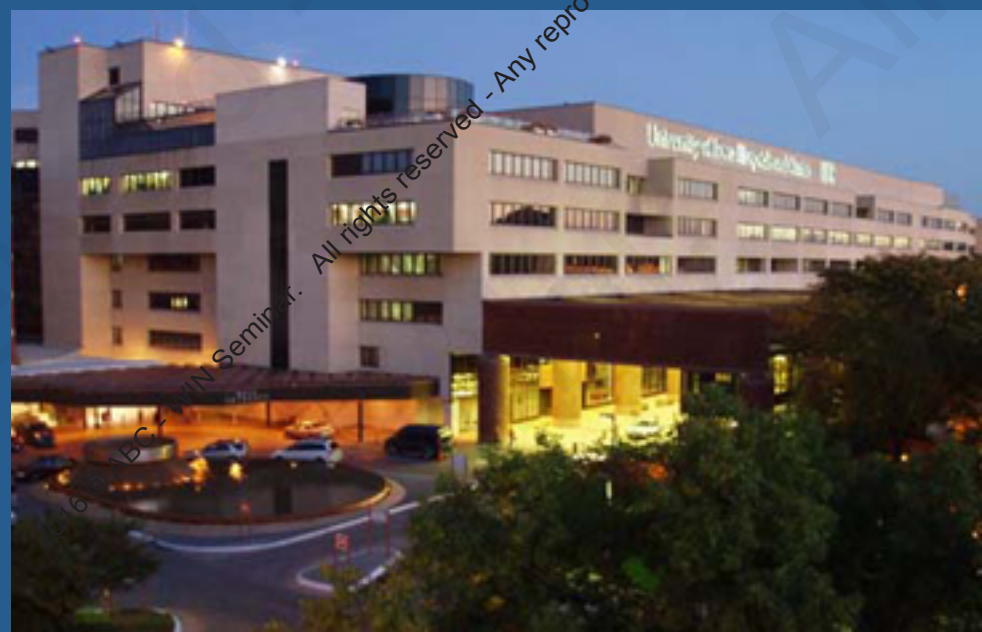


# Medical Therapy in the Prevention of Cerebral Aneurysm Rupture.

**Nohra Chalouhi M.D. and David Hasan, M.D.**

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# Background

- Inflammation plays an integral part of aneurysm formation and progression to rupture
- Human and animal tissue analysis confirmed that cerebral aneurysm walls are rich in macrophages and inflammatory molecules.

**Review Article**

**Biology of intracranial aneurysms:  
role of inflammation**

Nohra Chalouhi<sup>1</sup>, Muhammad S Ali<sup>1</sup>, Pascal M Jabbour<sup>1</sup>, Stavropoula I Tjoumakaris<sup>1</sup>,  
L Fernando Gonzalez<sup>1</sup>, Robert H Rosenwasser<sup>1</sup>, Walter J Koch<sup>2</sup> and Aaron S Dumont<sup>1</sup>

**Stroke**

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke  
Association<sup>SM</sup>

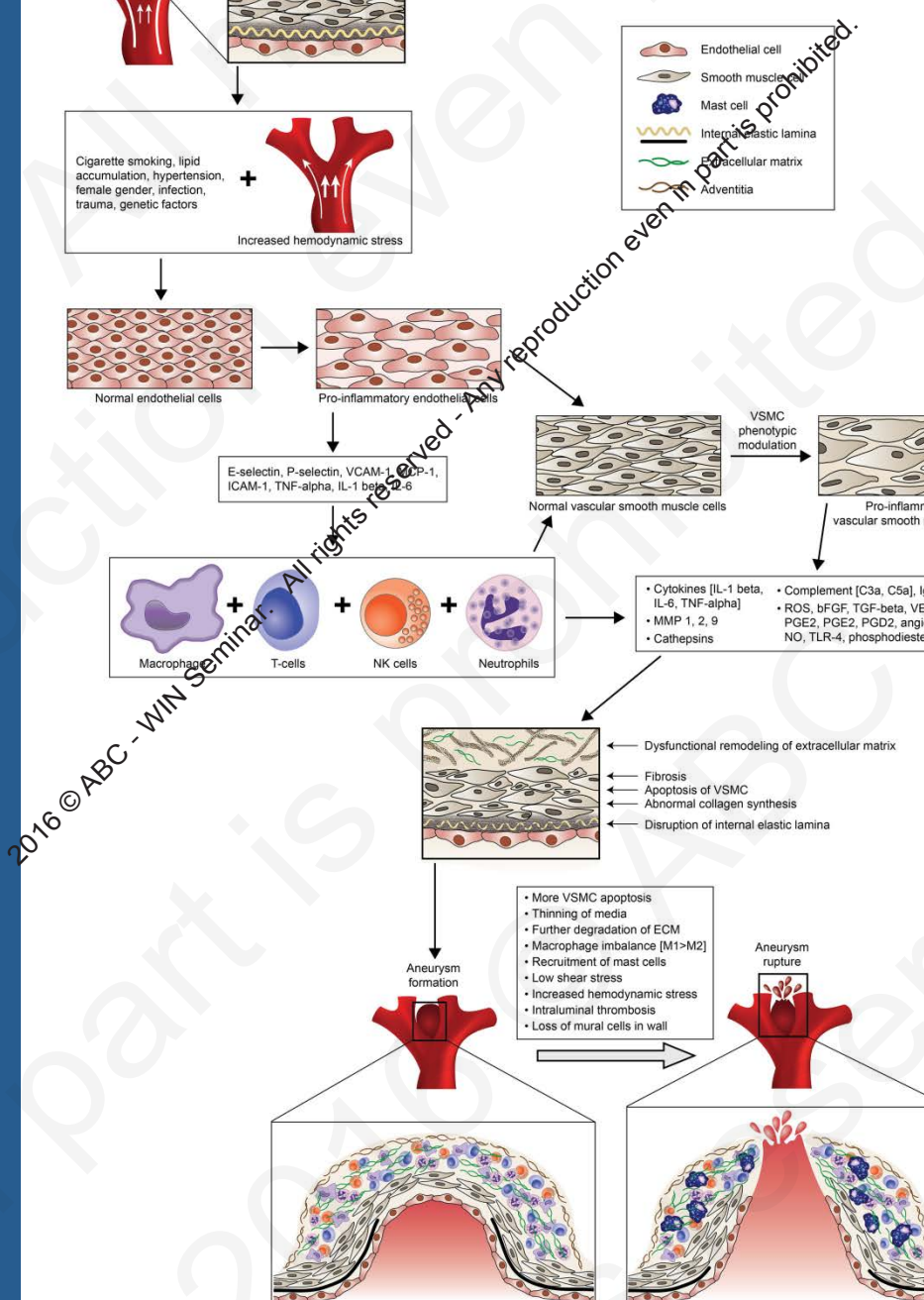
A Division of American  
Heart Association 

**Review of Cerebral Aneurysm Formation, Growth,  
and Rupture**

Nohra Chalouhi, MD; Brian L. Hoh, MD; David Hasan, MD



aneurysm formation, growth, and rupture. Stroke. 2013;44:3613-22



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# Tested Medical Therapies

Agent	Model	Efficacy
Nuclear factor- $\kappa$ B decoy ODN (Aoki <i>et al</i> , 2007c)	IA was induced in rats with administration of nuclear factor- $\kappa$ B decoy ODN ( $n=10$ ) or scrambled decoy ODN (control, $n=10$ )	Significant decrease in incidence of aneurysmal changes and aneurysm size when given at early stage of aneurysm formation
Statins (Marbacher <i>et al</i> , 2011)	Human. 300 cases of IA (265 with ruptured IA, 64.3% were female, 68.4% were $\geq 50$ years) and 900 matched controls (64.3% were women, 68.5% were $\geq 50$ years)	Cases and controls were similar with respect to statin intake (10.0% and 10.7%, respectively)
Simvastatin (Aoki <i>et al</i> , 2008b)	IA was induced in rats with ( $n=11$ ) or without ( $n=10$ ) administration of simvastatin	Significant increase in media thickness and reduction in IA size. Inhibition of IA enlargement and thinning of the media of preexisting IA
Simvastatin (Tada <i>et al</i> , 2011)	IA induced in rats with ( $n=13$ ) or without ( $n=8$ ) administration of simvastatin (5 mg/kg per day)	Higher incidence of IA in simvastatin-treated rats
Pravastatin (Tada <i>et al</i> , 2011)	IA induced in rats with or without ( $n=8$ ) administration of pravastatin (5, 25, and 50 mg/kg per day, $n=12$ each)	<ul style="list-style-type: none"> <li>- Inhibits IA formation at 5 mg/kg per day (but negligible effect compared with control)</li> <li>- Induces IA formation and possibly IA rupture at high dose (25 and 50 mg/kg per day)</li> </ul>
Pravastatin (Kimura <i>et al</i> , 2010)	IA induced in rats with or without ( $n=14$ ) administration of low (50 mg/kg per day, $n=10$ ) and high dose (100 mg/kg per day, $n=12$ ) pravastatin	Reduced formation of IA (50% in control, 10% in low dose, and 8% in high dose group)
Pitavastatin (Aoki <i>et al</i> , 2009a)	IA induced in rats with ( $n=10$ ) or without ( $n=10$ ) administration of pitavastatin (4 mg/kg per day)	Significant decrease in IA size and IEL score, and increase in media thickness. Media thickening in preexisting IA
Aspirin (Hasan <i>et al</i> , 2011)	Human. 271 nested case-control patients with untreated IA (58 cases, i.e., sustained an SAH, and 213 control). 74% were women, mean age 57 years	Significantly lower odds of hemorrhage in patients using aspirin three times weekly to daily





# More Medical Therapies

MMP inhibitor (Tolylsam) (Aoki <i>et al</i> , 2007a)	IA induced in rats with ( $n=10$ ) or without ( $n=21$ ) administration of tolylsam	Significant decrease in incidence of advanced IA (90% in control and 50% in treated group)
MCP1 inhibitor (7ND) (Aoki <i>et al</i> , 2009b)	IA induced in rats with ( $n=8$ ) or without ( $n=8$ ) administration of 7ND	Significant decrease in aneurysm size
Phosphodiesterase-4 inhibitor (Ibudilast) (Yagi <i>et al</i> , 2010)	IA induced in rats with or without ( $n=20$ ) administration of 30 mg/kg ( $n=15$ ) and 60 mg/kg ( $n=15$ ) of ibudilast	Significant decrease in aneurysmal stage only with 60 mg/kg
Cathepsin inhibitor (NC-2300) (Aoki <i>et al</i> , 2008)	IA induced in rats with ( $n=10$ ) or without ( $n=21$ ) administration of cathepsin inhibitor	Significant decrease in incidence of advanced IA (90% in control and 50% in treated group)
ARB (Olmesartan) (Kimura <i>et al</i> , 2010)	IA induced in rats with or without ( $n=14$ ) administration of low (3 mg/kg per day, $n=13$ ) and high dose (10 mg/kg per day, $n=12$ ) olmesartan	Reduced formation of IA (50% in control, 8% in low dose, and 0% in high dose group—but mainly via blood pressure reduction)
ARB (Valsartan) (Aoki <i>et al</i> , 2009d)	IA induced in rats with ( $n=10$ ) or without ( $n=10$ ) administration of valsartan	No change in IEL score, IA size, and media thickness
ARB (Candesartan) (Tamura <i>et al</i> , 2009)	IA induced in rats with ( $n=16$ ) or without ( $n=18$ ) administration of candesartan	Significant decrease in IA formation but mainly via blood pressure reduction
Mast cell degranulation inhibitor (Tranilast, cimetidine difumarate) (Ishibashi <i>et al</i> , 2010)	IA induced in rats with or without administration of mast cell degranulation inhibitor	Decrease in IA size and increase in media thickness
Free radical scavenger (Edaravone) (Aoki <i>et al</i> , 2009e)	IA induced in rats with ( $n=10$ ) or without ( $n=21$ ) administration of edaravone	Significant decrease in IA size, IEL score, and increase in media thickness

# Hypothesis

- Aspirin can attenuate the inflammatory process in the walls of cerebral aneurysms and decrease the incidence of aneurysm rupture.

# ISUIA: Nested case-control: SAH and controls (matched by site and size) – frequency of aspirin use

	Controls		Cases		Odds Ratio	P-value for linear association conditional odds*
	N	(%)	N	(%)		
Use of aspirin (grouped)						
Never	109	73.6	39	26.4	1	0.0246
<= Once a month	23	79.3	6	20.7	0.80	
> Once a month - 2 times a week	14	77.8	4	22.2	0.86	
3 times a week - daily	67	88.2	9	11.8	0.40	

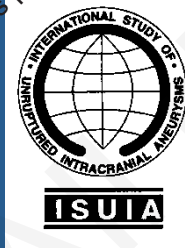
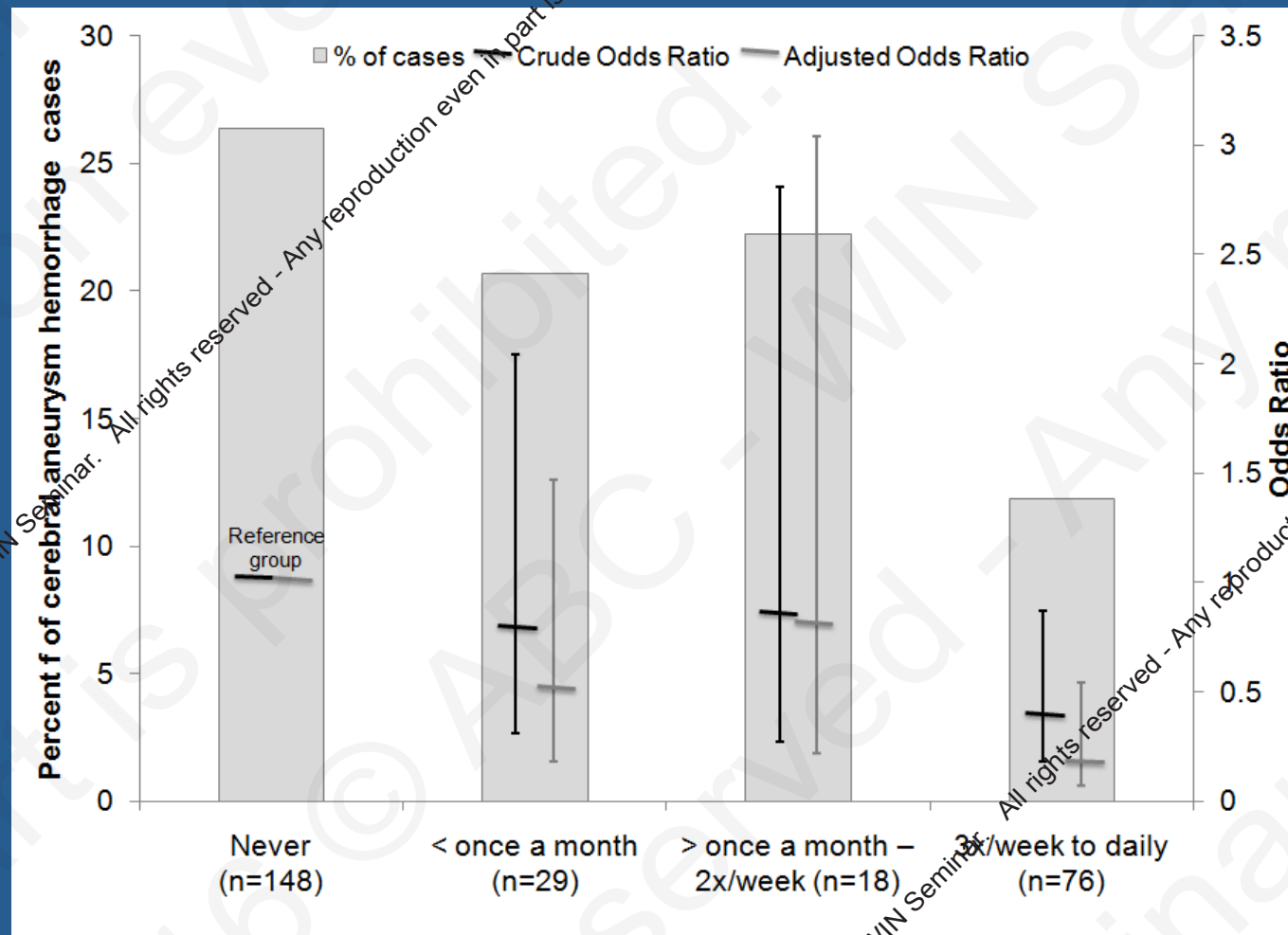


P-value =0.14 for these grouping. P-value of never versus ever=0.0529.

Hasan DM, et al: Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. Stroke 2011;42:3156–3162.



# ISUIA: Nested case-control: hemorrhages and controls (matched by site and size) – frequency of aspirin use



Hasan DM, et al: Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. Stroke 2011;42:3156–3162.

# Aspirin and SAH: More Human Data

- Garcia-Rodriguez et al:
  - 1797 patients with intracerebral hemorrhage
  - 1340 patients with SAH
  - 10,000 controls
- Results: chronic low dose aspirin protects against SAH

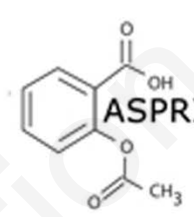
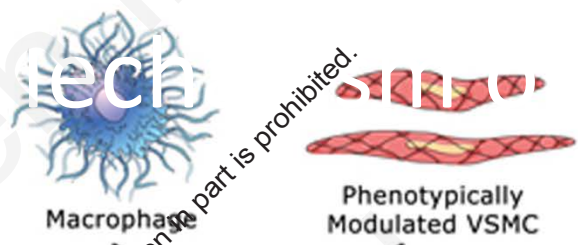
García-Rodríguez LA: Antithrombotic drugs and risk of hemorrhagic stroke in the general population. *Neurology* 2013; 81:566–574.

# Aspirin and SAH: More Human Data

- Gross et al: Review of 747 consecutive patients with cerebral aneurysms.
- The rate of hemorrhagic presentation was significantly lower in patients taking aspirin (28% vs. 40%;  $p=0.01$ ).

Gross BA, Aspirin and aneurysmal subarachnoid hemorrhage. World Neurosurg 2014; 82:1127–1130.





NFκB

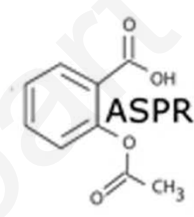
TNFα  
IL-1  
IL-6  
MCP-1  
MMP-2  
MMP-9



INFLAMMATION



INFLAMMATION



COX-1  
COX-2

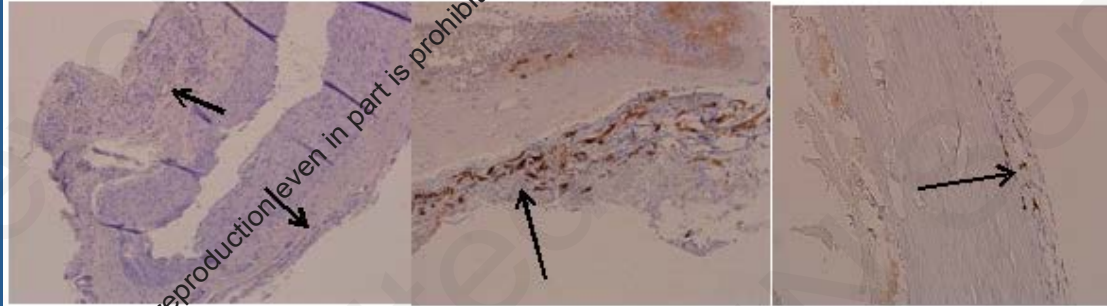
PGH2  
TXA2  
Prostacyclin  
PGD2  
PGE2  
PGF2α

Mechanism of Action??

# COX-2 in Human Aneurysm Tissue

Hasan D: Upregulation of cyclooxygenase-2 (COX-2) and microsomal prostaglandin E2 synthase-1 (mPGES-1) in wall of ruptured human cerebral aneurysms: preliminary results. Stroke 2012; 43: 1964–1967

**COX-2:**

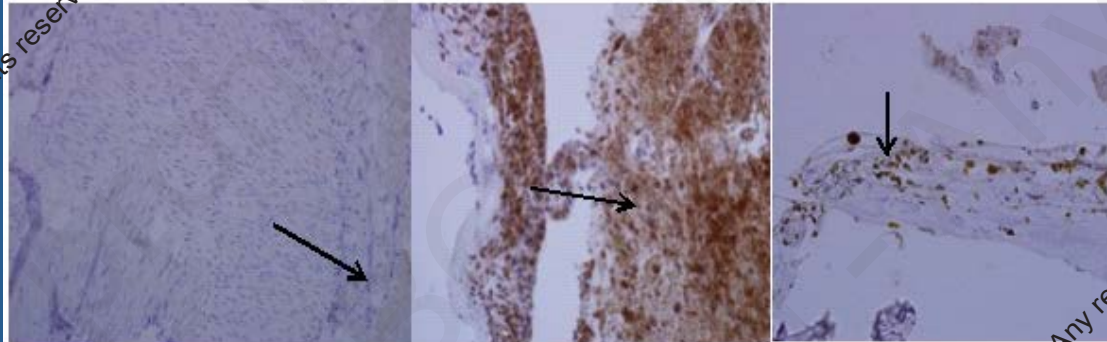


STA

Ruptured Aneurysm

Unruptured Aneurysm

**mPGES-1:**

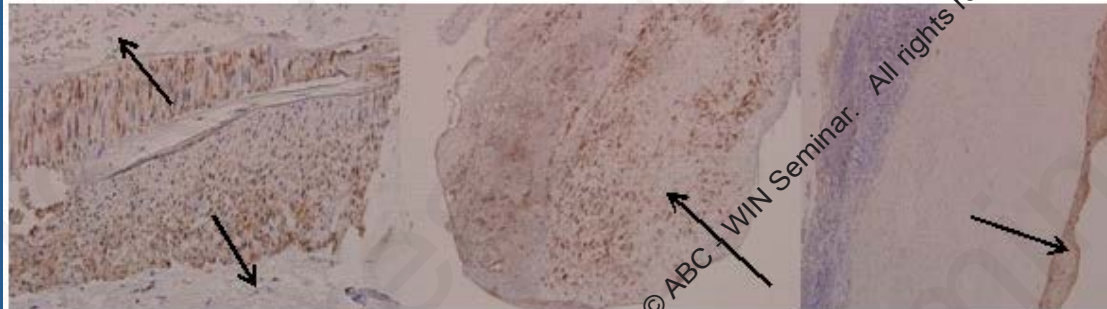


STA

Ruptured Aneurysm

Unruptured Aneurysm

**COX-1:**



STA

Ruptured Aneurysm

Unruptured Aneurysm

Figure 1

COX-2 in Human  
Aneurysm Tissue



ORIGINAL RESEARCH



## Evidence That Acetylsalicylic Acid Attenuates Inflammation in the Walls of Human Cerebral Aneurysms: Preliminary Results

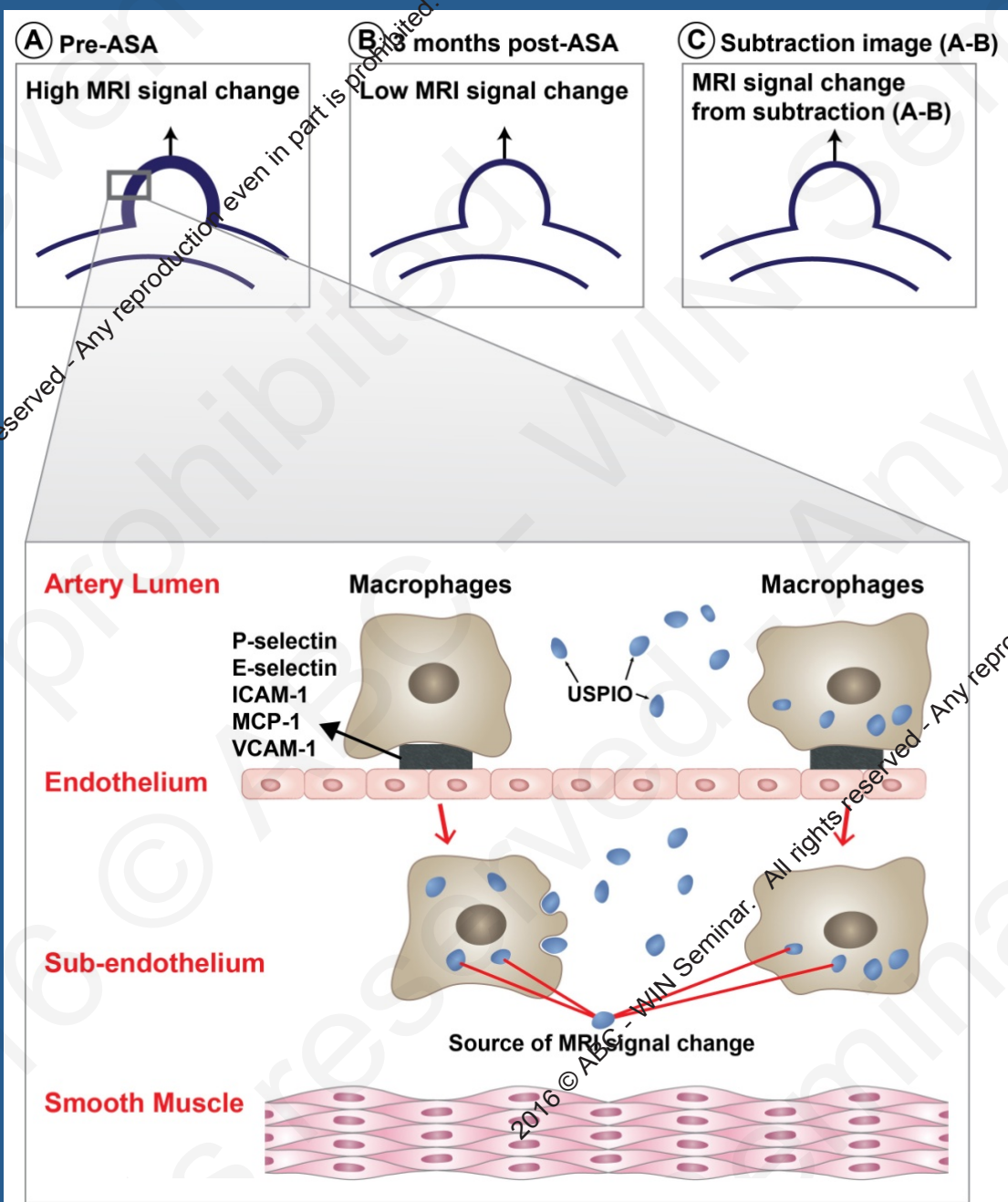
David M. Hasan, MD; Nohra Chalouhi, MD; Pascal Jabbour, MD; Aaron S. Dumont, MD; David K. Kung, MD; Vincent A. Magnotta, PhD; William L. Young, MD; Tomoki Hashimoto, MD; H. Richard Winn, MD; Donald Heistad, MD

11 prospectively enrolled patients randomized into an ASA-treated (81 mg daily) group (n=6) and an untreated (control) group (n=5)

- 1- Radiographic studies
- 2- Histological studies

Hasan DM, Chalouhi N, et al: Evidence that acetylsalicylic acid attenuates inflammation in the walls of human cerebral aneurysms: preliminary results. J Am Heart Assoc 2013; 2:e000019.

1- Radiographic studies

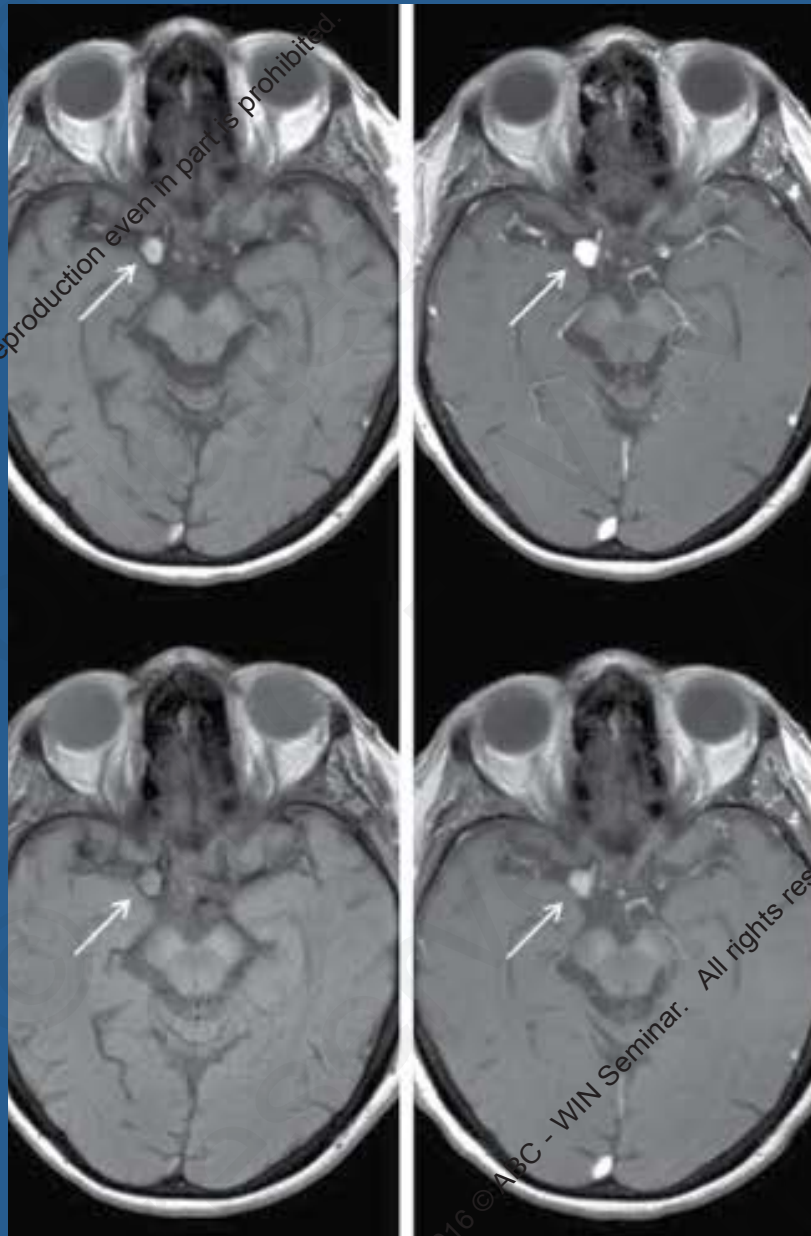


24h post Fe

72h post Fe

## 1- Radiographic studies

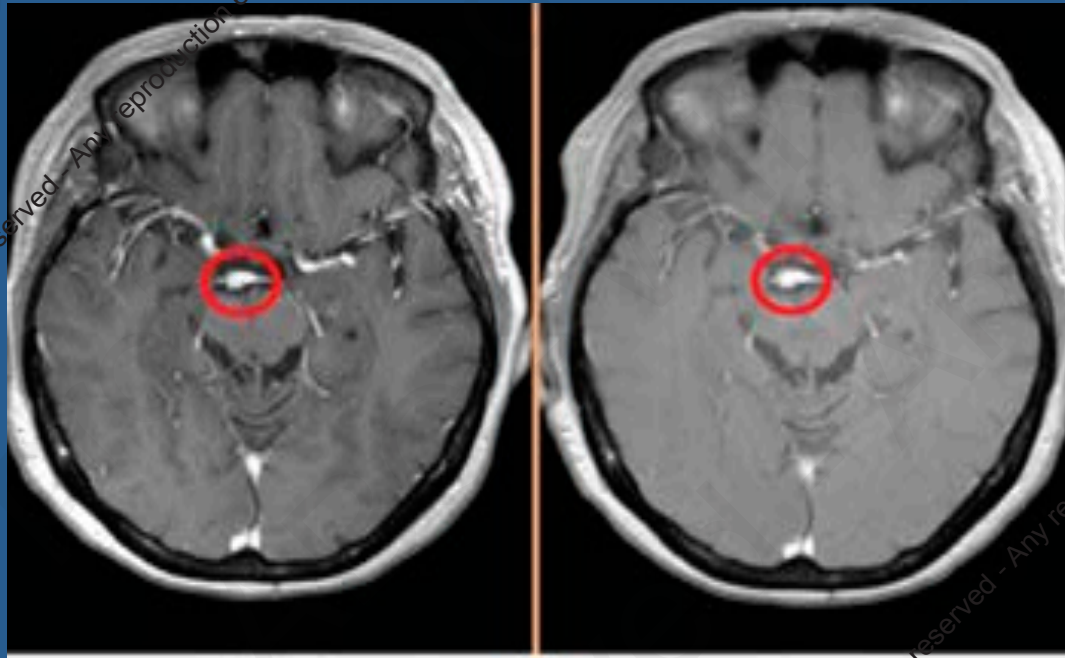
Baseline



After 3 months of ASA



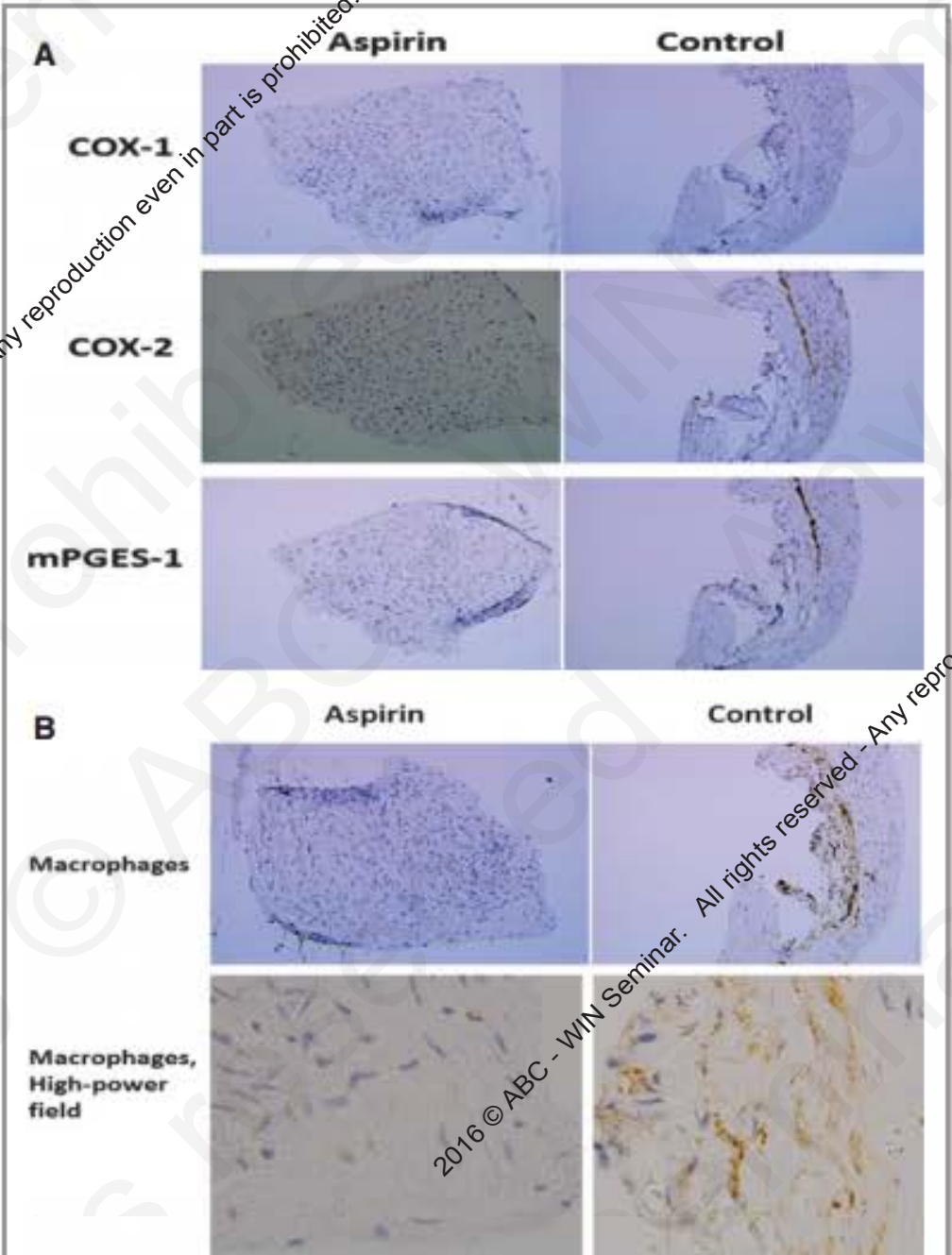
# Control group



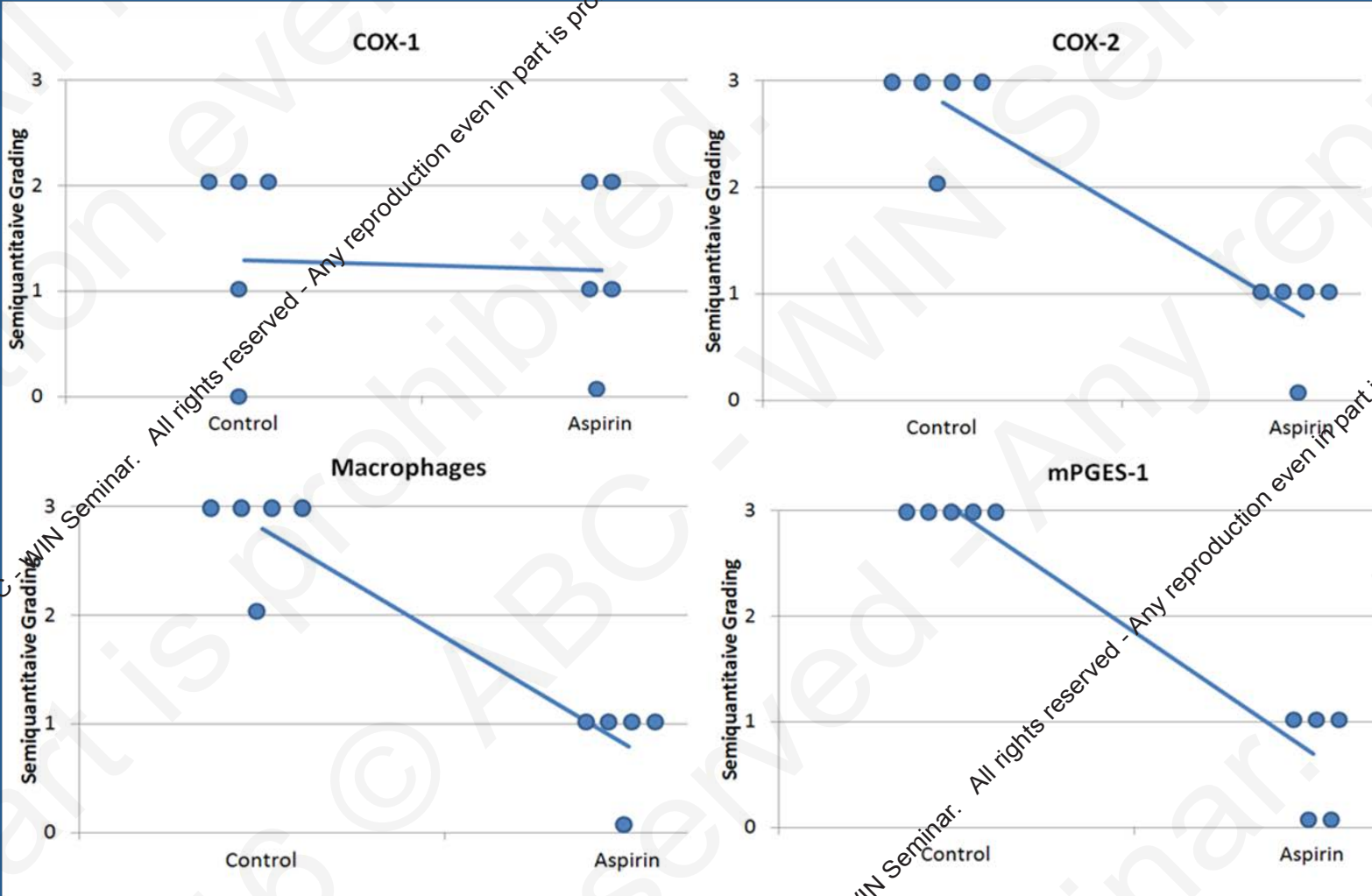
Baseline (72h post Fe)

After 3 months (72h post Fe)

2- Histological studies



2- Histological studies





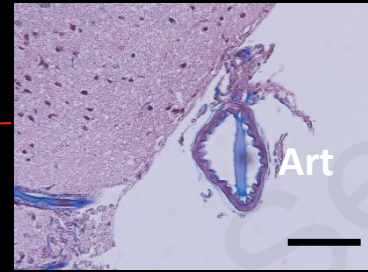
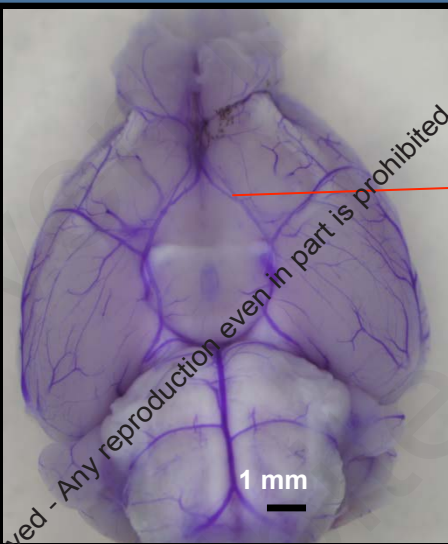
# Animal Data: Using a Mouse Model of Cerebral Aneurysm

## Differential Gender Response to Aspirin in Decreasing Aneurysm Rupture in Humans and Mice

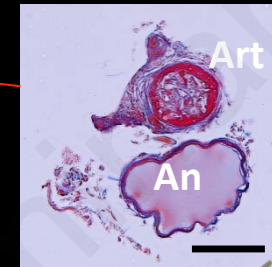
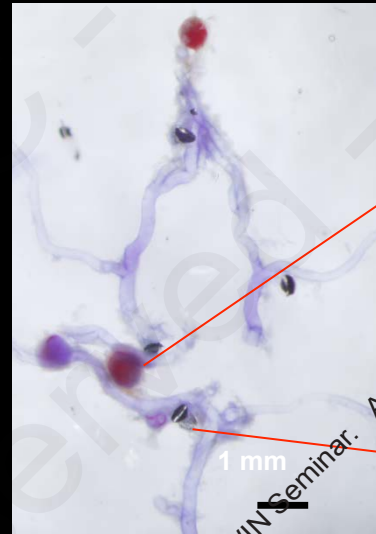
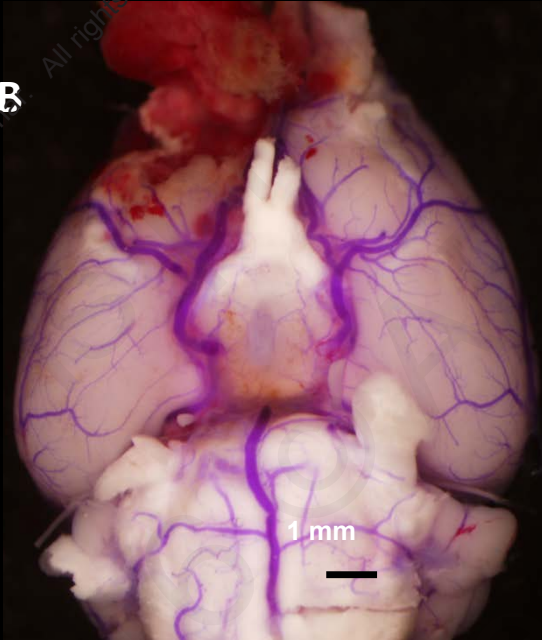
Nohra Chalouhi MD,<sup>1</sup> Robert M. Starke MD,<sup>2</sup> Tatiana Correa BS,<sup>3</sup> Pascal Jabbour MD,<sup>1</sup> Mario Zaidat MD,<sup>4</sup> Robert Brown Jr. MD,<sup>5</sup> James Torner MD,<sup>6</sup> and David Hasan MD<sup>4</sup>

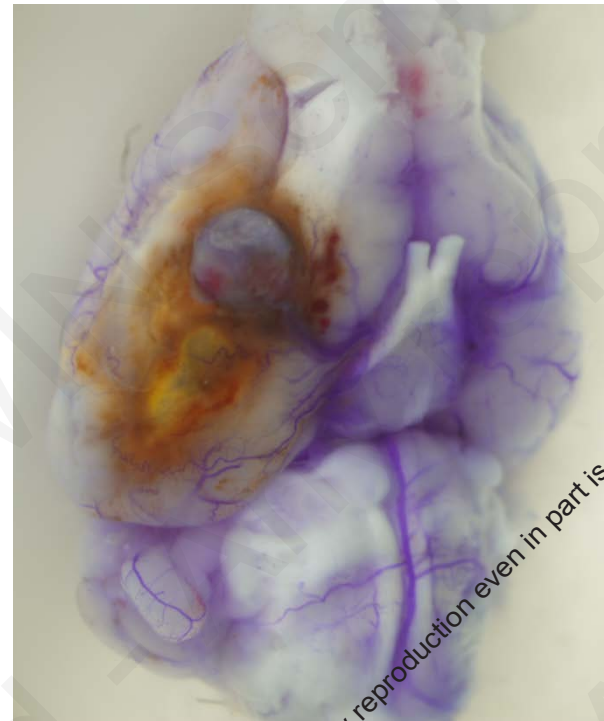
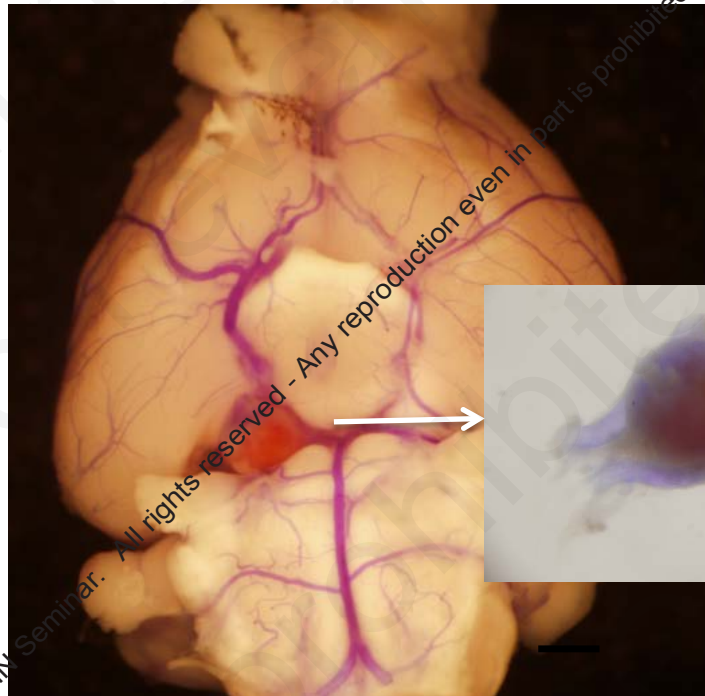
Circulation (under review)

A

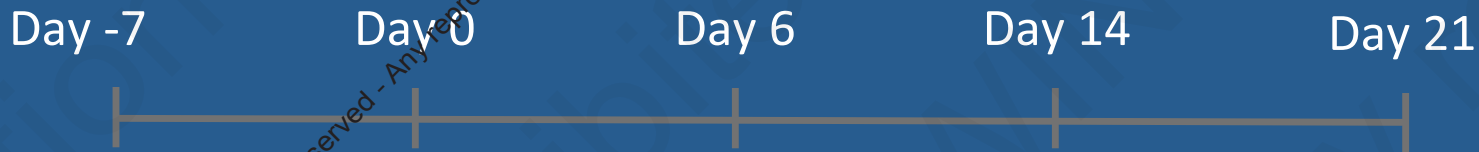


B





# Protocol: Aspirin + E35mU + AngII



▲ Elastase 35mU injection + Ang II mini pump implantation

1% saline

Aspirin (25mg/kg) IP daily

N=14

▲ sacrifice

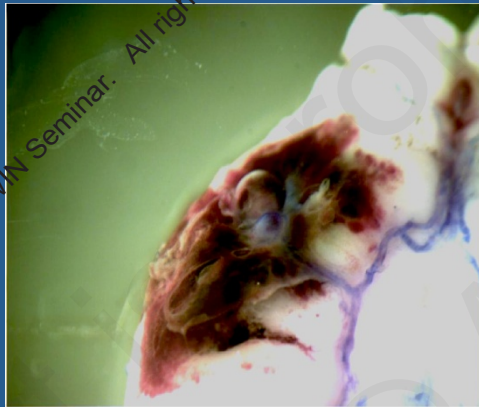


**Sacrifice criteria:**

**Reach 21 days**

**Weight loss > 10% from baseline or > 2g**

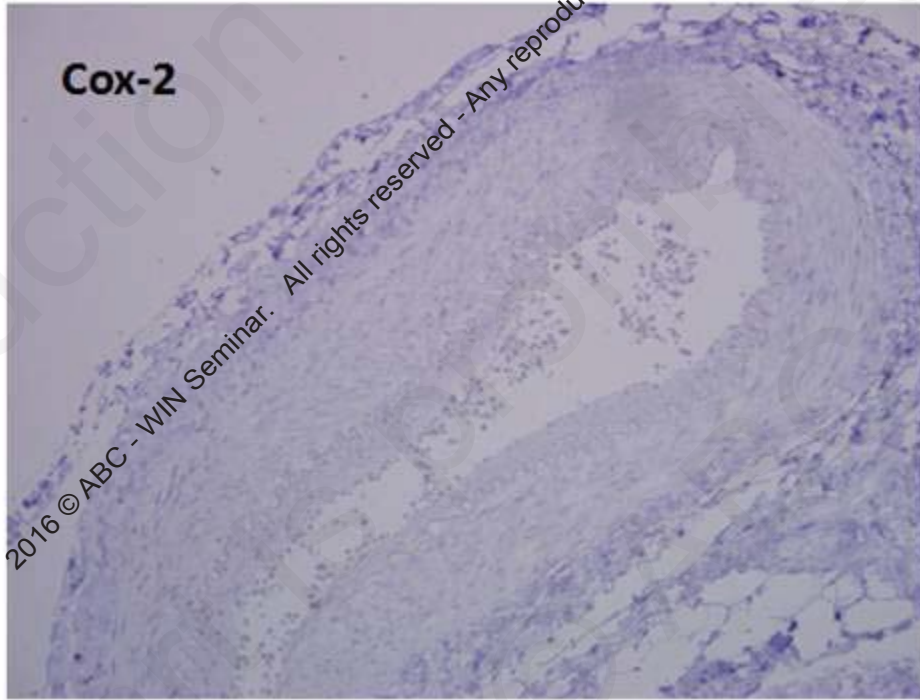
**Detection of aneurysmal rupture by symptoms**



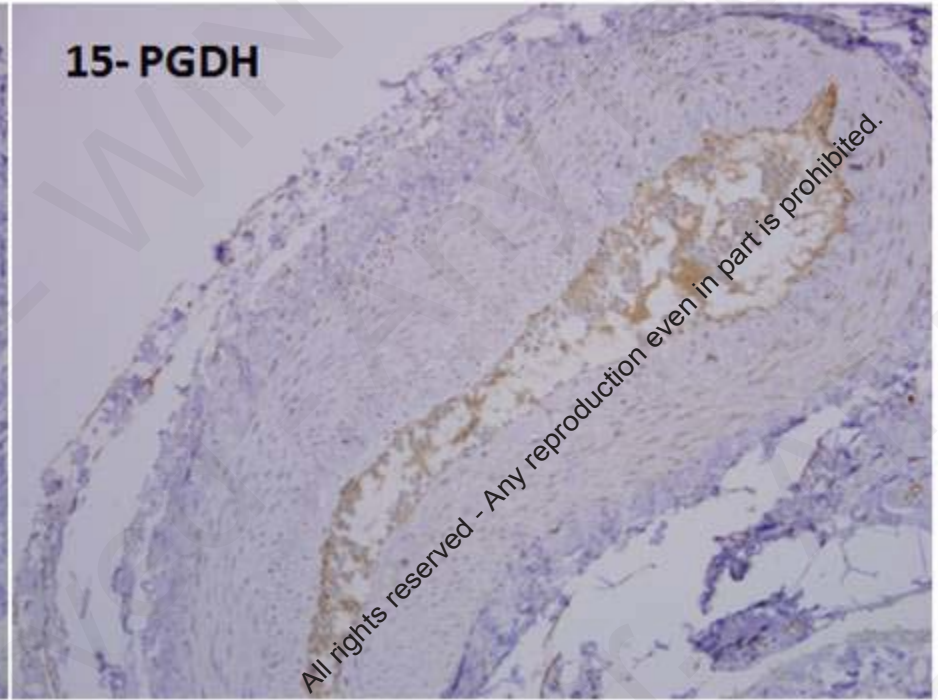
Grade	Signs
0	No abnormalities
1	Flexion of torso and forelimb upon lifting of the whole animal by the tail
2	Circling but normal posture at rest
3	Leaning to a side at rest
4	No spontaneous motor activity

# STA

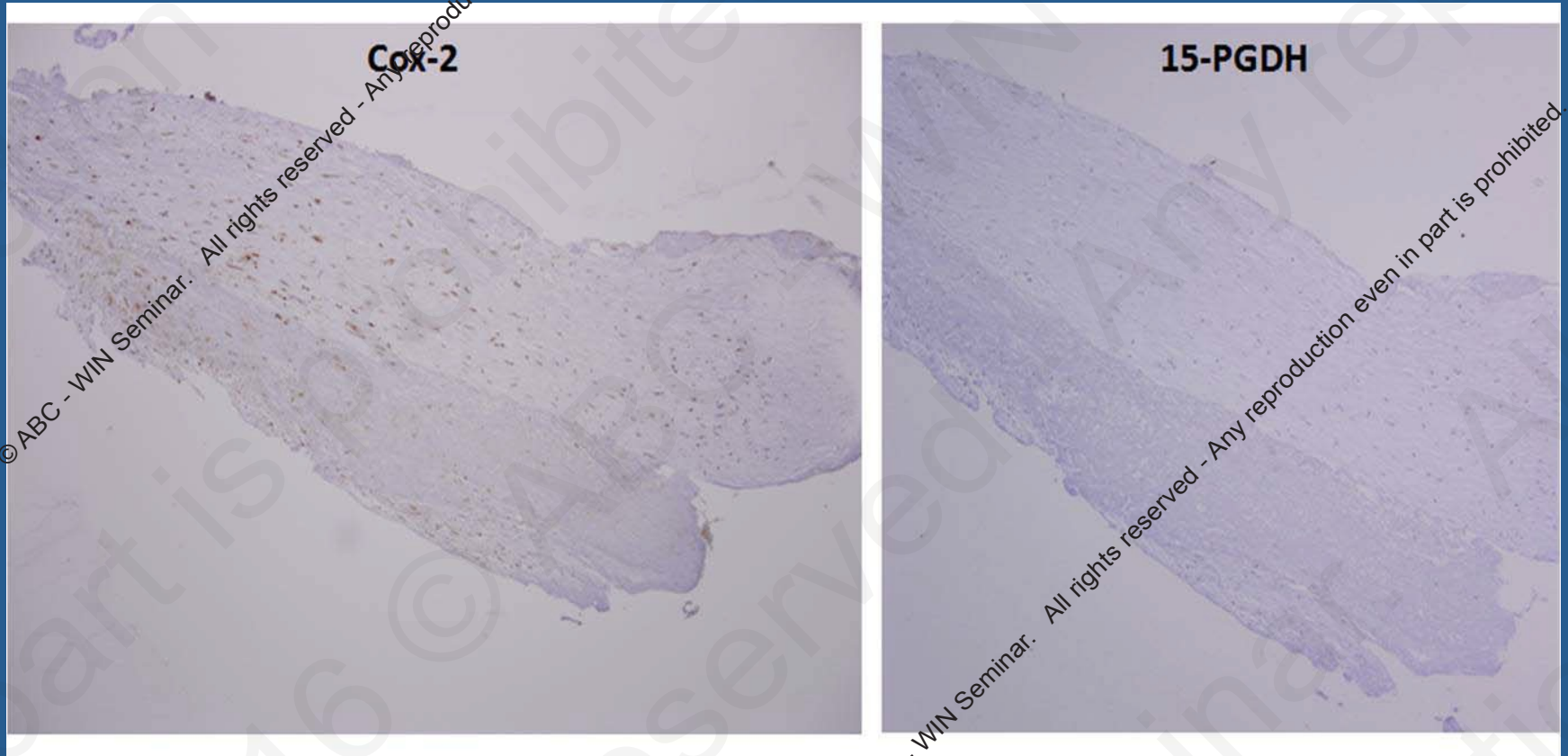
**Cox-2**



**15- PGDH**



# Intracranial Aneurysm from female patient



# More Animal Data

- Li et al showed that aspirin inhibited degenerative changes in the aneurysmal wall of a rat model of cerebral aneurysms and decreased inflammatory markers (MMP-2, MMP-9, MCP-1, VCAM-1, and NF-kB) in the wall.

Li S, Wang D, Tian Y, Zhou Z, Liu L, Wang D, et al: Aspirin inhibits degenerative changes of aneurysmal wall in a rat model. Neurochem Res. 2015 (June 21-Epub ahead of print)



# Potential Role of Aspirin in the Prevention of Aneurysmal Subarachnoid Hemorrhage

Robert M. Starke<sup>a</sup> Nohra Chalouhi<sup>b</sup> Dale Ding<sup>a</sup> David M. Hasan<sup>c</sup>

<sup>a</sup>Department of Neurological Surgery, University of Virginia, Charlottesville, Va., <sup>b</sup>Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, Pa., and <sup>c</sup>Department of Neurological Surgery, University of Iowa, Cedar Rapids, Iowa, USA

# Hypertension



## **Novel Role for Endogenous Hepatocyte Growth Factor in the Pathogenesis of Intracranial Aneurysms**

Ricardo A. Peña-Silva, Nohra Chalouhi, Lauren Wegman-Points, Muhammad Ali, Ian Mitchell, Gary L. Pierce, Yi Chu, Zuhair K. Ballas, Donald Heistad, David Hasan

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# Conclusion

- Human and animal data suggest that aspirin attenuates inflammation in the wall of cerebral aneurysms and may reduce the risk of rupture (with a gender-differential response). Medical treatment to halt aneurysm progression to rupture is attainable
- The stage is set for a human clinical trial!



## Neurosurgery

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# Aspirin for Prevention of Subarachnoid Hemorrhage: The Stage Is Set for a Randomized Controlled Trial

Chalouhi, Nohra; Jabbour, Pascal; Hasan, David; Starke, Robert M.



# Aneurysm Rupture Reduction and Expansion Stabilization Trial (ARREST)

- A randomized placebo-controlled clinical trial of aspirin therapy in patients with small unruptured aneurysms ( $3\text{mm} \leq \text{aneurysm} \leq 7\text{ mm}$ )
- Primary or secondary prevention
  - Primary aims of the trial:
    - Determination of effectiveness of aspirin on reducing the incidence of aneurysmal growth and rupture
  - Secondary aims:
    - Determination of effect of subgroups on response to aspirin
    - Determination of factors related to acute change in aneurysm size
    - Determination of the utility of serum myeloperoxidase levels in assessing response to aspirin

# Thank you!

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