

Surgical Management in Vascular Ehlers-Danlos Syndrome



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Vascular Genetics Symposium

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Disclosures

Advisory boards

- The Ehlers-Danlos Society
- Marfan Foundation





Surgical Management in Vascular Ehlers-Danlos Syndrome

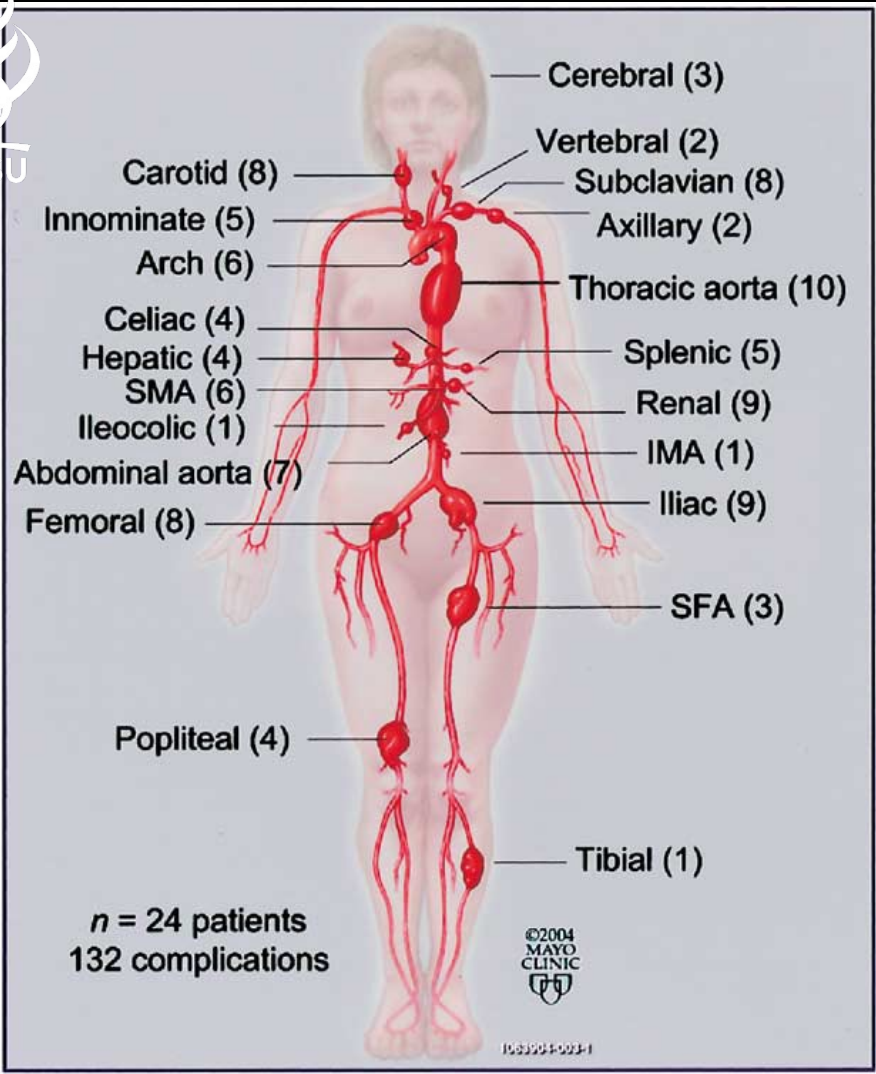
- We do not have VEDS specific guidelines for aneurysms but can extrapolate from current aneurysms/dissections recommendations
- General principles of open surgical techniques
- The role of endovascular approaches
- Knowing (or suspecting) the diagnosis in the preoperative setting improves the outcomes

1	Classical EDS	cEDS	AD	Major: <i>COL5A1</i> , <i>COL5A1</i> Rare: <i>COL1A1</i> c.934C>T, p.(Arg312Cys)	Type V collagen Type I collagen
2	Classical-like EDS	clEDS	AR	<i>TNXB</i>	Tenascin XB
3	Cardiac-valvular	cvEDS	AR	<i>COL1A2</i> (biallelic mutations that lead to <i>COL1A2</i> NMD and absence of pro $\alpha 2(I)$ collagen chains)	Type I collagen
4	Vascular EDS	vEDS	AD	Major: <i>COL3A1</i> Rare: <i>COL1A1</i> c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3227C>T, p.(Arg1093Cys)	Type III collagen Type I collagen
5	Hypermobile EDS	hEDS	AD	Unknown	Unknown
6	Arthrochalasia EDS	aEDS	AD	<i>COL1A1</i> , <i>COL1A2</i>	Type I collagen
7	Dermatosparaxis EDS	dEDS	AR	<i>ADAMTS2</i>	ADAMTS-2
8	Kyphoscoliotic EDS	kEDS	AR	<i>PLOD1</i> <i>FKBP14</i>	LH1 FKBP22
9	Brittle Cornea syndrome	BCS	AR	<i>ZNF469</i> <i>PRDM5</i>	ZNF469 PRDM5
10	Spondylodysplastic EDS	spEDS	AR	<i>B4GALT7</i> <i>B3GALT6</i> <i>SLC39A13</i>	$\beta 4$ GalT7 $\beta 3$ GalT6 ZIP13
11	Musculocontractural EDS	mcEDS	AR	<i>CHST14</i> <i>DSE</i>	D4ST1 DSE
12	Myopathic EDS	mEDS	AD or AR	<i>COL12A1</i>	Type XII collagen
13	Periodontal EDS	pEDS	AD	<i>C1R</i> <i>C1S</i>	C1r C1s

**Vascular EDS
(VEDS) is
5%
of all Ehlers-
Danlos
syndromes**

13 subtypes of EDS

EDS: Connective tissue disorders with a triad of joint hypermobility, skin hyperextensibility, and tissue fragility



Cerebrovascular 33%

Ascending Thoracic

Aorta 5%

Descending
Thoracic Aorta 7%

Hepatic 14%

Splenic 21%

Celiac 19%

LRA 12%

RRA 11%

SMA 7%

IMA 2%

Abdominal Aorta
12%

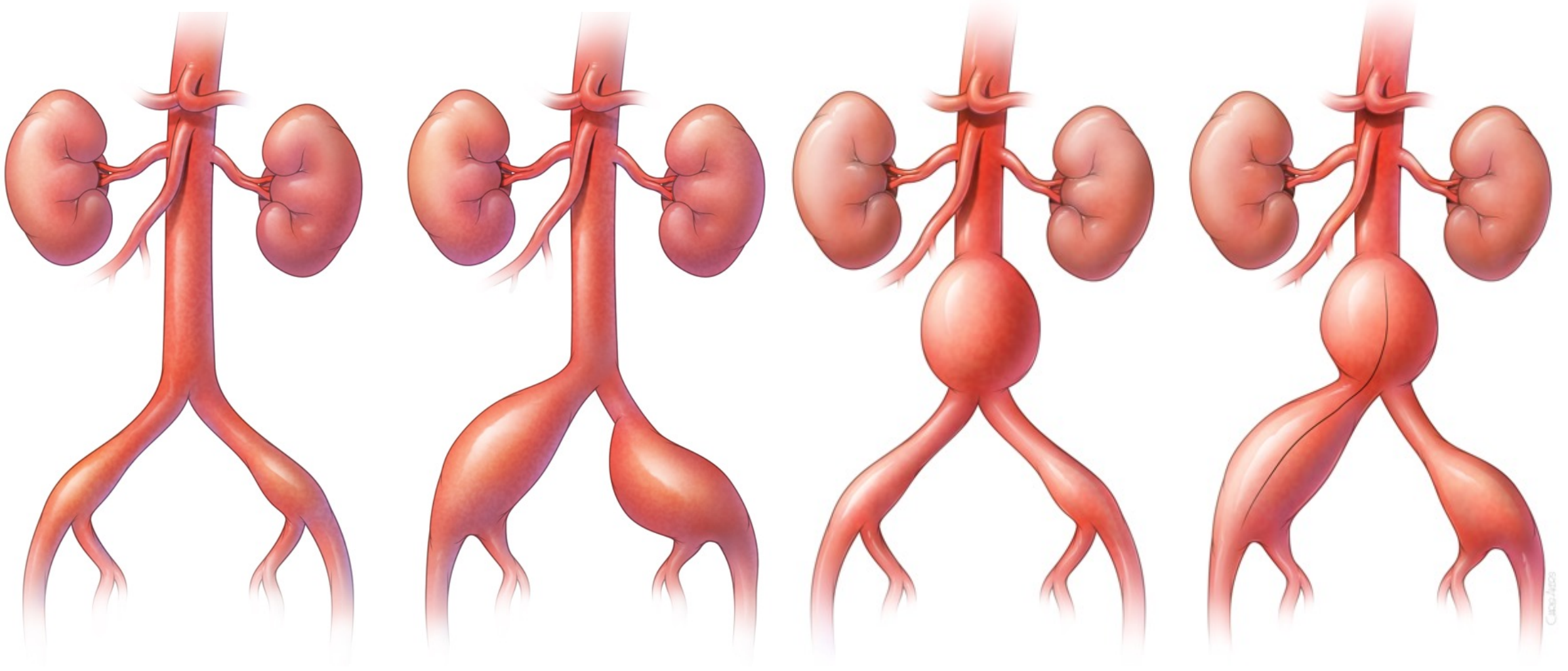
Iliac arteries 40%

139 aortic/arterial
pathologies in 53
individuals (51% Male,
median age 33 years)





VEDS has a unique morphology of the infrarenal abdominal aorta and common iliac arteries (Bell-Bottom iliacs)



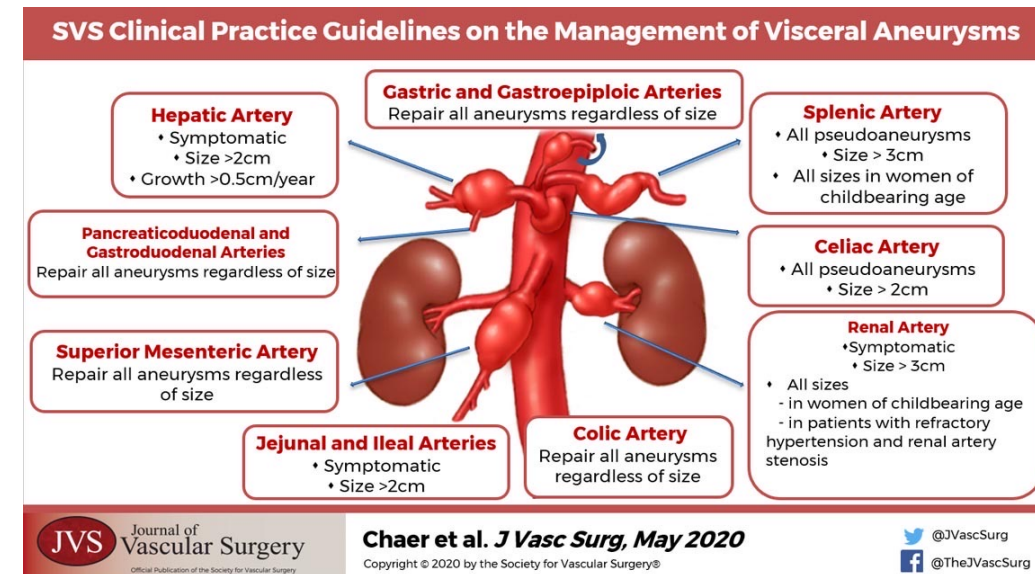
Bell Bottom Iliacs



42F, c.970G>A p.Gly324Ser

Aortic and arterial repair in VEDS is feasible

- Most aneurysms and dissections can be managed non-operatively
- Elective repairs have better outcomes than repairs in the emergency setting
- Knowing the diagnosis improves the outcomes
- Yes, there are risks but the outcomes are better when the repair is performed in an elective setting at a well supported setting
 - *Currently we do not have VEDS specific guidelines but can extrapolate from current aneurysms/dissections recommendations*
- When intervention is required for an enlarging arterial aneurysm or rupture, embolization and stenting are well tolerated



Vascular Surgery Principles

- Repair is indicated by size of aneurysm or complications of dissection
- Risk of surgery <<<<< Risk of aneurysm rupture or complications of dissection
- Management approach (medical and surgical) varies by type and location of the aortic and arterial pathology

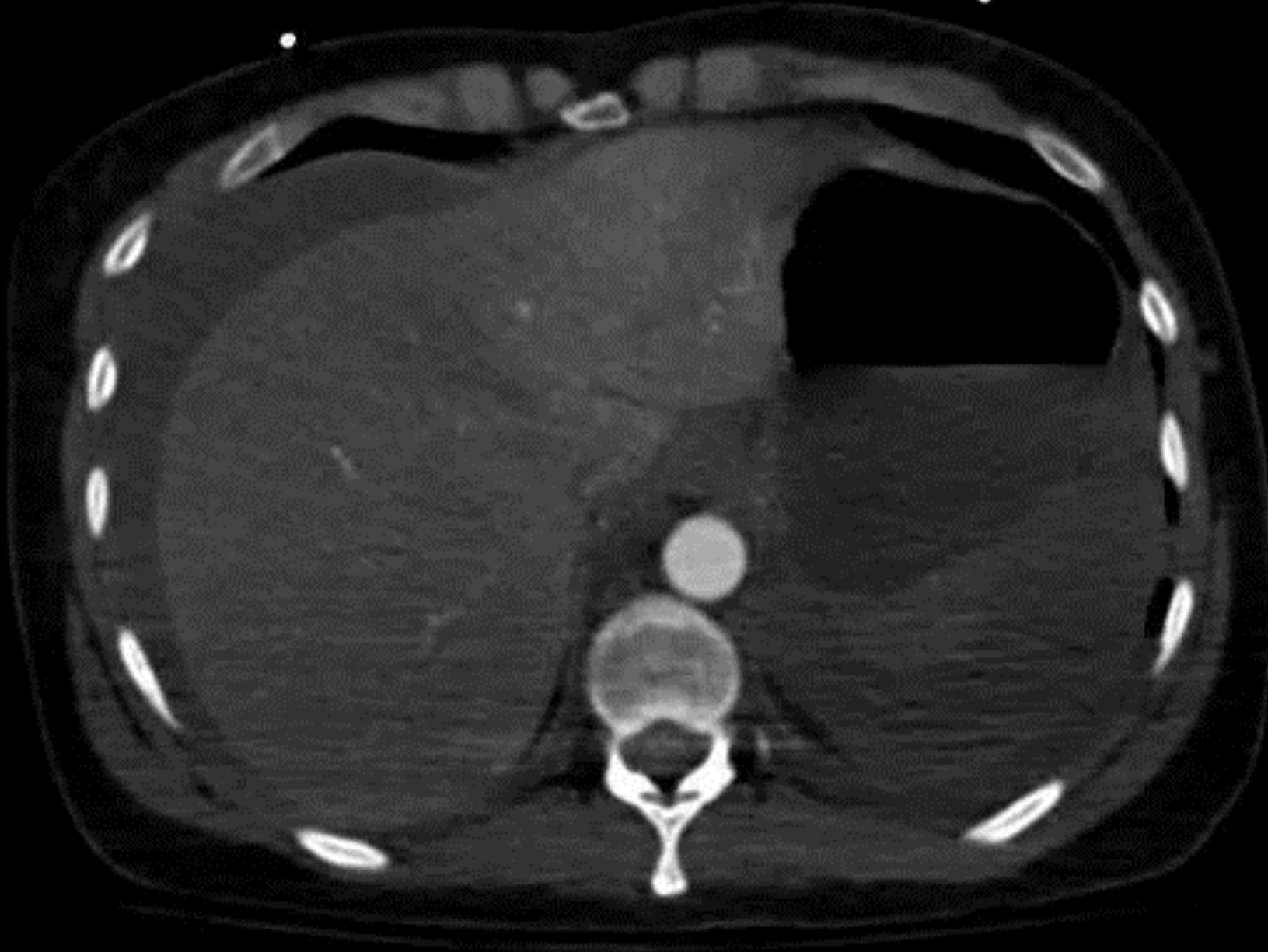




Case

- 38 y/o F with VEDS (*COL3A1* c.718G>C, p.Gly240Arg) diagnosed at age 15 y/o
- Family History
 - Father had VEDS
 - Died at 49 from descending thoracic aortic aneurysm rupture
 - Brother has VEDS
 - Alive, age 37 with history of aortic dissection and colonic perforation

R. renal infarct and hemoperitoneum of unclear source





Carotid Cavernous Fistula at age 32



Aorto-Iliac Aneurysm Progression



age 28



age 31



age 33



age 34

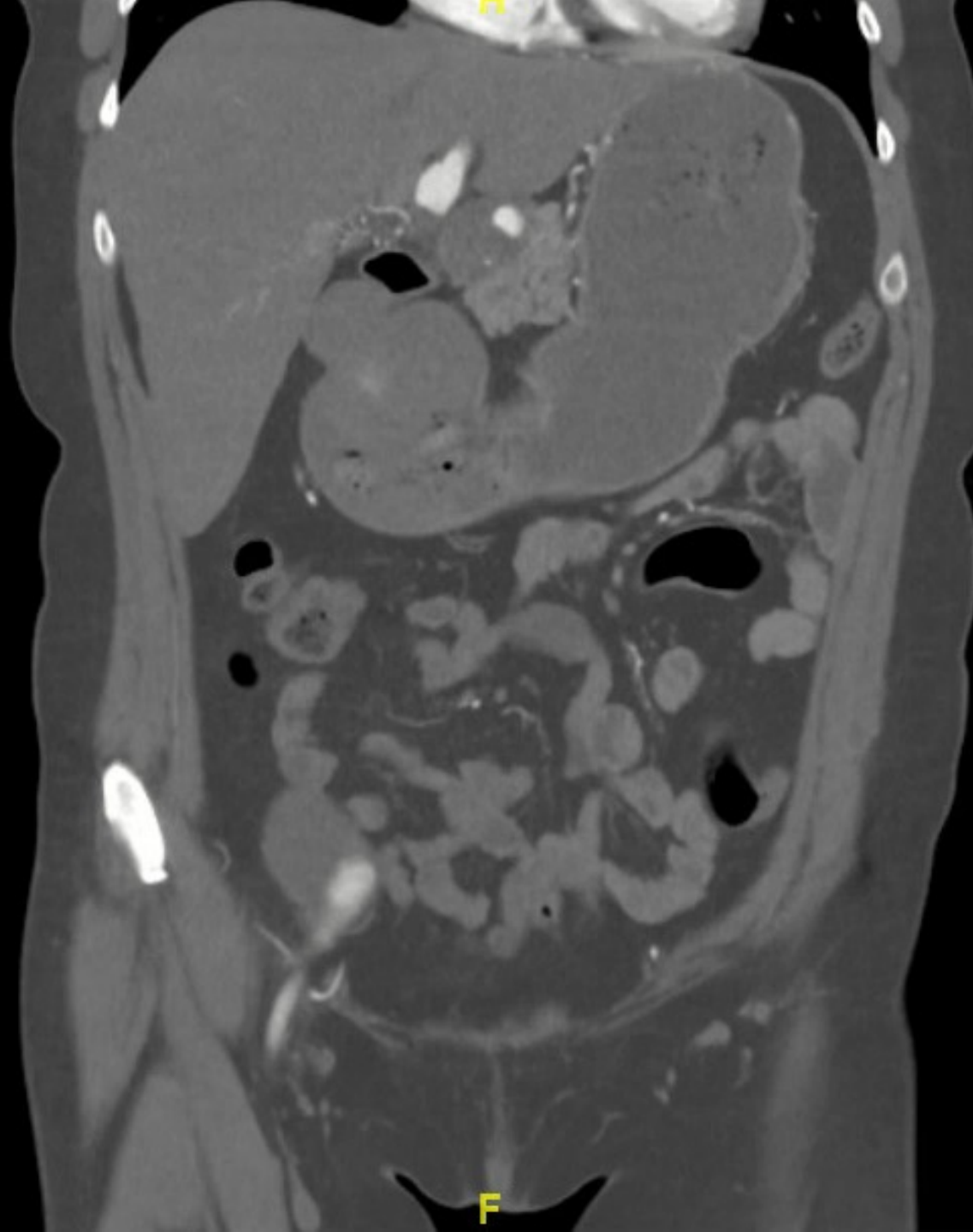


age 35



age 36

COL3A1: c.718G>C, p.Gly240Arg, Gly73Arg



Right External Iliac Mid

55

Hz
3Hz
Hz

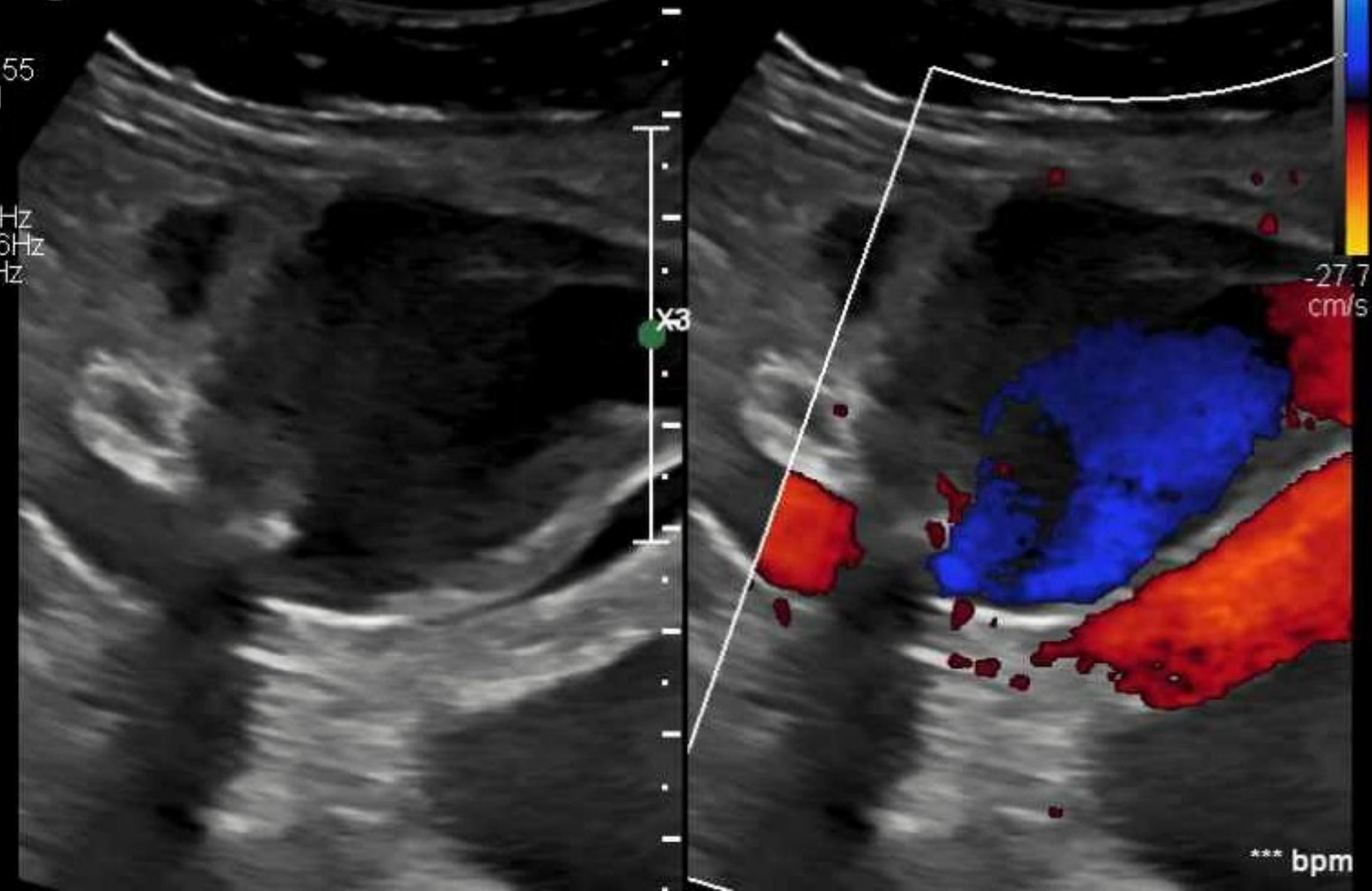
x3

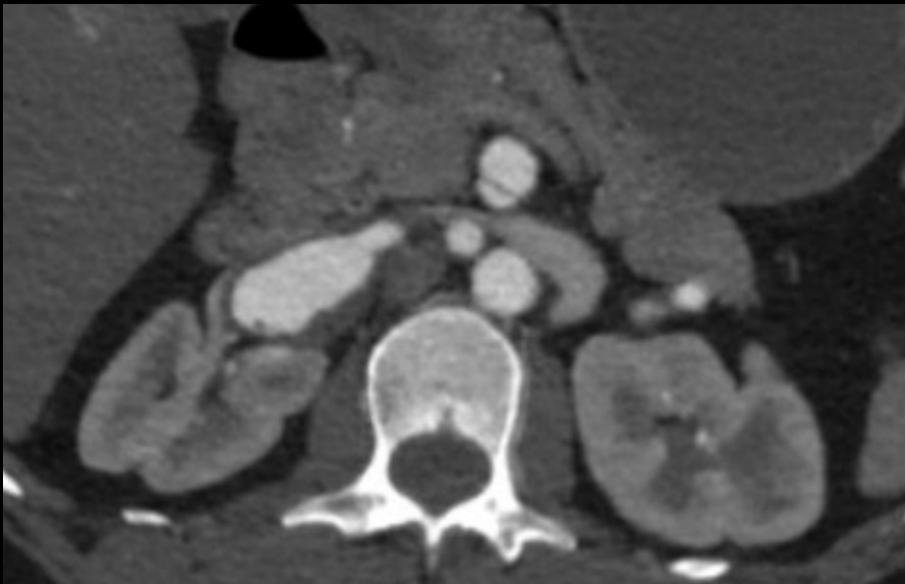
P

M7
+27.7

-27.7
cm/s

*** bpm







Medical management principles

Risk factor modification

- Smoking cessation
- Assessment and treatment for hypertension
- Moderate aerobic exercise

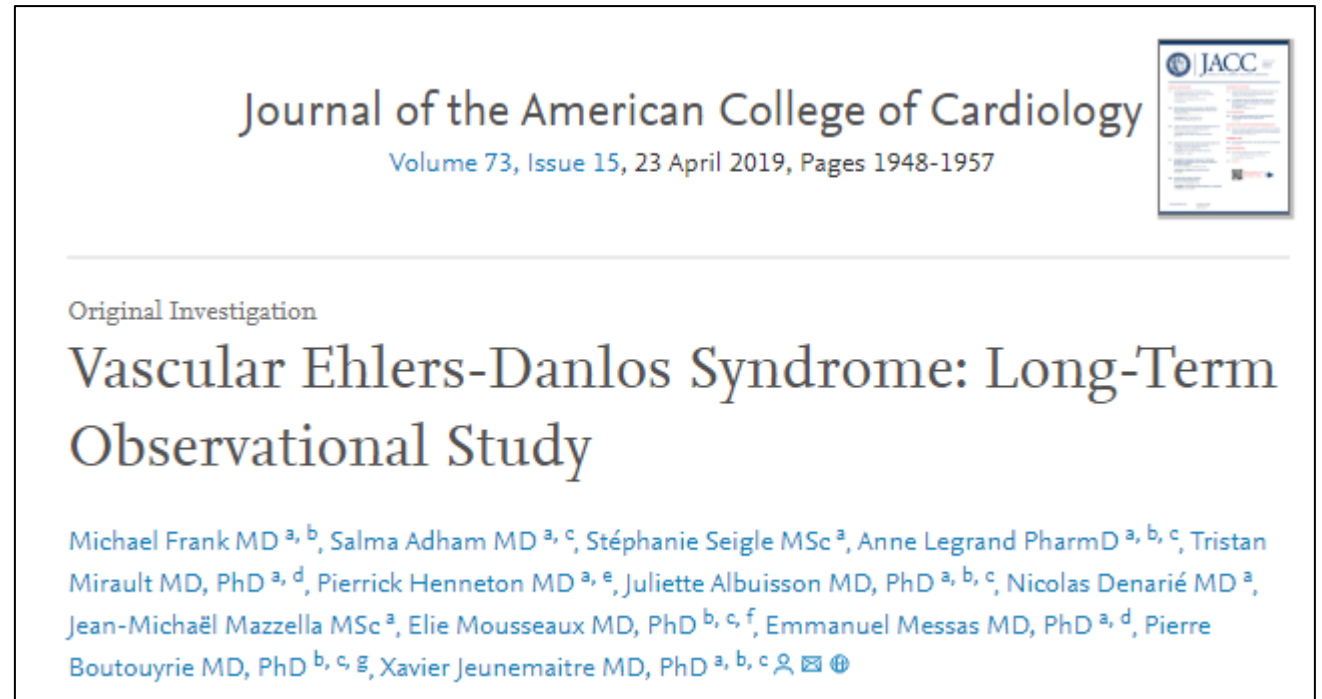
Medical Management

- Beta blockers, Angiotensin Receptor Blockers
- Vitamin C
- Low dose Aspirin (dissections)
- Stool softeners (avoid constipation)

Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial

Lancet, 2010

Kim-Thanh Ong, Jérôme Perdu, Julie De Backer, Erwan Bozec, Patrick Collignon, Joseph Emmerich, Anne-Laure Fauret, Jean-Noël Fiessinger, Dominique P Germain, Gabriella Georgesco, Jean-Sebastien Hulot, Anne De Paepe, Henri Plauchu, Xavier Jeunemaitre, Stéphane Laurent, Pierre Boutouyrie





U.S. Department of Health and Human Services



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Drug Safety and Availability

Avelox (moxifloxacin)
Baxdela (delafloxacin)
Cipro (ciprofloxacin)
Factive (gemifloxacin)
Levaquin (levofloxacin)
Generic ofloxacin

[Information for Patients and
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FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects



SHARE



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EMAIL



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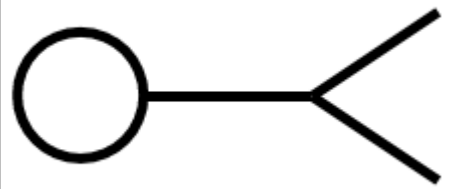
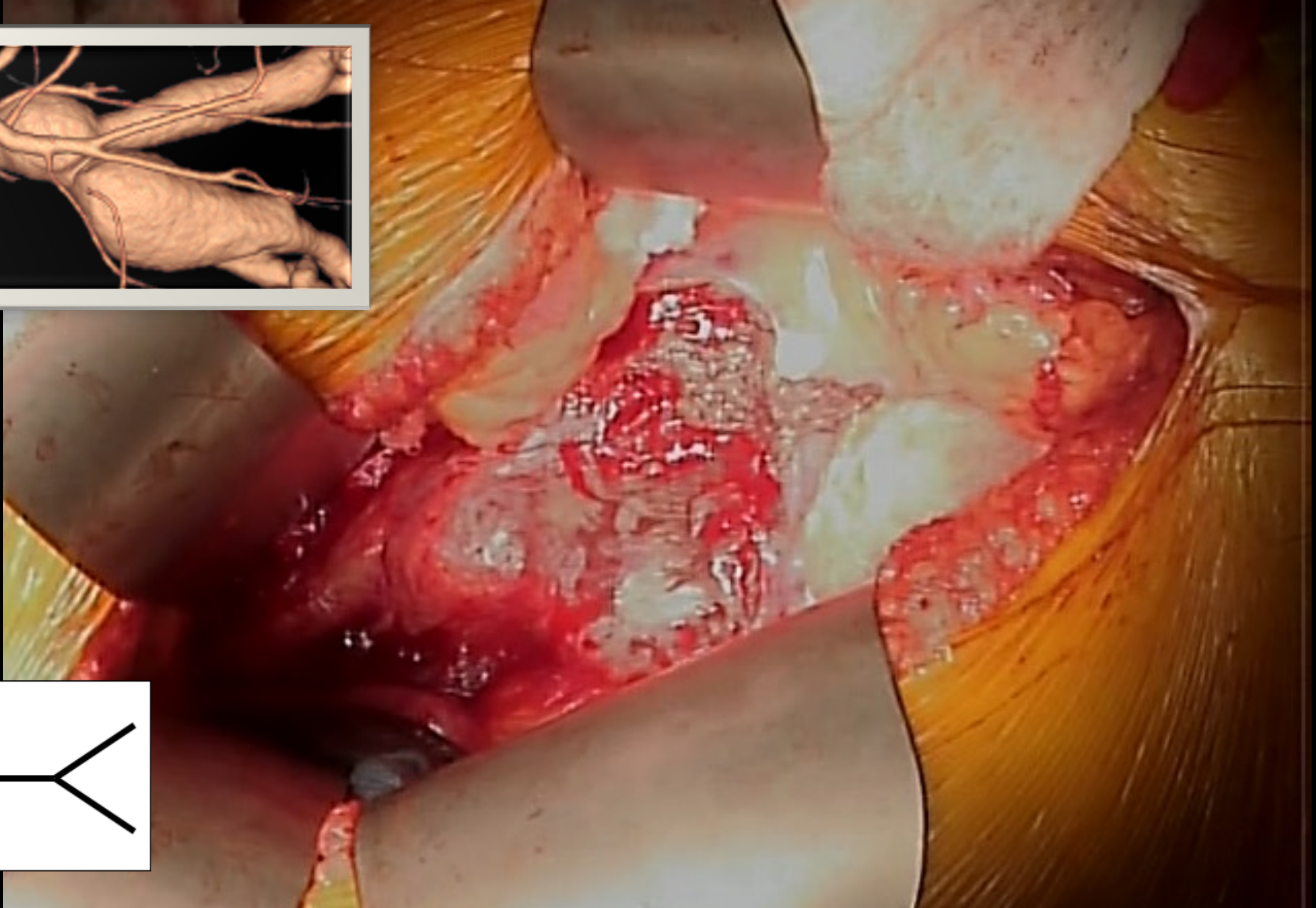
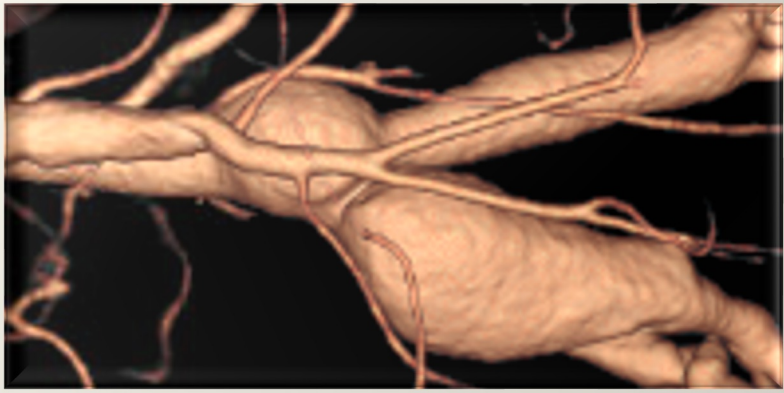
This information is an update to the FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together issued on **May 12, 2016**

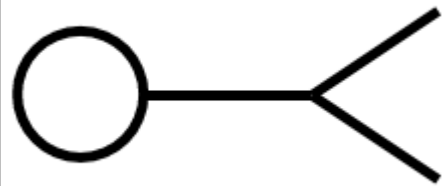
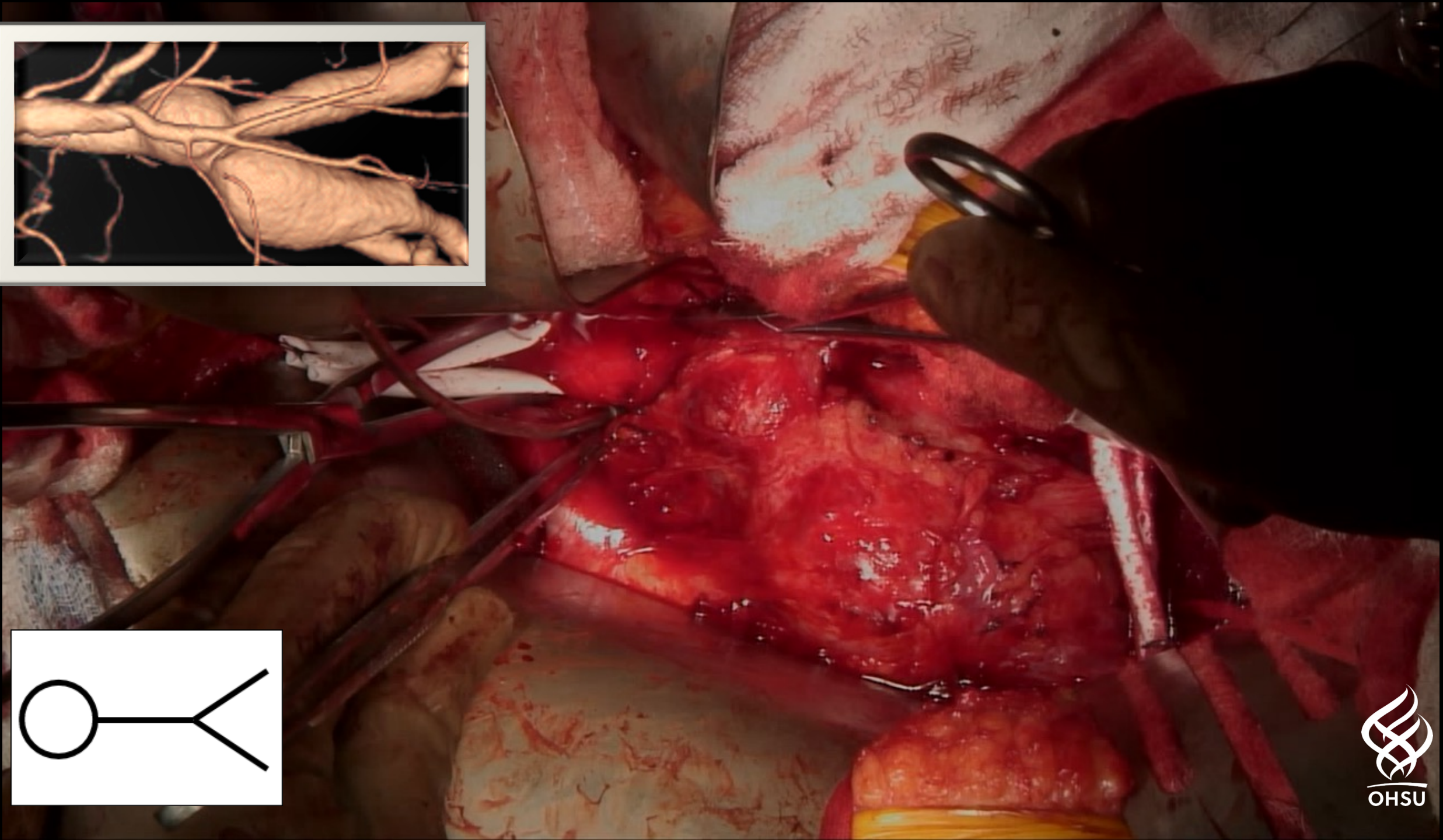
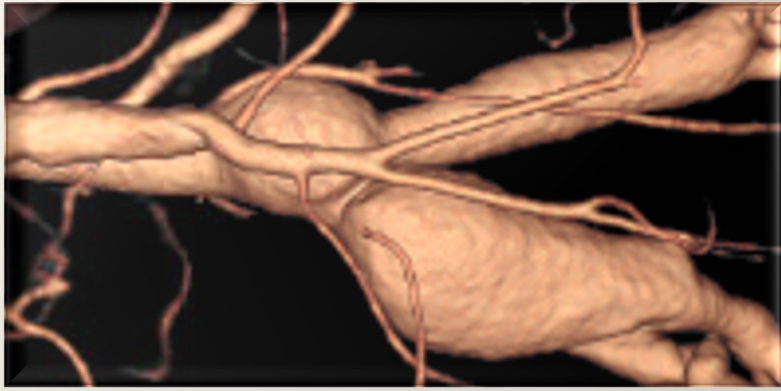


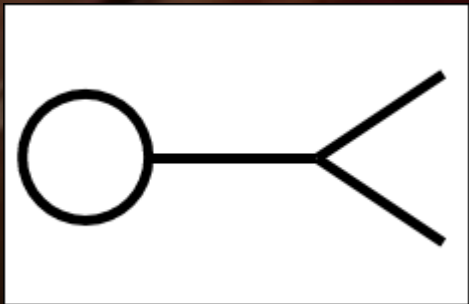
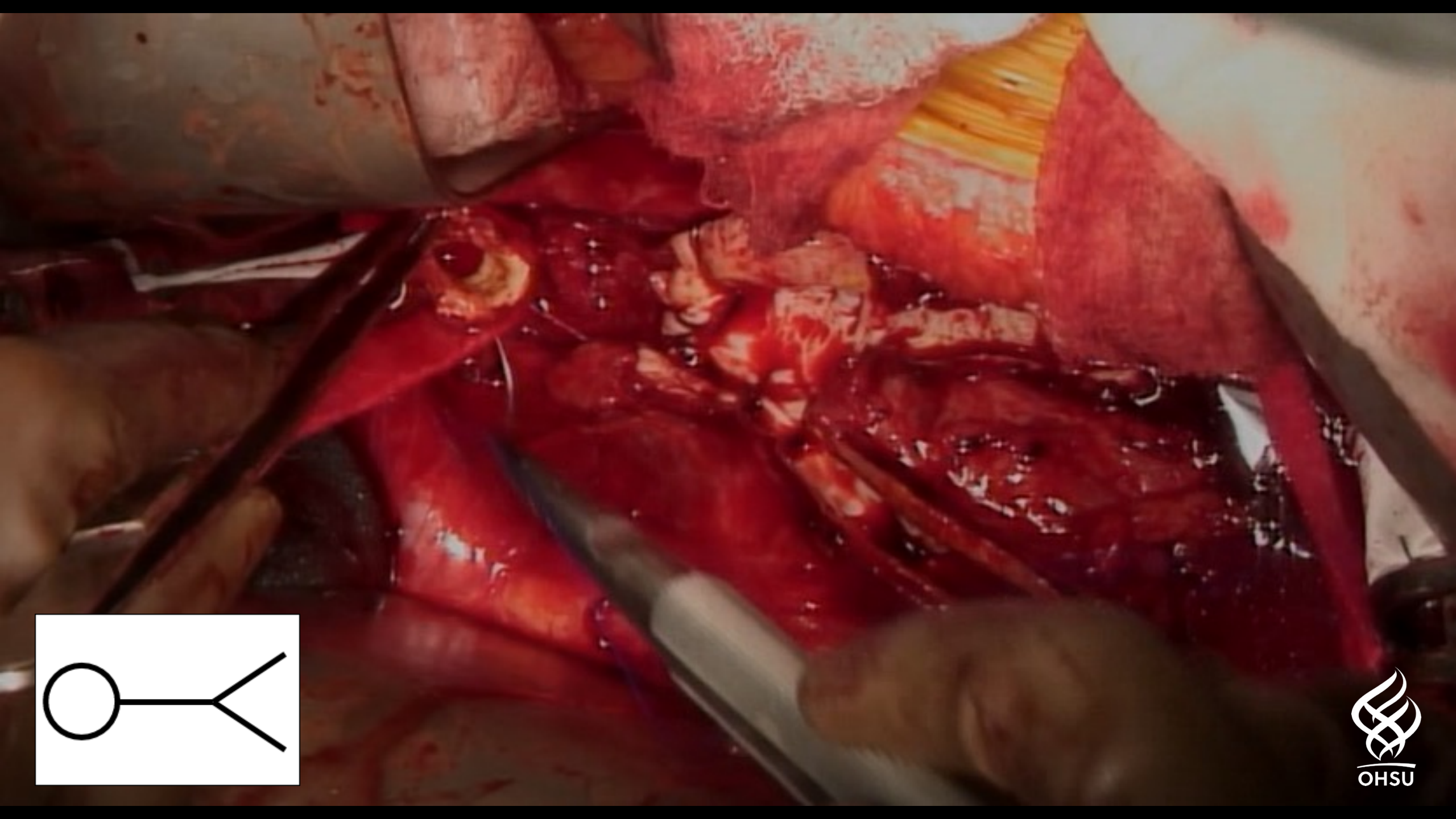
Operation

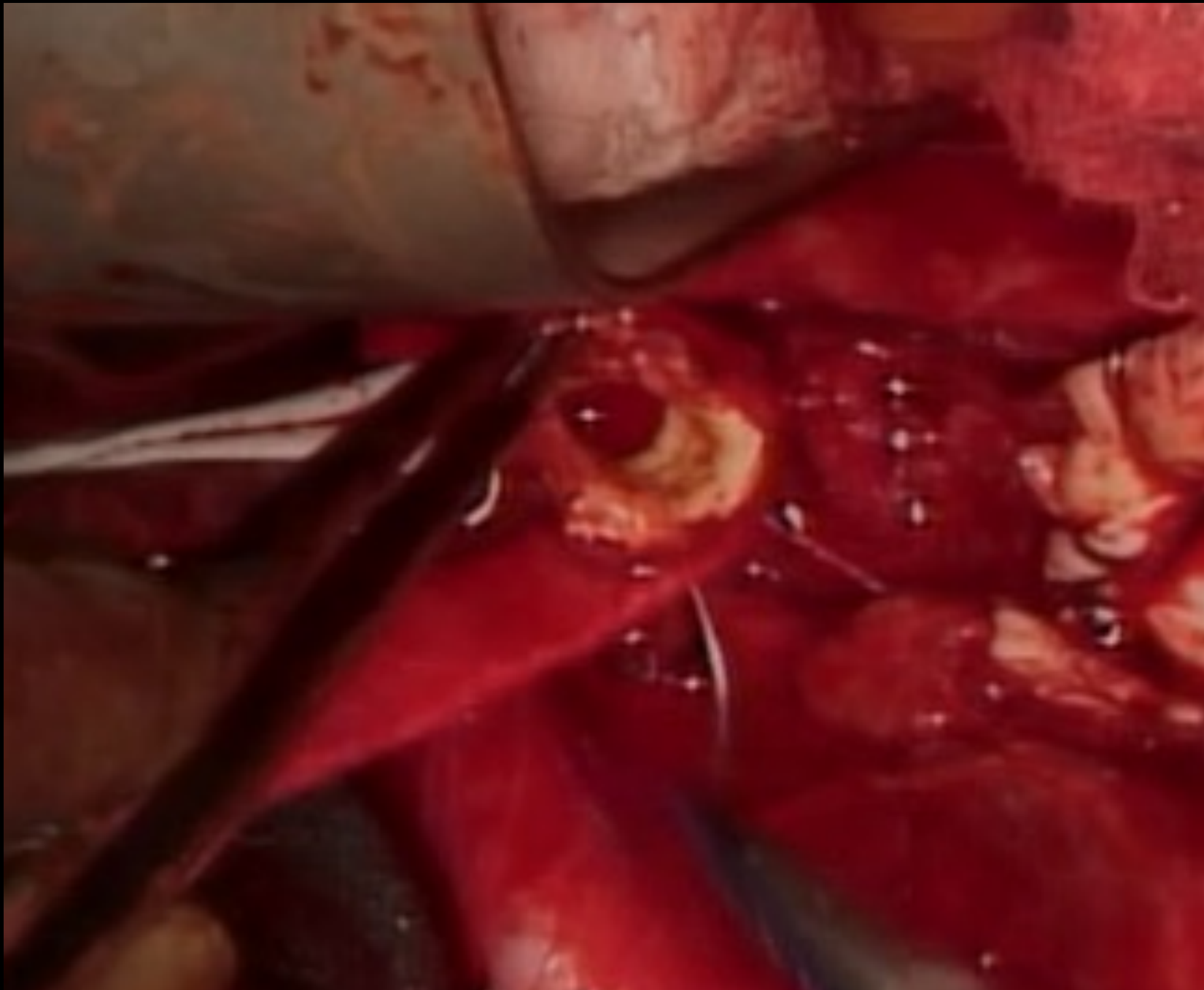
- Right Common Femoral Artery Exposure

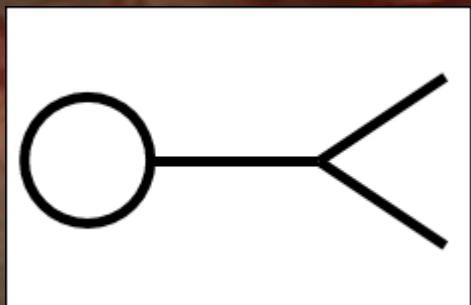
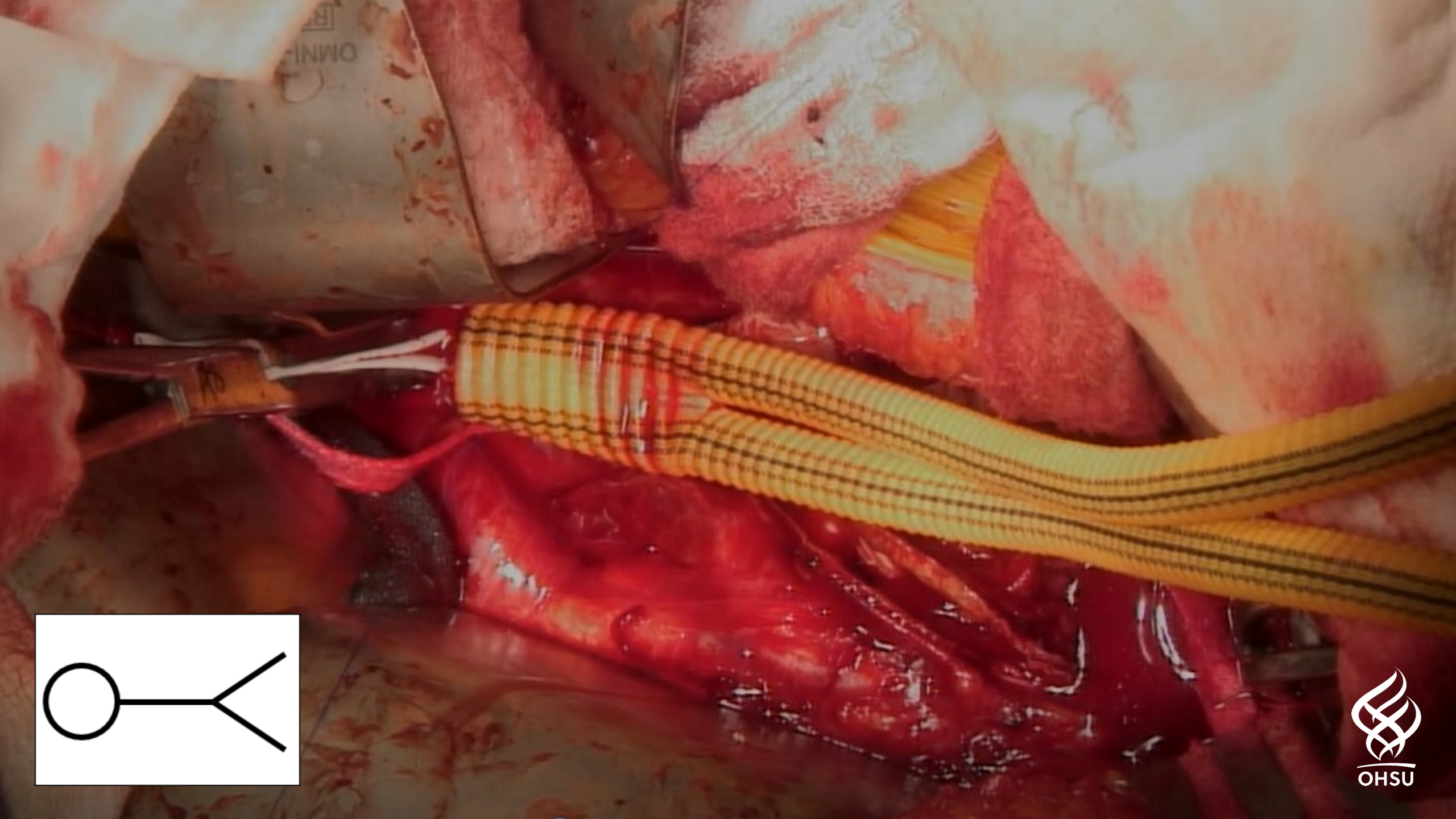


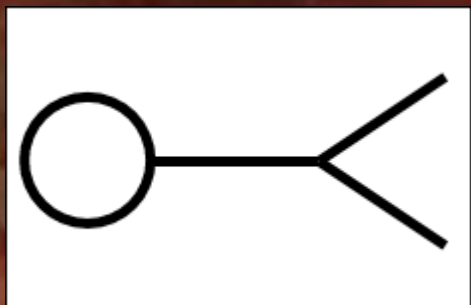
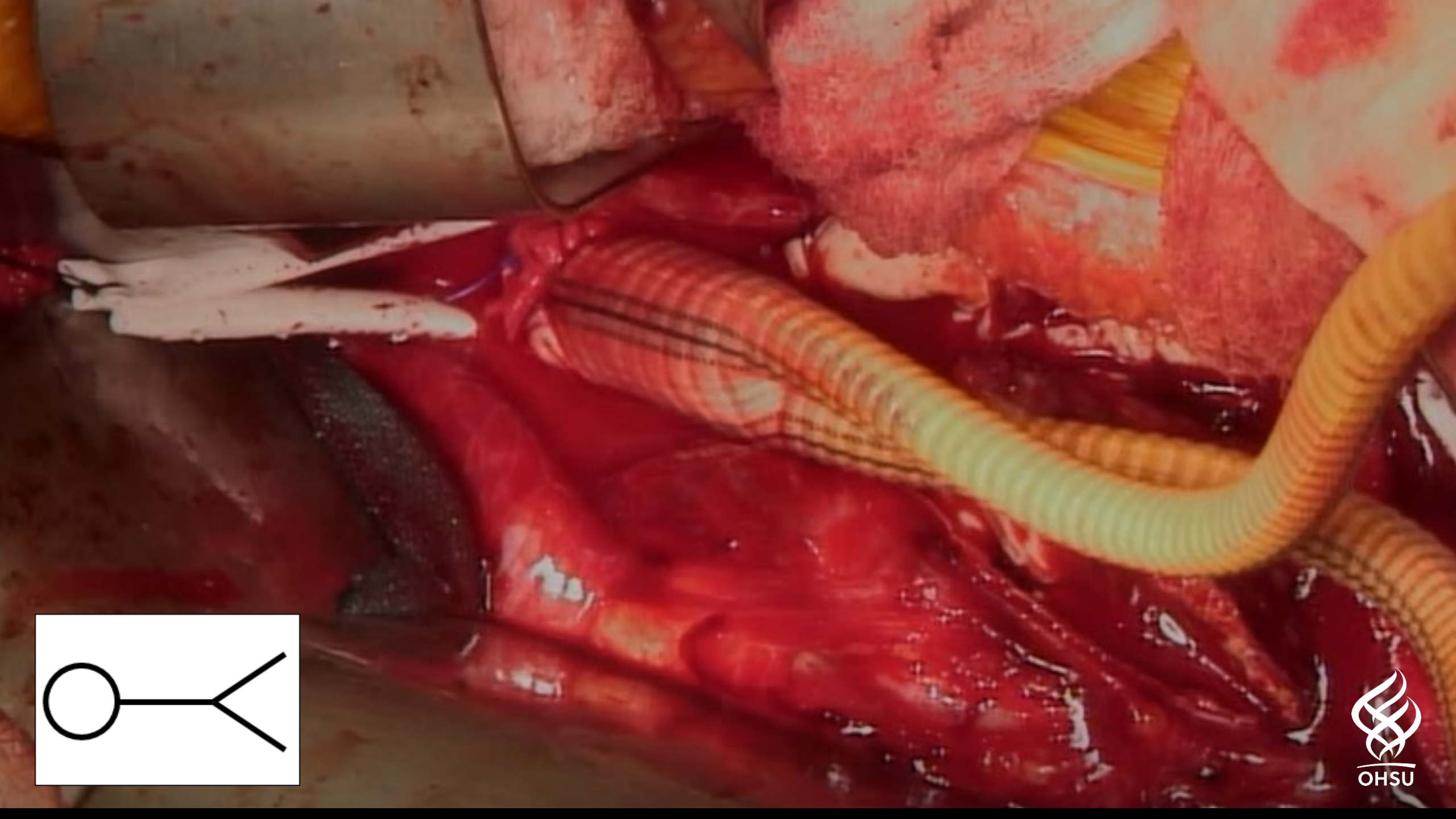


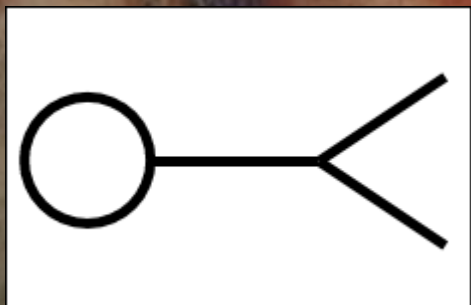
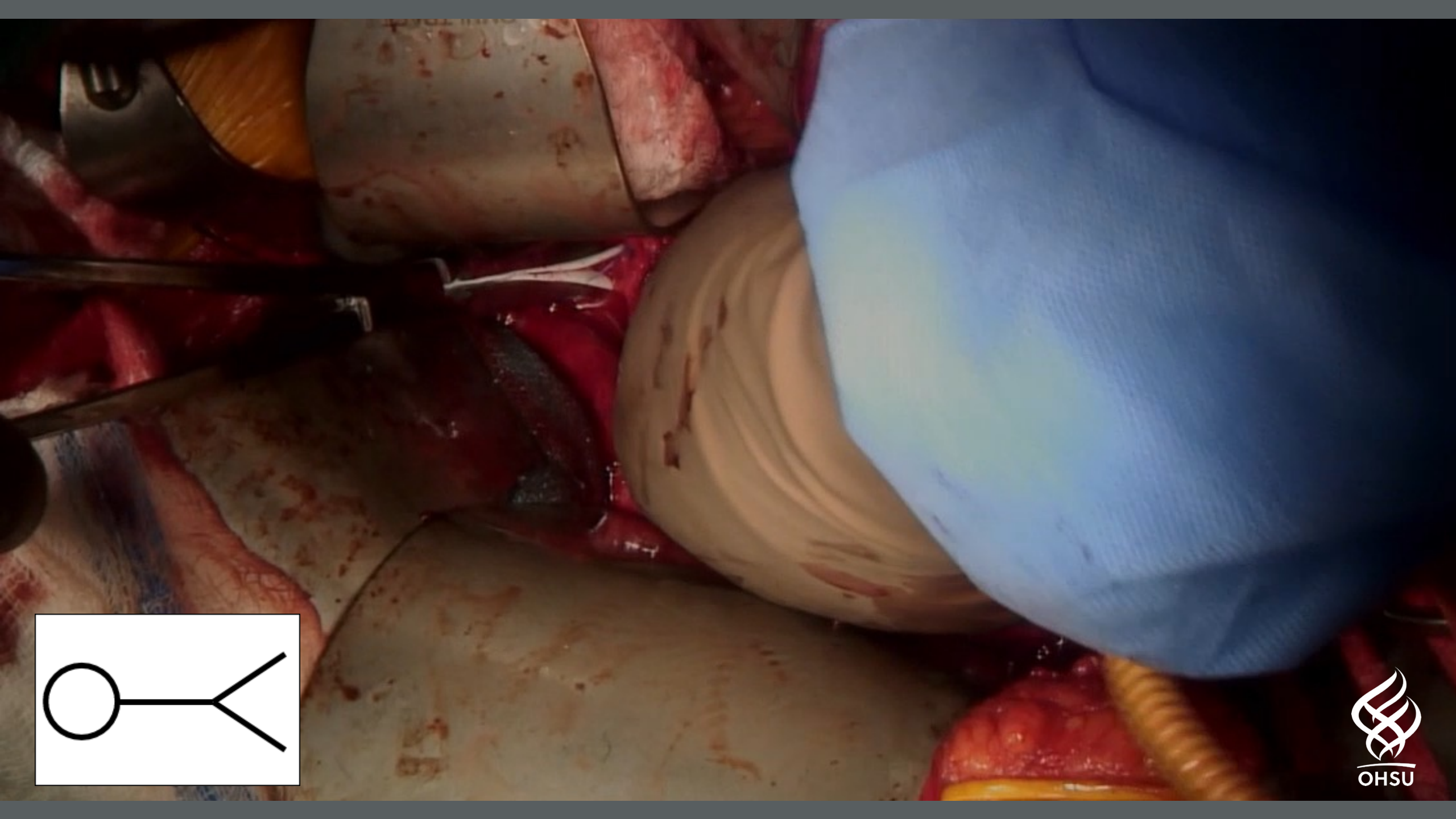


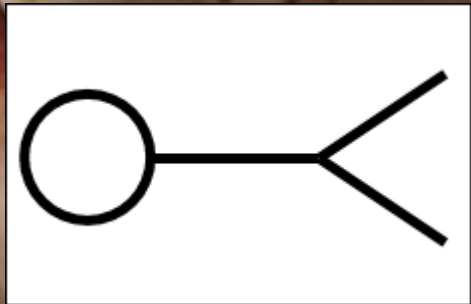
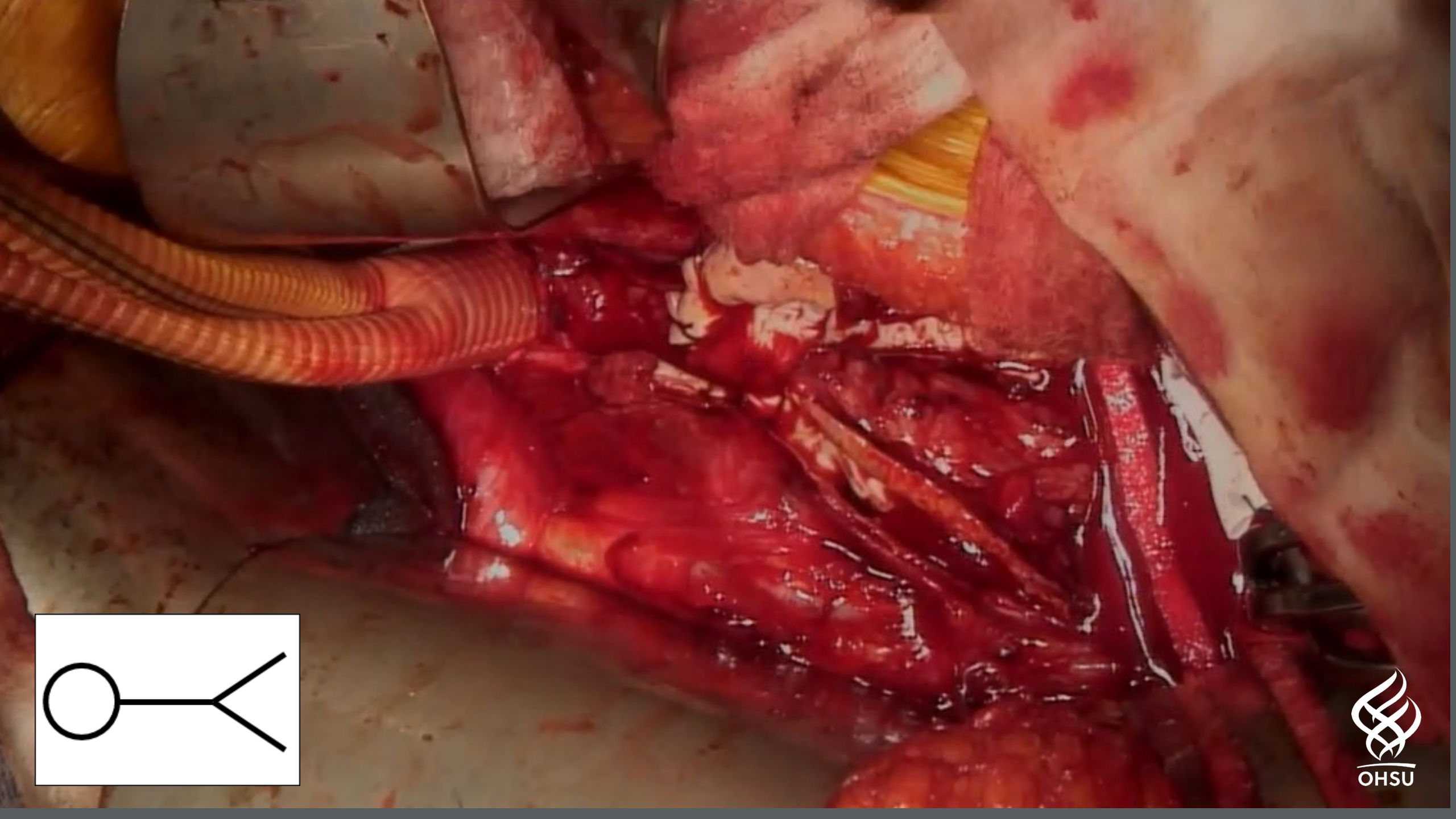




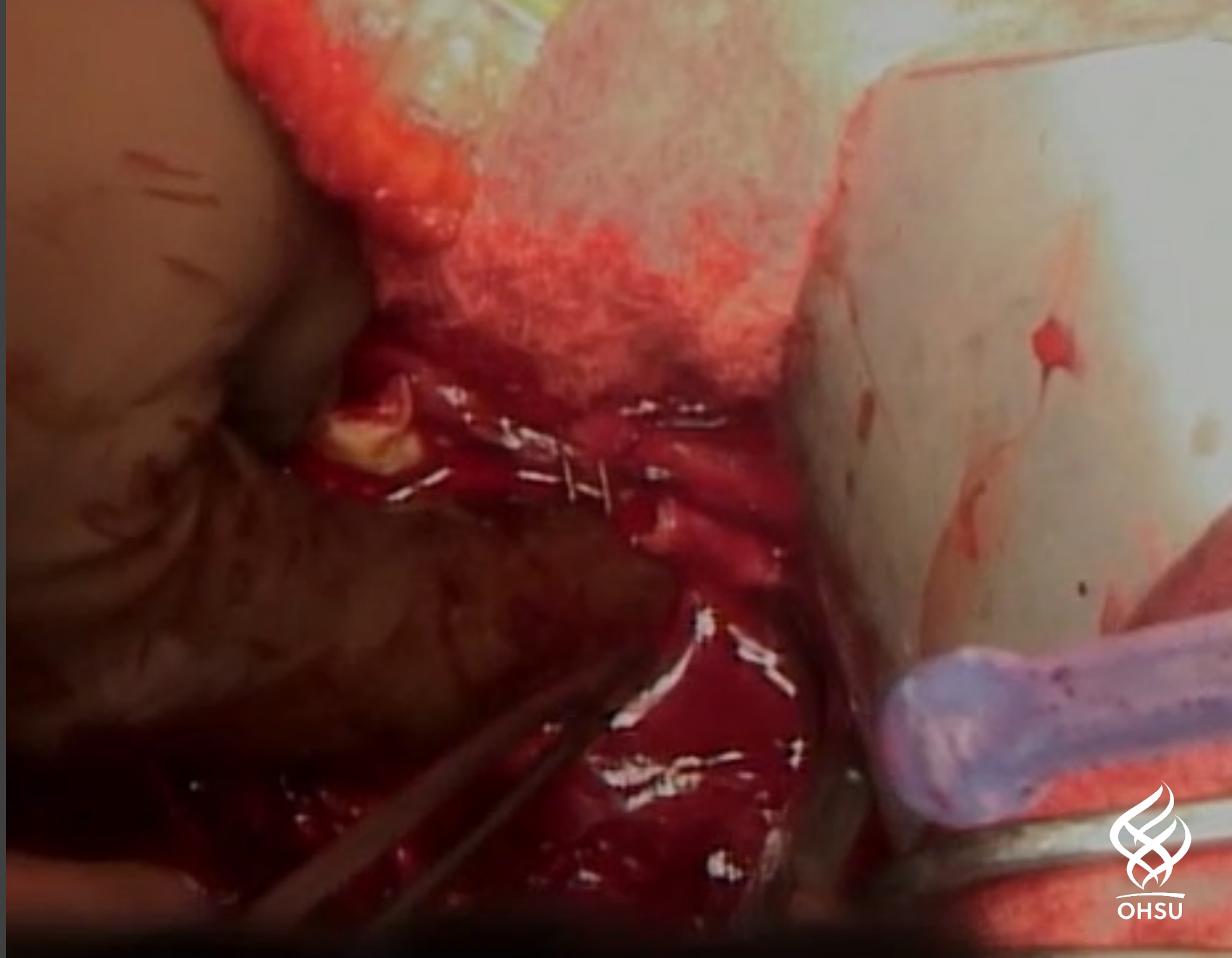
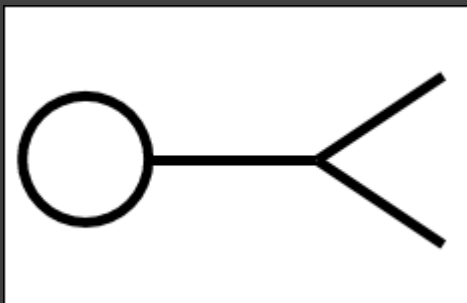


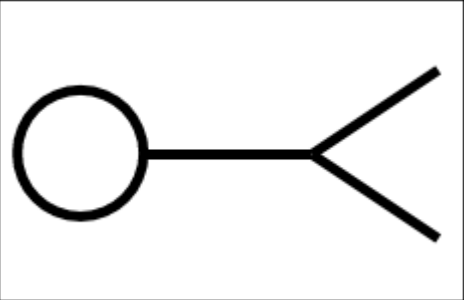


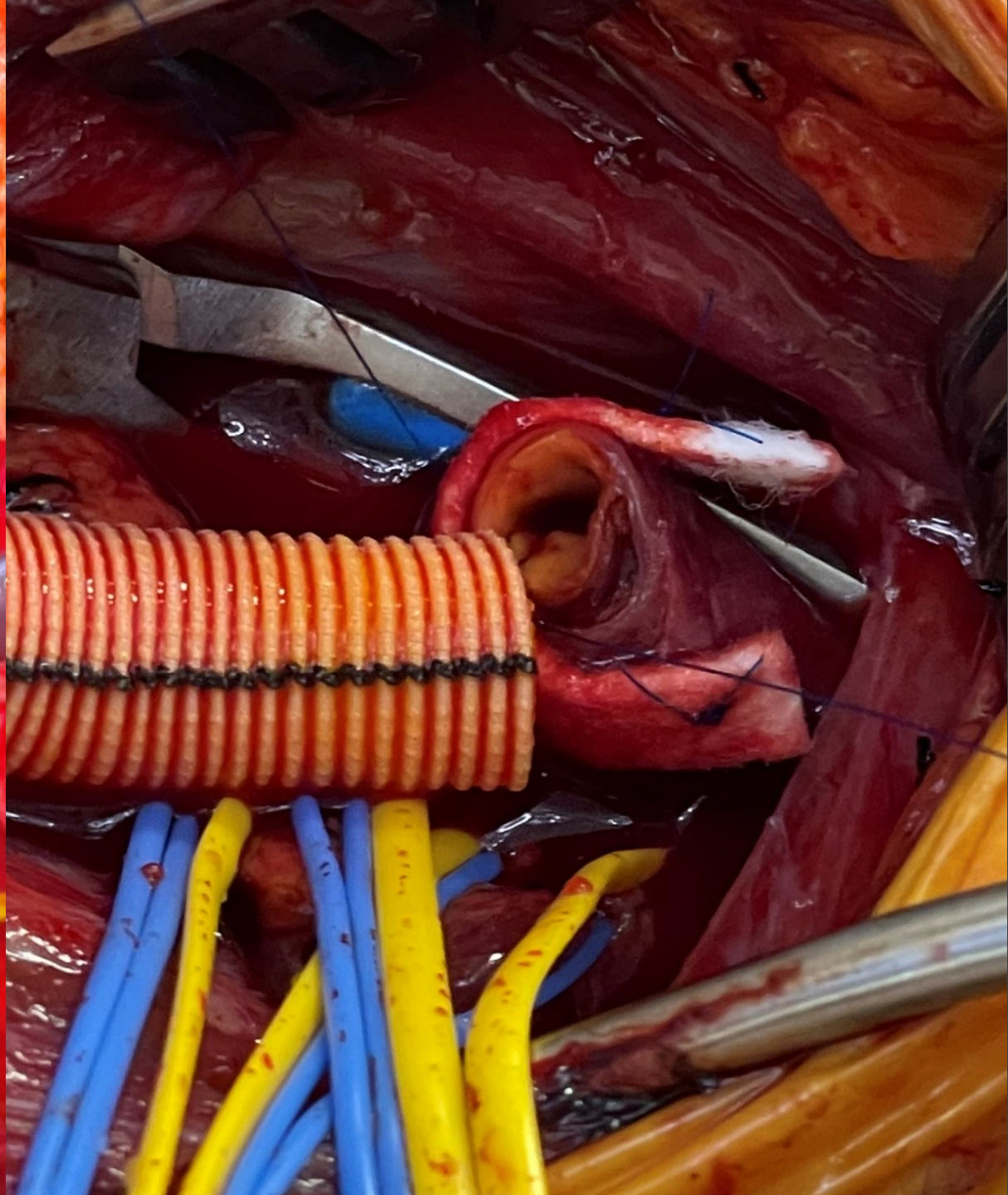
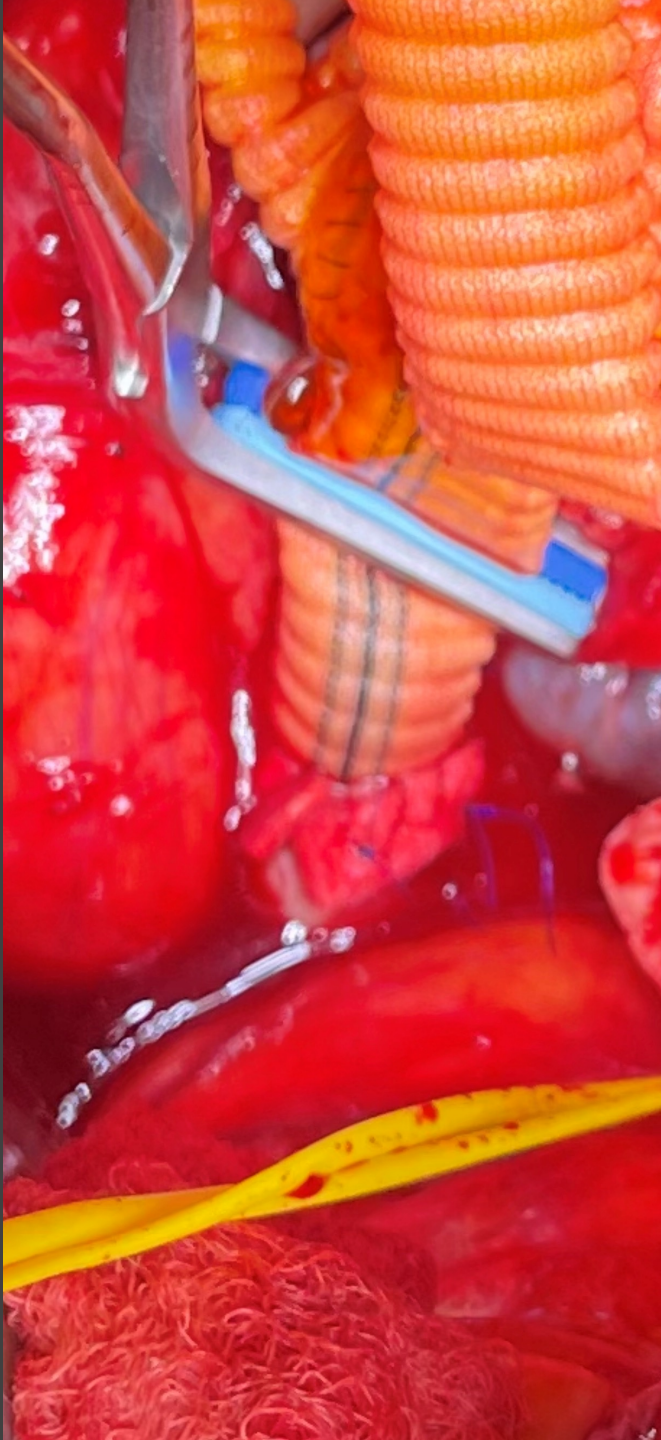


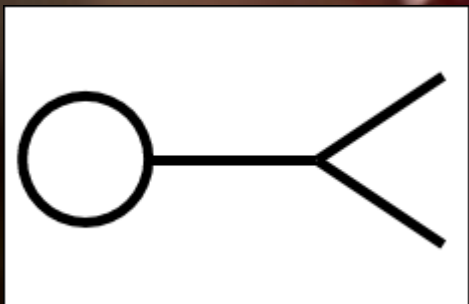
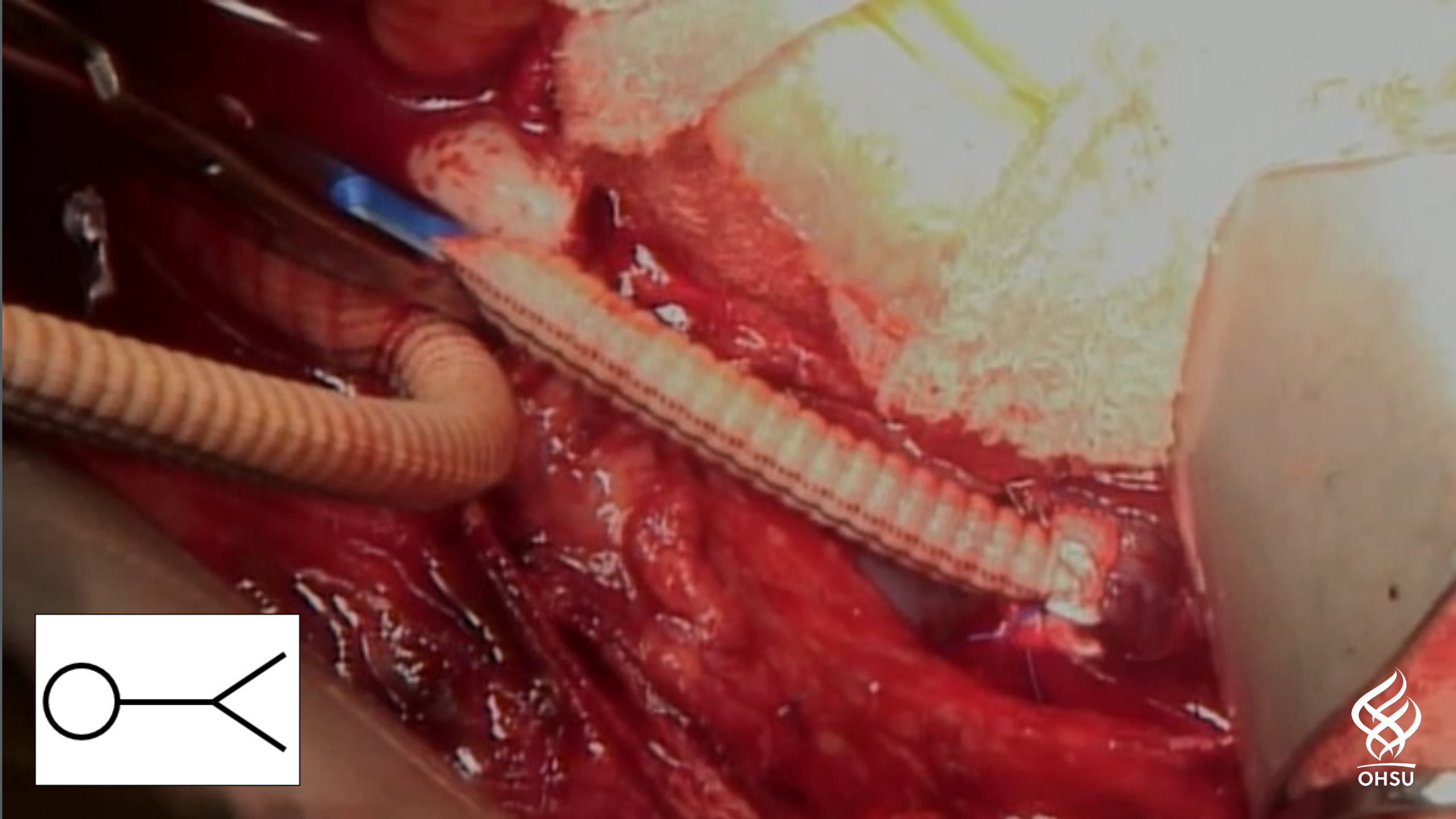


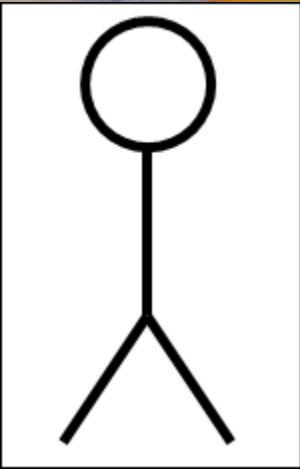
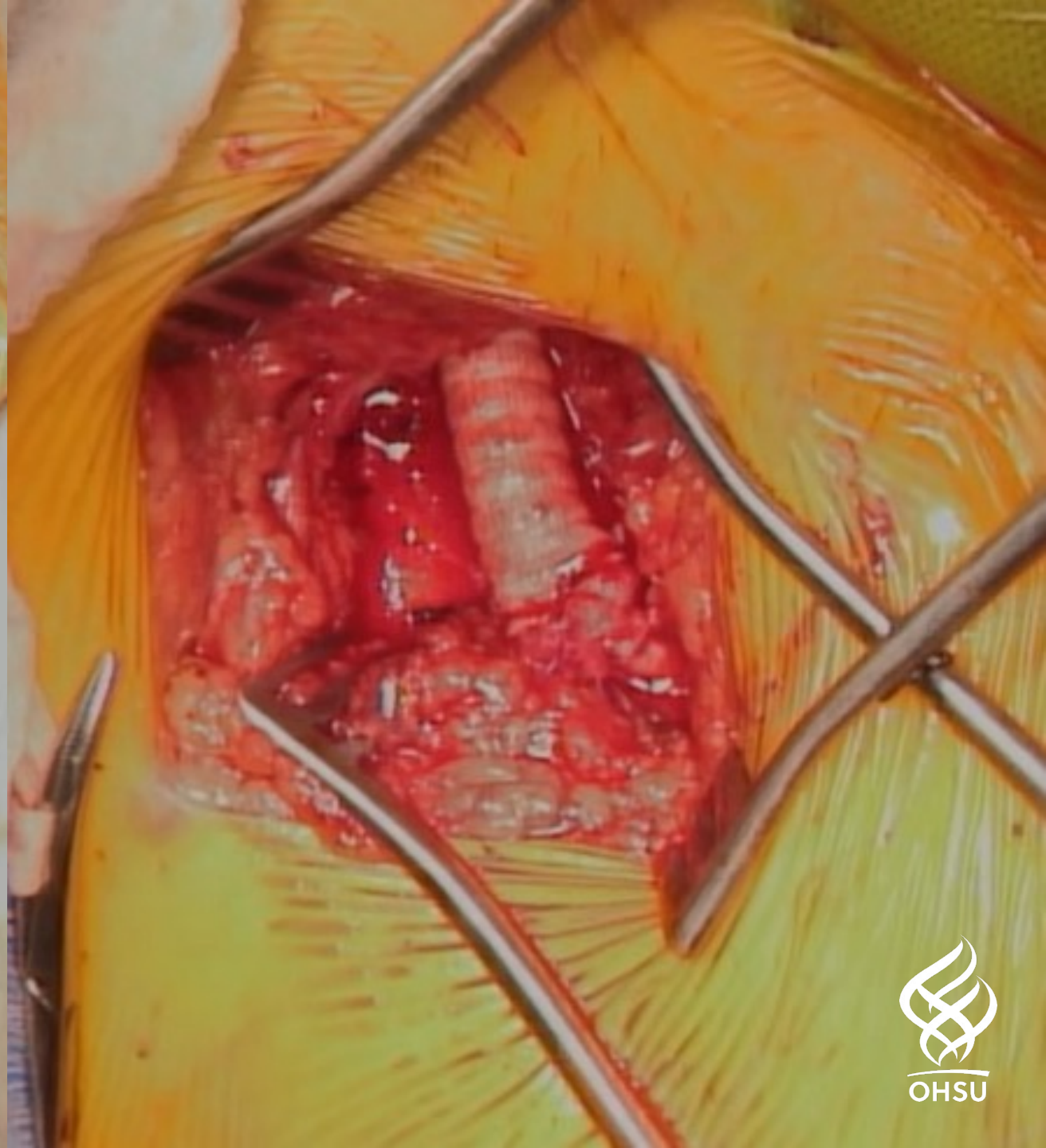
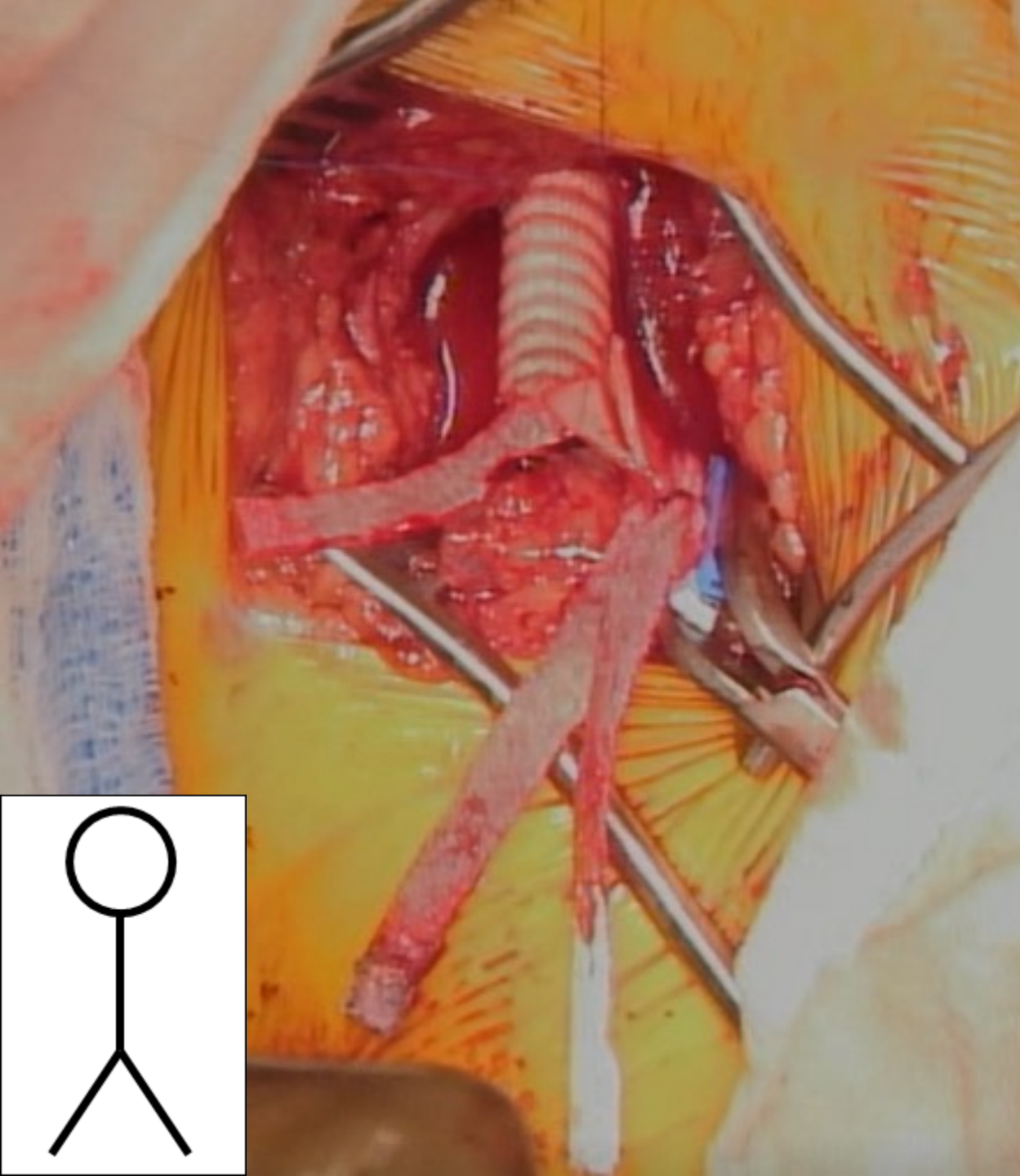
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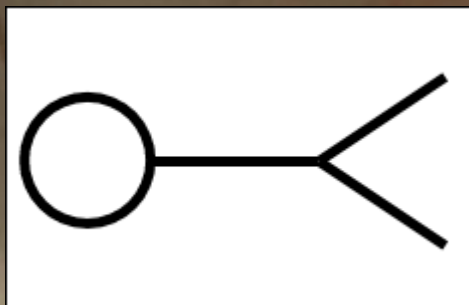
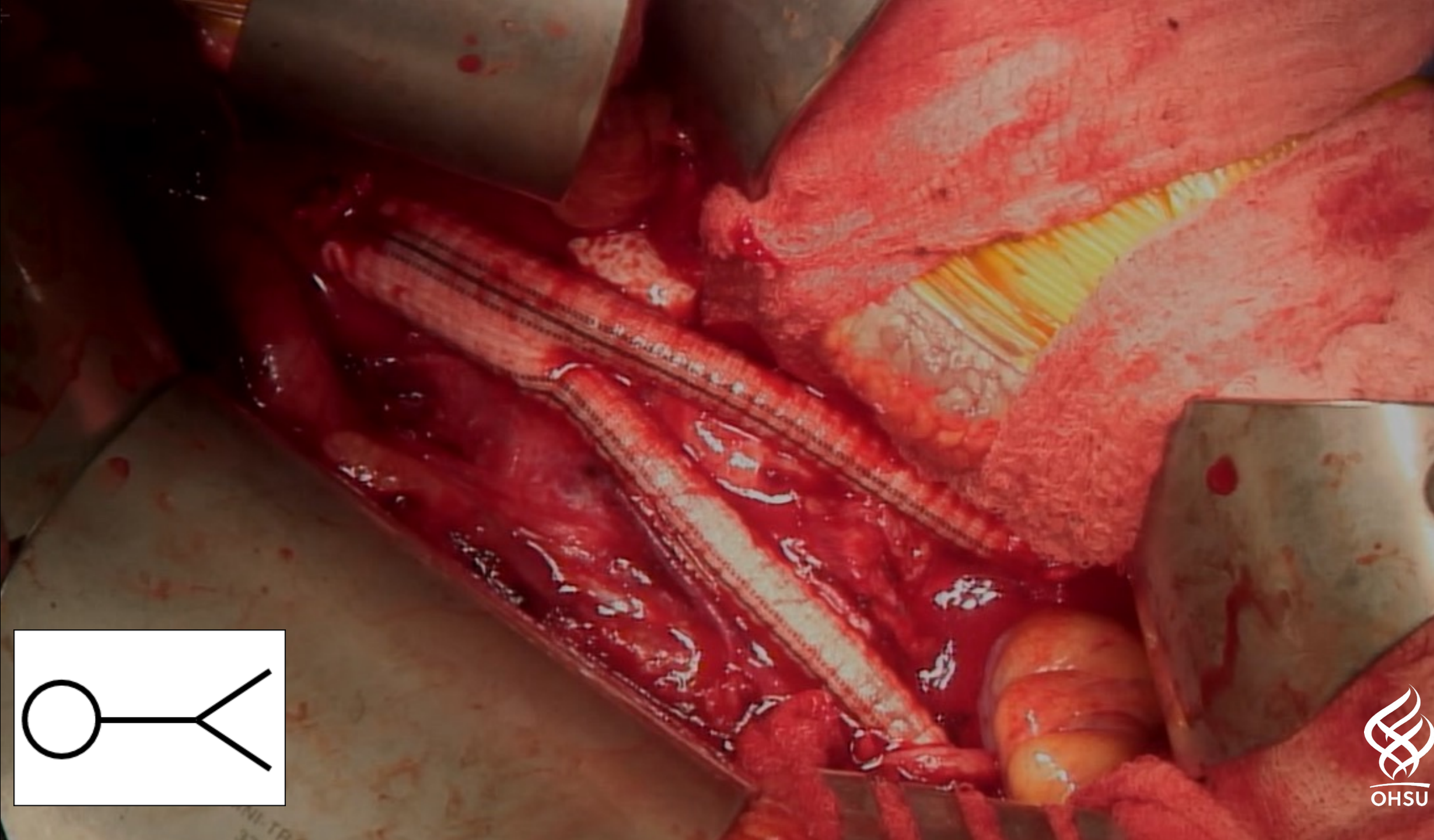




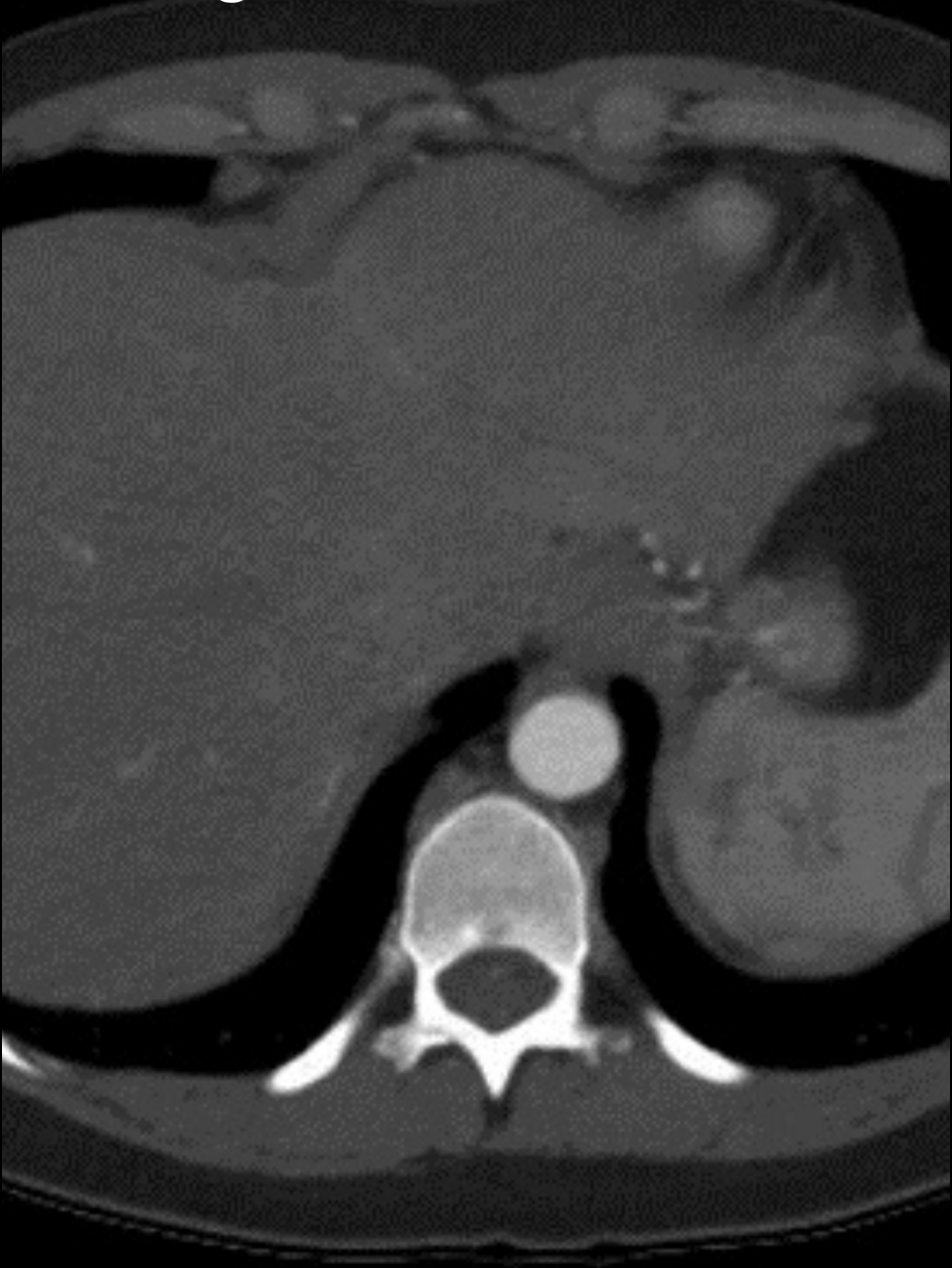








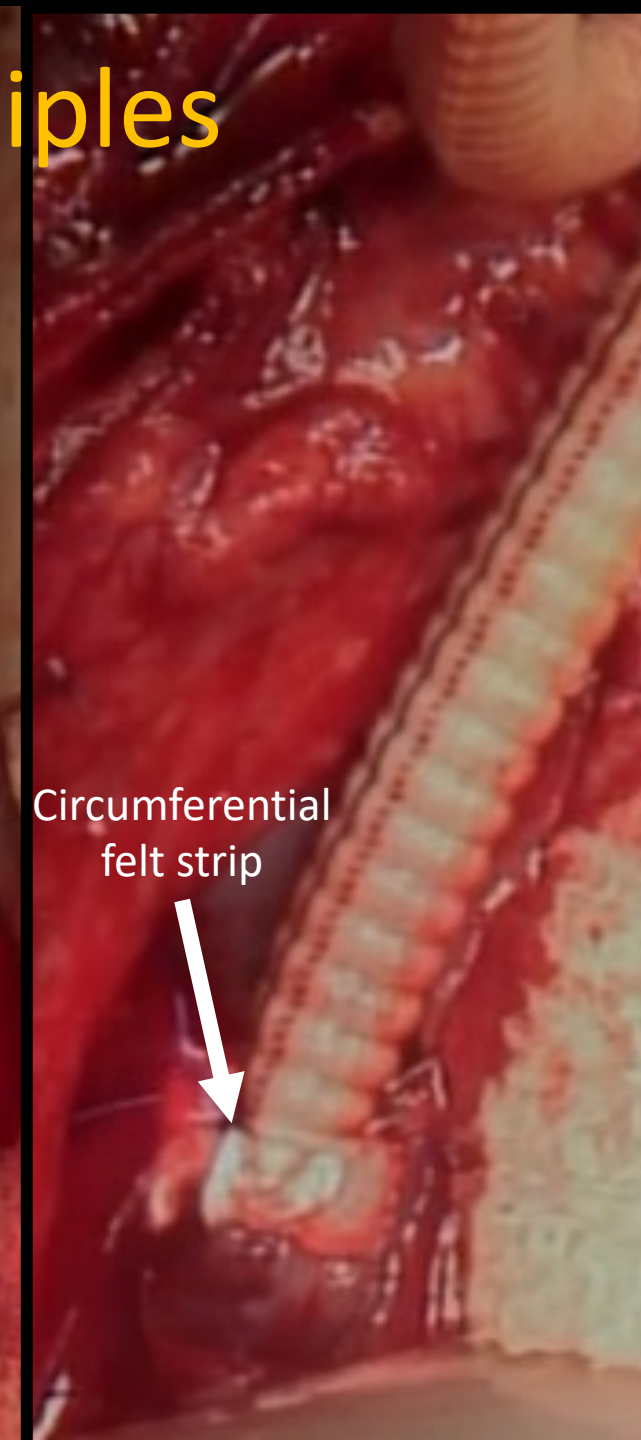
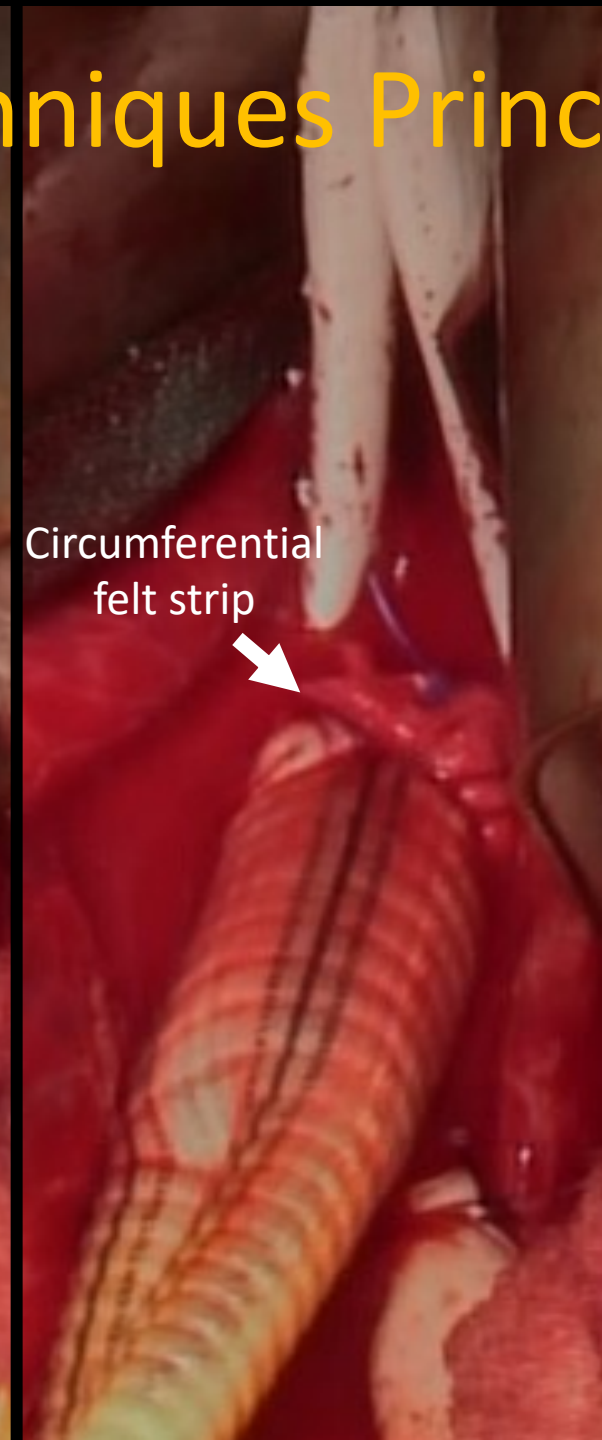
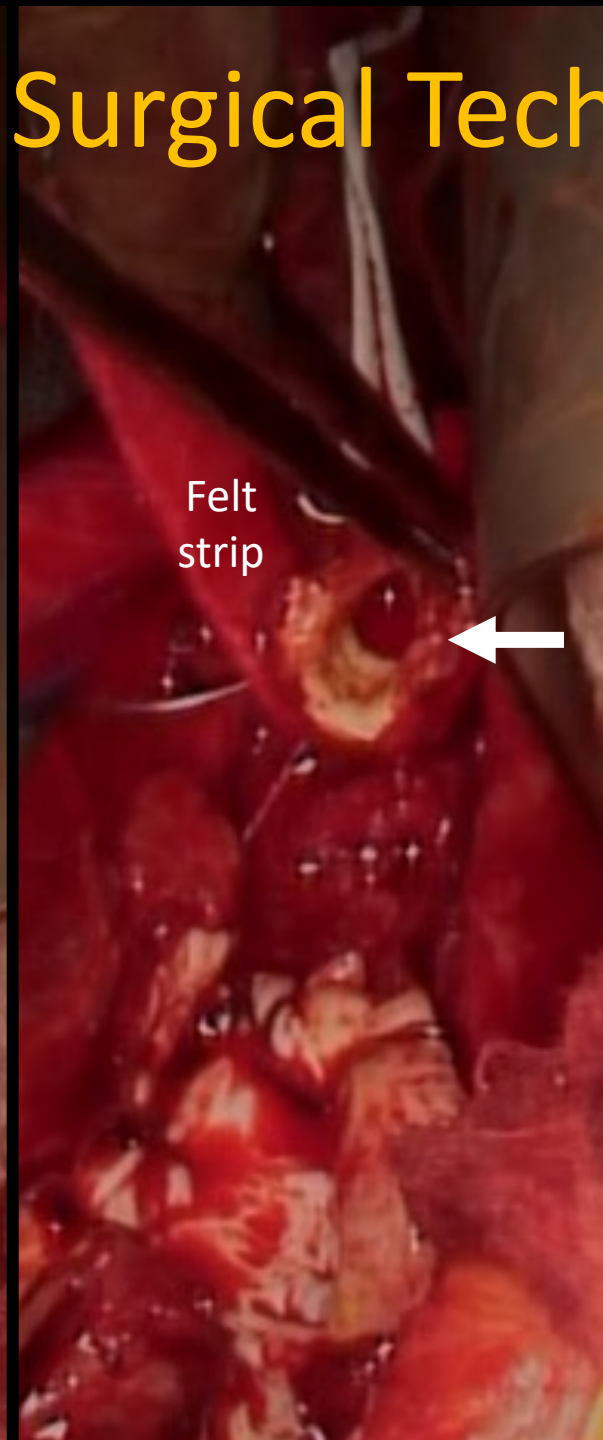
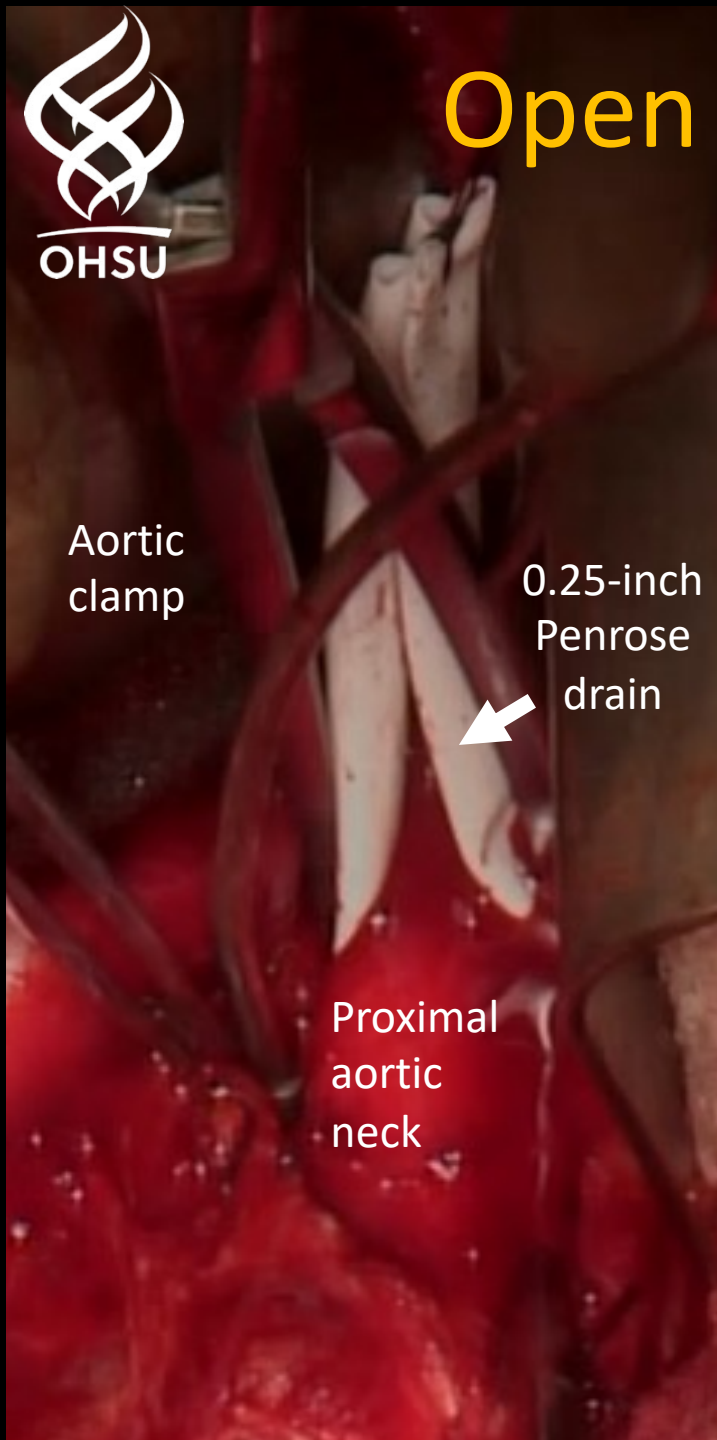
Discharged to home on POD 15



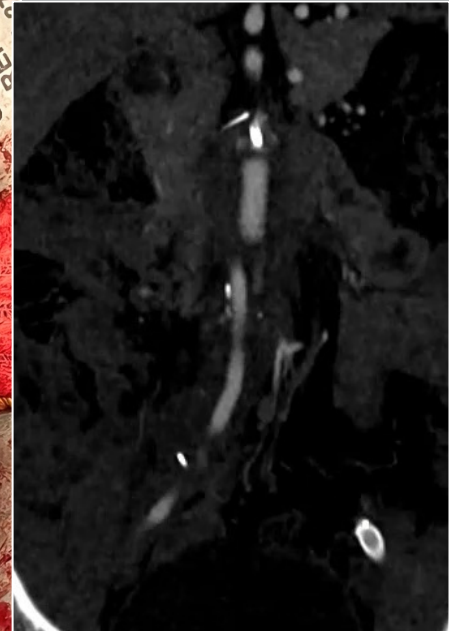
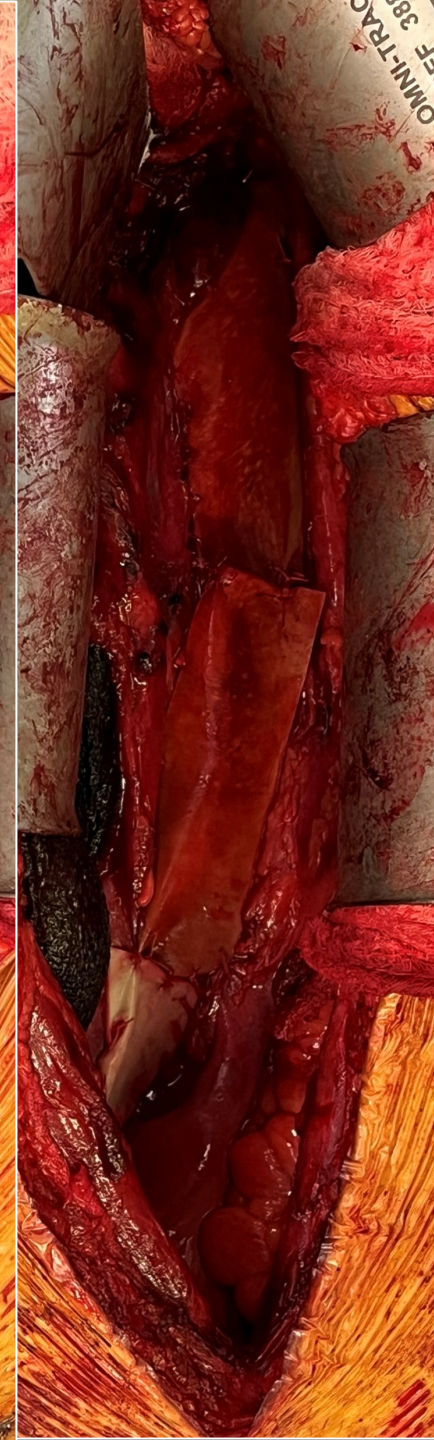
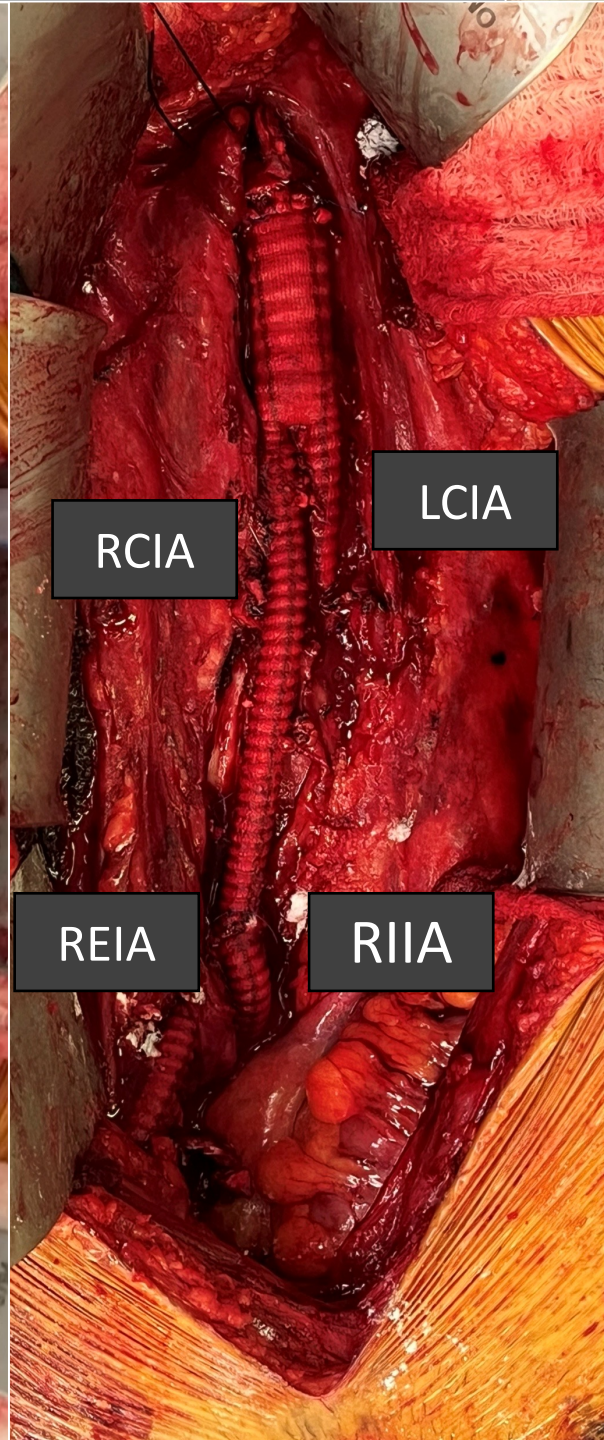
3 years post op



Open Surgical Techniques Principles



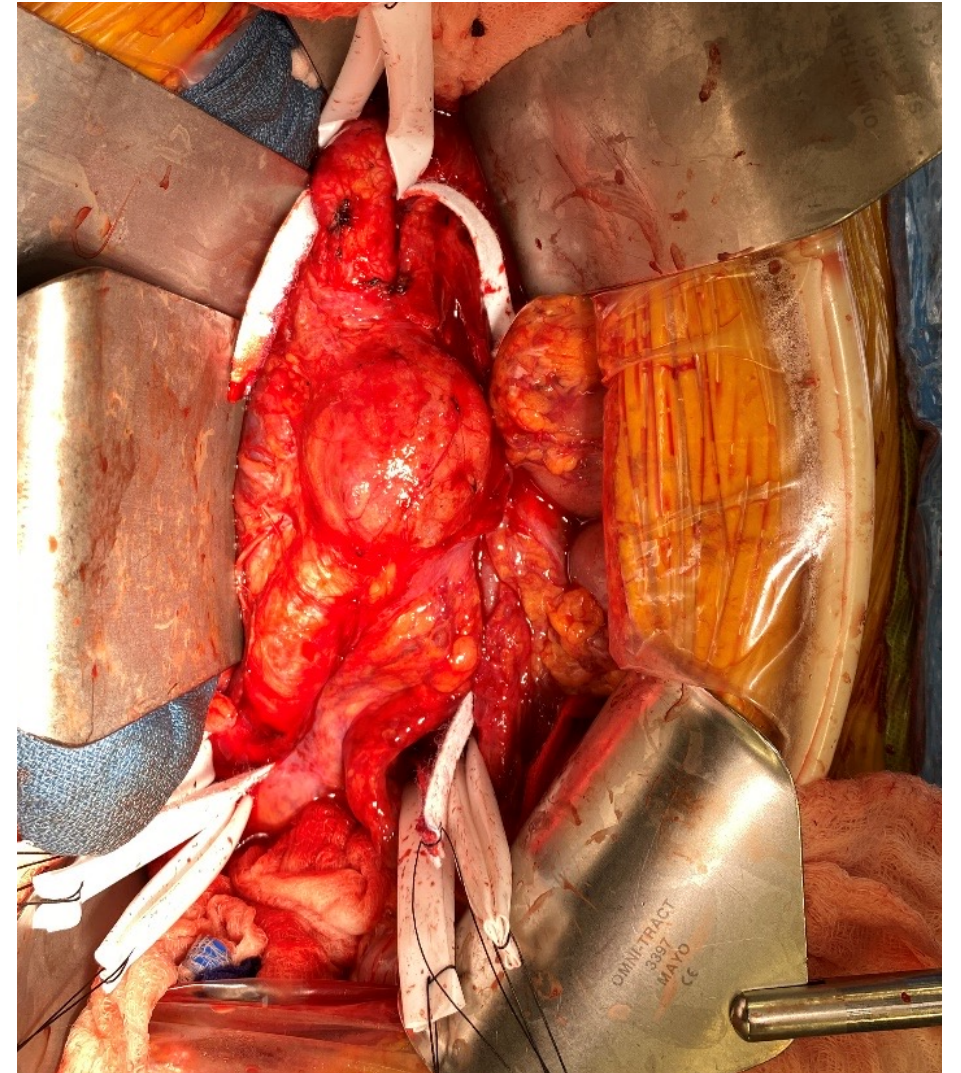
26 (COL3A1 c.1347+1G>A)



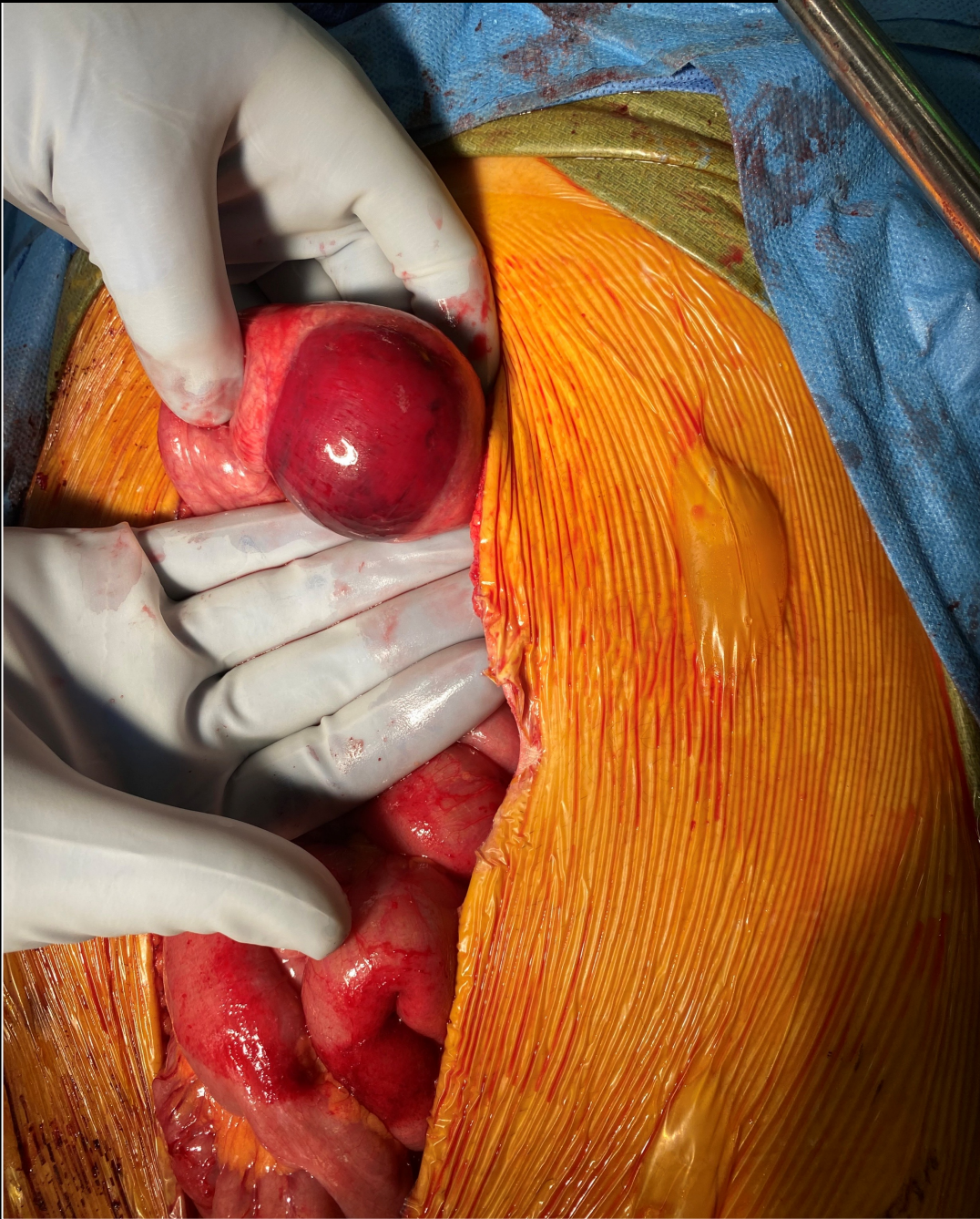


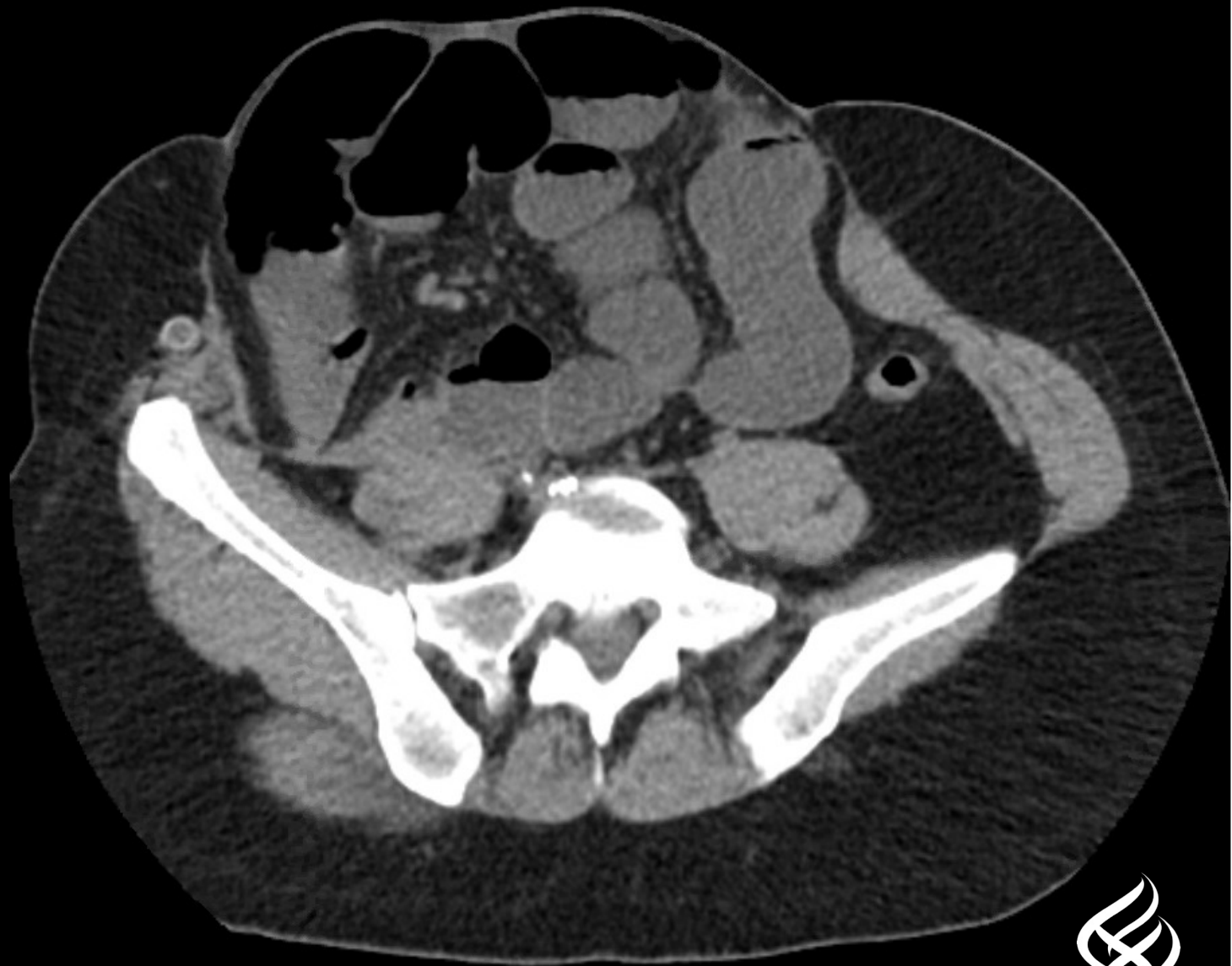
Open Surgical Techniques Principles

- Gentle retraction
- Minimize excessive tissue manipulation
- Padded clamps/avoid repeated application
- Avoid vessel loops or umbilical tape if the genotype corresponds to a severe phenotype
- Felt strips for the anastomosis
- Pledged repairs
- Avoid hypertension



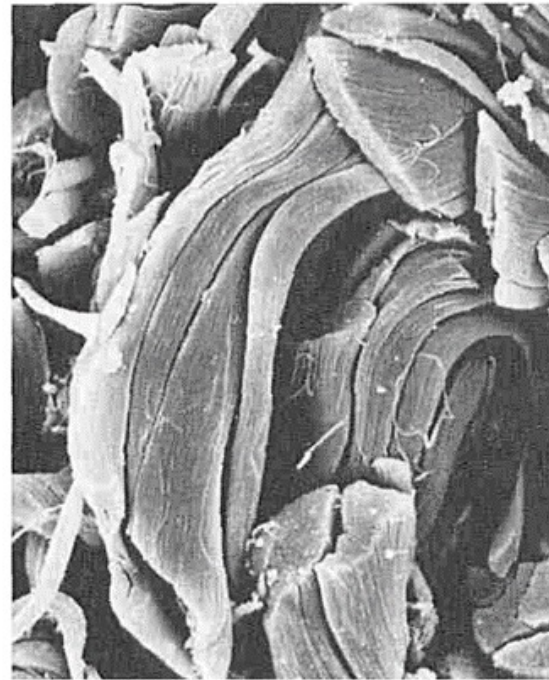
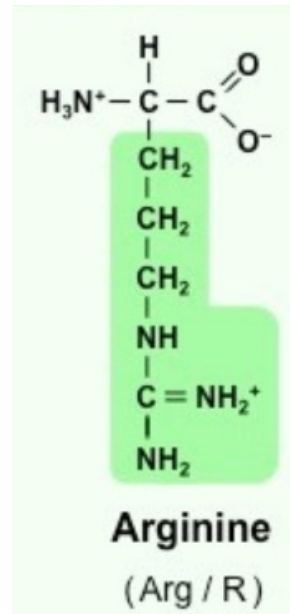
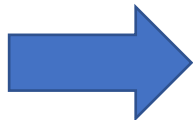
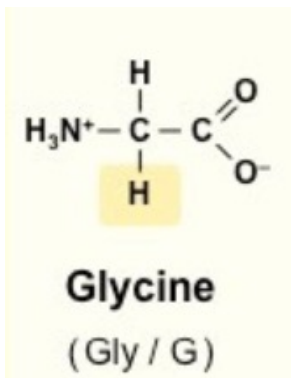
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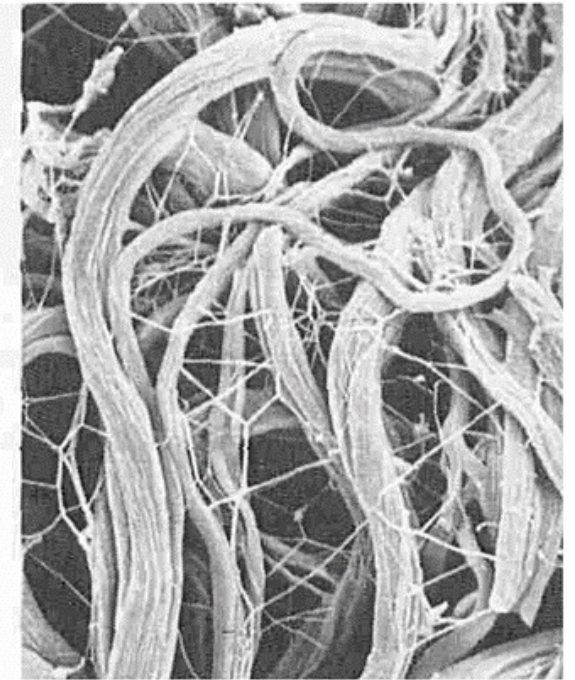


Tissue quality variability by genotype

- Variability in tissue quality in arterial tissues in VEDS can be appreciated
- Glycine substitution affects collagen
 - Size
 - Charge



Control

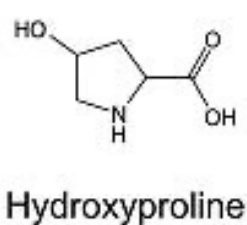
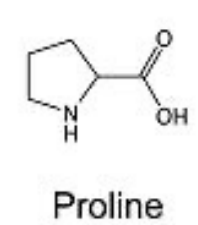
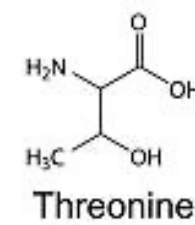
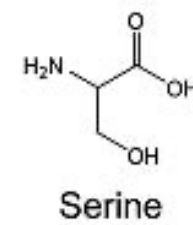
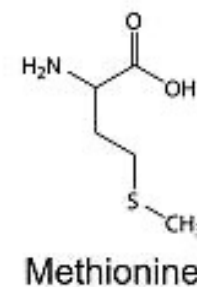
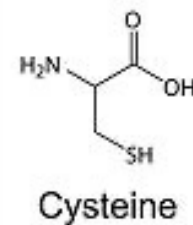
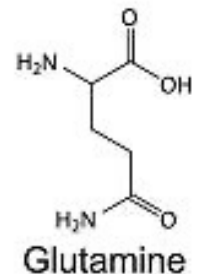
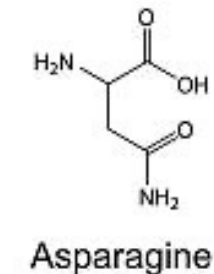
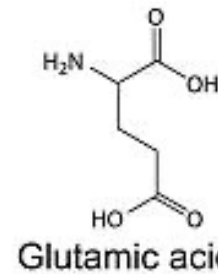
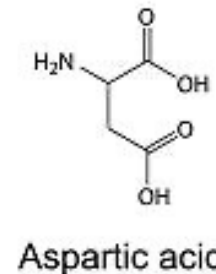
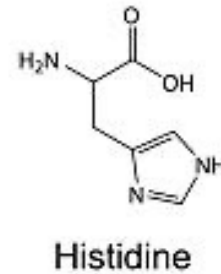
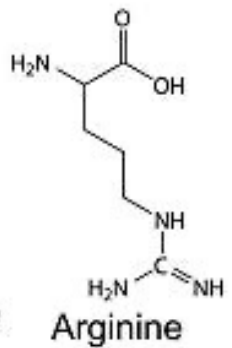
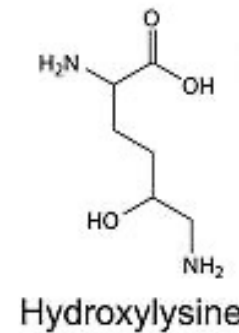
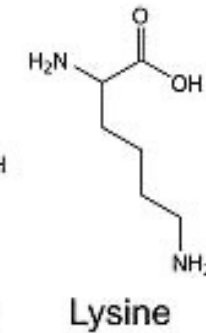
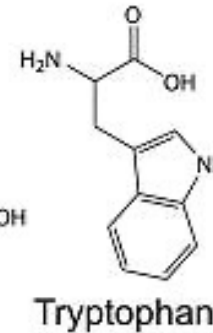
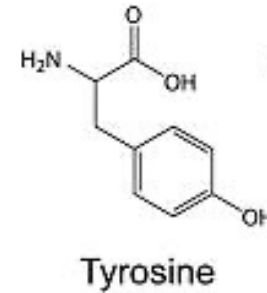
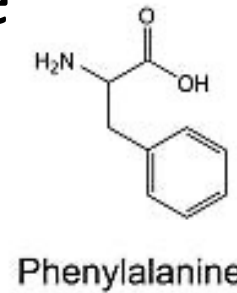
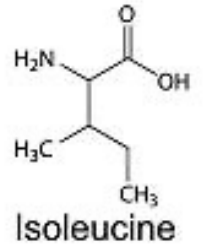
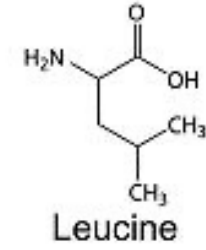
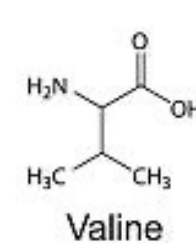
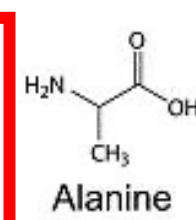
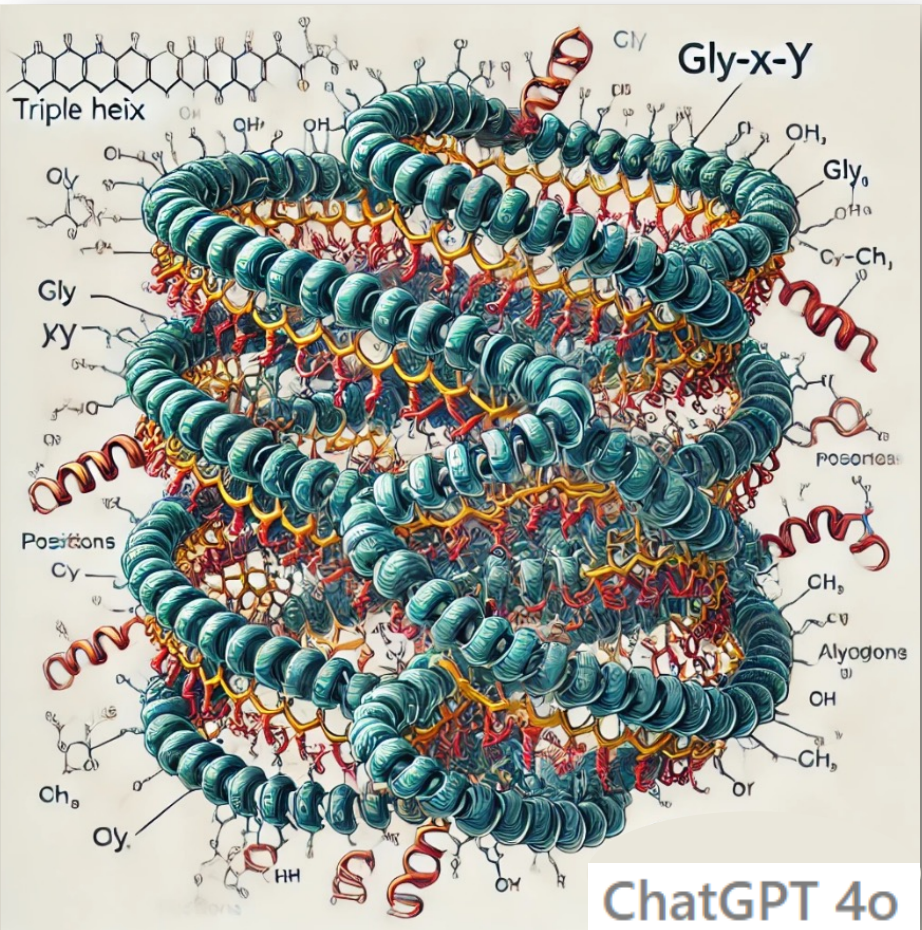


p.Gly373Arg

Smith LT. J Invest Derm, 1997

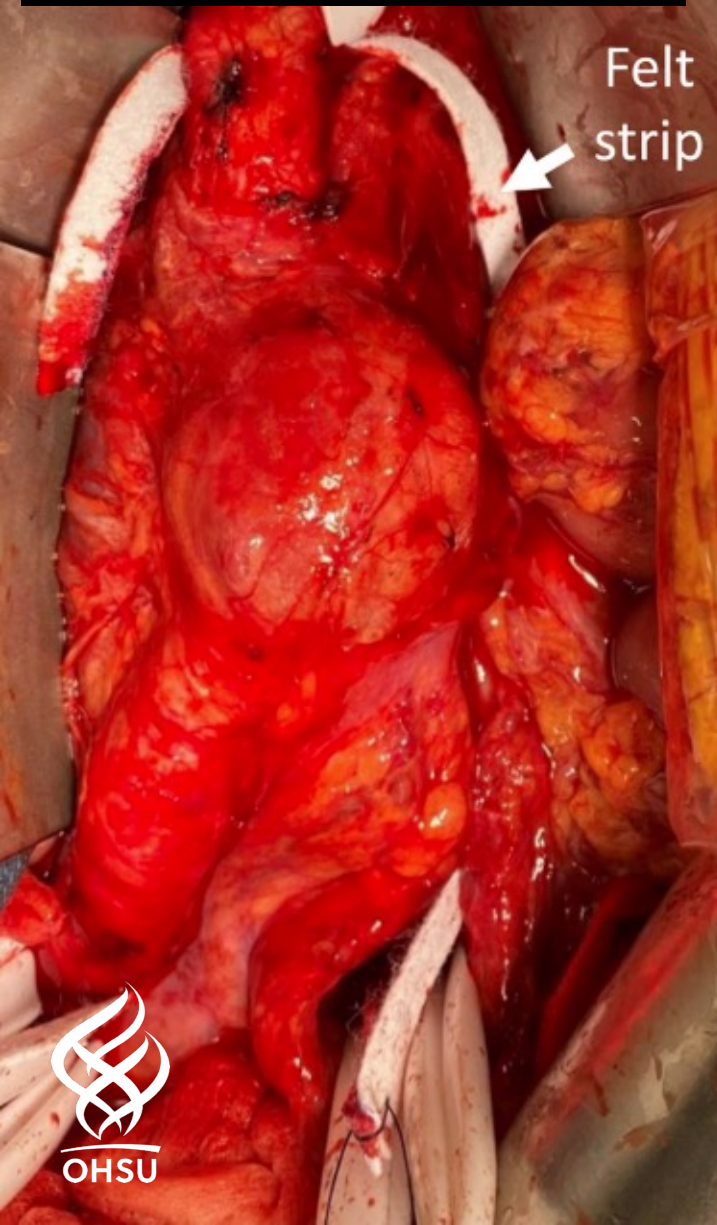
Collagen triple helix Gly-x-y

Glycine substitution affects collagen folding: Size, Charge



Pathogenic *COL3A1* variant types have different impact on tissue quality

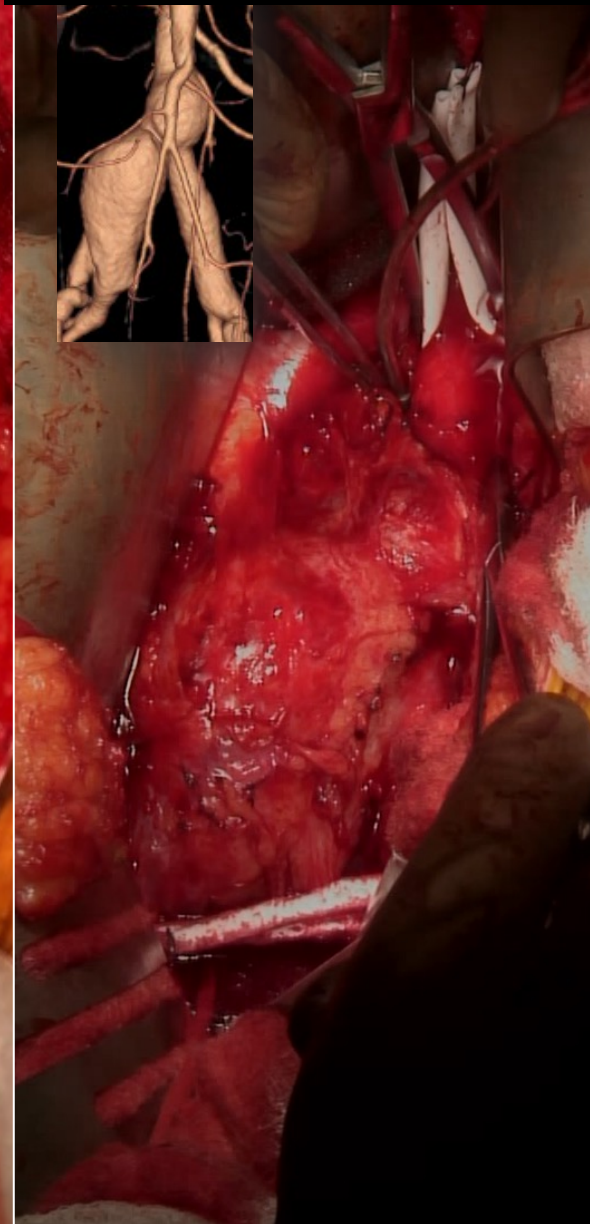
64 (c.2200C>A, p.Leu734Ile)



45 (c.1347+1delG)

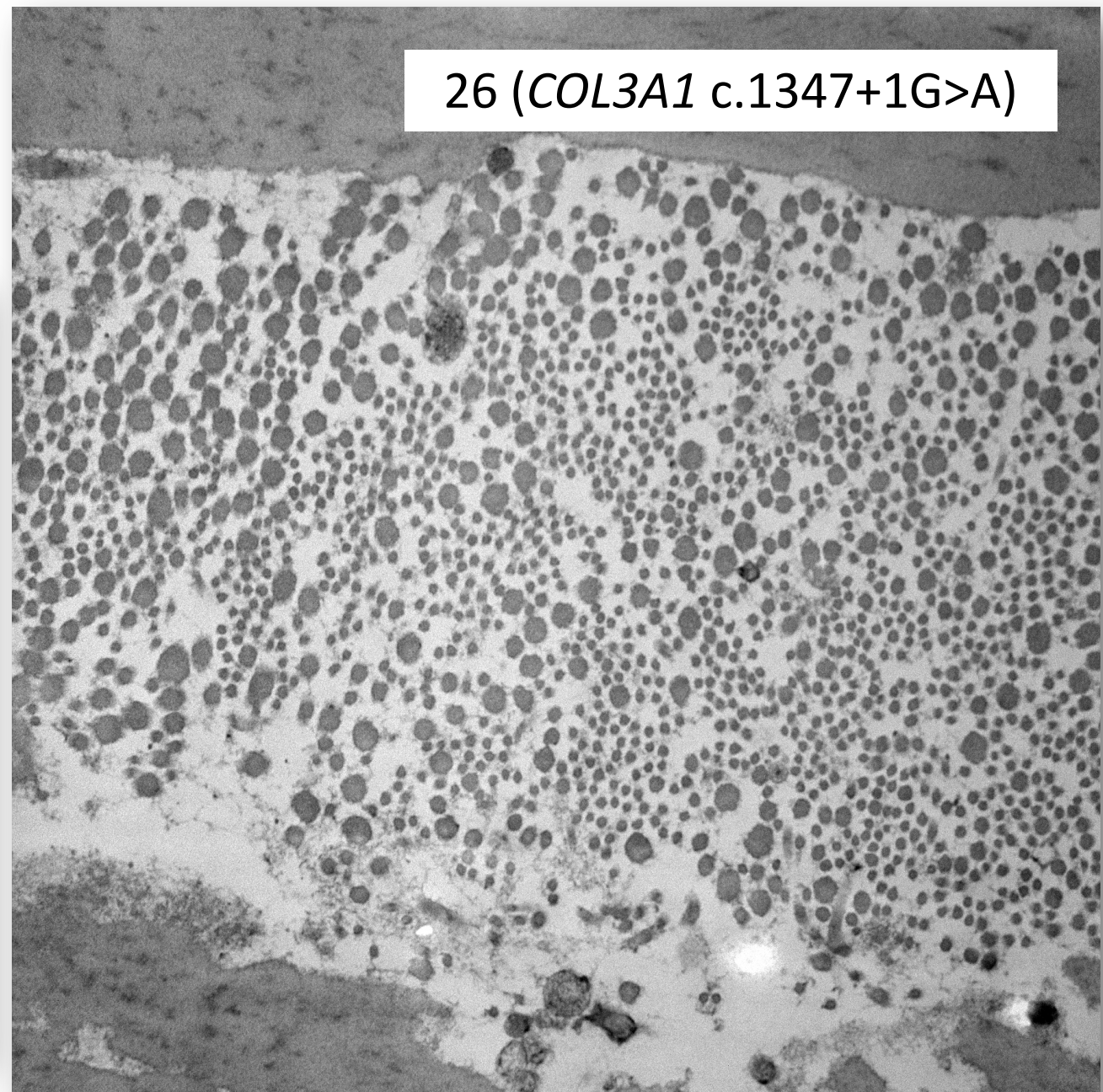


38 (c.718G>C, p.Gly240Arg)



26 (c.1347+1G>A)





10-23-24 LYS GR008 Iliac :
Cal: 0.002563 µm/pix

Iliac artery

500 nm
Direct Mag: 25000x
Tilt:0.02

Skin

Abdominal aorta

26 (*COL3A1* c.1347+1G>A)

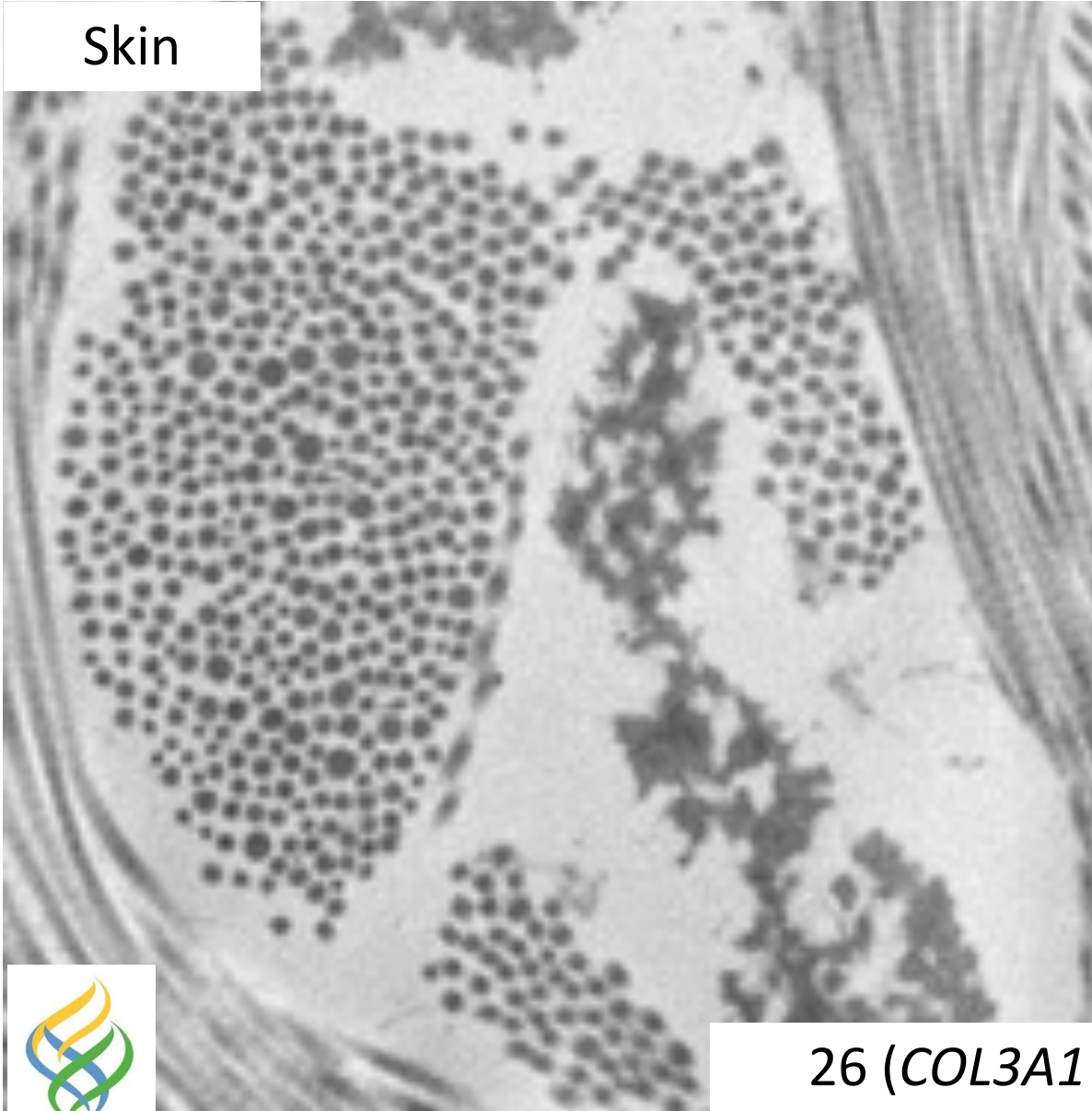
10-23-24 LYS GR008 skin_037
Cal: 0.006260 µm/pix

2 µm
Direct Mag: 9600x
Tilt: 0.00

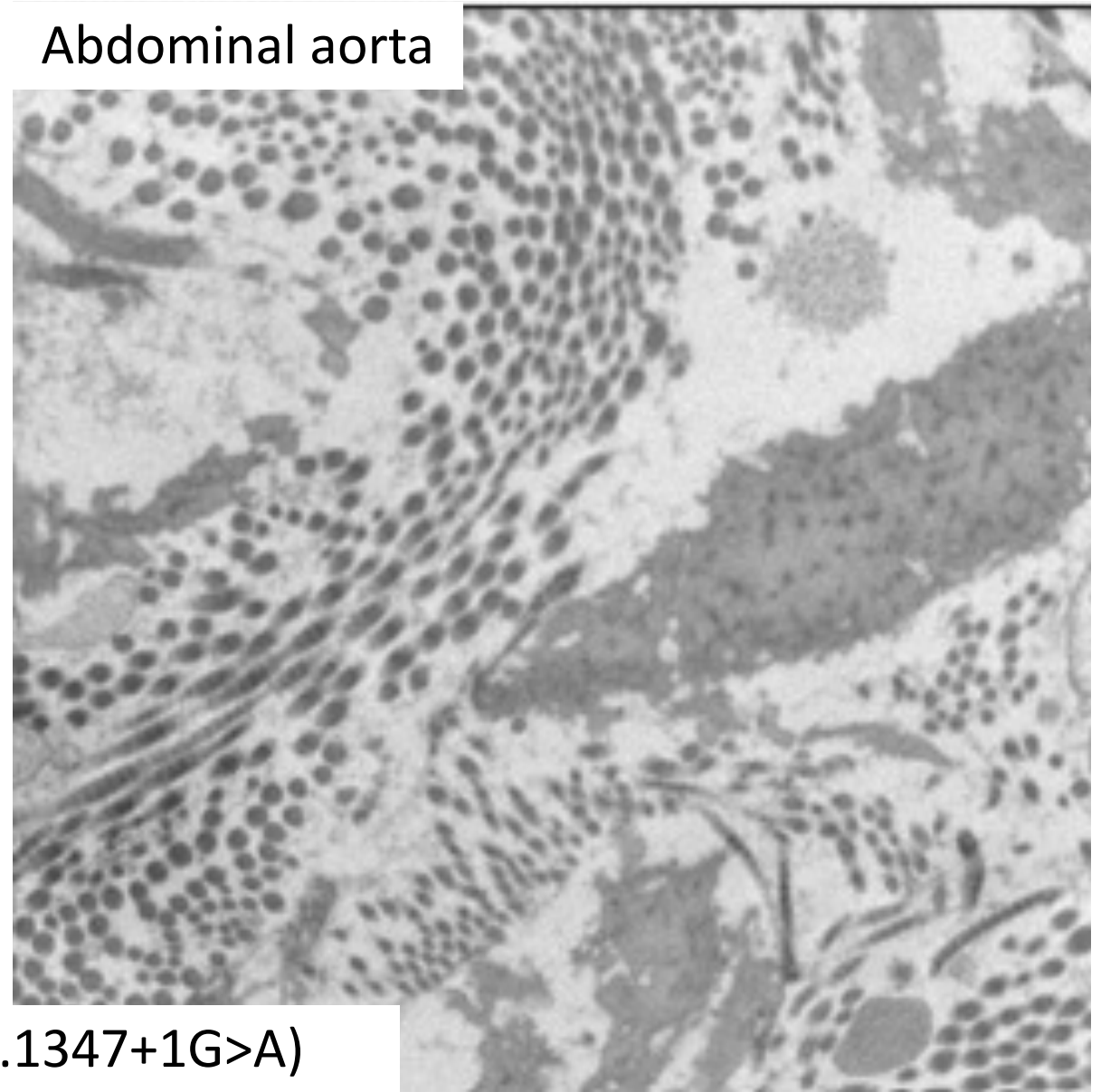
YS GR008 abd aorta_029
60 µm/pix

2 µm
Direct Mag: 9600x
Tilt: 0.02

Skin



Abdominal aorta



26 (*COL3A1* c.1347+1G>A)



genTAC

Endovascular thoracic aortic repair in confirmed or suspected genetically triggered thoracic aortic dissection

Sherene Shalhub, MD, MPH,^a Kim A. Eagle, MD,^b Federico M. Asch, MD,^c Scott A. LeMaire, MD,^{d,e} and Dianna M. Milewicz, MD, PhD,^f on behalf of the GenTAC Investigators for the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) Consortium, *Seattle, Wash; Ann Arbor, Mich; Washington, D.C.; and Houston, Tex*

August 2018

REVIEW ARTICLE

Braz J Cardiovasc Surg 2020 -

The Role of Thoracic Endovascular Aortic Repair (TEVAR) of Thoracic Aortic Diseases in Patients with Connective Tissue Disorders – A Literature Review

Amer Harky¹, MBChB, MSc, MRCS; Syed Mohammad Asim Hussain¹, MBChB, MSc, MRCS; Beverly MacCarthy-Ofosu¹, MBChB, BSc; Mohammad Usman Ahmad³, MBChB

JAMA Surgery | Original Investigation

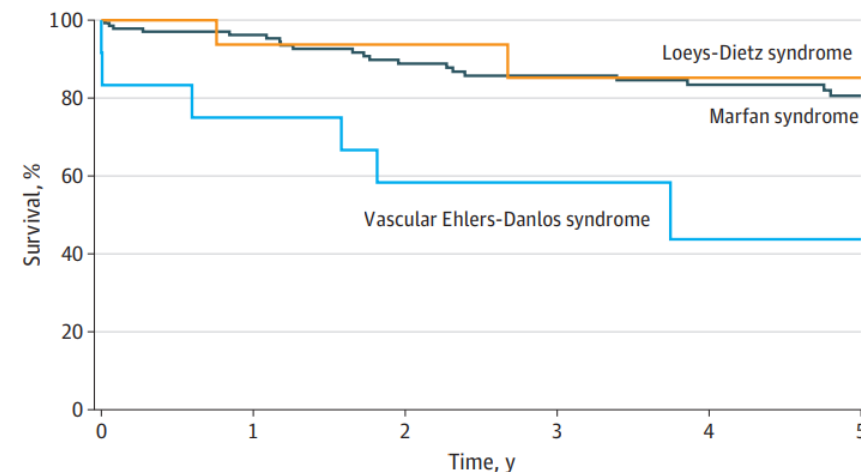
Outcomes After Endovascular Aortic Intervention in Patients With Connective Tissue Disease

Karl Wilhelm Olsson, MD, PhD; Kevin Mani, MD, PhD; Anne Burdess, MD, PhD; Suzannah Patterson, BS; Salvatore T. Scali, MD; Tilo Kölbel, MD, PhD; Giuseppe Panuccio, MD, PhD; Ahmed Eleshra, MD; Luca Bertoglio, MD; Vincenzo Ardita, MD, PhD; Germano Melissano, MD; Amish Acharya, MD; Colin Bicknell, MD;

Endovascular Aortic Intervention in Patients With Connective Tissue Disease (EVICTUS)

- N=171 (2005-2020)
- 18 aortic centers in Europe, Asia, North America, & New Zealand.
- Marfan syndrome: Clinical diagnosis
- Loeys-Dietz syndrome: genetic testing
- VEDS: Clinical diagnosis
- Median follow-up: 4.7 years (1.9-9.2)

Figure. Kaplan-Meier Estimate of Survival for Patients With Connective Tissue Disease After Endovascular Treatment of Aortic Pathology



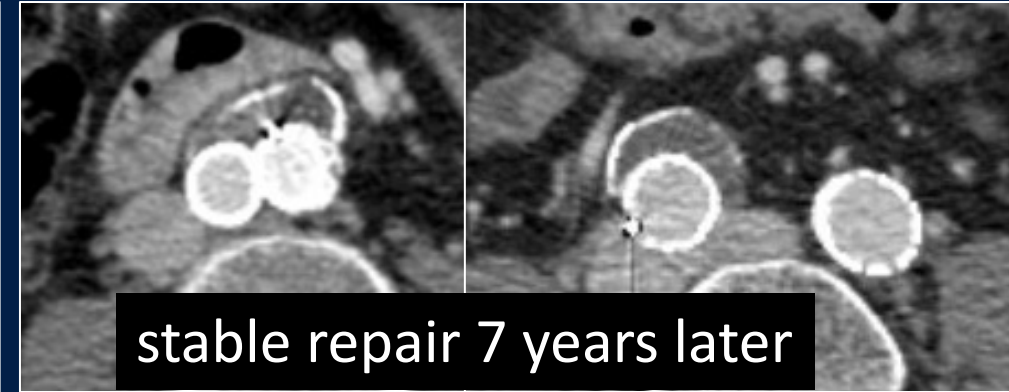
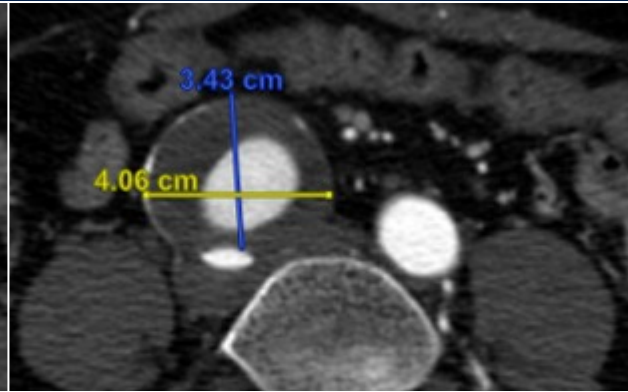
No. at risk	142	110	92	81	69	57
Marfan syndrome	17	15	12	11	7	4
Loeys-Dietz syndrome	12	10	8	7	4	3
Vascular Ehlers-Danlos syndrome						



Biological twinning & Shared Decision Making

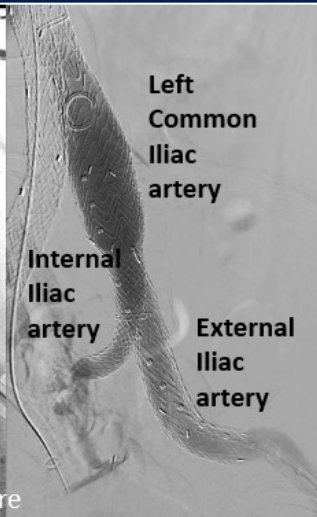
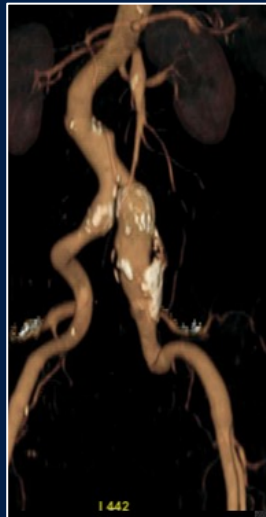
Using pre-existing data from family members (or similar variants)

60-year-old female



stable repair 7 years later

65-year-old male

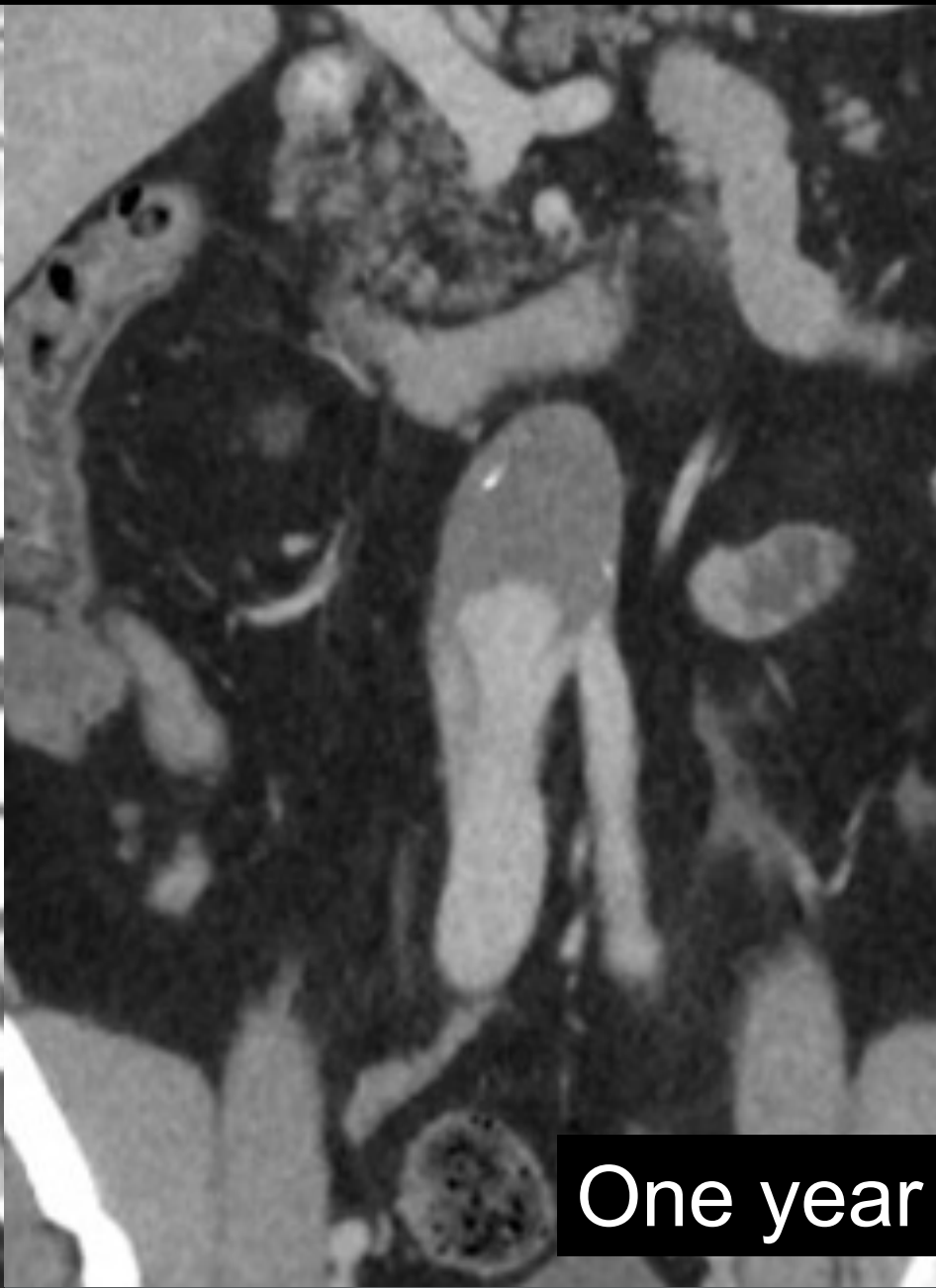
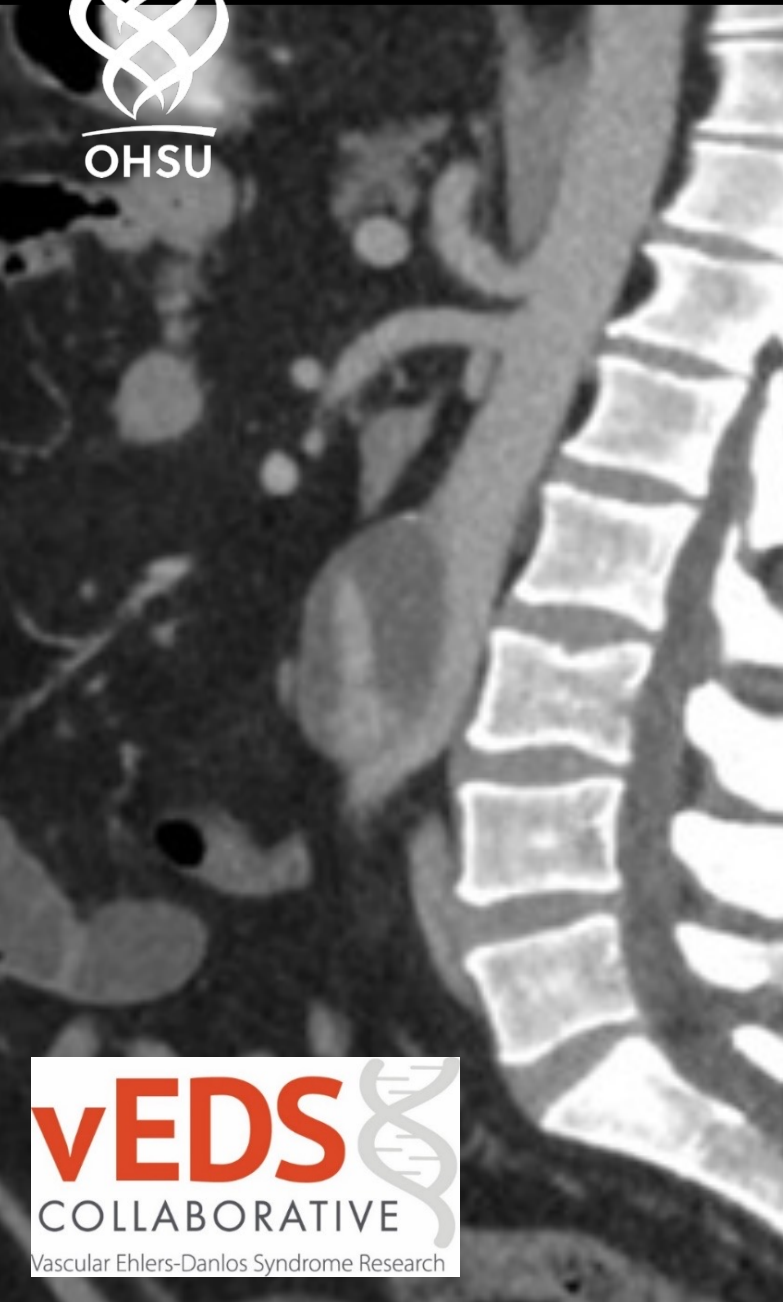


stable repair 4 years later

VEDS *COL3A1* c.555delT p.Gly186Valfs*36, Null variant



39-year-old male (*COL3A1* c.970G>A p.Gly0324Ser Missense variant)



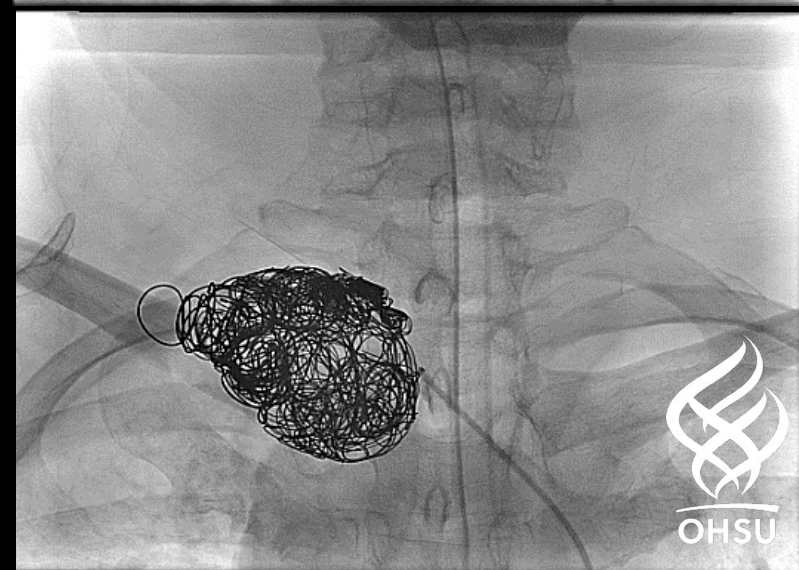
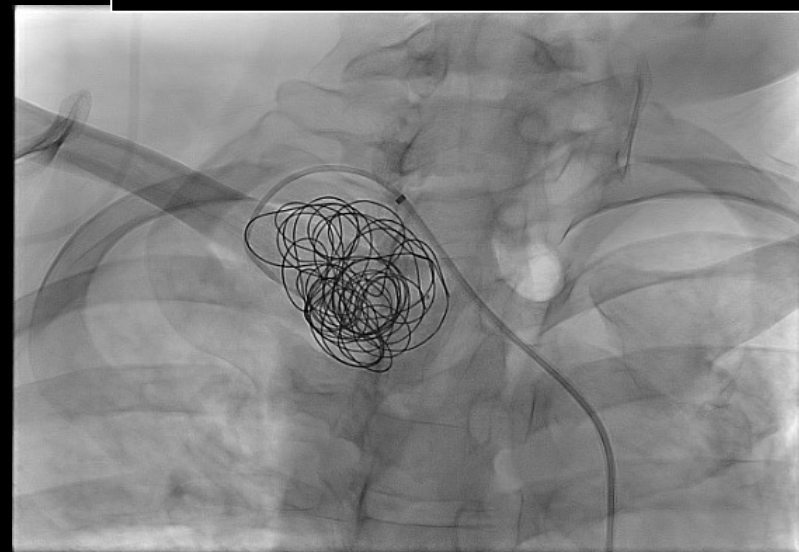
One year follow up

Subclavian Artery aneurysm embolization



Journal of
Vascular Surgery
Cases, Innovations and Techniques

Published: December 16, 2022



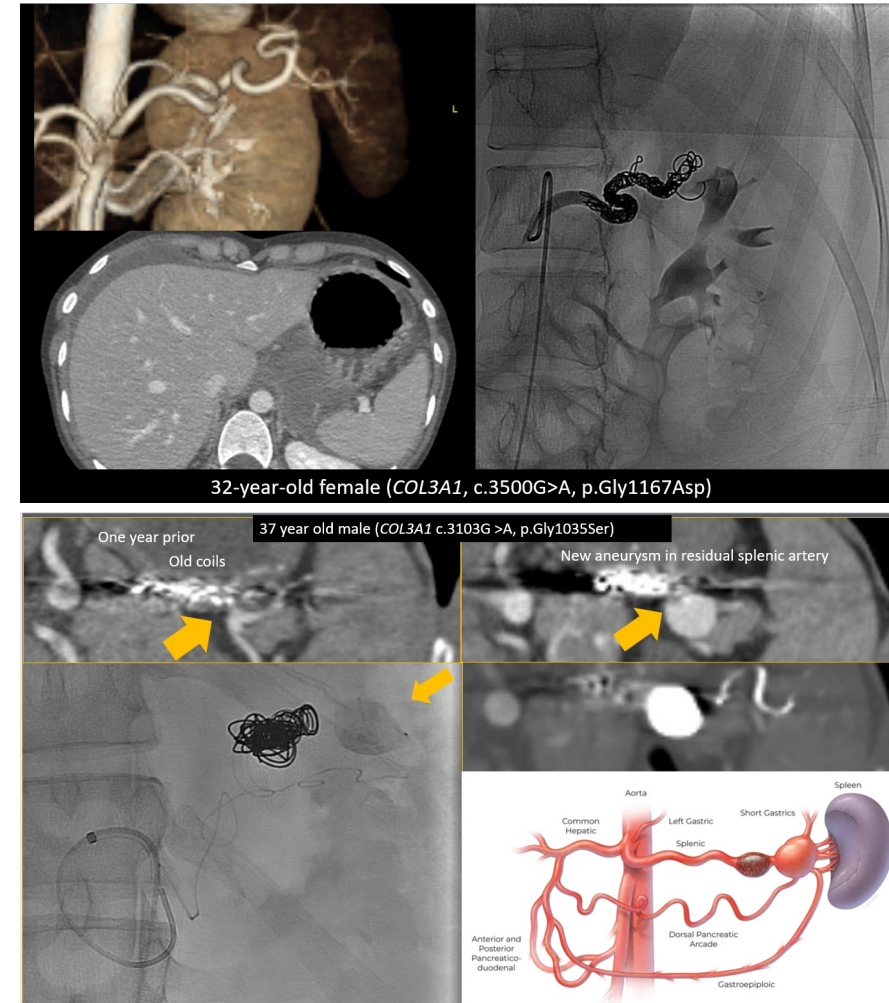
4.09 cm

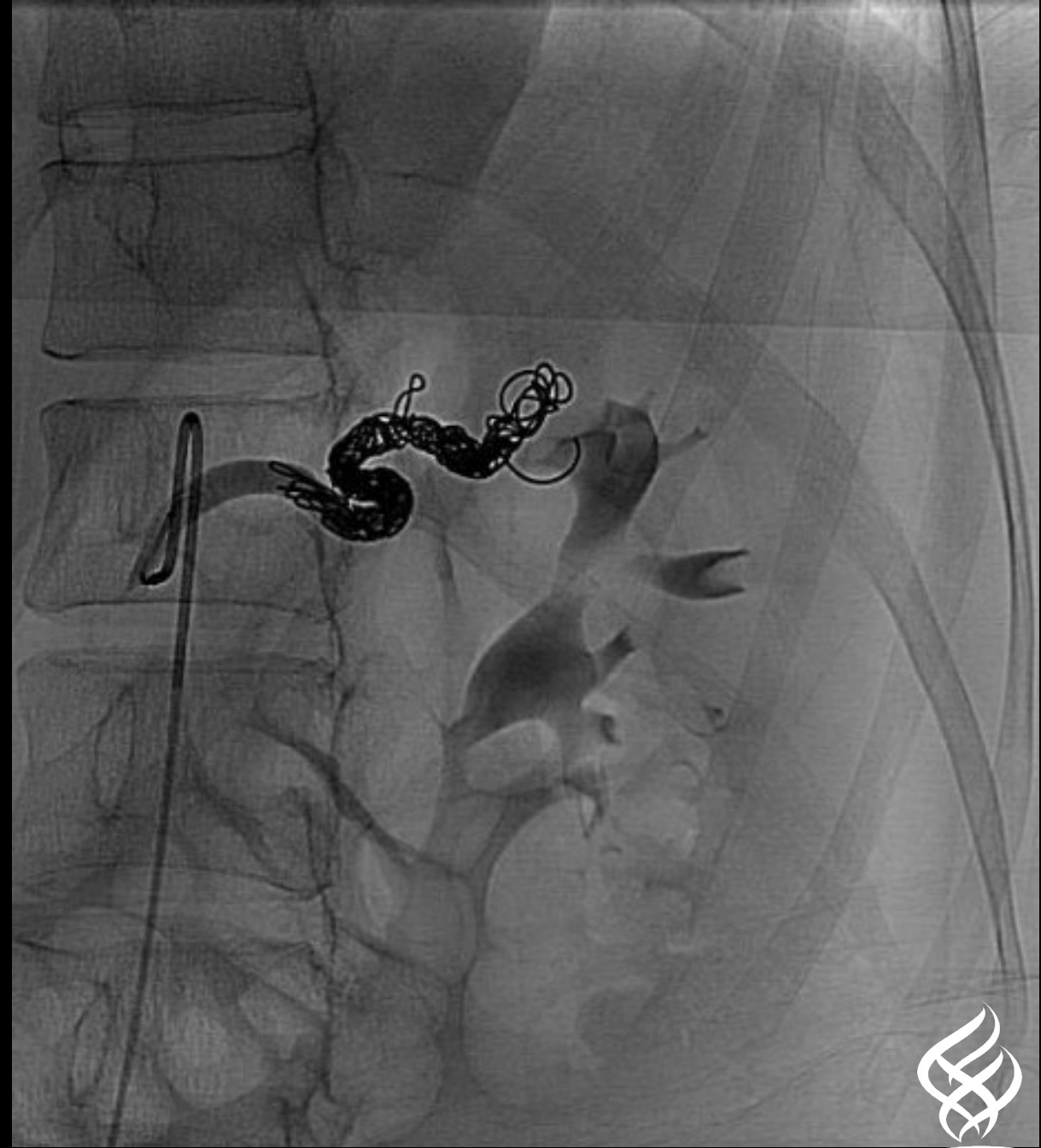
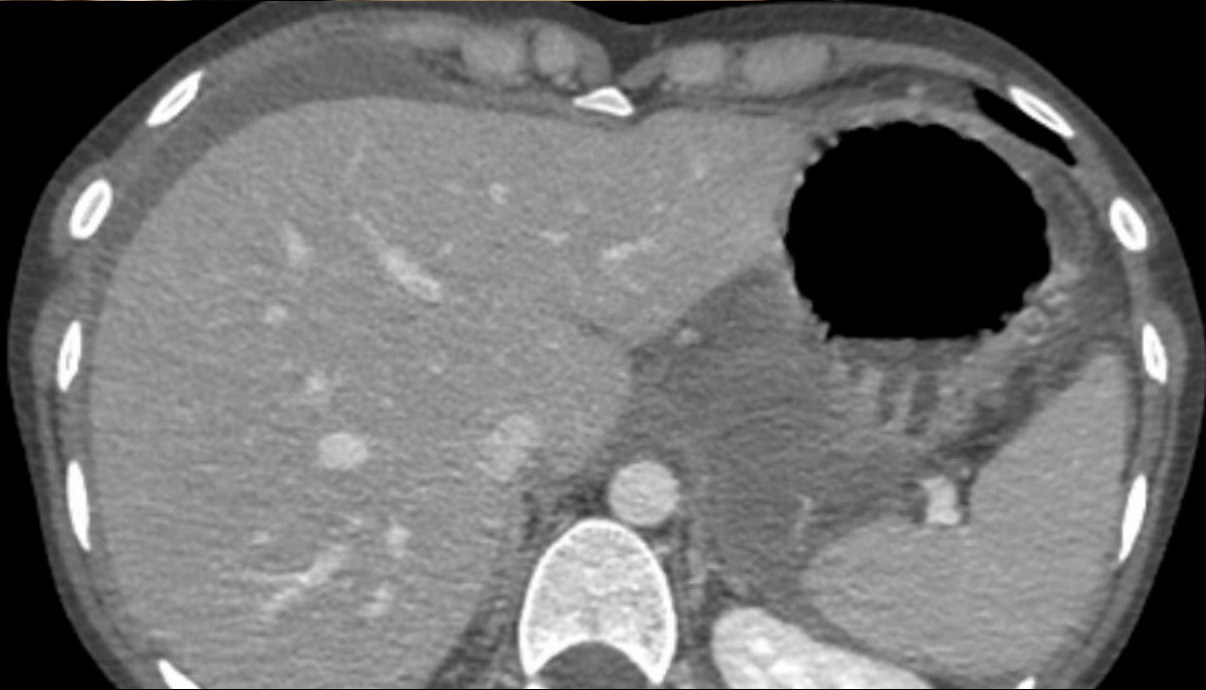


Splenic artery pathology presentation, operative interventions, and outcomes in 88 patients with vascular Ehlers-Danlos syndrome

Sherene Shalhub, MD, MPH, FACS, DFSVS,^a Reginald Nkansah, MD,^b Asmaa El-Ghazali, MD,^c Charles J. Hillenbrand, MD,^b Sandeep S. Vaidya, MBBS,^d Ulrike Schwarze, MD,^e and Peter H. Byers, MD,^e
Portland, OR and Seattle, WA

- Cross-sectional analysis of 1547 individuals presented between 1992 and 2021 with pathogenic variants in COL3A1
- N=88 / 40 interventions in 34 patients (38.6%)
 - 6 (18%) more than one intervention
- **21 Open surgical repairs**
 - 10 Splenectomies
 - 17 (81%) ruptured splenic artery/spleen rupture
 - 19% intraoperative mortality / 1 AVF 2 years later
- **18 Endovascular interventions (Embolization (Most since 2010))**
 - 8 (47%) ruptured aneurysms
 - No deaths or access site complications
 - *Four patients (23.5%) had a new SAA in the remaining splenic artery*





32-year-old female (*COL3A1*, c.3500G>A, p.Gly1167Asp)

Permissive Hypotension

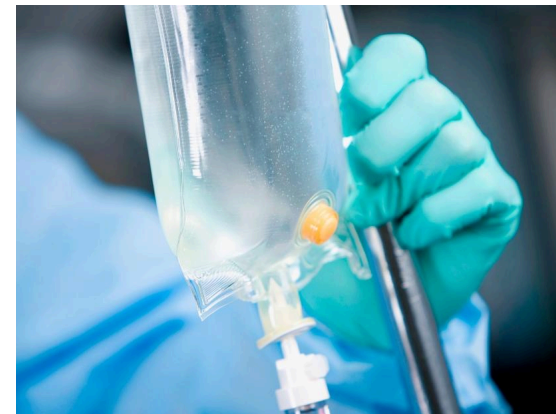
“Permissive hypotension to maintain a systolic blood pressure of 80 mm Hg limits volume overload and appears sufficient to maintain critical end-organ perfusion”

The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm

Elliot L. Chaikof, MD, PhD,^a Ronald L. Dalman, MD,^b Mark K. Eskandari, MD,^c Benjamin M. Jackson, MD,^d W. Anthony Lee, MD,^e M. Ashraf Mansour, MD,^f Tara M. Mastracci, MD,^g Matthew Mell, MD,^b M. Hassan Murad, MD, MPH,^h Louis L. Nguyen, MD, MBA, MPH,ⁱ Gustavo S. Oderich, MD,^j Madhukar S. Patel, MD, MBA, ScM,^{a,k} Marc L. Schermerhorn, MD, MPH,^a and Benjamin W. Starnes, MD,^l
Boston, Mass; Palo Alto, Calif; Chicago, Ill; Philadelphia, Pa; Boca Raton, Fla; Grand Rapids, Mich; London, United Kingdom; Rochester, Minn; and Seattle, Wash

JVS 2018 Jan;67:2-77

The risk of secondary events may increase with the severity of the initial event, the length of the hospital stay, the invasive character of treatment, and the extent of fluid overload



37-year-old male (*COL3A1* c.3103G >A, p.Gly1035Ser)

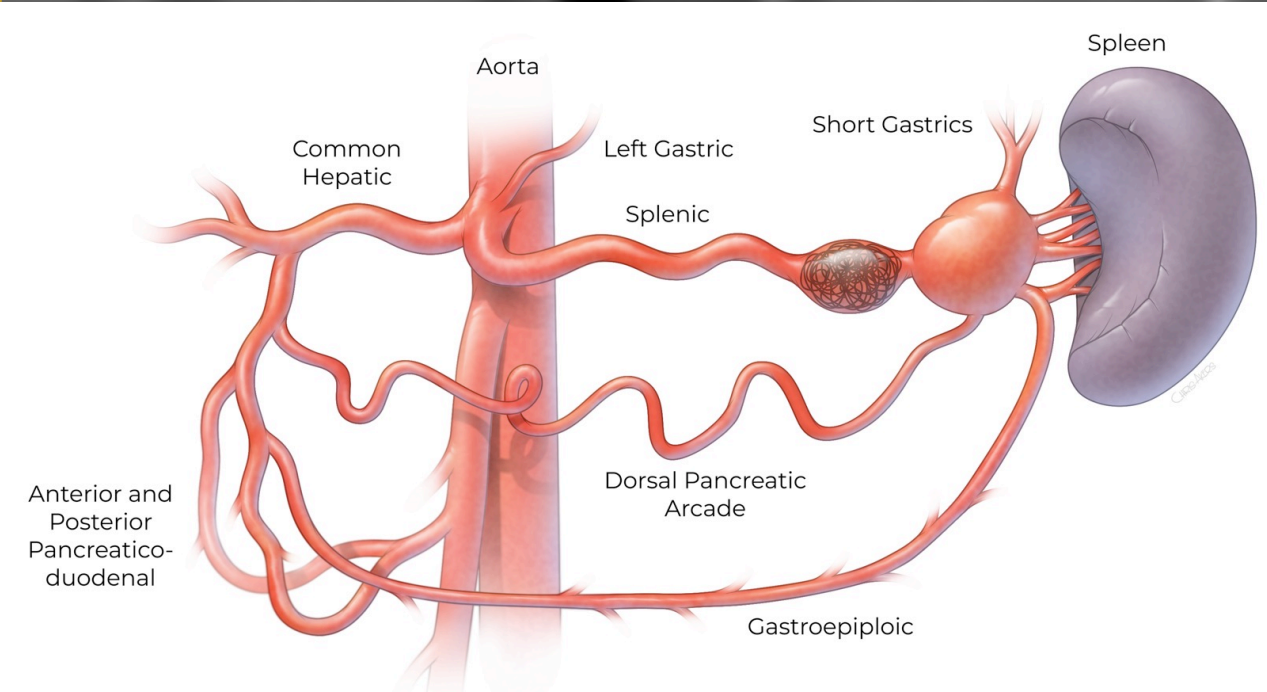
One year prior
Old coils

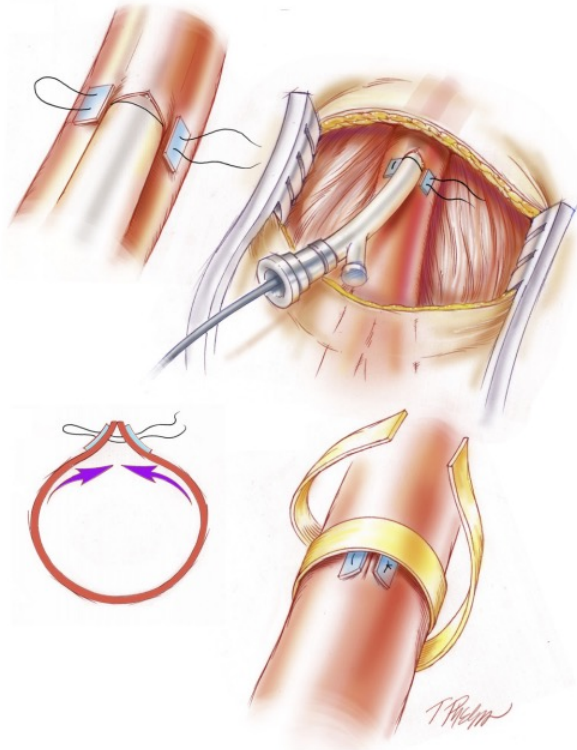


New aneurysm in residual splenic artery



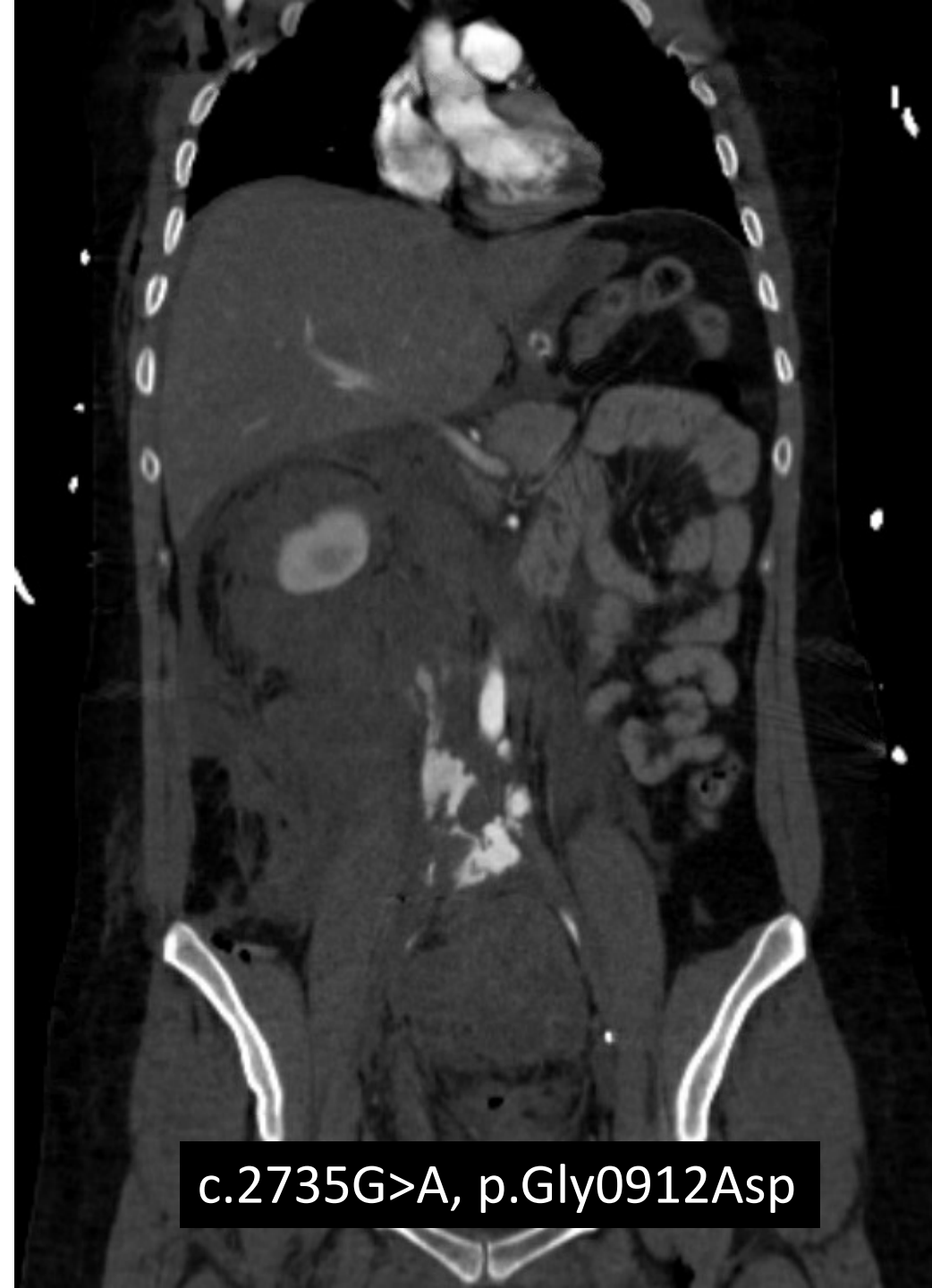
Ruptured middle colic artery 2 years later requiring laparotomy. Iatrogenic injury to spleen → splenectomy





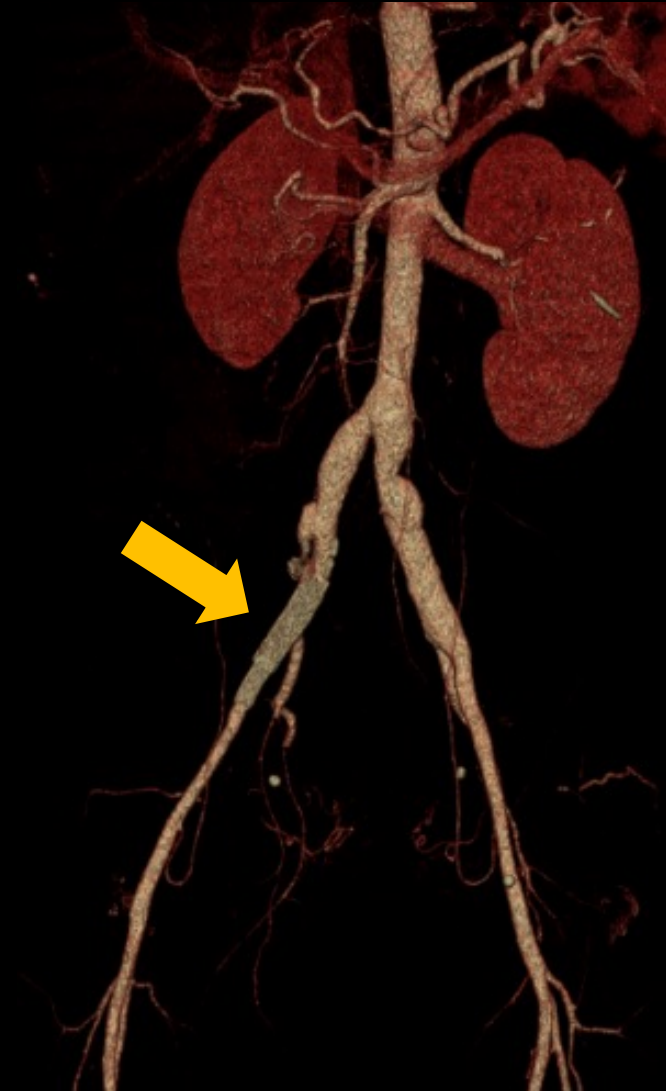
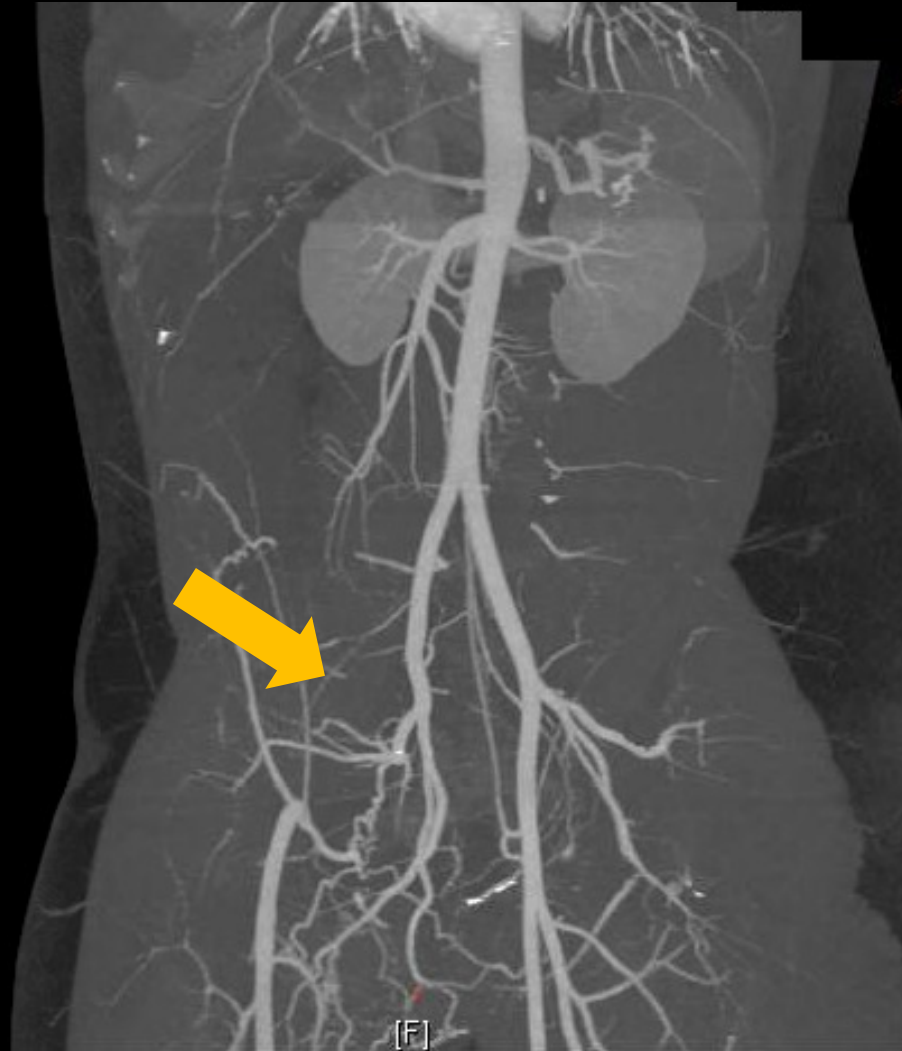
Wei Lum et al, *Annals of Vascular Surgery*, 2012

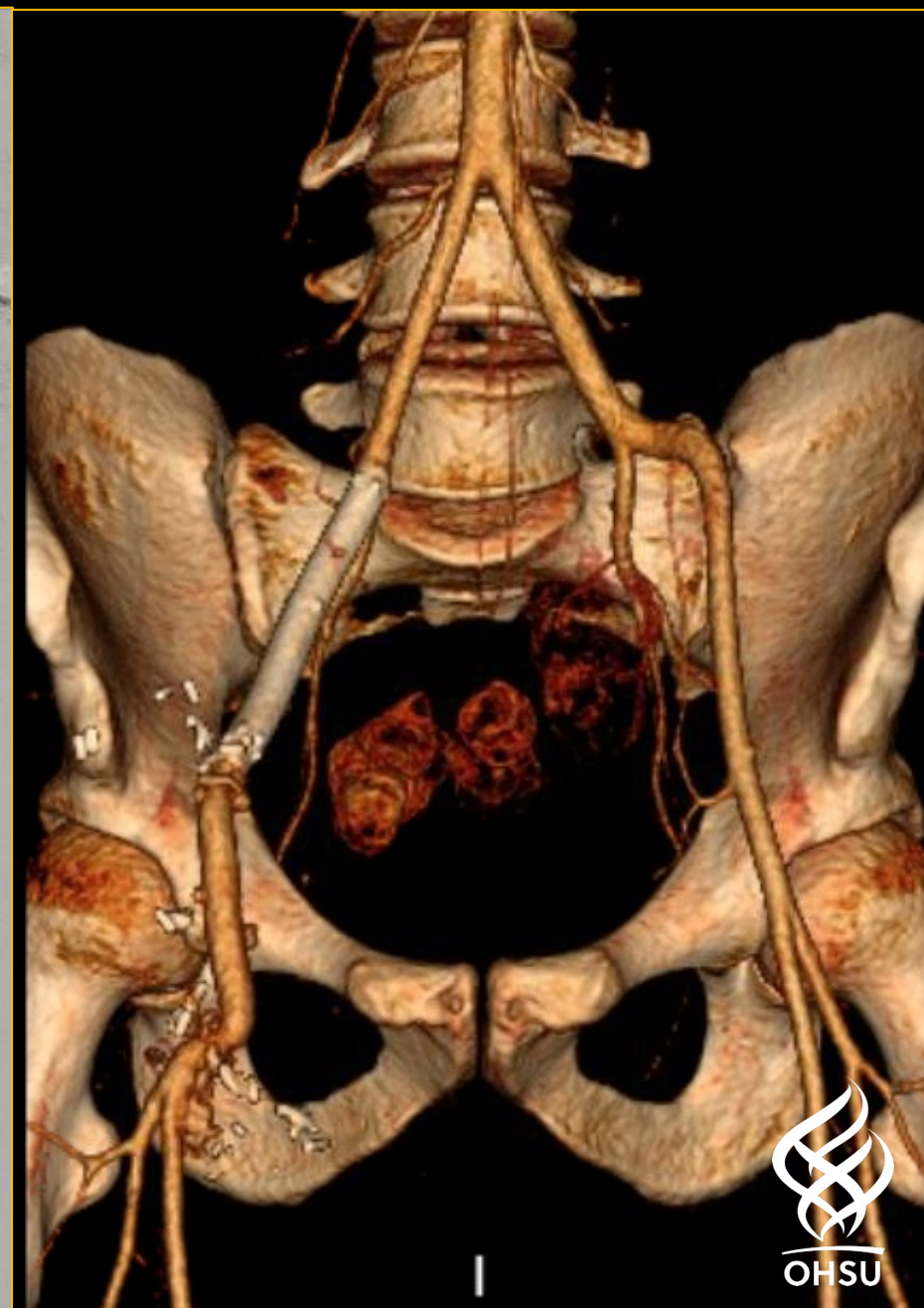
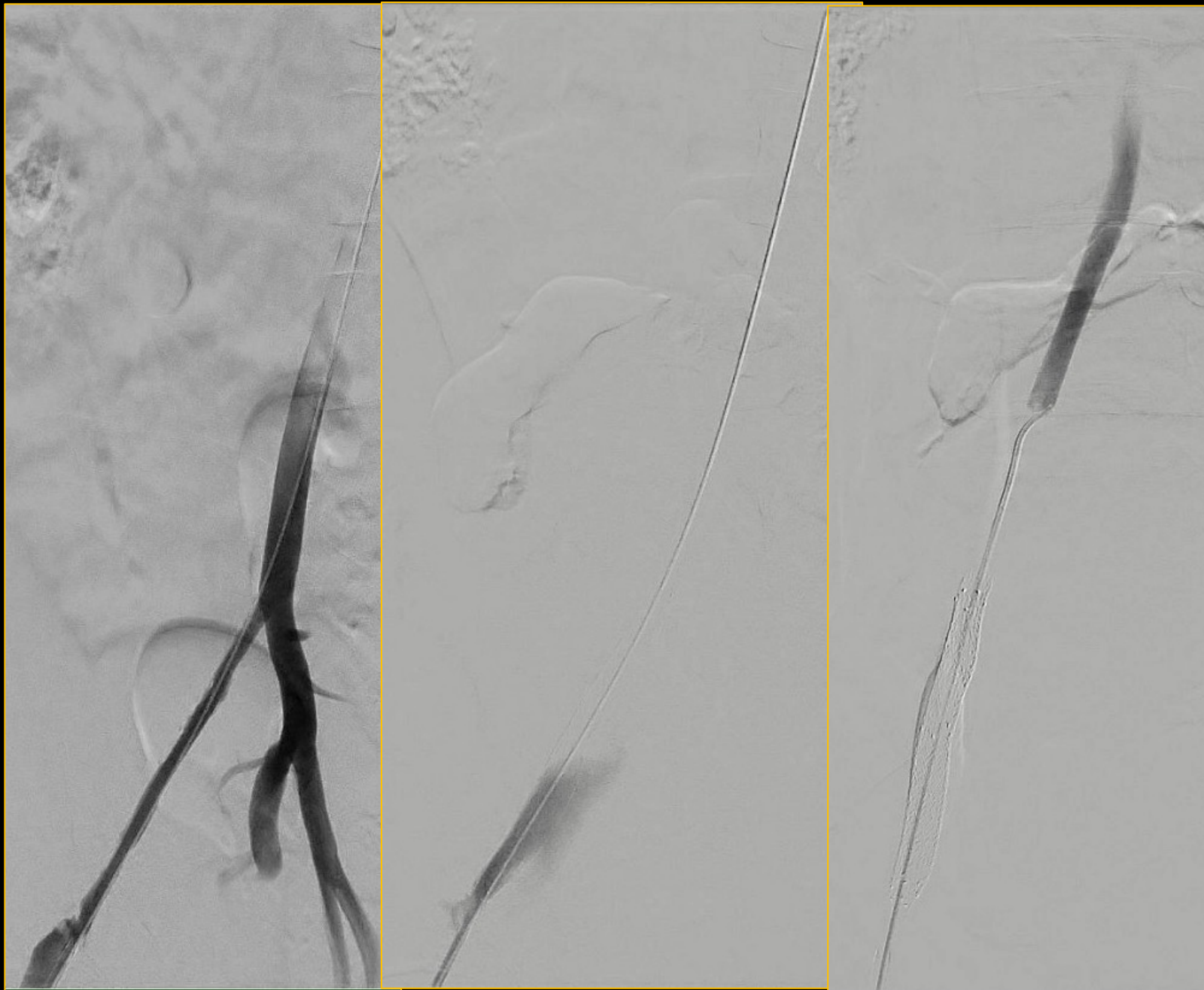
- Gentle wire manipulation
- Softer wires/catheters
- Access site complications (early and delayed) – consider open exposure and repair of the femoral arteries



c.2735G>A, p.Gly0912Asp

External Iliac Artery







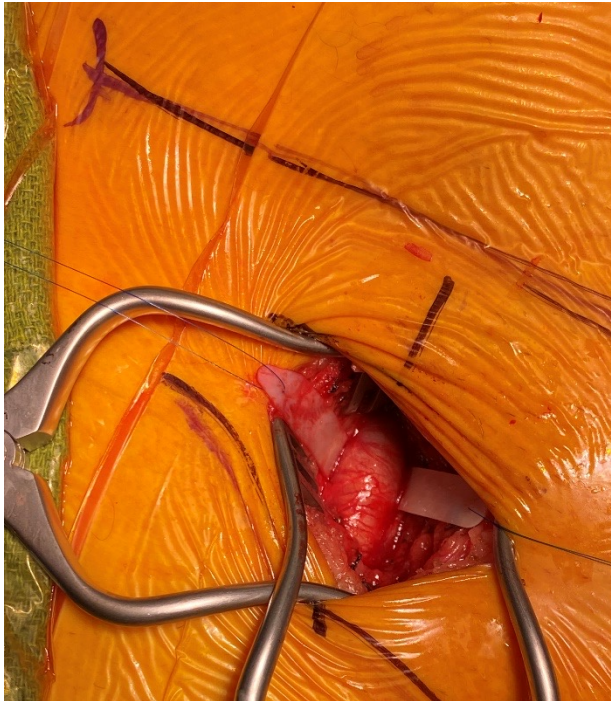
Endovascular Technical Tips

- Minimal to no oversizing
- No ballooning of seal zones
- Prefer devices with lower radial force
- Ideally, graft to graft
- Be mindful of potential access site complications (early and delayed)

Avoid repeated sheath exchanges

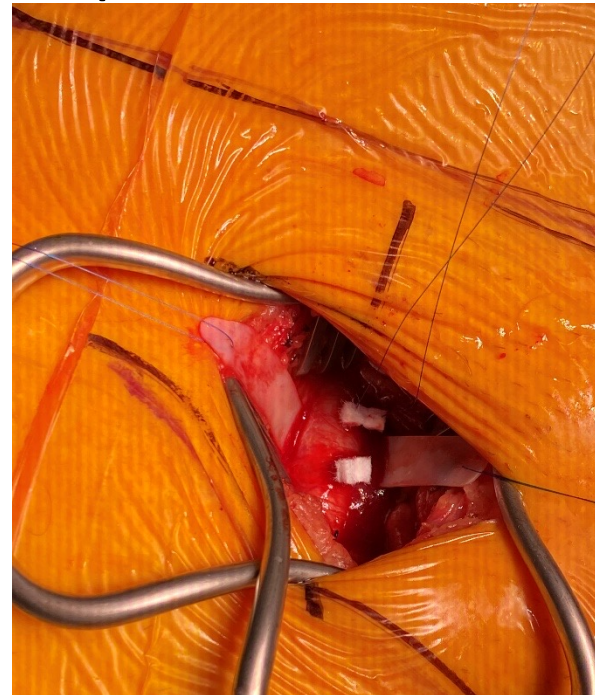


Plan for open
exposure of
the common
femoral artery
Avoid vessel
loops



Access site considerations

“U” stitch
monofilament
pledgeted
repair



Avoid
repeated
sheath
exchanges



Circumferential
artery
reinforcement





NW GAAP S

Living Better with Marfan, Loeys-Dietz, & VEDS

Saturday, May 11, 2024
Oregon Health & Science University
Portland, Oregon



DOERNBECHER
CHILDREN'S
Hospital

