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von Willebrand Factor Degradation Fragments Are A Mechanistic Link Between Continuous-Flow LVAD Support And Gastrointestinal Angiodysplasia And Bleeding

Carlo Bartoli, MD, PhD

Department of Surgery
Division of Cardiovascular Surgery
Hospital of the University of Pennsylvania
University of Pennsylvania, Perelman School of Medicine
Philadelphia, PA
USA

The Society of Thoracic Surgeons

EACTS European Association For Cardio-Thoracic Surgery

Penn Medicine

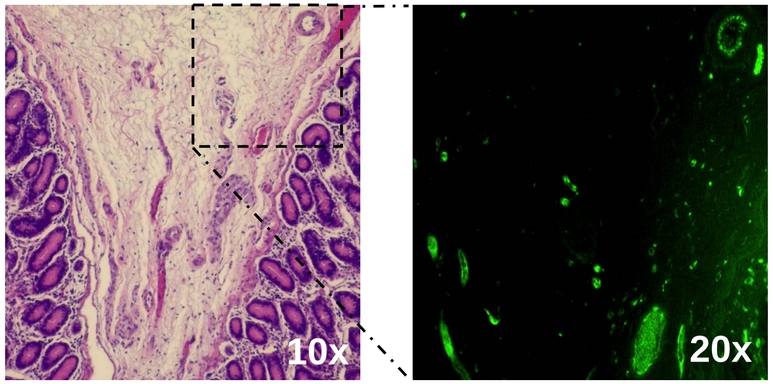
Disclosures

- No relevant disclosures

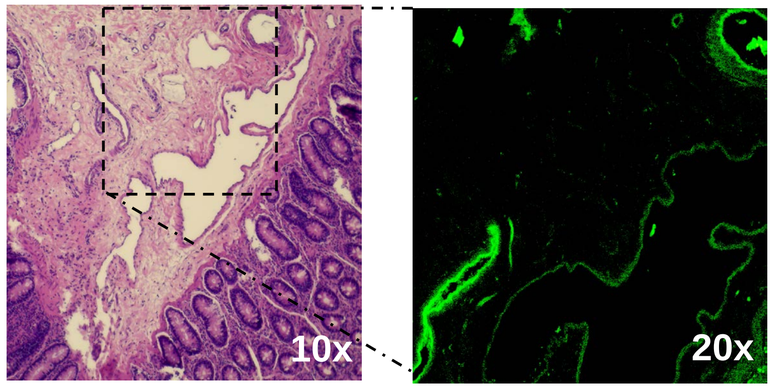
Gastrointestinal Bleeding During LVAD Support

- 25 – 40% of patients
- Most frequent cause of hospital readmission
- Gastrointestinal angiodysplasia is the most common source
- LVAD support causes **a distinct form of intestinal angiodysplasia**

Control Small Bowel



LVAD Small Bowel

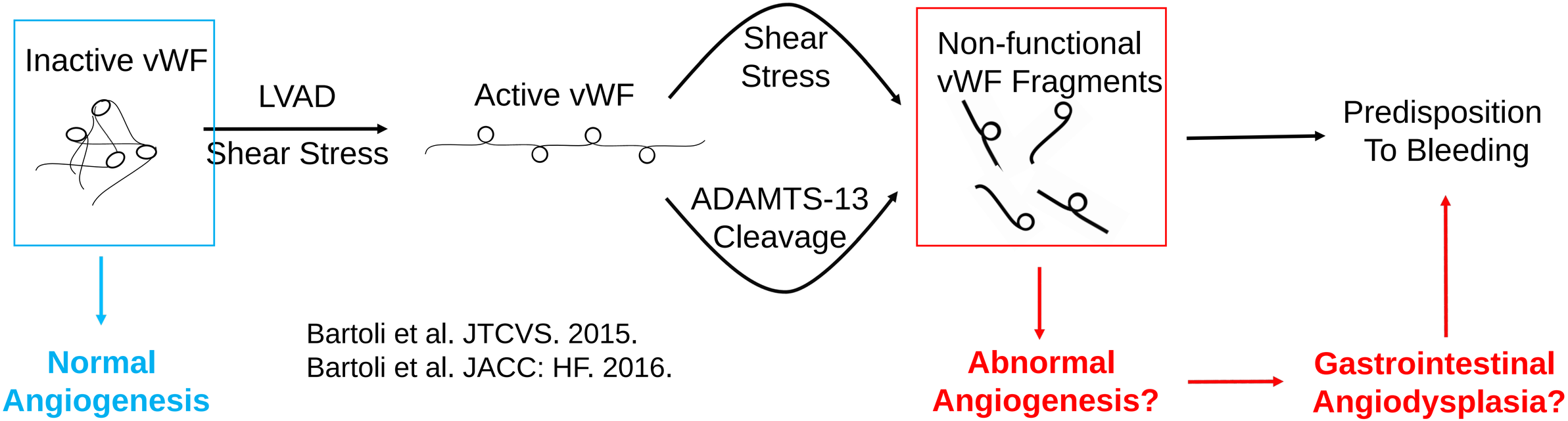


- LVAD support causes **abnormal intestinal vascular architecture**

What is the mechanism of angiodysplasia formation during LVAD support?

Kang et al. Circulation Research. In Press, 2017.

LVAD Support Causes von Willebrand Factor (vWF) Degradation



Bartoli et al. JTCVS. 2015.
Bartoli et al. JACC: HF. 2016.

- vWF is an important regulator of angiogenesis
- LVAD support causes marked degradation of vWF into small vWF fragments

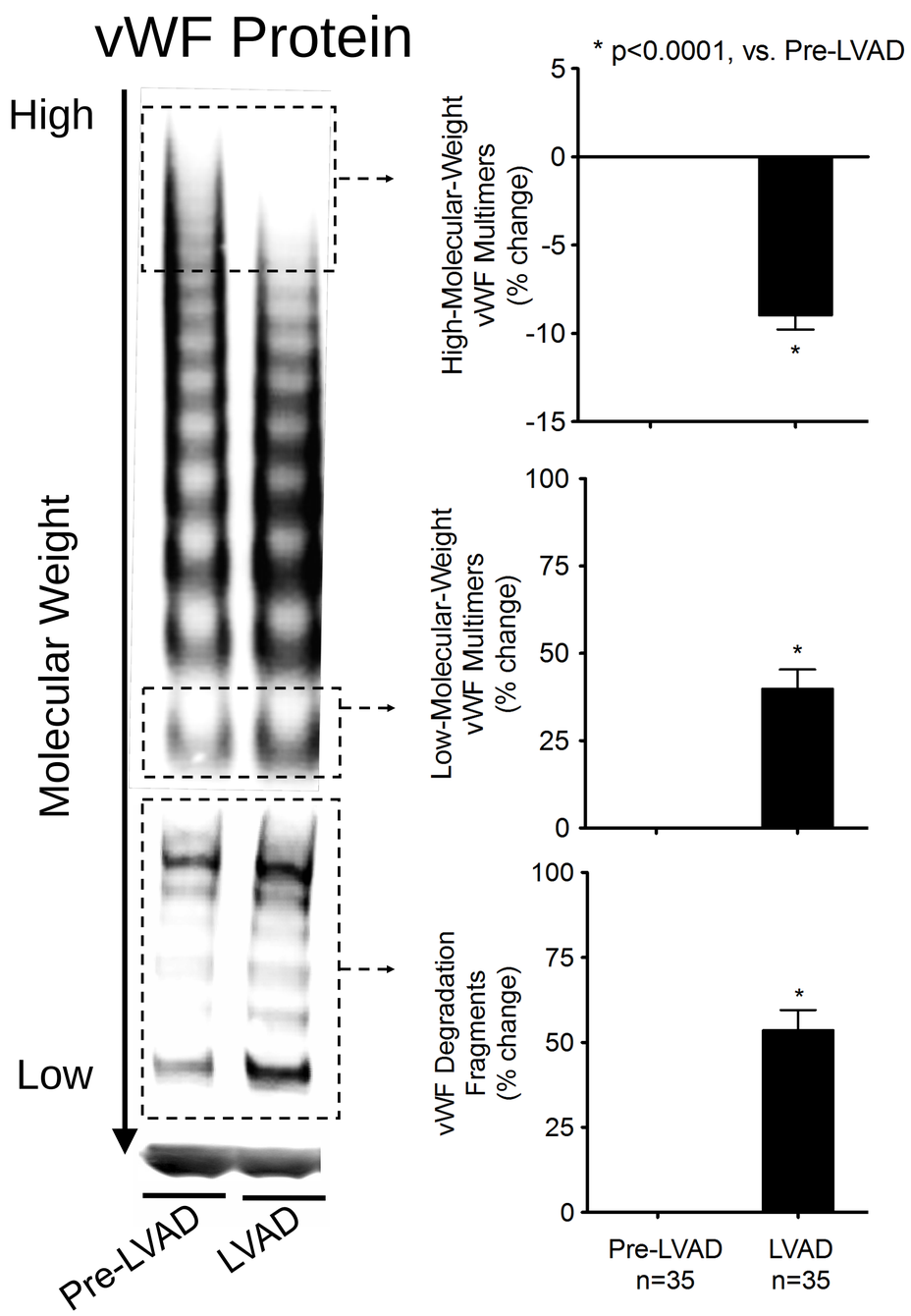
What is the relationship between vWF degradation and angiodysplasia?

Clinical Study

What is the profile of vWF in LVAD patients with gastrointestinal bleeding?

- Continuous-flow LVAD patients (n=35, 417±53 days support)
- Paired blood samples
- Quantified vWF
- Stratified patients as non-bleeders or gastrointestinal bleeders
- Confirmed angiodysplasia via endoscopy

Clinical Results – All Patients

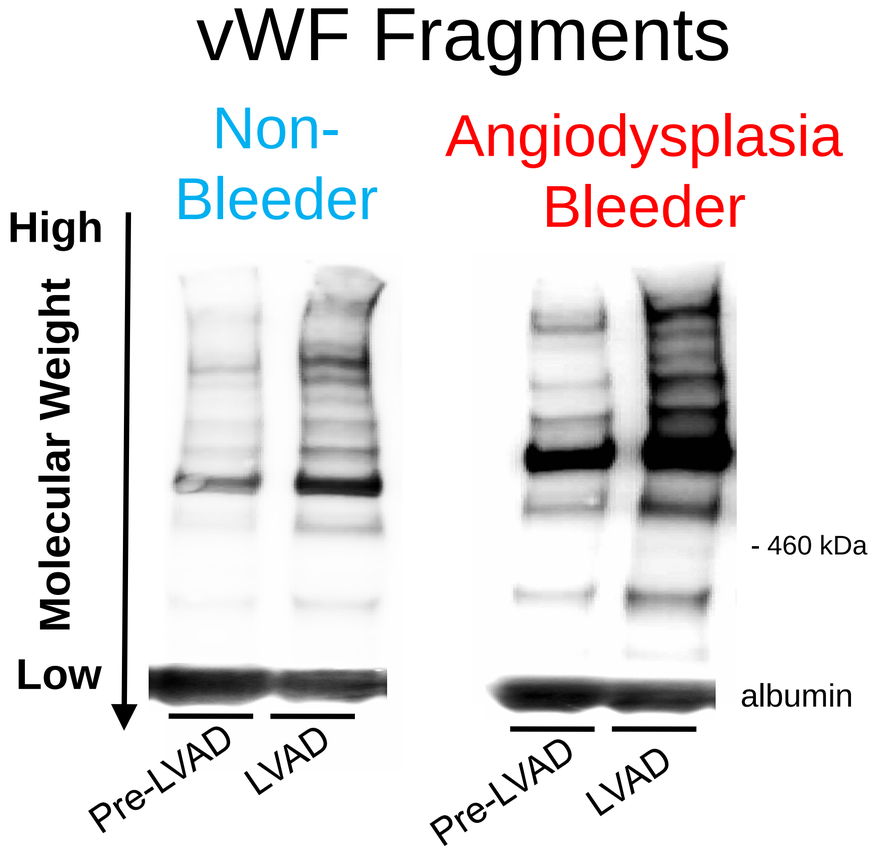


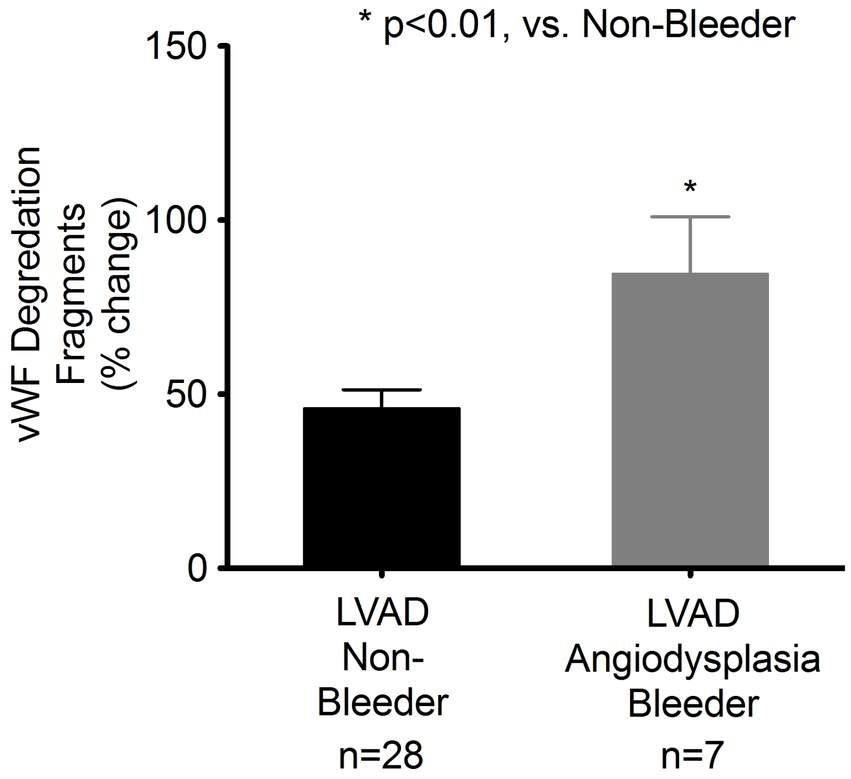
- In all patients, LVAD support caused significant degradation of vWF protein

Kang et al. Circulation Research. 2017.

Clinical Results – Non-Bleeders vs. Angiodysplasia Bleeders

- 28 non-bleeders
- 7 bleeders from intestinal angiodysplasia



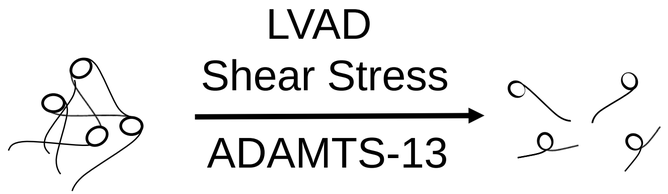


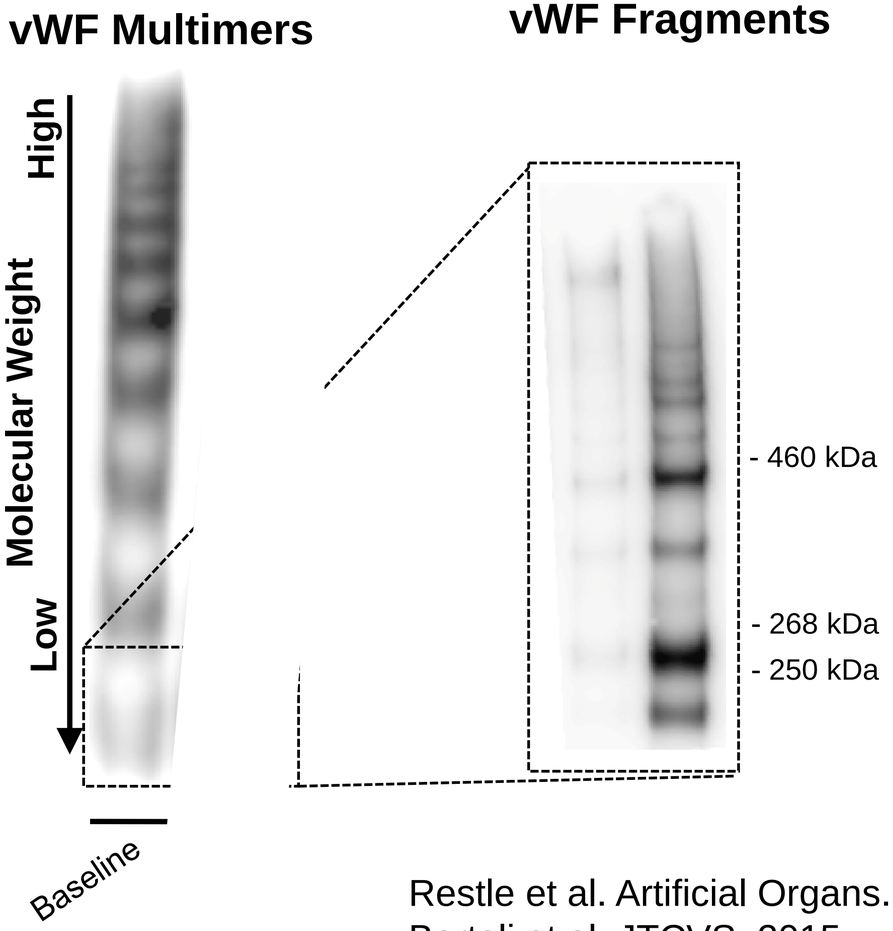
- vWF fragments were significantly higher in LVAD patients with gastrointestinal angiodysplasia and bleeding

What is the biological mechanism?

In Vitro Study

Do vWF fragments alter angiogenesis?

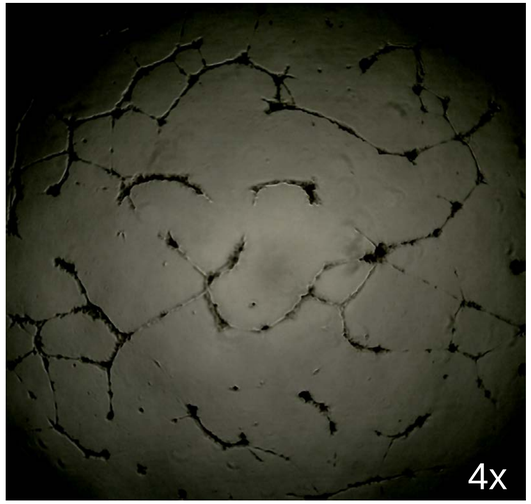




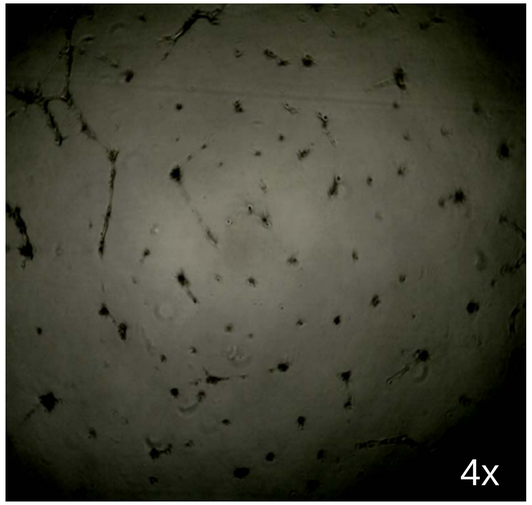
- Production of vWF pure fragments
- Endothelial cell culture with vWF fragments
- Quantification of angiogenesis

Restle et al. Artificial Organs. 2014.
Bartoli et al. JTCVS. 2015.

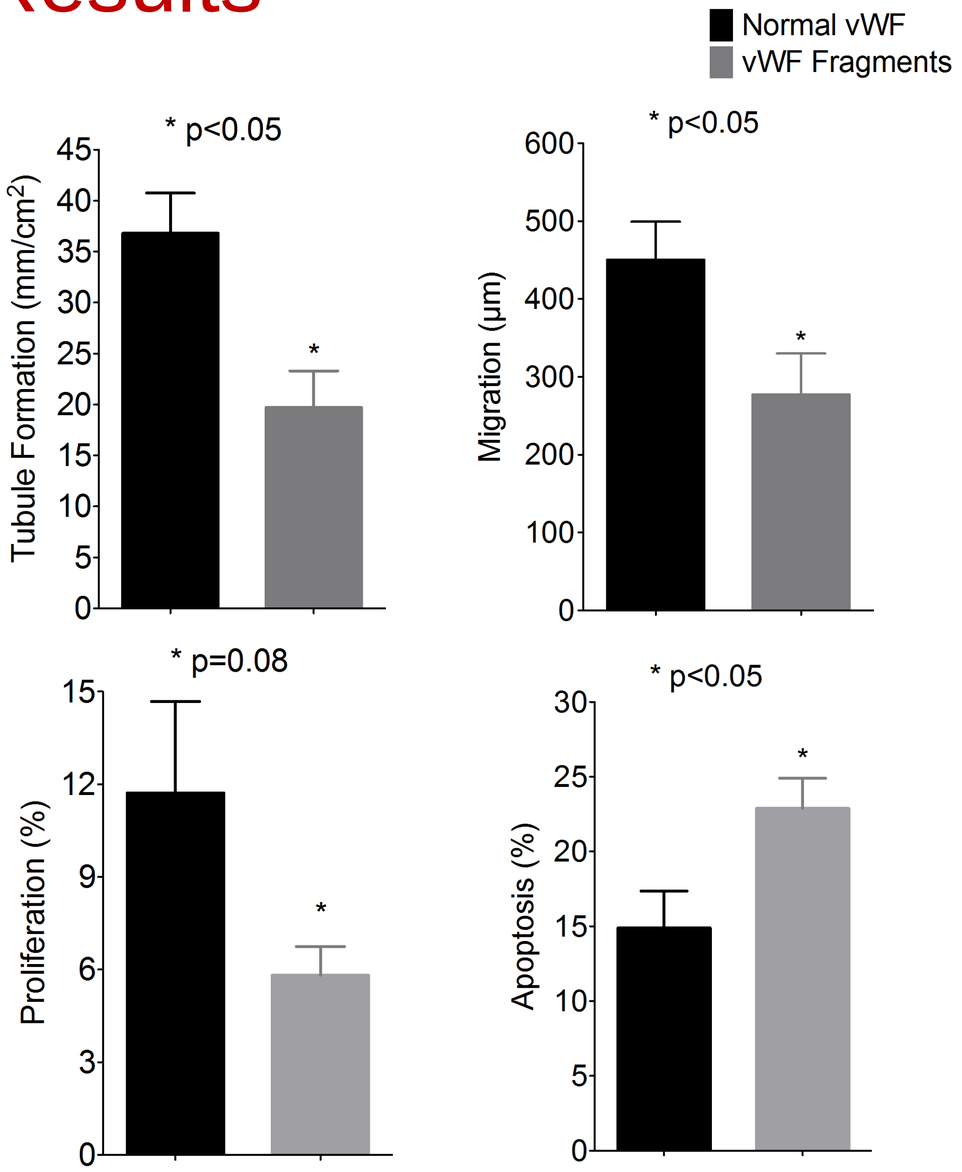
In Vitro Study - Results



Normal vWF



vWF Fragments



vWF fragments caused abnormal angiogenesis *in vitro*

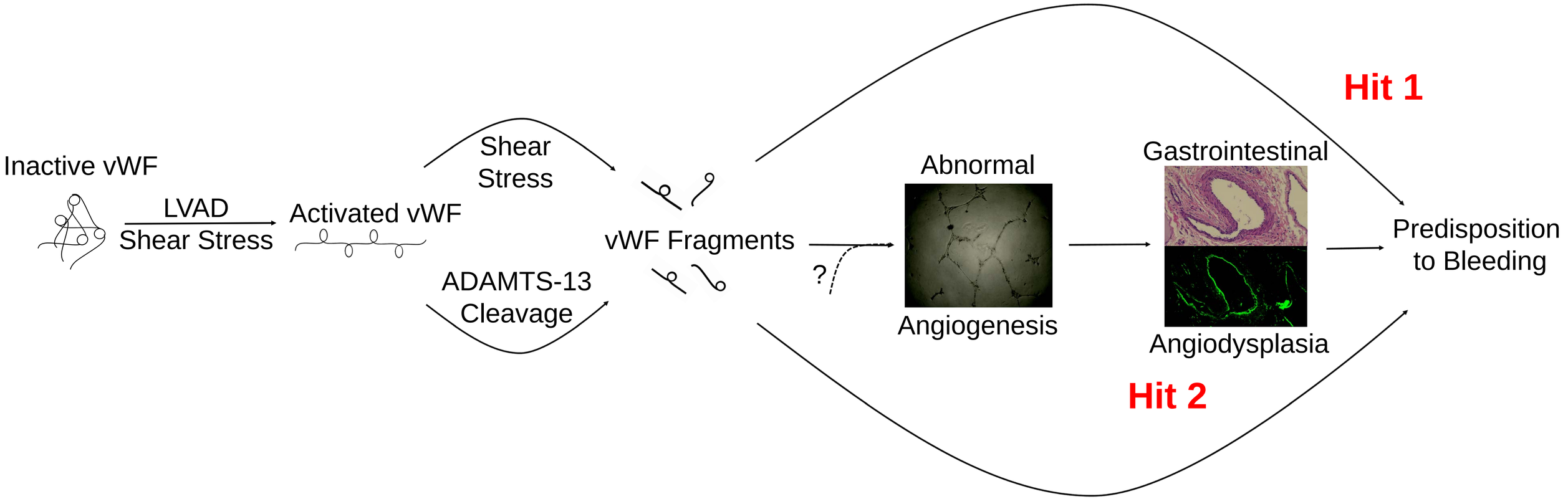
Conclusions

1. LVAD patients with bleeding from angiodyplasia have higher levels of vWF fragments than non-bleeders

2. vWF fragments cause abnormal angiogenesis *in vitro*:
(tubule formation, migration, proliferation, apoptosis)

3. **Two-hit hypothesis** for LVAD-associated gastrointestinal bleeding:
    A. vWF degradation alone
    B. vWF fragments alter angiogenesis and promote angiodysplasia

Proposed Mechanism Of LVAD-Associated Gastrointestinal Angiodysplasia And Bleeding



vWF Metabolism May Be A Clinical Target To Reduce Gastrointestinal Bleeding In LVAD Patients

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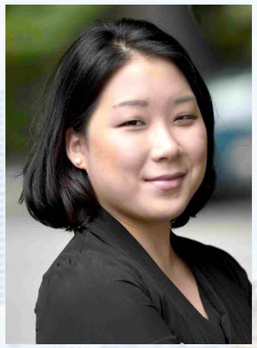
Thank You

Samson Hennessy-Strahs
BSE



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