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Loss of tissue inhibitor of metalloproteinase-3 (Timp3) leads to abdominal aortic aneurysm (AAA)

Zamaneh Kassiri, PhD
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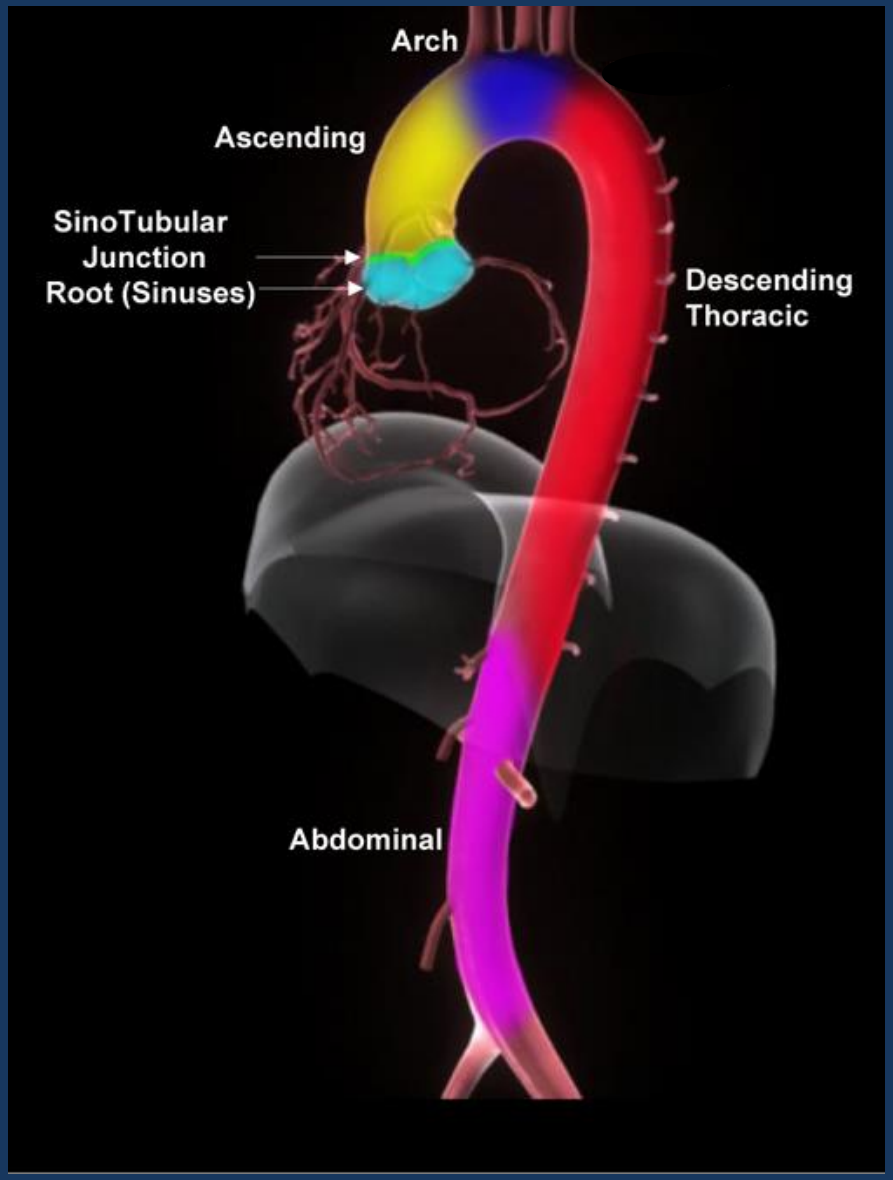
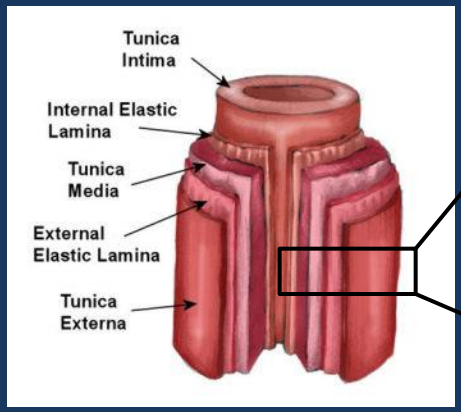
Edmonton, AB
Canada

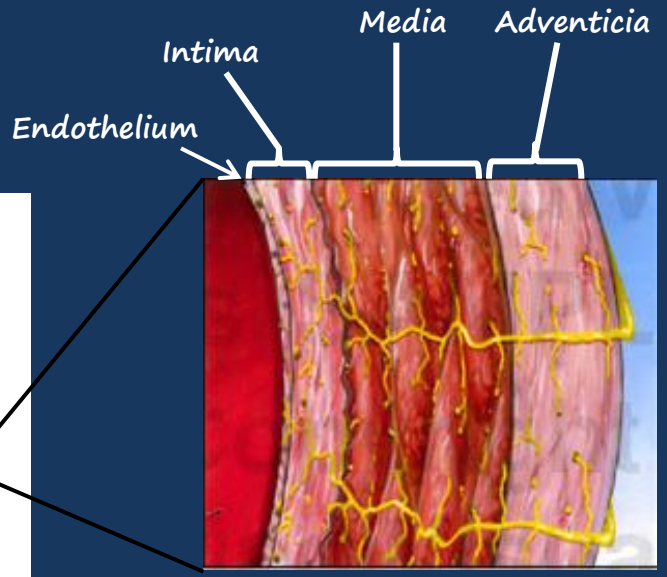
Aorta

- Largest Artery in the body.

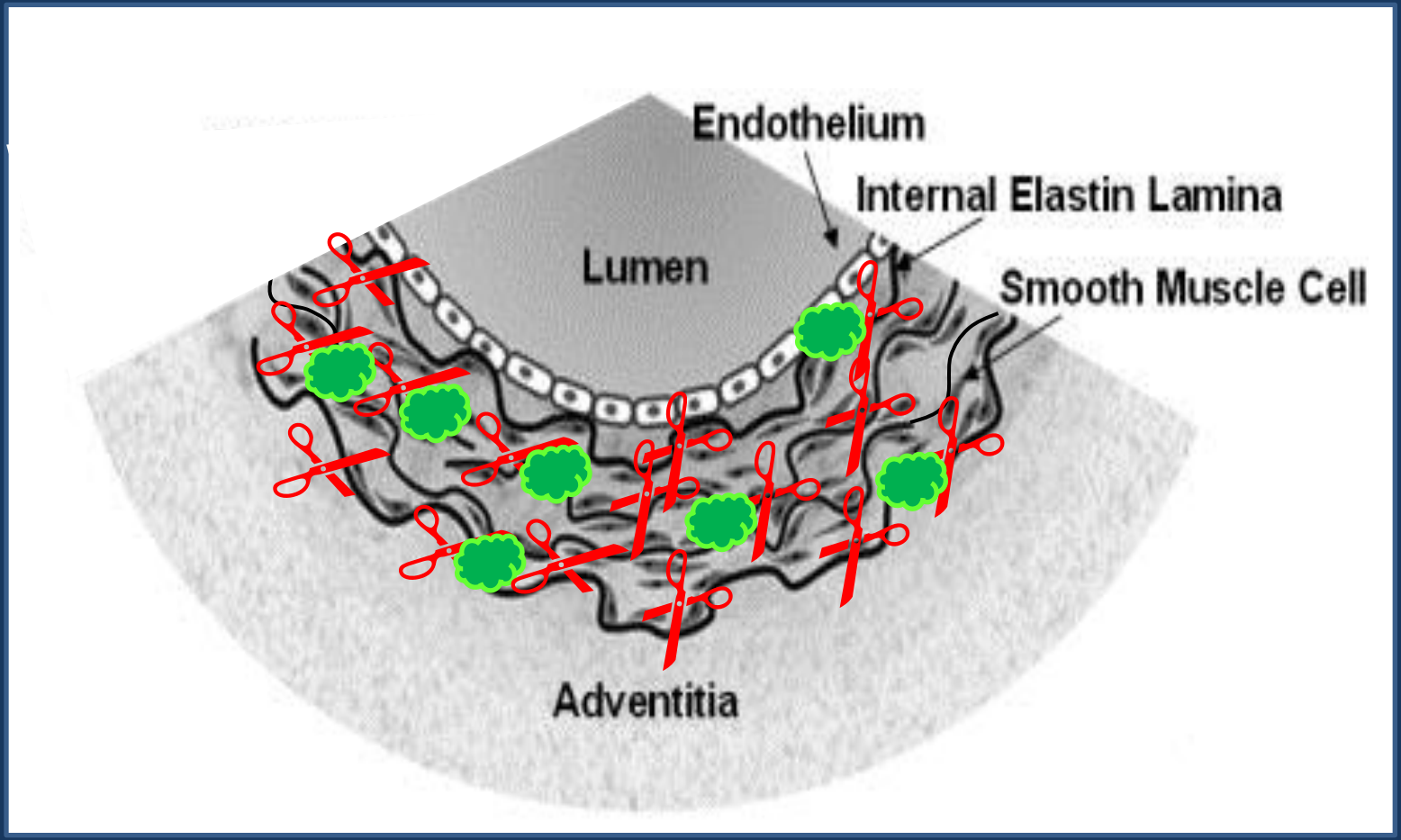
- Functions:
  1) Conduit function.
  2) Cushion / Capacitor function
  3) Pump function.




Tunica Intima
Internal Elastic Lamina
Tunica Media
External Elastic Lamina
Tunica Externa


Endothelium
Intima
Media
Adventicia

Vascular ECM turnover

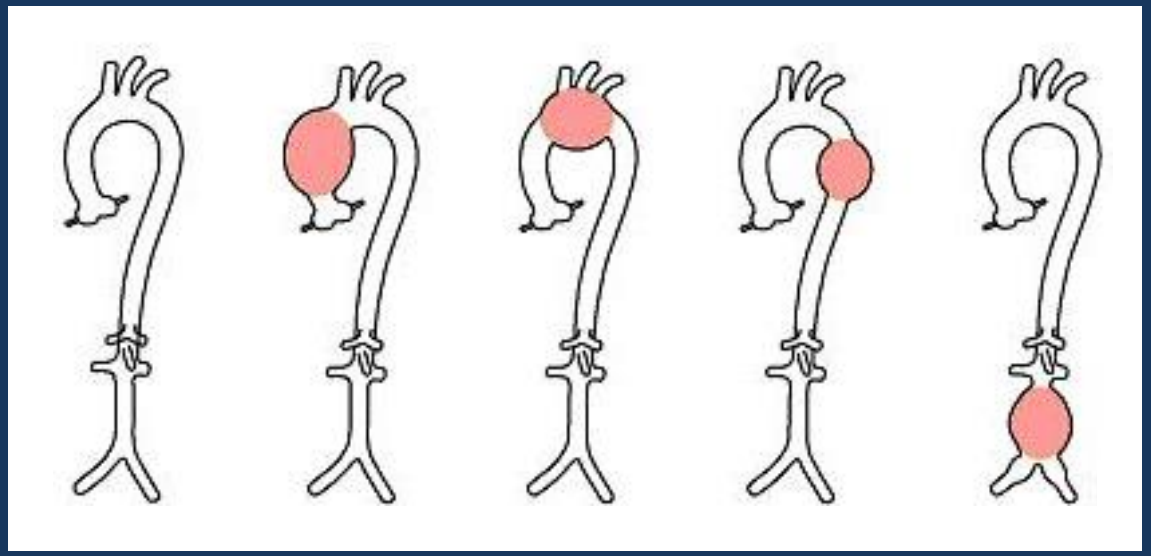


MMPs (matrix metalloproteinases)

TIMPs (Tissue inhibitor of metalloproteinases)

Aneurysm: A localized, pathological, blood-filled dilatation of a blood vessel caused by a disease or weakening of the vessel's wall.

Various locations of Aortic Aneurysm



Normal | Ascending aorta | Aortic arch | Descending aorta | Abdominal aorta

Abdominal Aortic Aneurysm

•AAAs are usually asymptomatic until rupture occurs.

• Abdominal Aortic Aneurysm rupture has been recognized as a significant cause of mortality of adults aged >60 years in the developed world.

U.S. Department of Health and Human Services Centers for Disease Control and Prevention National Center for Health Statistics. MD LCWK1. **Deaths, percent of total deaths, and death rates for the 15 leading causes of death in 5-year age groups, by race and sex: United States**, 2006, 2009:7–9. http://www.cdc.gov/nchs/data/dvs/ LCWK1_2006.pdf.

• Screening programs have been shown to reduce mortality in men aged >65 years

Fleming ,C. et al. Screening for AAA: a best-evidence systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2005;142:203–211.

• **Currently, no recognized treatment for AAAs (Golledge & Norman, *ATVB*, 2010)**
(ACE inhibitors, β-blockers and statins have been ineffective)

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Aortic Aneurysm

Is Aortic Dilatation an Atherosclerosis-Related Process?

Clinical, Laboratory, and Transesophageal Echocardiographic Correlates of Thoracic Aortic Dimensions in the Population With Implications for Thoracic Aortic Aneurysm Formation

Yoram Agmon, MD,* Bijoy K. Khandheria, MD,* Irene Meissner, MD,† Gary L. Schwartz, MD,‡ JoRean D. Sicks, MS,§ Angela J. Fought, BS,§ W. Michael O'Fallon, PHD,§ David O. Wiebers, MD,† A. Jamil Tajik, MD*

Rochester, Minnesota

OBJECTIVES The study determined, in a population-based setting, whether dilatation of the thoracic aorta is an atherosclerosis-related process.

BACKGROUND The role of atherosclerosis in thoracic aortic dilatation and aneurysm formation is poorly defined.

METHODS The dimensions of the thoracic aorta were measured with transesophageal echocardiography in 373 subjects participating in a population-based study (median age 66 years; 52% men). The associations between clinical and laboratory atherosclerosis risk factors, aortic atherosclerotic plaques, and aortic dimensions were examined.

RESULTS Age, male gender, and body surface area (BSA) jointly accounted for 41%, 31%, 38%, and 47% of the variability in diameters of the sinuses of Valsalva, ascending aorta, aortic arch, and descending aorta, respectively. Adjusting for age, gender, and BSA: 1) smoking was associated with a greater aortic arch diameter, and diastolic blood pressure and diabetes were each associated with a greater descending aorta diameter ($p < 0.05$); 2) atherosclerotic plaques in the descending aorta were associated with a greater descending aorta diameter (0.18 ± 0.08-mm increase in diameter per 1-mm increase in plaque thickness; $p = 0.02$); and 3) minor negative associations were noted between atherosclerotic plaques and risk factors for atherosclerosis and the dimensions of the proximal thoracic aorta. Notably, atherosclerosis risk factors and plaque variables each accounted for <2% of the variability in aortic dimensions, adjusting for age, gender, and BSA.

CONCLUSIONS Age, gender, and BSA are major determinants of thoracic aortic dimensions. Atherosclerosis risk factors and aortic atherosclerotic plaques are weakly associated with distal aortic dilatation, suggesting that atherosclerosis plays a minor role in aortic dilatation in the population. (J Am Coll Cardiol 2003;42:1076–83) © 2003 by the American College of Cardiology Foundation

Atherosclerosis in Abdominal Aortic Aneurysms: A Causal Event or a Process Running in Parallel? The Tromsø Study

Stein Harald Johnsen, Signe Helene Forsdahl, Kulbir Singh, Bjarne Koster Jacobsen

Objective—The pathogenesis of abdominal aortic aneurysm (AAA) formation is poorly understood. We investigated the relationship between carotid, femoral, and coronary atherosclerosis and abdominal aortic diameter, and whether atherosclerosis was a risk marker for AAA.

Methods and Results—Ultrasound of the right carotid artery, the common femoral artery, and the abdominal aorta was performed in 6446 men and women from a general population. The burden of atherosclerosis was assessed as carotid total plaque area, common femoral lumen diameter, and self-reported coronary heart disease. An AAA was defined as maximal infrarenal aortic diameter ≥30 mm. No dose-response relationship was found between carotid atherosclerosis and abdominal aortic diameter <27 mm. However, significantly more atherosclerosis and coronary heart disease was found in aortic diameter ≥27 mm and in AAAs. The age- and sex-adjusted odds ratio (OR) (95% CI) for AAA in the top total plaque area quintile was 2.3 (1.5 to 3.4), as compared with subjects without plaques. The adjusted OR (95% CI) was 1.7 (1.1 to 2.6). No independent association was found between femoral lumen diameter and AAA.

Conclusion—The lack of a consistent dose-response relationship between atherosclerosis and abdominal aortic diameter suggests that atherosclerosis may not be a causal event in AAA but develops in parallel with or secondary to aneurismal dilatation. (*Arterioscler Thromb Vasc Biol.* **2010;30:1263-1268.**)

TIMP3 and aneurysm

• TIMP3 mRNA levels are increased in dilated aorta from patients with aortic aneurysm whereas other TIMPs were not altered (Tsarouhas, K et al. *Thromb Res* **2010)**.

• A significant interaction between polymorphism of TIMP3, but not TIMP1 or TIMP2, occurs in patients with AAA and with a positive family history of AAA (Ogata, T. et al. *J Vasc Surg.* 2005).

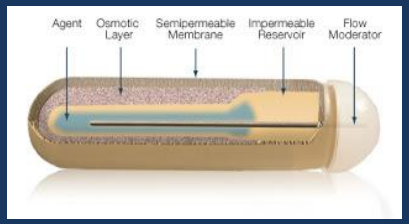
Model of Hypertension

Elevated Ang II levels

WT & TIMP3$^{-/-}$

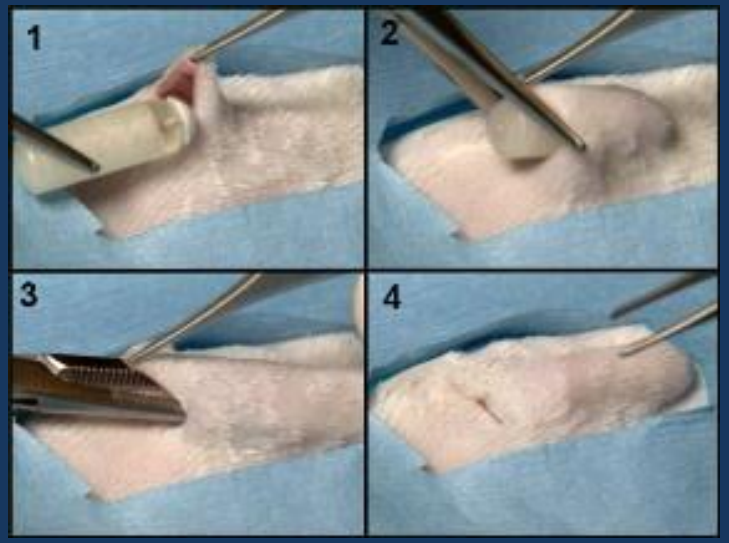
C57BL/6

Alzet micro-osmotic pump



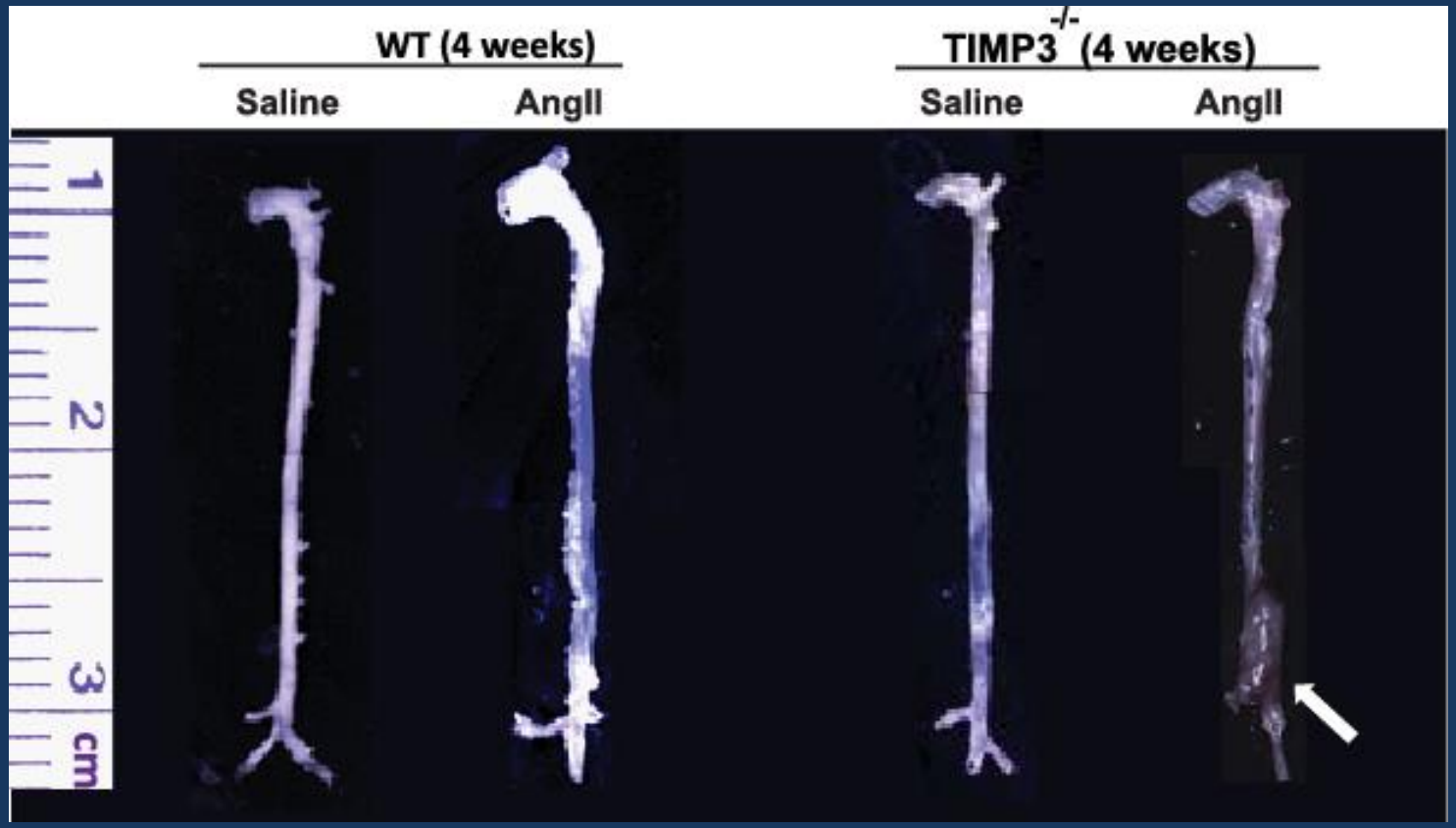
Micro-pump was filled with Ang II to deliver **1.5mg/Kg/d**. (control: saline)

Dorsal sub-cutaneous implantation of Alzet micro-osmotic pump

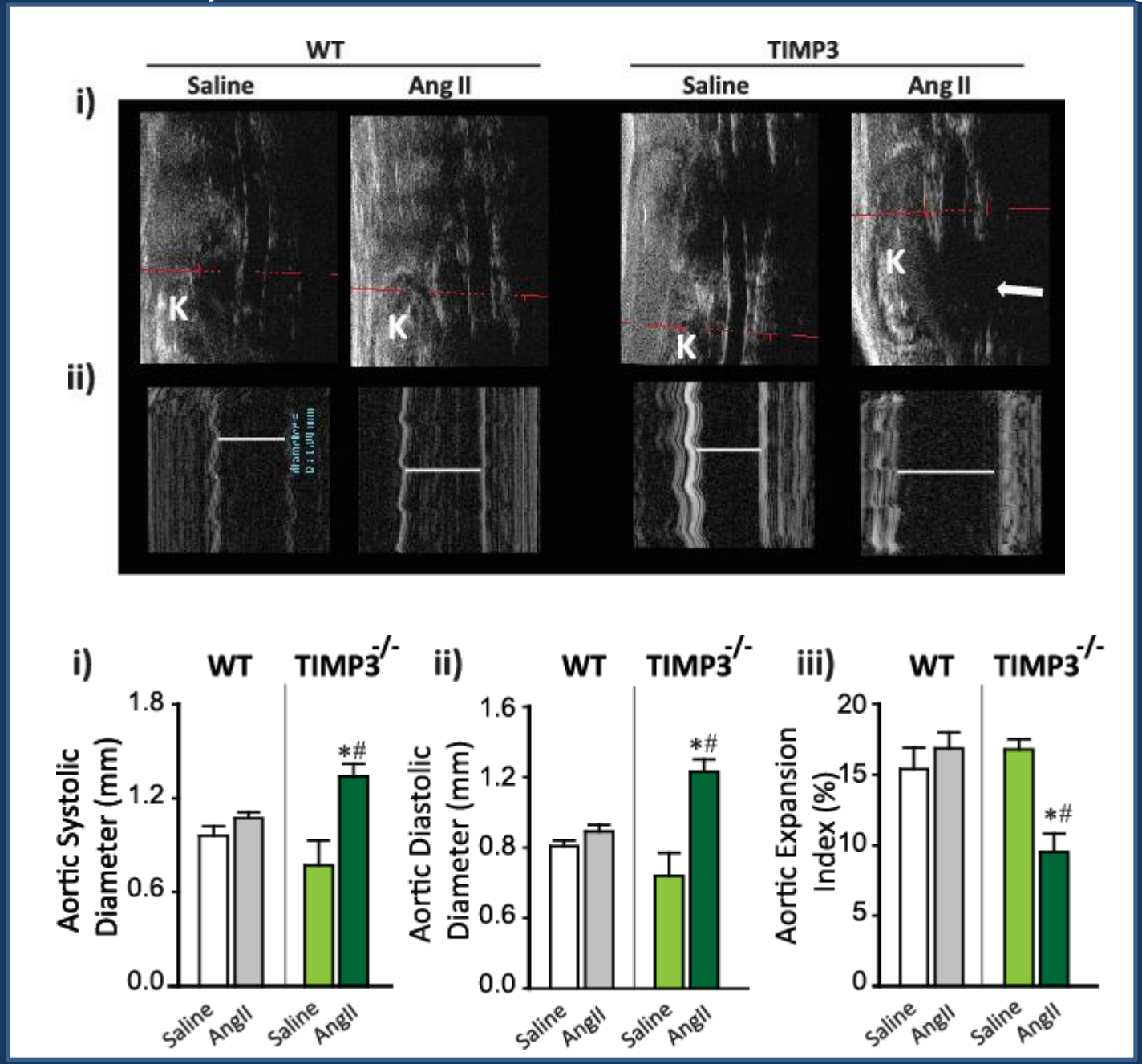


alzet® OSMOTIC PUMPS

After **4 weeks** of Ang II infusion, we detected swelling of the aorta at the supra-renal level in TIMP3$^{-/-}$-Ang II mice.

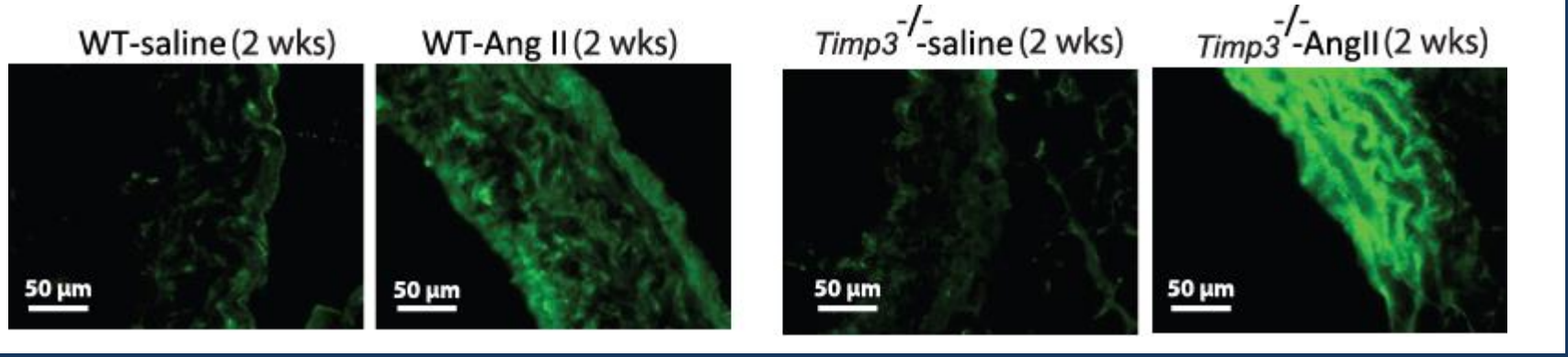


Aortic Aneurysm was well reflected in the ultrasound images

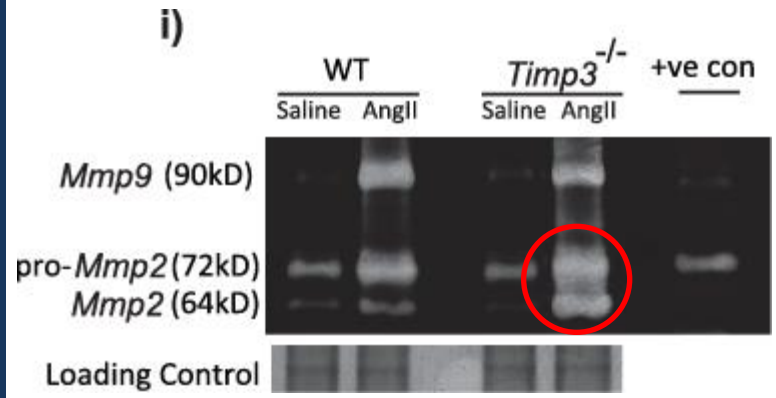


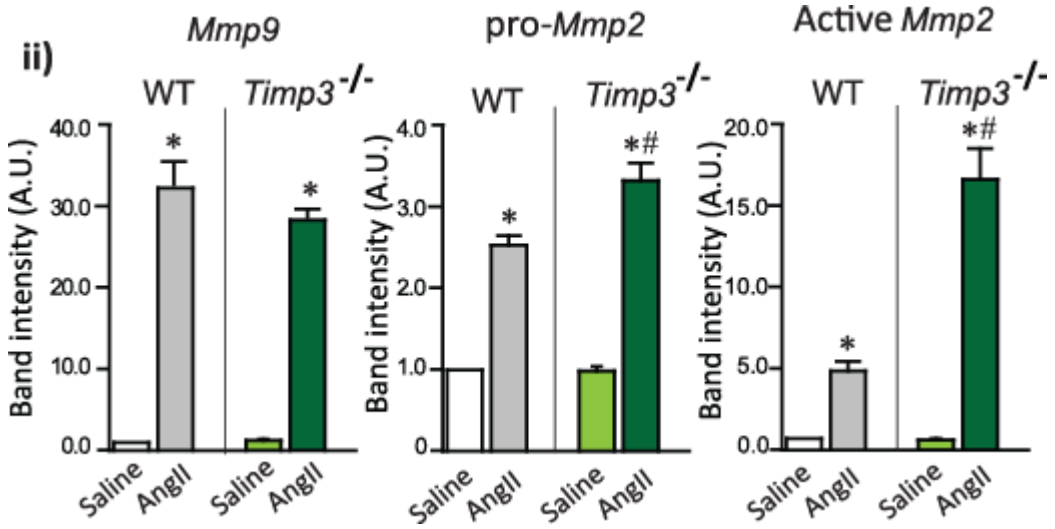
Elevated gelatinase activity, specifically MMP2 in TIMP3$^{-/-}$-Ang II compared to WT-Ang II aorta after **2 weeks** of Ang II infusion

In Situ gelatin Zymography



In Vitro gelatin Zymography





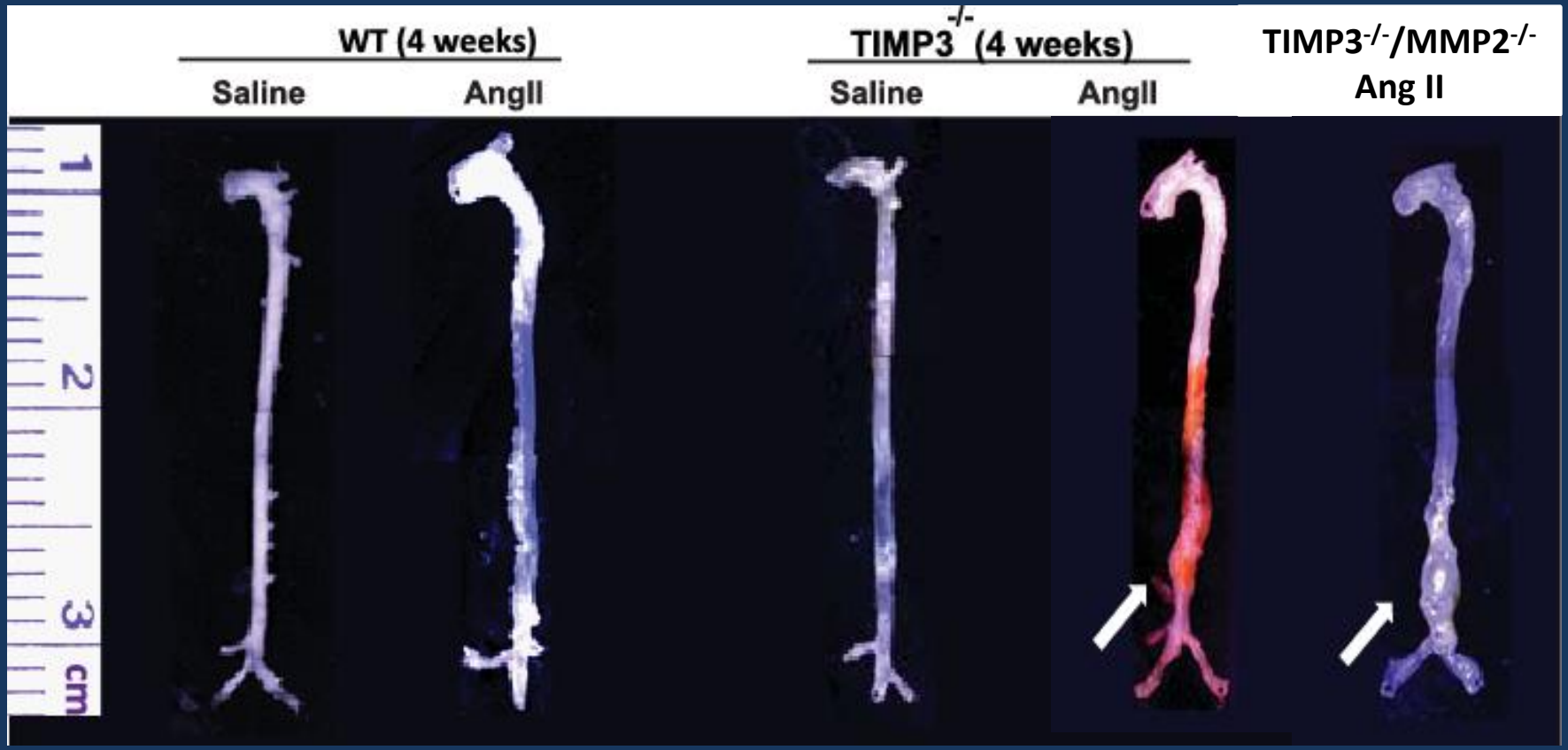
Targeted inhibition of MMP2 in TIMP3$^{-/-}$ mice

TIMP3$^{-/-}$

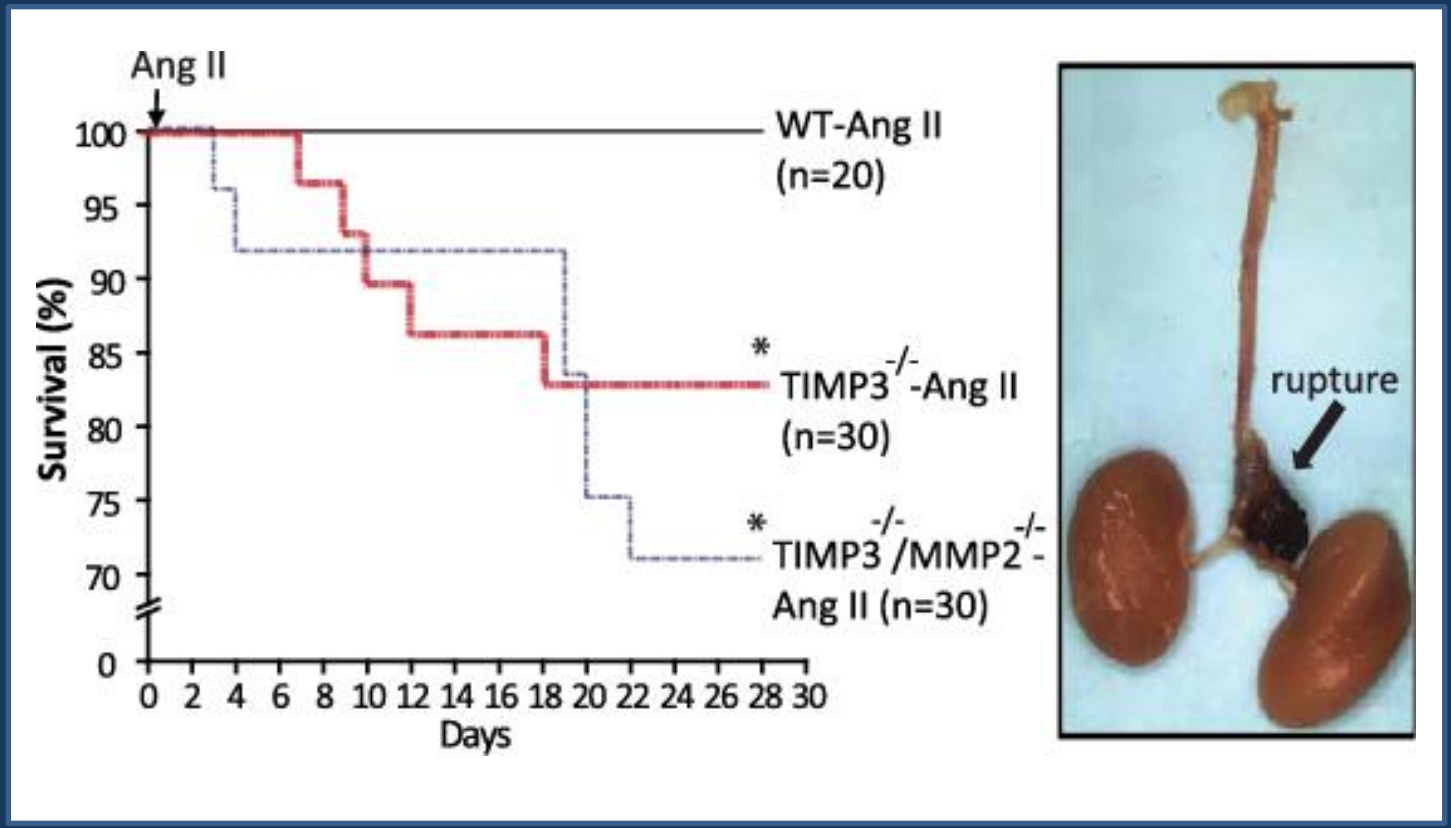
MMP2$^{-/-}$

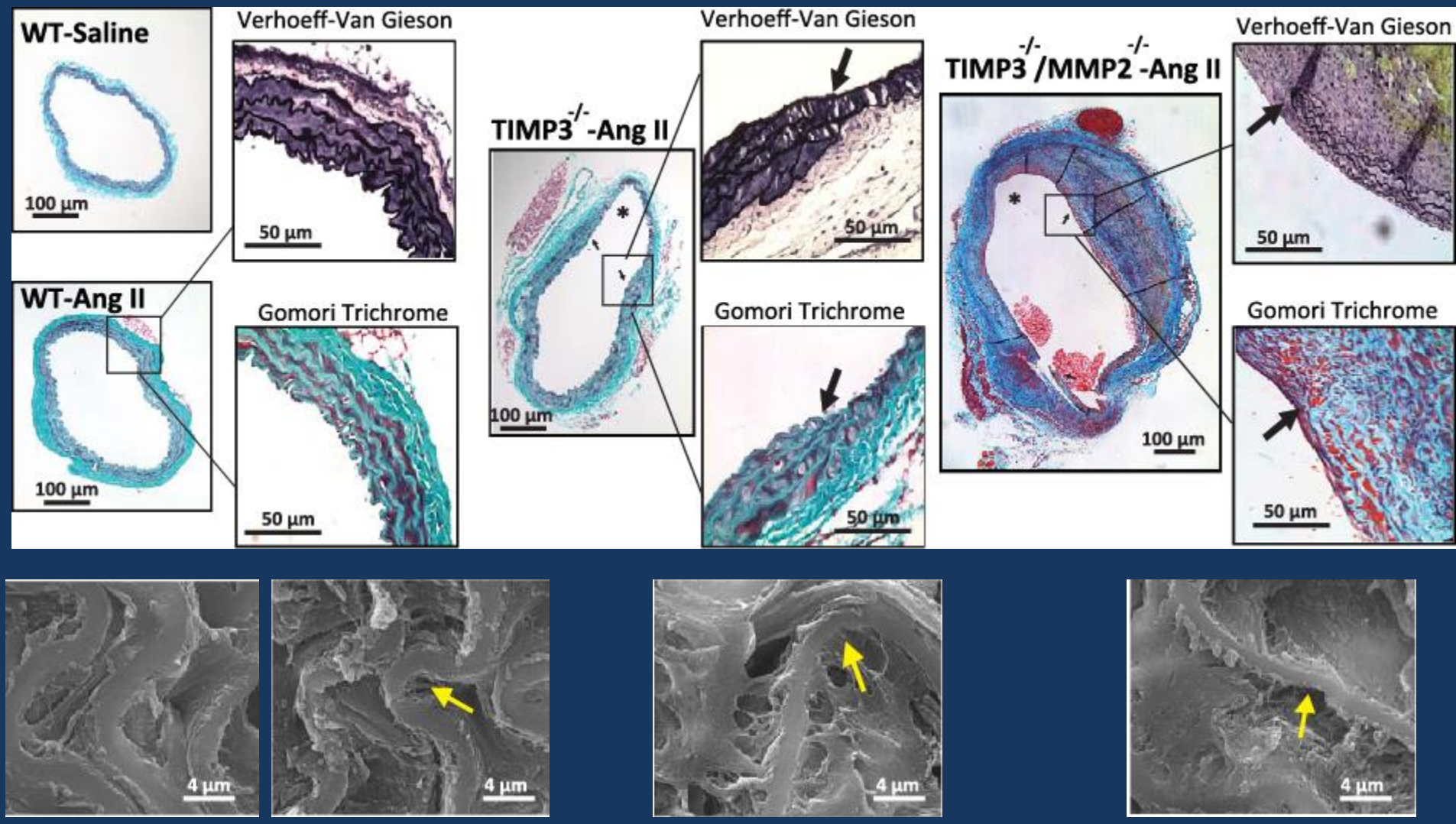
TIMP3$^{-/-}$/MMP2$^{-/-}$

After 4 weeks of Ang II infusion ...



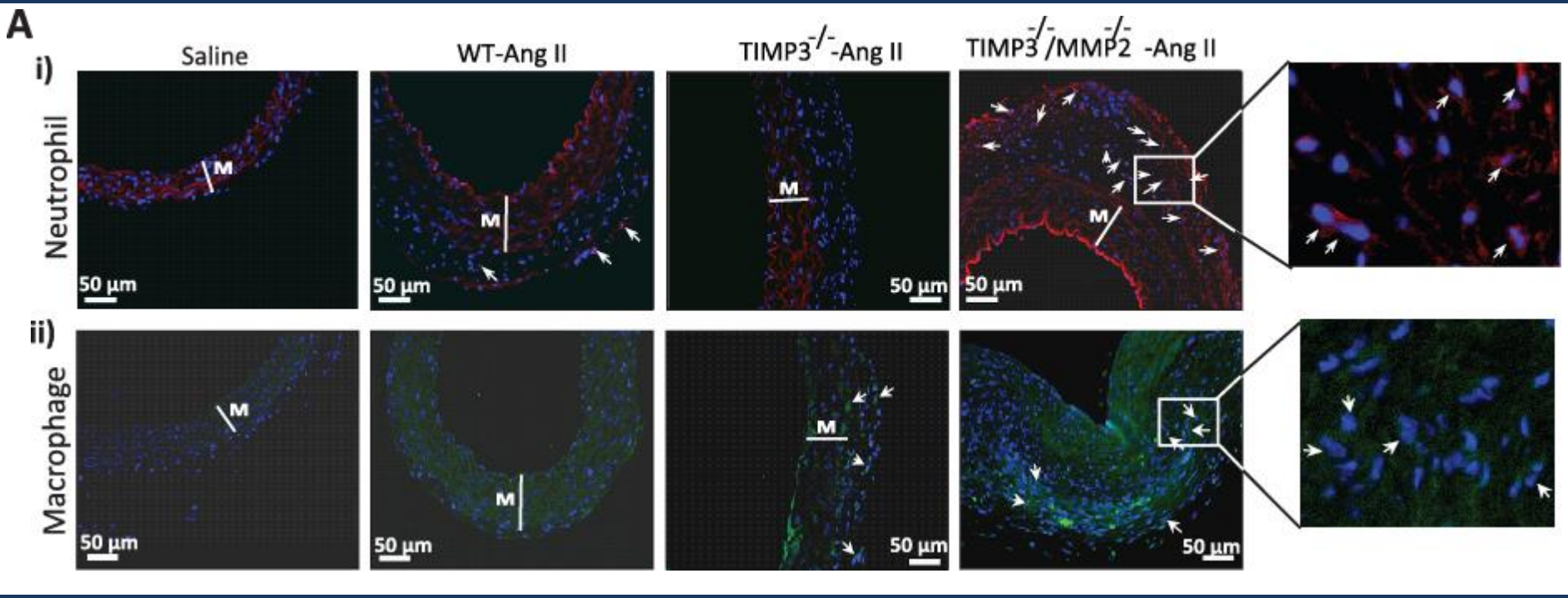
MMP2 deletion in the background of TIMP3-deficiency exacerbated the AAA outcomes

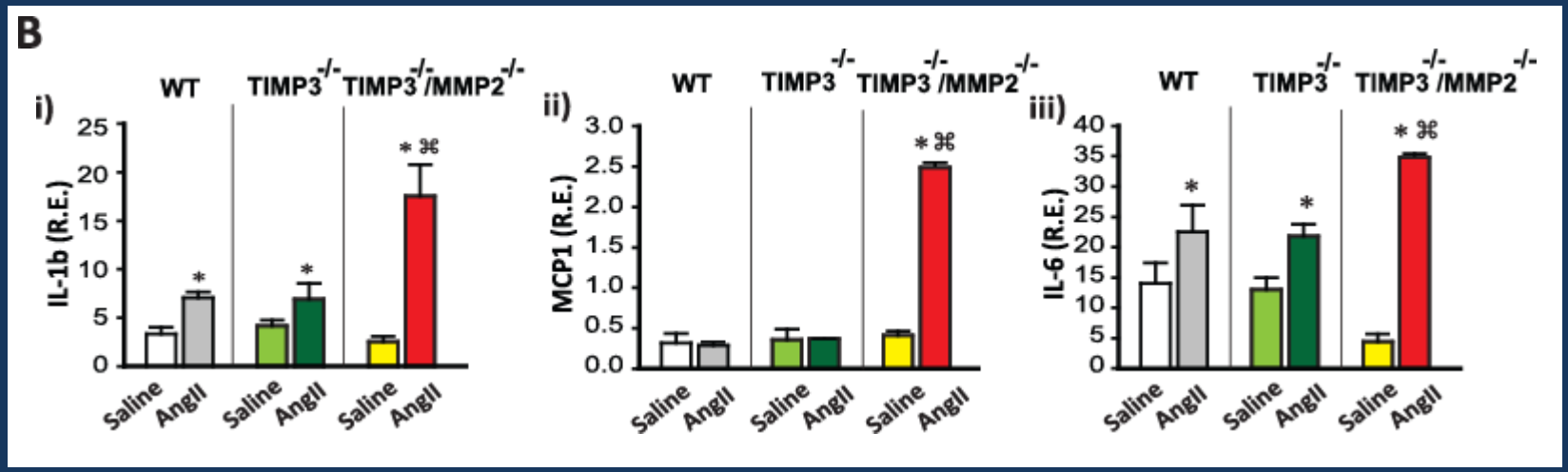




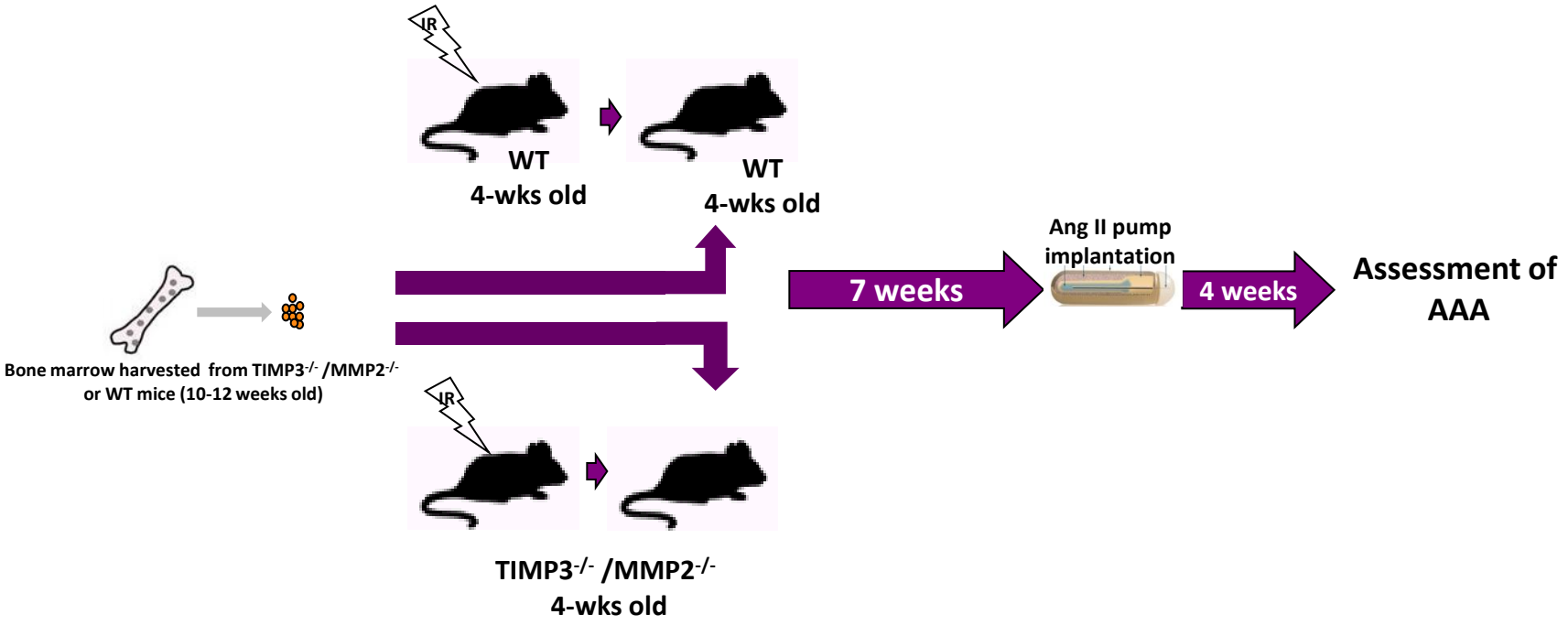
Saline | WT-Ang II | TIMP3$^{-/-}$-Ang II | TIMP3$^{-/-}$/MMP2$^{-/-}$-Ang II

Elevated inflammation in TIMP3$^{-/-}$/MMP2$^{-/-}$ abdominal aortas (4 wks of Ang II infusion)

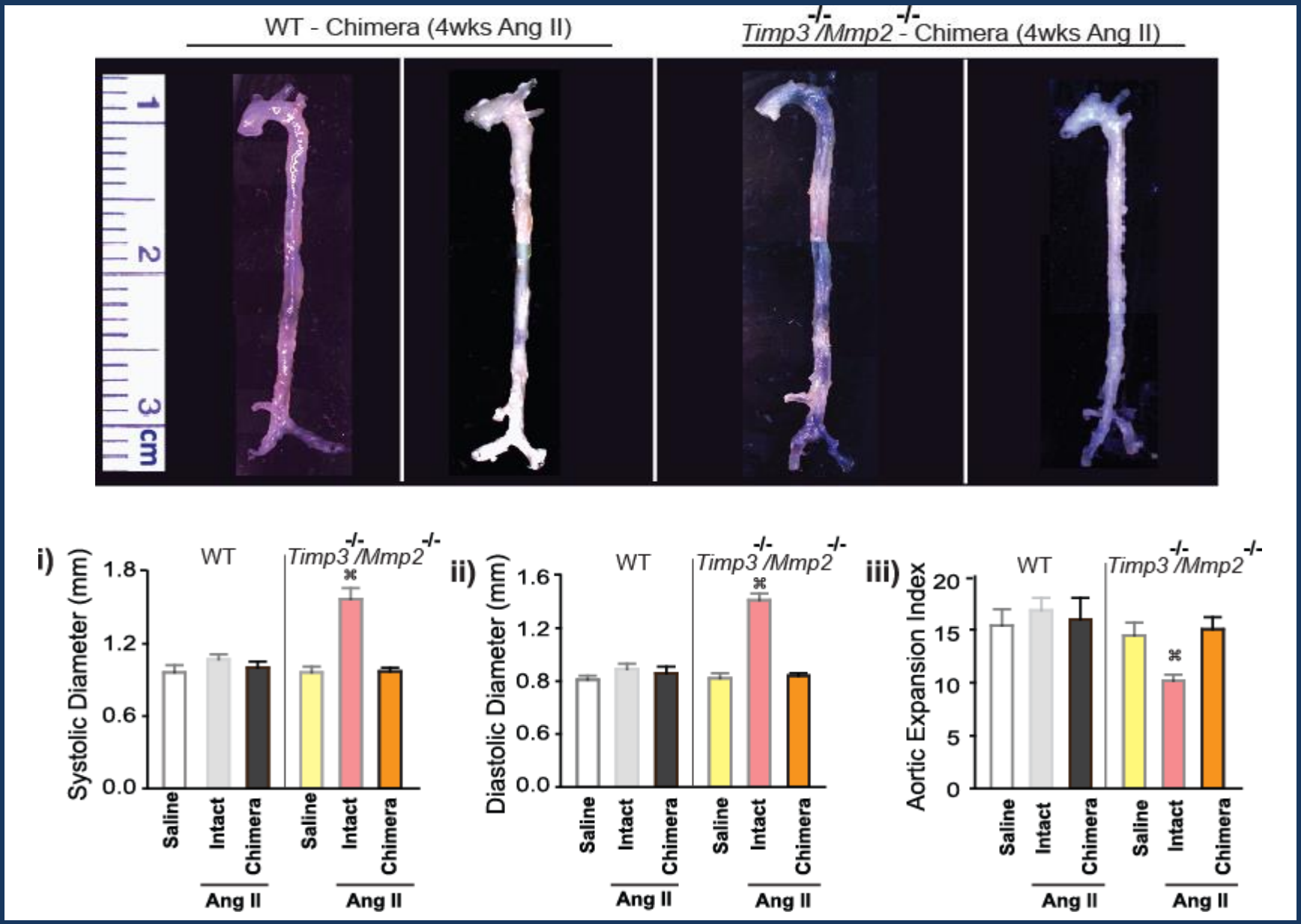




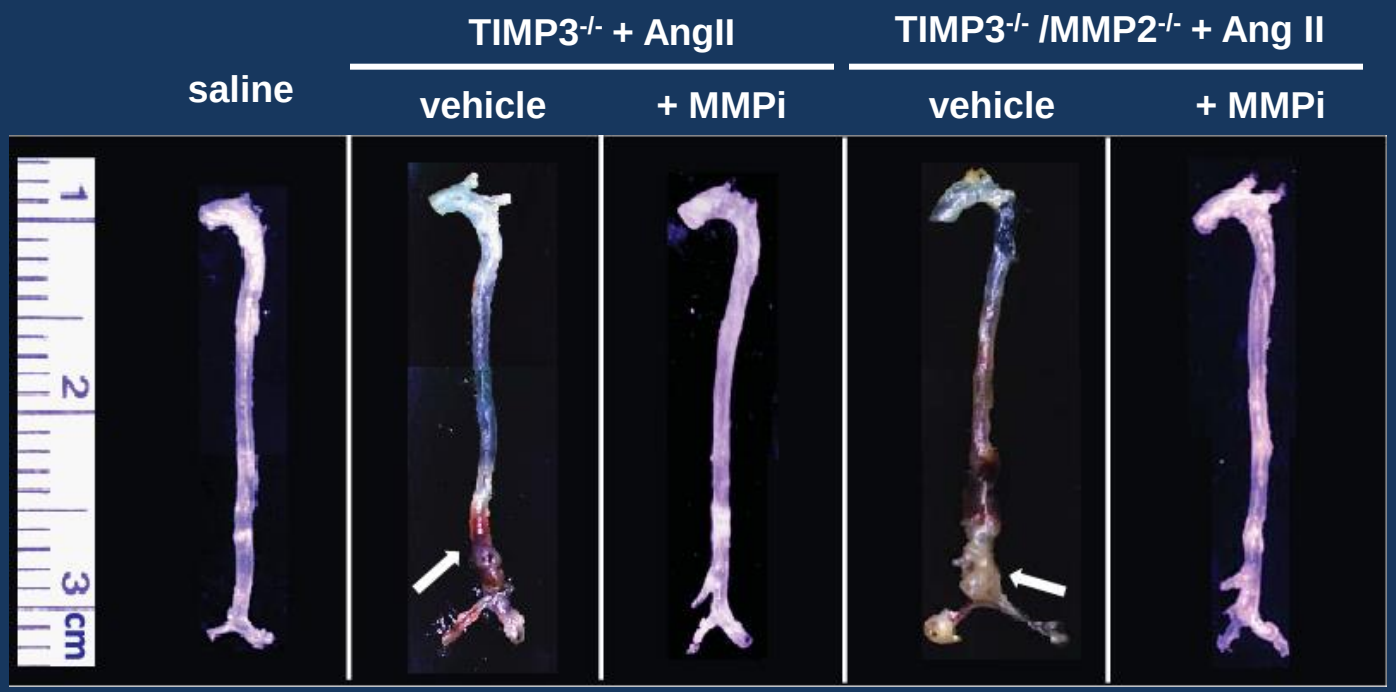
Bone marrow swap between WT and TIMP3$^{-/-}$ /MMP2$^{-/-}$ mice

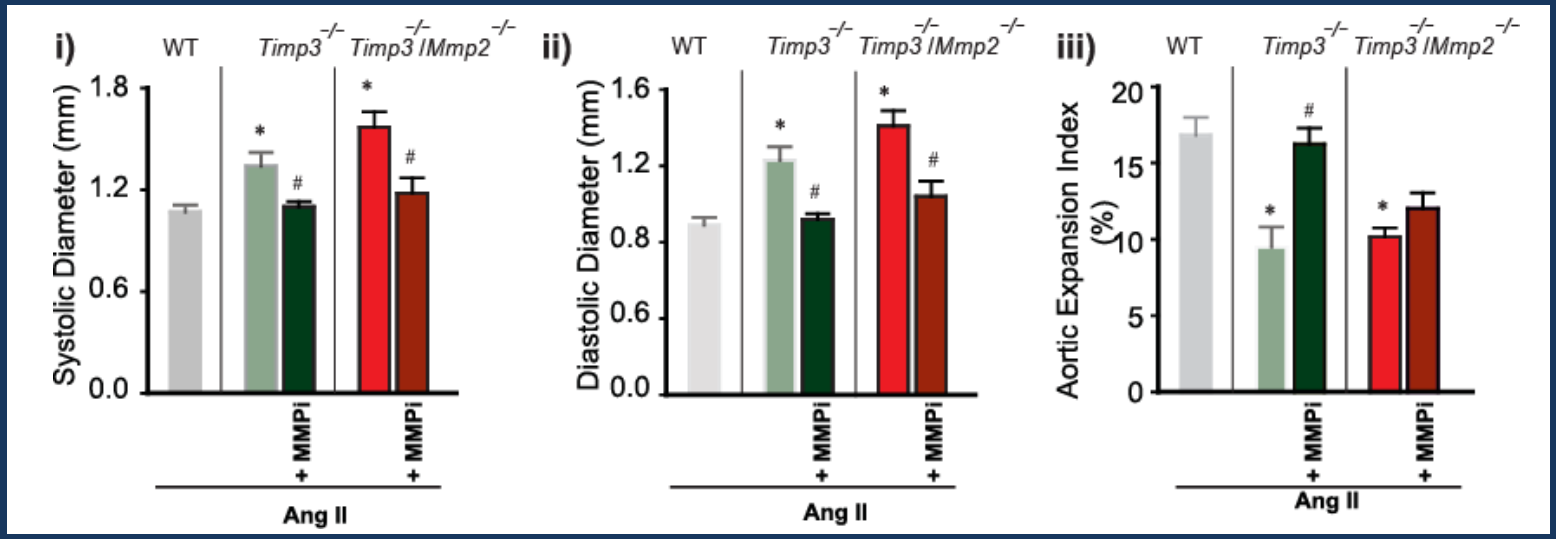


Reconstitution of WT bone marrow prevented AAA in TIMP3$^{-/-}$ /MMP2$^{-/-}$ mice



Broad-spectrum MMP inhibition prevented AAA





MMPi: 25mg/Kg/day of PD166739 by daily gavage.

SUMMARY

- **TIMP3-deficiency enhances susceptibility to AAA.**

- **Despite early elevation in MMP2, deletion of this MMP in TIMP3$^{-/-}$ mice exacerbated the AAA, due to heightened inflammation.**

- **Broad-spectrum MMP inhibition prevented the Ang II-induced AAA in both, TIMP3$^{-/-}$ and TIMP3$^{-/-}$ /MMP2$^{-/-}$ mice.**

- **TIMP3 is required for optimal vascular remodeling in response to Ang II.**

- **The elevated TIMP3 levels (in the aorta) is an adaptive mechanism towards optimal vascular remodeling.**

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Review

Current status of medical management for abdominal aortic aneurysm

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[b] School of Surgery, University of Western Australia, Perth, Australia

Table 4
Studies assessing the association of statin prescription with small AAA expansion.

Study	Year	Number of patients	Average follow-up	Adjusted analysis	Analysis methods	Associations with statin prescription
Thompson et al. [83]	2010	1231	3.2	Yes	Hiearchical	None
Sweeting et al. [84]	2010	1701	1.9	Yes	Linear regression	None
Ferguson et al. [85]	2010	652	5.0	Yes	Logistic regression	None
Karlsson et al. [86]	2009	213	NS	No	Linear regression	Reduced growth
Mosorin et al. [87]	2008	121	3.6	Yes	Linear regression	Reduced need for AAA repair
Schlosser et al. [88]	2008	147	3.3	Yes	Linear regression	Reduced growth
Schouten et al. [89]	2006	150	3.1	Yes	Linear regression	Reduced growth
Sukhija et al. [90]	2006	130	2.0	No	NS	Reduced growth

NS = not stated; follow-up given in years.

Table 6
Studies assessing the association of ARB and ACE inhibitor prescription with outcomes of small AAAs.

Study	Year	Number of patients	Follow-up	ARB/ACEI	Associations with prescription
Thompson et al. [83]	2010	1269	3.2	ARB	Reduced growth
Sweeting et al. [84]	2010	1701	1.9	ARB	No association
Ferguson et al. [85]	2010	652	5.0	ARB	No association
Hackam et al. [107]	2006	15,326	CC	ARB	No association
Thompson et al. [83]	2010	1269	3.2	ACEI	No association
Sweeting et al. [84]	2010	1701	1.9	ACEI	Increased growth
Ferguson et al. [85]	2010	652	5.0	ACEI	No association
Hackam et al. [107]	2006	15,326	CC	ACEI	Reduced rupture

ARB = angiotensin receptor blocker; ACEI = angiotensin converting enzyme inhibitor; CC = case-control study; follow-up given in years.

Doxycycline has been found to inhibit aneurysm development and progression in at least 14 separate studies

Two large randomized trials examine the efficacy of Doxycycline in patients with small AAA. Trials expected to be completed in 2014:

Curci J. Medical therapy of aortic aneurysm. Presented at The Atheroscelrosis, Thrombosis and Vascular Biology Conference. San Francisco, April 2010, available at http://www.americanheart.org/presenter.jhtml?identifier=3073618.

Golledge J, Lindeman J. Potential strategies for medical management of aortic aneurysm. In: Presented at the 2nd International Meeting on Aortic Diseases in Leige. 2010.

[19] Sheth RA, Maricevich M, Mahmood U. In vivo optical molecular imaging of matrix metalloproteinase activity in abdominal aortic aneurysms correlates with treatment effects on growth rate. Atherosclerosis 2010;212:181–7.
[20] Yang HH, Kim JM, Chum E, van Breemen C, Chung AW. Effectiveness of combination of losartan potassium and doxycycline versus single-drug treatments in the secondary prevention of thoracic aortic aneurysm in Marfan syndrome. J Thorac Cardiovasc Surg 2010;140:305–12.
[21] Turner GH, Olzinski AR, Bernard RE, et al. In vivo serial assessment of aortic aneurysm formation in apolipoprotein E-deficient mice via MRI. Circ Cardiovasc Imaging 2008;1:220–6.
[22] Tedesco MM, Terashima M, Blankenberg FG, et al. Analysis of in situ and ex vivo vascular endothelial growth factor receptor expression during experimental aortic aneurysm progression. Arterioscler Thromb Vasc Biol 2009;29:1452–7.
[23] Chung AW, Yang HH, Radomski MW, van Breemen C. Long-term doxycycline is more effective than atenolol to prevent thoracic aortic aneurysm in marfan syndrome through the inhibition of matrix metalloproteinase-2 and -9. Circ Res 2008;102:e73–85.
[24] Xiong W, Knispel RA, Dietz HC, Ramirez F, Baxter BT. Doxycycline delays aneurysm rupture in a mouse model of Marfan syndrome. J Vasc Surg 2008;47:166–72.
[25] Vinh A, Gaspari TA, Liu HB, et al. A novel histone deacetylase inhibitor reduces abdominal aortic aneurysm formation in angiotensin II-infused apolipoprotein E-deficient mice. J Vasc Res 2008;45:143–52.
[26] Bartoli MA, Parodi FE, Chu J, et al. Localized administration of doxycycline suppresses aortic dilatation in an experimental mouse model of abdominal aortic aneurysm. Ann Vasc Surg 2006;20:228–36.
[27] Manning MW, Cassis LA, Daugherty A. Differential effects of doxycycline, a broad-spectrum matrix metalloproteinase inhibitor, on angiotensin II-induced atherosclerosis and abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 2003;23:483–8.
[28] Prall AK, Longo GM, Mayhan WG, et al. Doxycycline in patients with abdominal aortic aneurysms and in mice: comparison of serum levels and effect on aneurysm growth in mice. J Vasc Surg 2002;35:923–9.
[29] Pyo R, Lee JK, Shipley JM, et al. Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. J Clin Invest 2000;105:1641–9.
[30] Sho E, Chu J, Sho M, et al. Continuous periaortic infusion improves doxycycline efficacy in experimental aortic aneurysms. J Vasc Surg 2004;39:1312–21.
[31] Curci JA, Petrinec D, Liao S, Golub LM, Thompson RW. Pharmacologic suppression of experimental abdominal aortic aneurysms: a comparison of doxycycline and four chemically modified tetracyclines. J Vasc Surg 2007;27:461–9.
[32] Petrinec D, Liao S, Holmes DR, et al. Doxycycline inhibition of aneurysmal degeneration in an elastase-induced rat model of abdominal aortic aneurysm: preservation of aortic elastin associated with suppressed production of 92 kD gelatinase. J Vasc Surg 1996;23:336–46.

CONCLUSION

Therapies aiming to preserve aortic ECM integrity offer an effective approach in treating/limiting growth of AAA .

Lab members

- **Dr. Ratnadeep Basu (PhD Candidate)**
- Abhijit Takawale (PhD Candidate)
- Ji-Won Lee (MSc Candidate)
- Dr. Dong Fan (Post-doctoral Fellow)
- Dr. Sue Wang (Lab technician/Manager/surgeon)

Lab Alumni

Vijay Kandalam (PhD)- 2007-2012
Ahmed Awad (MSc) – 2008-2010

Collaborators:

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  - Dr. Jude Morton
- Troy Baldwin (MMI)
- Dr. Gavin Oudit
  - Subhash Das

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Alberta Innovates Health Solutions

Collaborators:

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  - Dr. Jude Morton
- Troy Baldwin (MMI)
- Dr. Gavin Oudit
  - Subhash Das

CVRC core:

- Donna Becker (vascular ultrasound)

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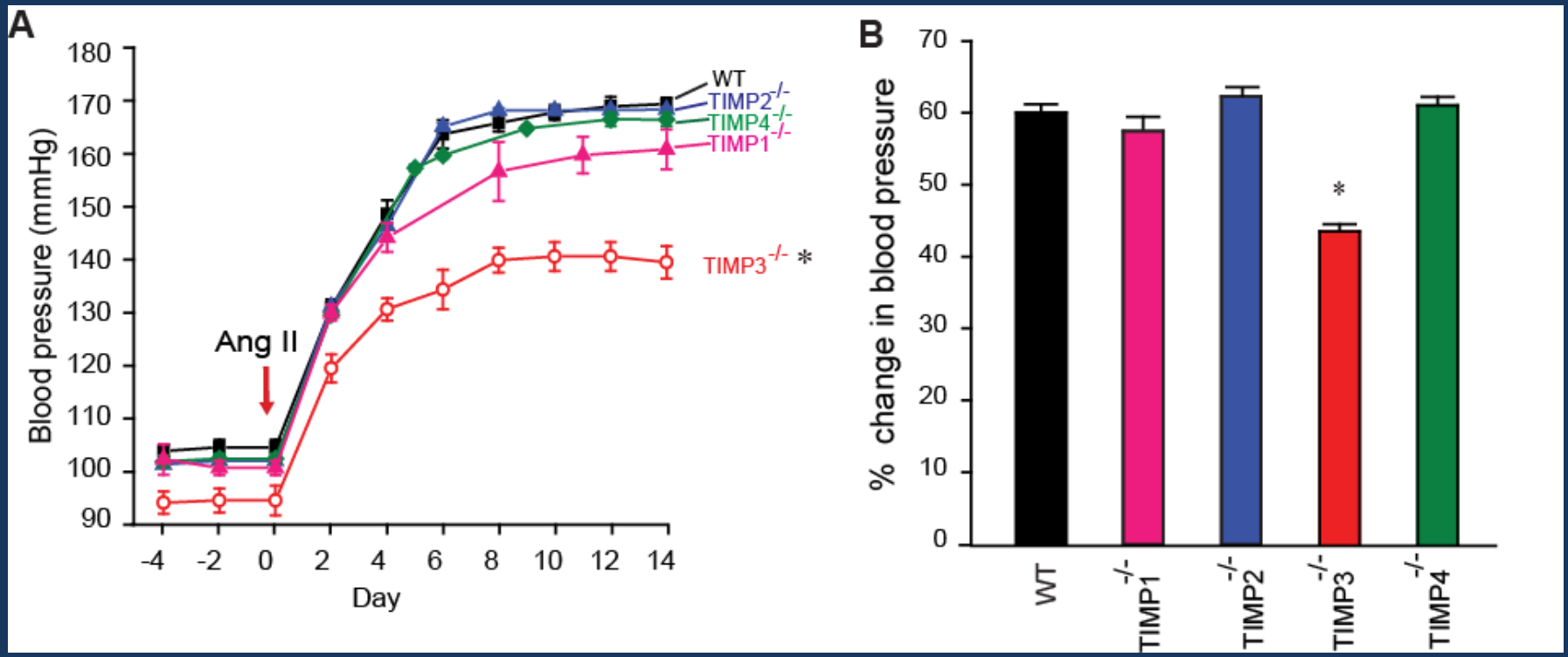
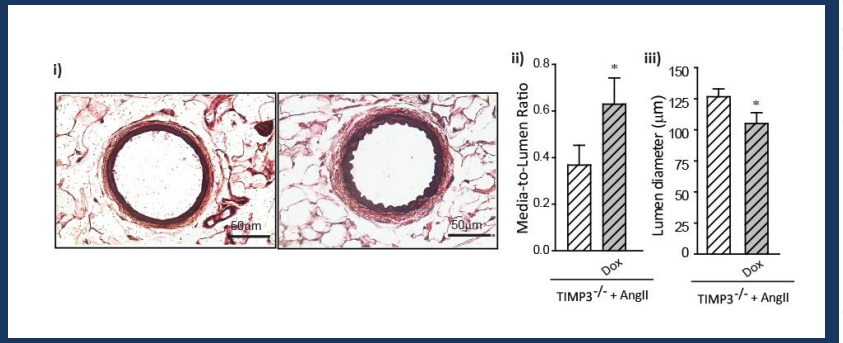
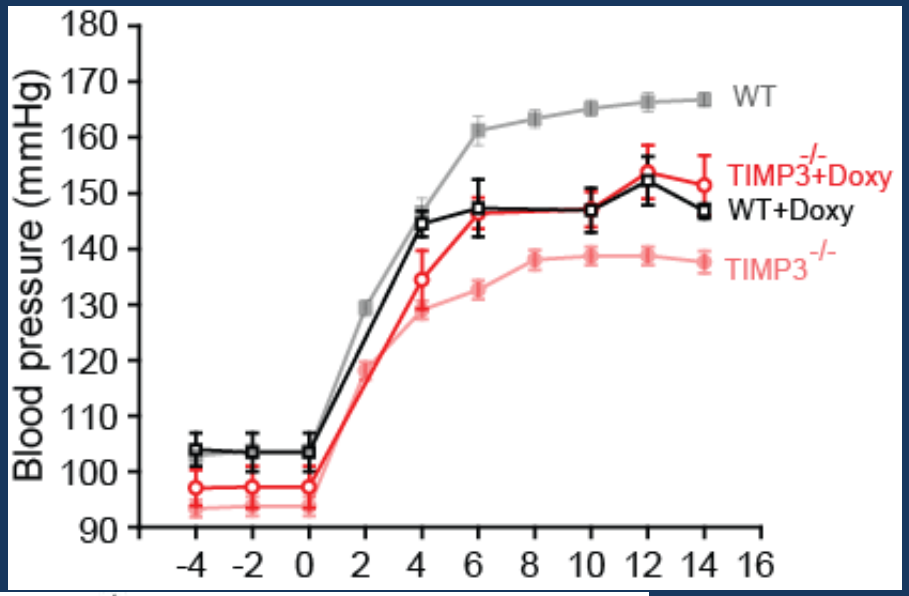
HEART & STROKE FOUNDATION

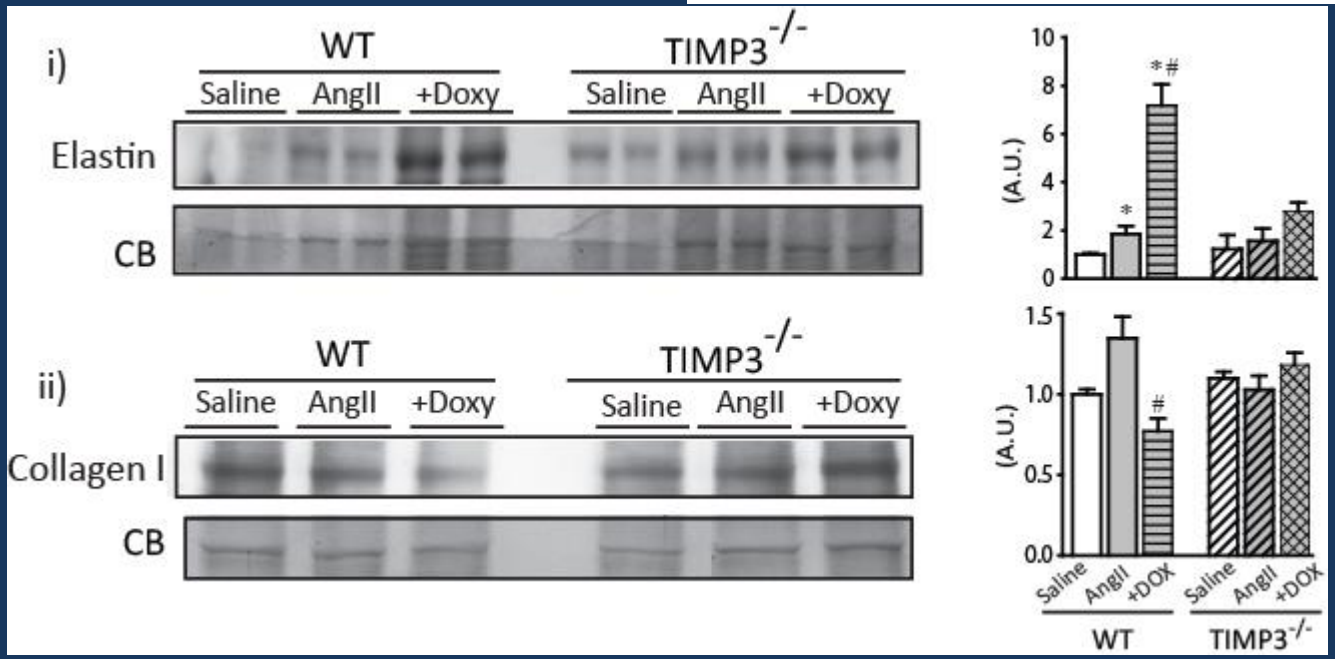
Alberta Innovates Health Solutions


A
Blood pressure (mmHg)
180
170
160
150
140
130
120
110
100
90
-4
-2
0
2
4
6
8
10
12
14
Day
Ang II
WT
TIMP2-/-
TIMP4-/-
TIMP1-/-
TIMP3-/- *
B
% change in blood pressure
70
60
50
40
30
20
10
0
*
WT
-/- TIMP1
-/- TIMP2
-/- TIMP3
-/- TIMP4

Treatment with doxycylclin prevented the adverse remodeling in the TIMP3$^{-/-}$-Ang II small arteries, but altered elastin and collagen protein levels differently.

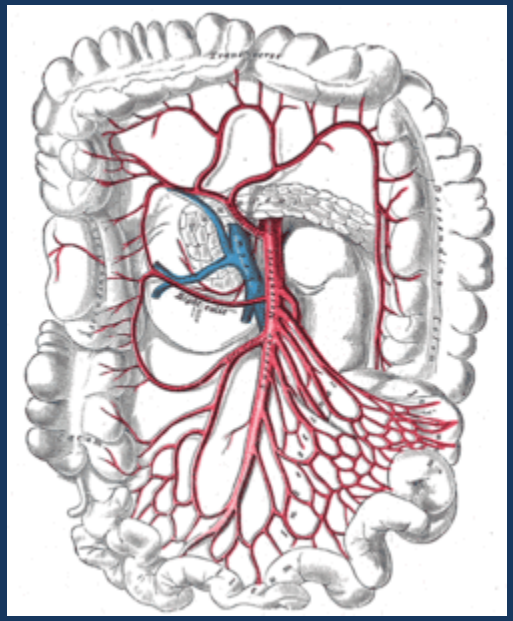






HYPERTENSION

A number of factors can cause hypertension, endothelial dysfunction, SMC, ECM ... I will talk ab

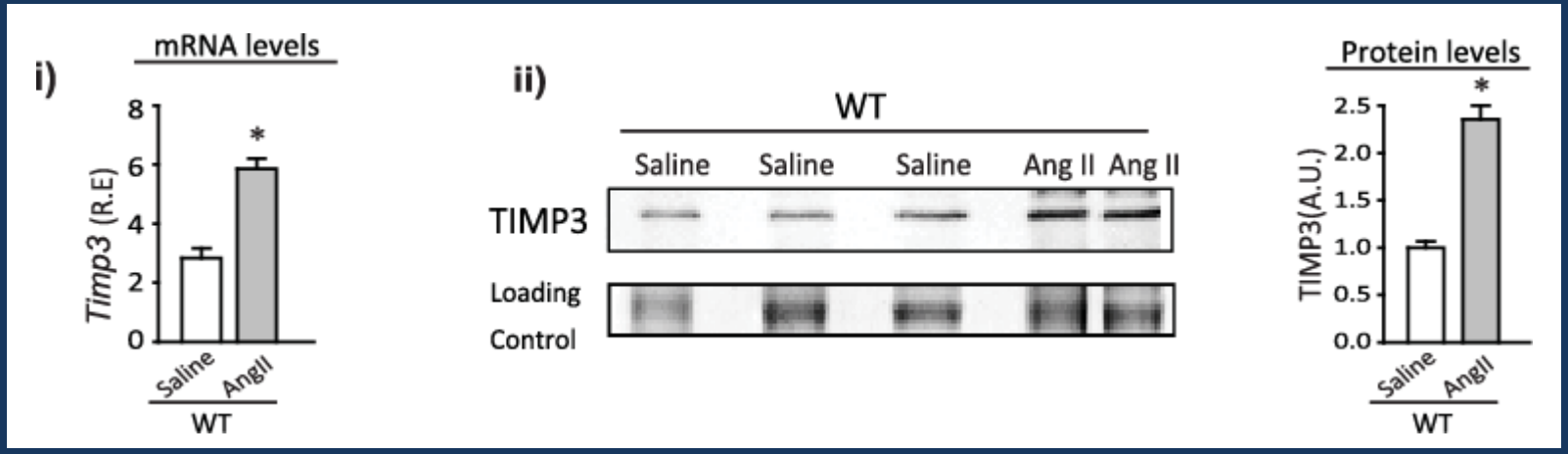


TIMP3 and aneurysm

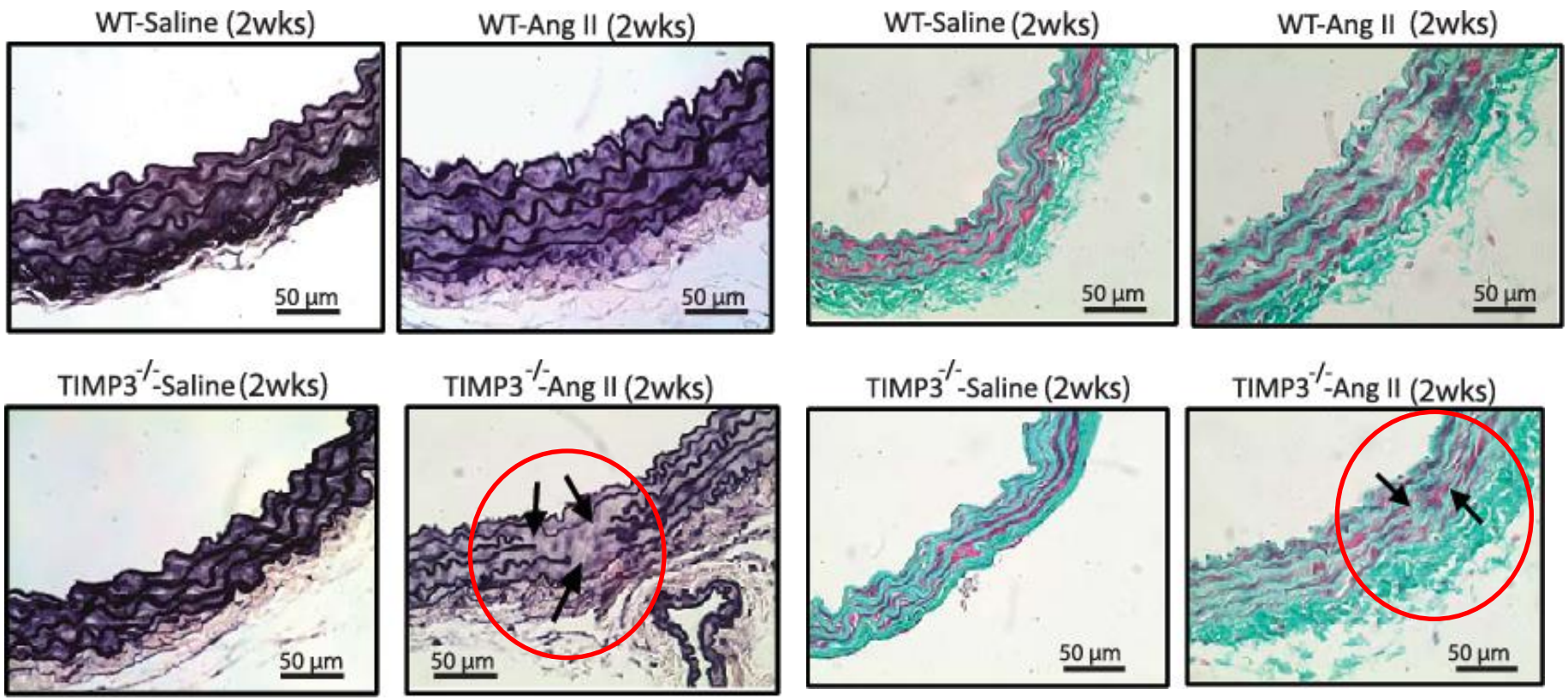
• TIMP3 mRNA levels are increased in dilated aorta from patients with aortic aneurysm whereas other TIMPs were not altered (Tsarouhas, K et al. *Thromb Res* **2010)**.

• A significant interaction between polymorphism of TIMP3, but not TIMP1 or TIMP2, occurs in patients with AAA and with a positive family history of AAA (Ogata, T. et al. *J Vasc Surg.* 2005).

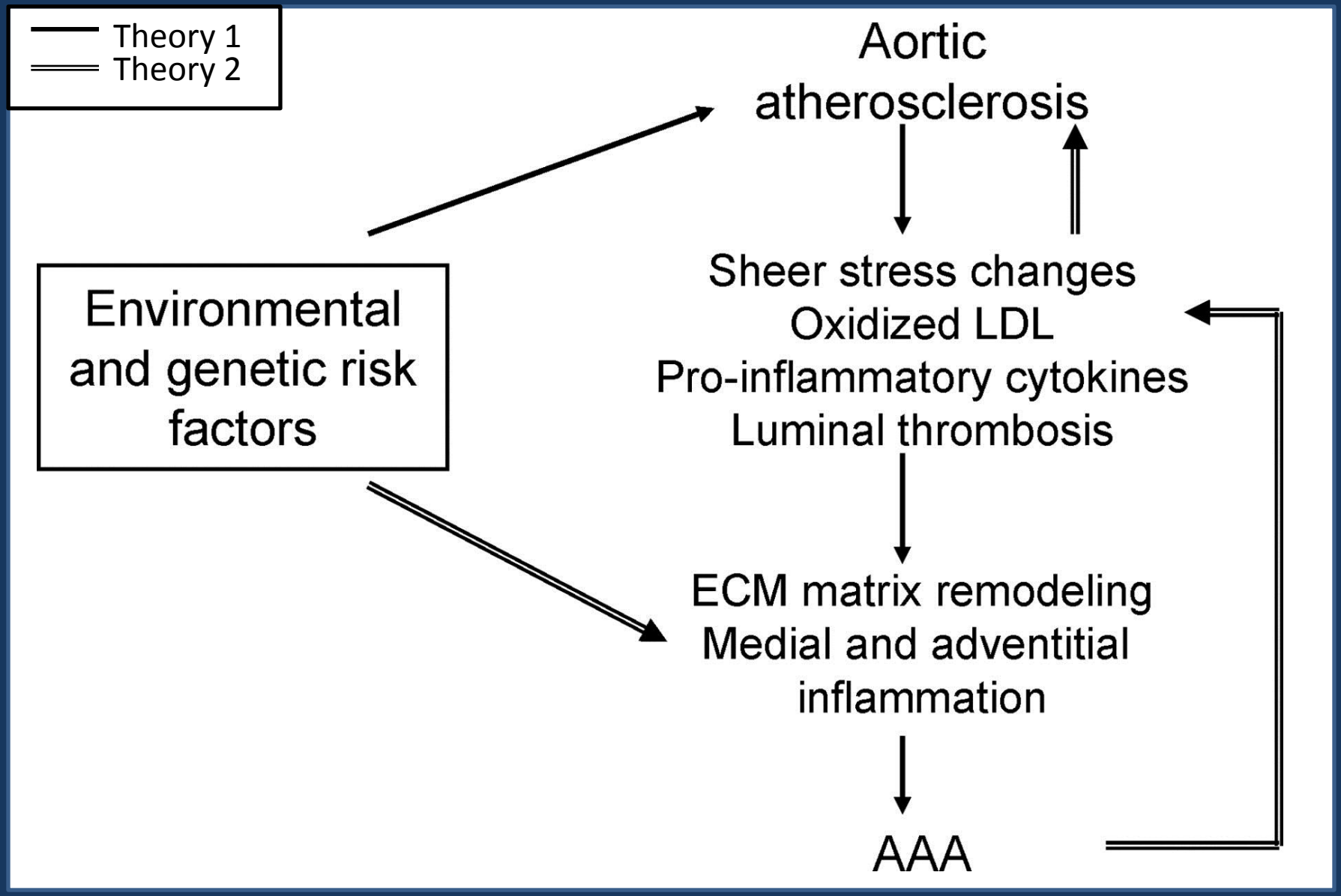
• **We found elevated TIMP3 levels in the abdominal aorta following Ang II infusion.**



After **2 weeks** of Ang II infusion, elastin and collagen fibre interruption and disarray detected in TIMP3$^{-/-}$-Ang II aorta (but no aortic aneurysm).

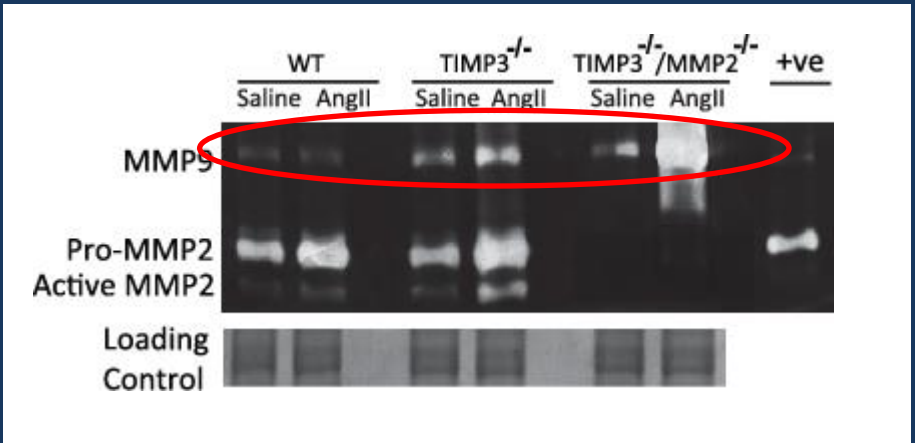


Causes of abdominal aortic aneurym



Golledge J , and Norman P E *Arterioscler Thromb Vasc Biol* 2010;30:1075-1077
(*Editorial on the Tromsø study*)

MMP9 levels are elevated in TIMP3$^{-/-}$/MMP2$^{-/-}$ abdominal aortas (4 wks of Ang II infusion)



Thanks' for your kind attention!!!!!!

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