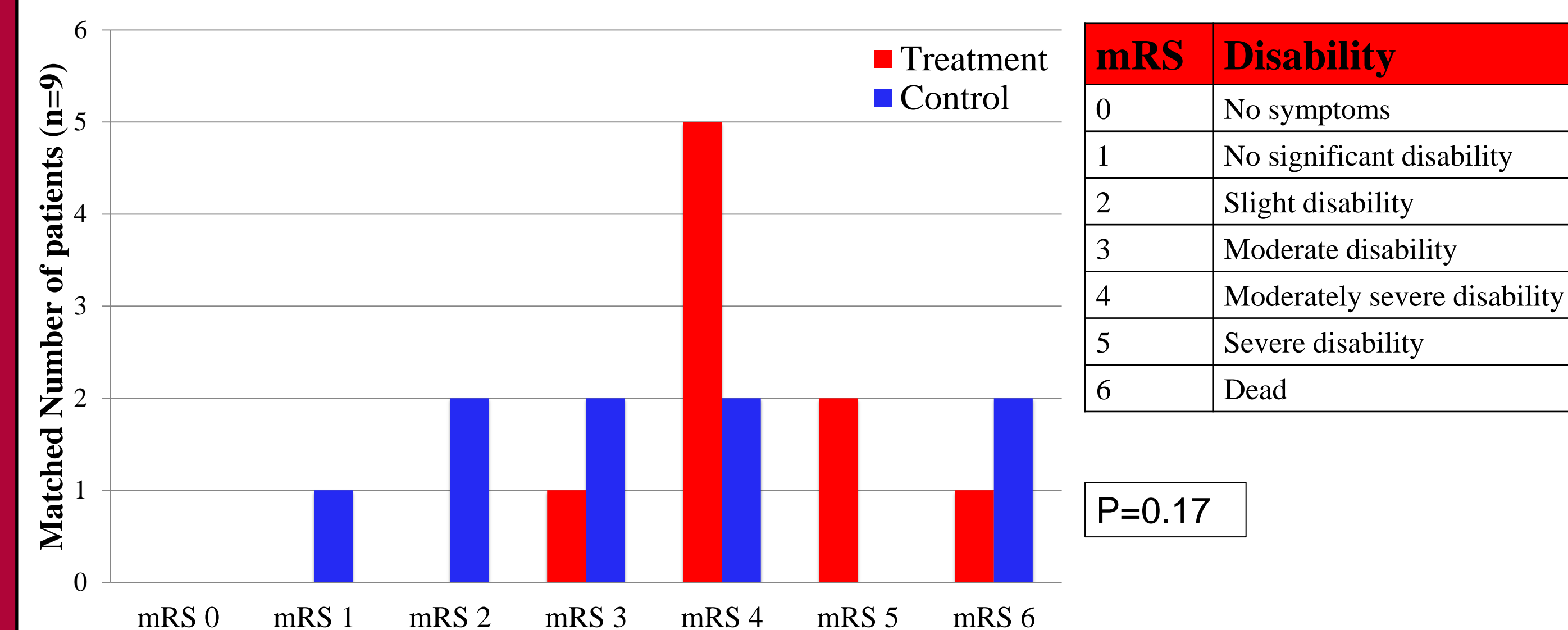
	VanDerwall et al. (n=9)	Lannes et. al. (n=88)	Fraticeilli et. al. (n=22)
<b>Duration of milrinone infusion</b>			
Mean days (SD)	<b>10 (3.42)</b>	9.8 (5.1)	7 (3)
<b>24 hour infusion rate of milrinone</b>			
Mean, mCg/kg/min (SD)	<b>0.23 (0.11)</b>	0.75	1 (0.55)

**Table 1. Average duration of treatment group milrinone infusion.** Average infusion rate for treatment IV milrinone was 0.23 mCg/kg/min.



**Figure 2. Median cerebral blood flow velocity per treatment day as measured by TCD** Vasospasm is suspected with a cerebral blood flow velocity >120cm/second.

### Results



**Figure 3. Modified Rankin score on discharge.** 15 patients (83%) had poor outcomes (mRS  $\geq 3$ ), Plausible cause of poor functional outcomes could be low dose average infusion.

### Conclusion

- Small trial limits ability to make conclusion
- No difference seen in TCDs or mRS at discharge milrinone vs. control
  - Larger sample size and standardized dosing needed for significance
- Future Direction:
  - September 2014 – mandatory 90 day mRS documented on all aSAH patients per protocol
  - April 2016 – Prospective randomized controlled trial starting at IU Health<sup>8</sup>

### References

- Pierot L, Aggour M, Moret J. Vasospasm after aneurysmal subarachnoid hemorrhage: recent advances in endovascular management. *Curr Opin Crit Care*. 2010 Apr;16(2):110-6.
- Liu-DeRyke X, Rhoney DH. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage; an overview of pharmacologic management. *Pharmacotherapy* 2006;26:182-203
- Dabus G, Nogueira RG. Current options for the management of aneurysmal subarachnoid hemorrhage-induced cerebral vasospasm: a comprehensive review of the literature. *Interv Neurol*. 2013 Oct;2(1):30-51.
- Baumann A, Derelle AL, et al. Seeking new approaches: milrinone in the treatment of cerebral vasospasm. *Neurocrit Care*. 2012 Jun;16(3):351-3.
- Romero CM, Morales D, et al. Milrinone as a rescue therapy for symptomatic refractory cerebral vasospasm in aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2009;11(2):165-71.
- Fraticeilli AT, Cholley BP, Losser MR, Saint Maurice JP, Payen D. Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2008 Mar;39(3):893-8.
- Lannes M, Teitelbaum J, et al. Milrinone and homeostasis to treat cerebral vasospasm associated with subarachnoid hemorrhage: the Montreal Neurological Hospital protocol. *Neurocrit Care*. 2012 Jun;16(3):354-62.
- Shapiro, S. et al. Milrinone in Addition to Hyperdynamic Therapy in the Treatment of Vasospasm Following Aneurysmal Subarachnoid Hemorrhage. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2016 March 15]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02712788> NLM Identifier: NCT02712788.

Contact: Rebecca VanDerwall, PharmD, BCPS

(rvanderwall@iuhealth.org)