Thrombus Management in STEMI – Insights from the CHEETAH Trial

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• ***Research Support***	• **Abbott Vascular, Boston Scientific, Shockwave Medical, TriReme Medical, Surmodics, MedAlliance, Veryan Medical, Concept Medical, Acotec**
• ***Consulting Fees/Honoraria***	• **Terumo, Abiomed, Inari, Penumbra, Canon**
• ***Advisory Board***	• **Abbott, Medtronic, Boston Scientific, R3, Philips, Cordis**
• ***Equity***	• **ANT, Encompass Vascular, eFemoral**

Background on Coronary Thrombus

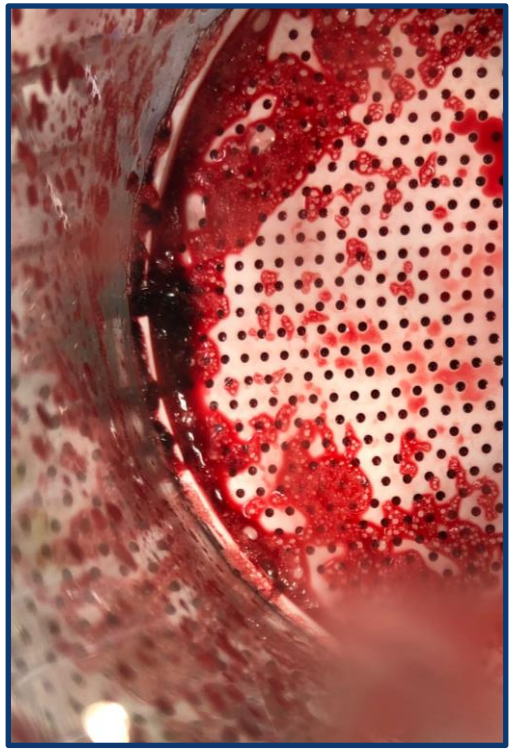
Coronary Thrombus

- Large thrombus burden in PCI may increase the likelihood of:
  - PCI MACE rates[,2]
  - Stent thrombosis
  - No reflow[3]
- Potential consequences of no reflow:
  - Lower survival rate at 5 years[4]
  - Threefold increase in mortality or heart failure–related hospitalizations for patients who develop microvascular obstruction[5, a]

2. Vecchio S, Varani E, Chechi T, et al. Coronary thrombus in patients undergoing primary PCI for STEMI: prognostic significance and management. *World J Cardiol*. 2014 Jun 26;6(6):381–392. doi:10.4330/wjc.v6.i6.381.
3. Yang L, Cong H, Lu Y, et al. Prediction of no-reflow phenomenon in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Medicine (Baltimore)*. 2020 Jun 26;99(26):e20152. doi:10.1097/MD.0000000000020152.
4. Ndrepepa G, Tiroch K, Fusaro M, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol*. 2010 May 25;55(21):2383–2389. doi:10.1016/j.jacc.2009.12.054.
5. de Waha S, Patel MR, Granger CB, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. *Eur Heart J*. 2017 Dec 14;38(47):3502–3510. doi:10.1093/eurheartj/ehx414.
The clinical results presented herein are for informational purposes only, and may not be predictive for all patients. Image used with permission. Consent on file at Penumbra, Inc. Individual results may vary depending on patient-specific attributes and other factors.

Addressing Thrombus in the Coronaries

- Traditional treatment options are limited
- Past trials have shown limited to no difference with manual aspiration[1]
- Thrombus remains a barrier of procedural success

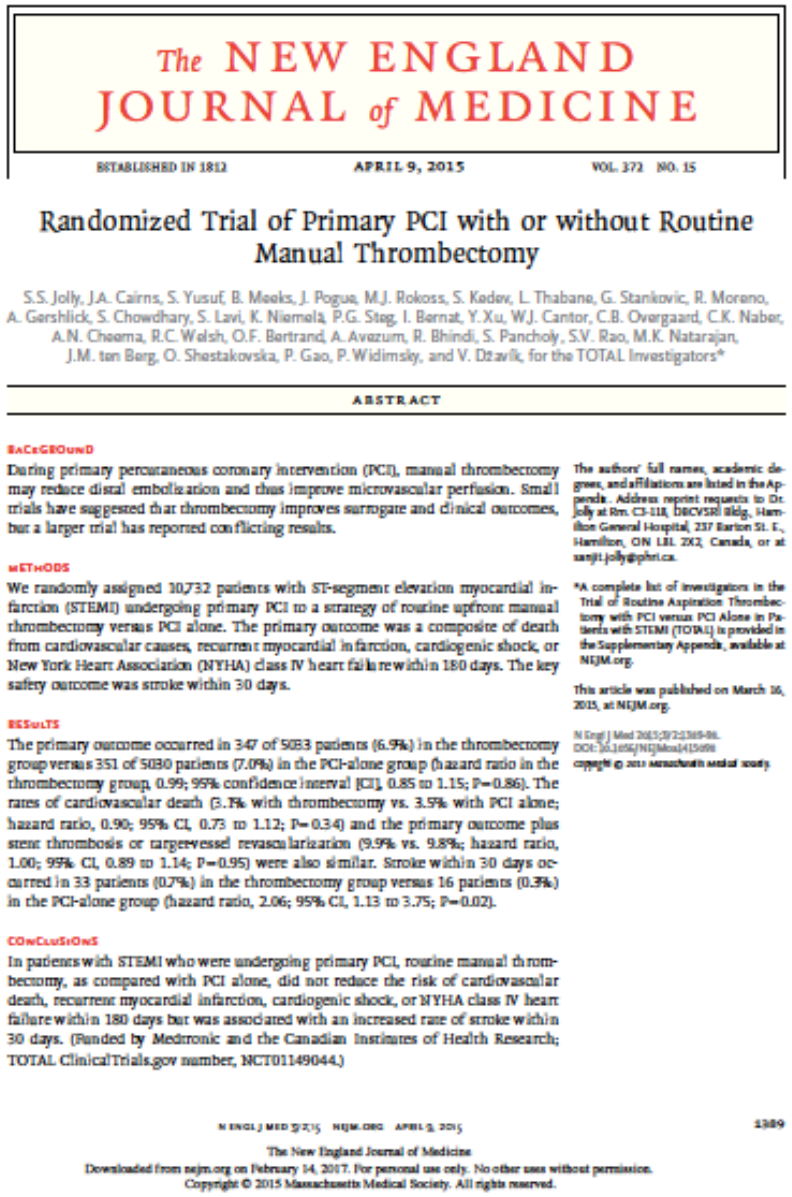


Current Evidence Landscape

TOTAL Trial

Key Points

- Utilized manual aspiration
  - Export® – Older Technology
  - Did not improve outcomes
- Treated all patients with or without clot
- Increased rate of stroke at 30 days



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Randomized Trial of Primary PCI with or without Routine Manual Thrombectomy

S.S. Jolly, J.A. Cairns, S. Yusuf, B. Meeks, J. Pogue, M.J. Rokoss, S. Kedev, L. Thabane, G. Stankovic, R. Moreno, A. Gershlick, S. Chowdhary, S. Lavi, K. Niemelä, P.G. Steg, I. Bernat, Y.Xu, W.J. Cantor, C.B. Overgaard, C.K. Naber, A.N. Cheema, R.C. Welsh, O.F. Bertrand, A. Avezum, R. Bhindi, S. Pancholy, S.V. Rao, M.K. Natarajan, J.M. ten Berg, O. Shestakovska, P. Gao, P. Widimsky, and V. Džavík, for the TOTAL Investigators*

ABSTRACT

BACKGROUND

During primary percutaneous coronary intervention (PCI), manual thrombectomy may reduce distal embolization and thus improve microvascular perfusion. Small trials have suggested that thrombectomy improves surrogate and clinical outcomes, but a larger trial has reported conflicting results.

METHODS

We randomly assigned 10,732 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI to a strategy of routine upfront manual thrombectomy versus PCI alone. The primary outcome was a composite of death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within 180 days. The key safety outcome was stroke within 30 days.

RESULTS

The primary outcome occurred in 347 of 5033 patients (6.9%) in the thrombectomy group versus 351 of 5030 patients (7.0%) in the PCI-alone group (hazard ratio in the thrombectomy group, 0.99; 95% confidence interval [CI], 0.85 to 1.15; P=0.86). The rates of cardiovascular death (3.7% with thrombectomy vs. 3.5% with PCI alone; hazard ratio, 0.90; 95% CI, 0.73 to 1.12; P=0.34) and the primary outcome plus stent thrombosis or target-vessel revascularization (9.9% vs. 9.8%; hazard ratio, 1.00; 95% CI, 0.89 to 1.14; P=0.95) were also similar. Stroke within 30 days occurred in 33 patients (0.7%) in the thrombectomy group versus 16 patients (0.3%) in the PCI-alone group (hazard ratio, 2.06; 95% CI, 1.13 to 3.75; P=0.02).

CONCLUSIONS

In patients with STEMI who were undergoing primary PCI, routine manual thrombectomy, as compared with PCI alone, did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days but was associated with an increased rate of stroke within 30 days. (Funded by Medtronic and the Canadian Institutes of Health Research; TOTAL ClinicalTrials.gov number, NCT01149044.)

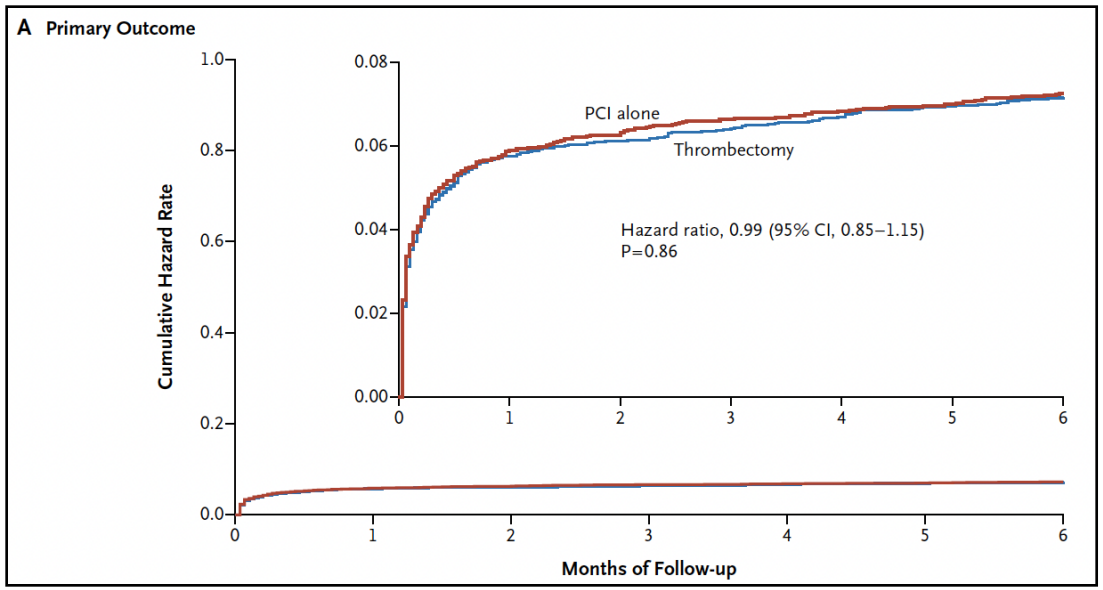
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jolly at Rm. C3-118, HSCVSRI Bldg., Hamilton General Hospital, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at sanjit.jolly@phri.ca.

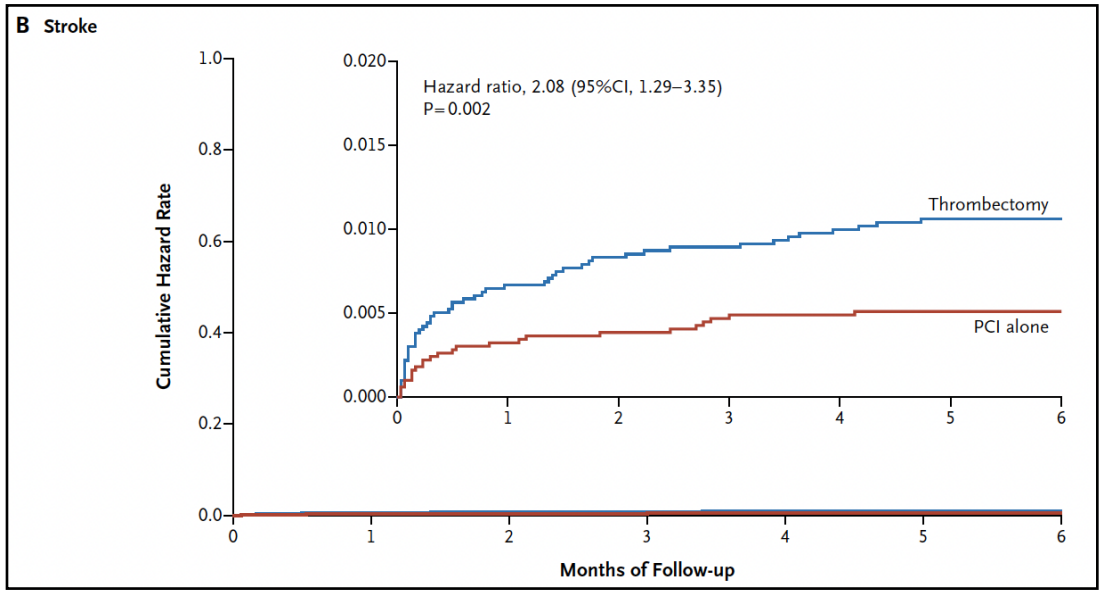
*A complete list of investigators in the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 16, 2015, at NEJM.org.

N Engl J Med 2015;372:1389-98.
DOI: 10.1056/NEJMoa1415096

TOTAL Trial





- Primary and Secondary Outcomes: **No difference** between thrombectomy group and PCI alone group
- increase in stroke rate for patients who received manual thrombectomy

Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med. 2015;372:1389-1398. doi: 10.1056/NEJMoa1415098.

Thrombus Aspiration in Patients with High Thrombus Burden in the TOTAL Trial

Discussion

There may be a potential for future thrombus removal devices to reduce mortality if they are able to avoid an increased stroke risk. Further innovation and research are needed in this high-risk population.

Conclusion

Thrombus burden remains an important risk factor for mortality during primary PCI and new therapies are needed to improve the outcomes of these patients.

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Thrombus Aspiration in Patients With High Thrombus Burden in the TOTAL Trial

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ABSTRACT

BACKGROUND Routine thrombus aspiration in patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) does not improve clinical outcomes. However, there is remaining uncertainty about the potential benefit in those patients with high thrombus burden, where there is a biological rationale for greater benefit.

OBJECTIVES The purpose of this study was to evaluate the benefit of thrombus aspiration among STEMI patients with high thrombus burden.

METHODS TOTAL (ThrOmbectomy with PCI vs. PCI ALone in patients with STEMI) was a randomized trial of routine manual thrombectomy versus PCI alone in patients with STEMI (n = 10,732). High thrombus burden (thrombolysis In Myocardial Infarction thrombus grade ≥3) was a pre-specified subgroup.

RESULTS The primary outcome of cardiovascular (CV) death, MI, cardiogenic shock, or heart failure was not different at 1 year with thrombus aspiration in patients with high thrombus burden (8.1% vs. 8.3% thrombus aspiration; hazard ratio [HR]: 0.97; 95% confidence interval [CI]: 0.84 to 1.13) or low thrombus burden (6.0% vs. 5.0% thrombus aspiration; HR: 1.22; 95% CI: 0.73 to 2.05; interaction p = 0.41). However, among patients with high thrombus burden, stroke at 30 days was more frequent with thrombus aspiration (31 [0.7%] thrombus aspiration vs. 16 [0.4%] PCI alone, HR: 1.90; 95% CI: 1.04 to 3.48). In the high thrombus burden group, thrombus aspiration did not significantly improve CV mortality at 30 days (HR: 0.78; 95% CI: 0.61 to 1.01; p = 0.06) and at 1 year (HR: 0.88; 95% CI: 0.72 to 1.09; p = 0.25). Irrespective of treatment assignment, high thrombus burden was an independent predictor of death (HR: 1.78; 95% CI: 1.05 to 3.01).

CONCLUSIONS In patients with high thrombus burden, routine thrombus aspiration did not improve outcomes at 1 year and was associated with an increased rate of stroke. High thrombus burden is still an important predictor of outcome in STEMI. (A Trial of routine aspiration ThrOmbectomy with PCI vs. PCI ALone in patients with STEMI [TOTAL]; NCT01149044) (J Am Coll Cardiol 2018;72:1589–96) © 2018 by the American College of Cardiology Foundation.

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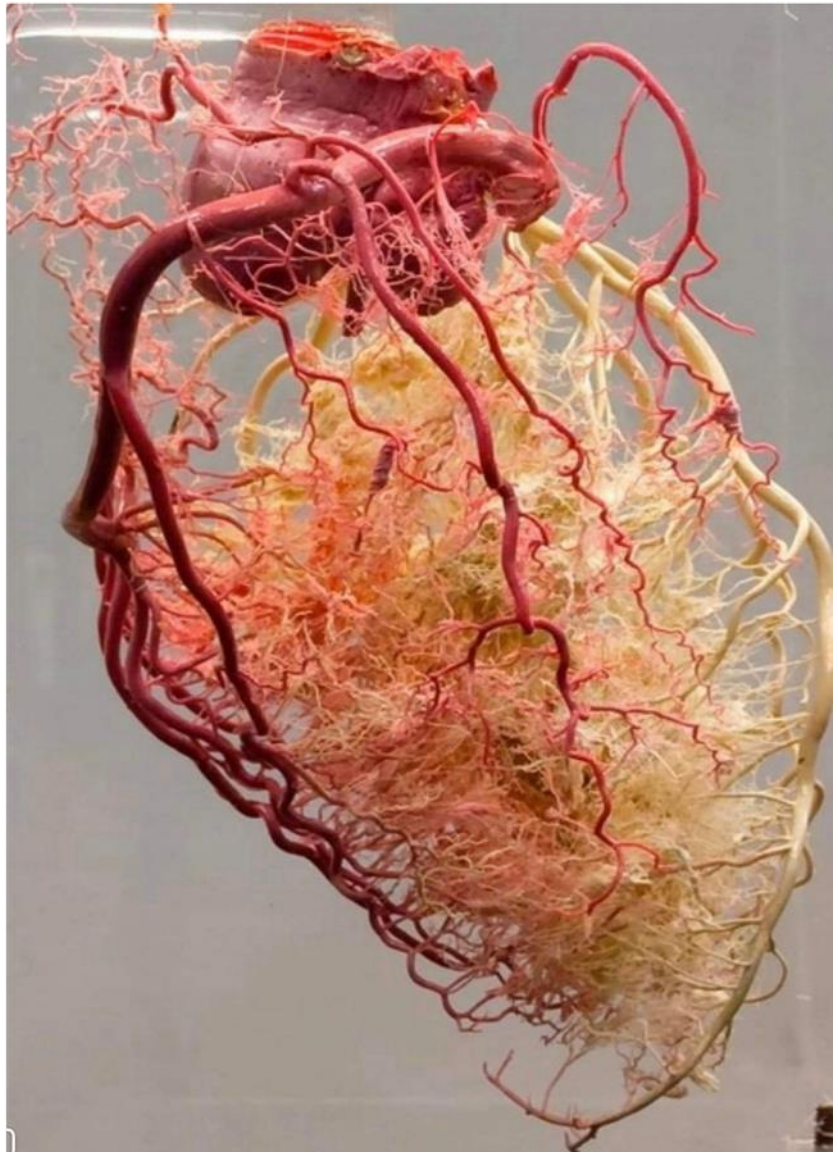
Jolly SS, Cairns JA, Lavi S, et al. Thrombus aspiration in patients with high thrombus burden in the TOTAL trial. JACC 2018, 72 (14) 1589-1596. doi: 10.1016/j.jacc.2018.07.047.

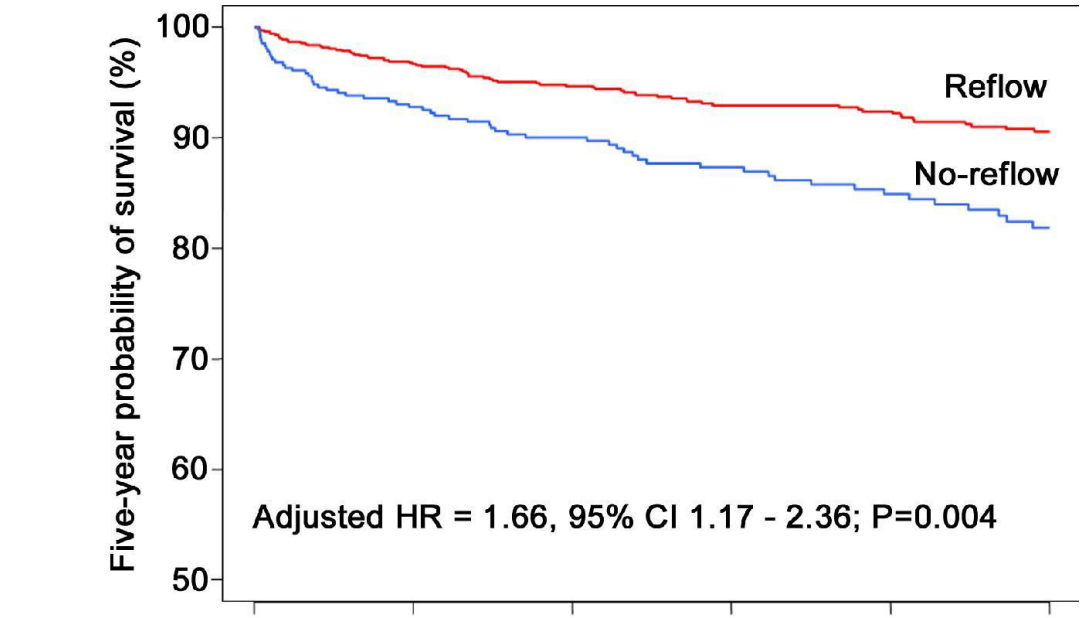


90% of myocardial blood flow is supplied by the microcirculation

No Reflow Phenomenon

Implications of No Reflow

- Lower survival rate at 5 years
- 3X increase in mortality or heart failure–related hospitalizations for patients who develop microvascular obstruction



Patients at Risk						
Reflow	996	890	742	591	485	374
No-reflow	410	355	291	234	191	139

Incidence of no-reflow in acute MI

PRIMARY PCI	MANUAL ASPIRATION	PRIMARY STENTING	CAT RX
16-26%	25-27%	20.8%	.75% MBG 3 in 99.75%
Wang, 2015	*Bayramglu, 2017*	*Bayramglu, 2017*	*Matthews, 2022*

No-reflow from primary PCI & subsequent stroke results in **death rate of 7%** in a metanalysis of 3872 patients.

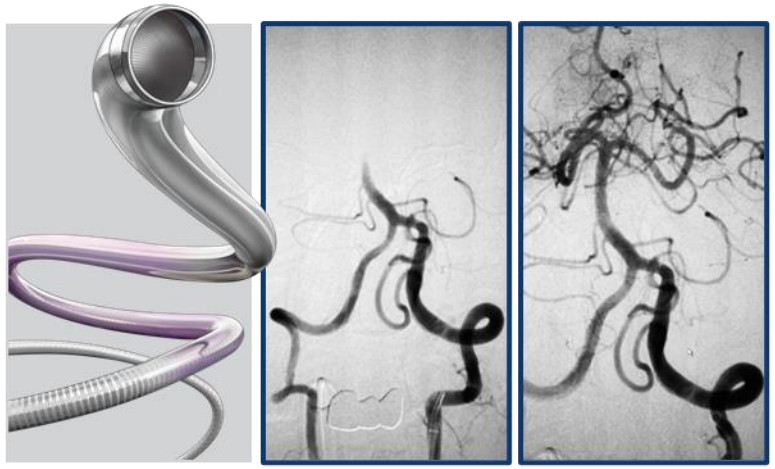
- Keeley UTSW 2003

“ The best way to **TREAT** no reflow is to **PREVENT** no reflow ”

Evolution of Mechanical Aspiration

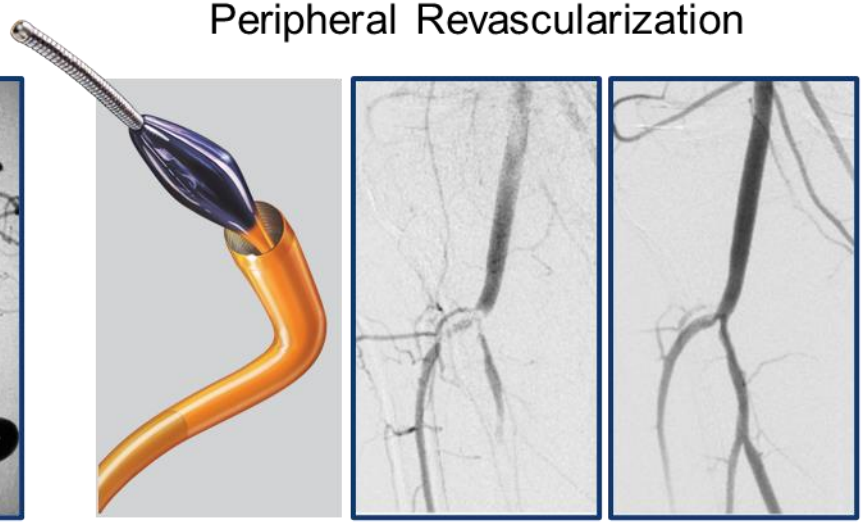
Evolution of Mechanical Power Aspiration

2008 — Stroke Revascularization



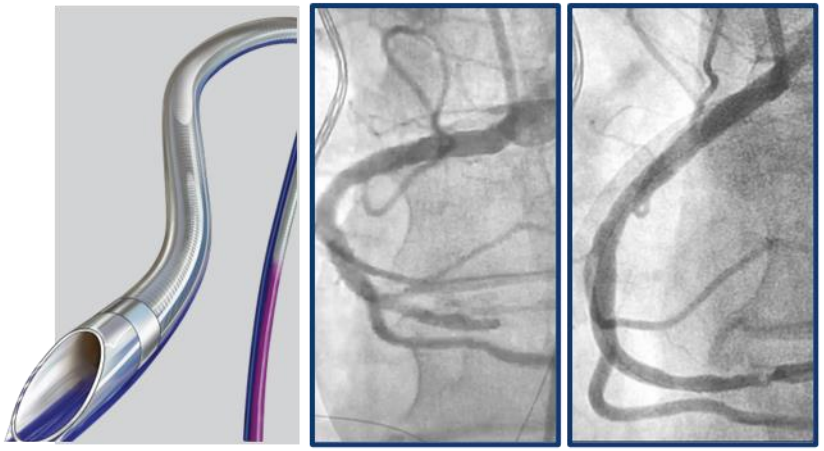
Penumbra System®

2015 — Peripheral Revascularization



Indigo System

2018 — **Coronary Revascularization**



CAT **RX** Aspiration Catheter Introduced

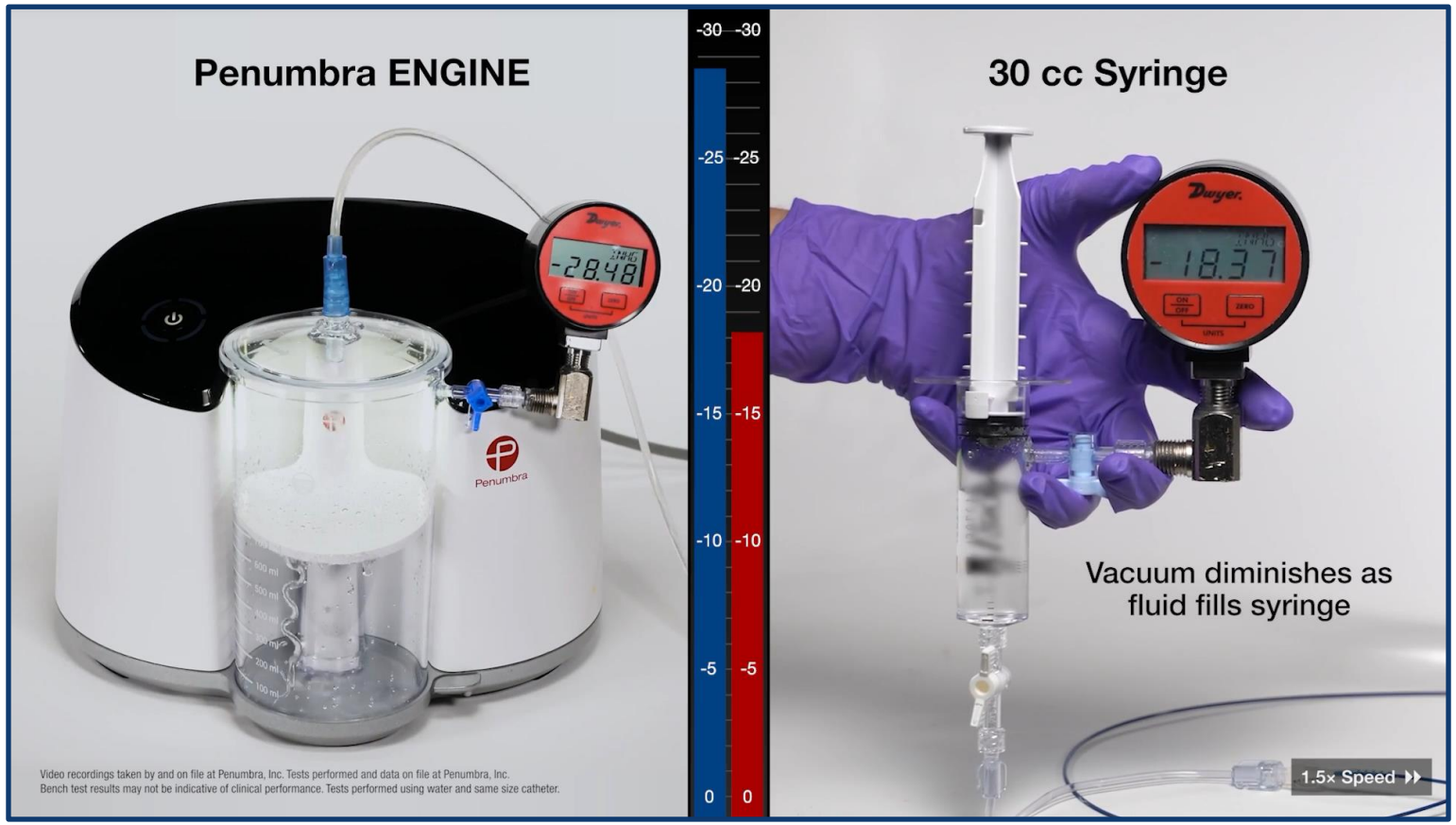
Aspiration Thrombectomy Goals

- Deliver highest aspiration source to thrombus-filled vasculature
  - Catheter designed to deliver mechanical power aspiration
  - Generate sustained, mechanical power aspiration

Penumbra ENGINE®

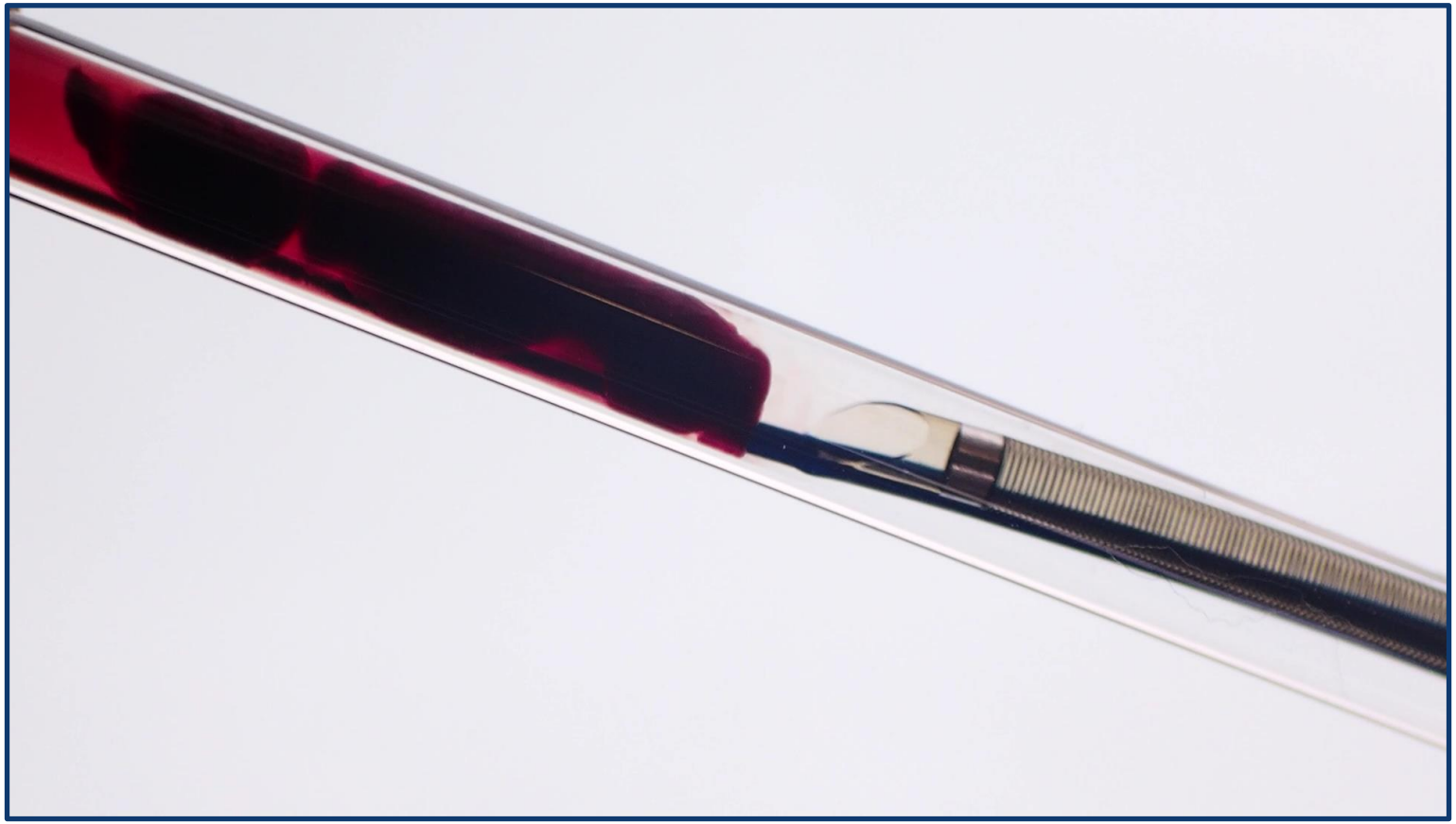
Sustained, Mechanical Power Aspiration

Click to play video



CAT RX Mechanical Power Aspiration

Click to play video



Video recording taken by and on file at Penumbra, Inc. Tests performed and data on file at Penumbra, Inc. Bench test results may not be indicative of clinical performance.

CHEETAH Study

Objective:

Demonstrate the safety and performance of the Indigo Aspiration System using the CAT **RX** aspiration catheter in a population presenting with acute high thrombus burden coronary vessel occlusion who are referred for Percutaneous Coronary Intervention (PCI)

Design


Prospective Study


400 Patients


25 Sites


High Thrombus Burden in ACS

Study Population:

Frontline treatment with Indigo Aspiration System using the CAT **RX** Aspiration Catheter, prior to PCI

CHEETAH Study

- **Primary Endpoint:**
  - Major Adverse Cardiovascular Events, a composite of 30-day cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or new or worsening New York Heart Association Class IV heart failure
- **Secondary Endpoints:**
  - **Procedure:**
    - *Final TIMI Flow Grade*
    - *Final TIMI Thrombus Grade*
    - *Myocardial Blush Grade*
    - *Distal Embolization Rate*
  - **Within 30 days:**
    - *Stroke*
    - *Major Bleeding*
  - **Within 180 days:**
    - *Stent Thrombosis*
    - *All-Cause Mortality*
    - *Cardiovascular Death*
    - *Recurrent MI*
    - *Cardiogenic Shock*
    - *Class IV Heart Failure*
    - *Incident of Device Related SAEs*

CHEETAH Study

Primary Composite Endpoint Met
Safe in High-Risk Patient Population

96.5%
Freedom from MACE at 30 days[a]

0
Device related SAEs (including stroke[b])

Successful Thrombus Removal
High Rates of Flow Achieved
Core lab adjudicated

85%
TIMI 2–3 flow post CAT **RX**

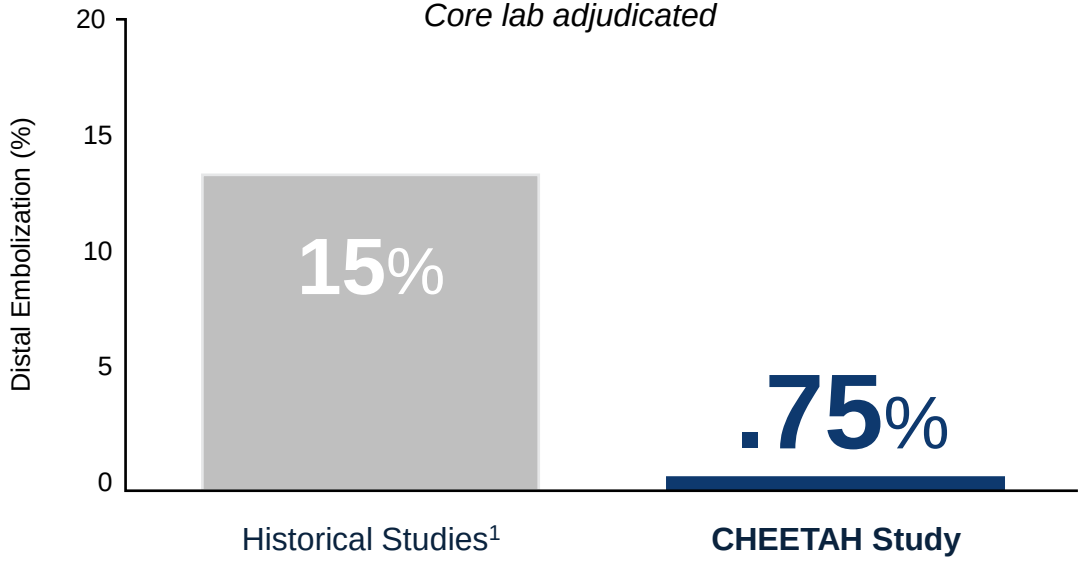
97.5%
TIMI 3 flow at final angiography

a. Composite of 30 day cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or new or worsening New York Heart Association Class IV heart failure.
b. There were 3 (.75%) incidence of non-device related strokes as adjudicated by Independent Medical Reviewer.
As presented at TCT 2021 by Dr. Jay Mathews, Manatee Memorial Hospital, FL. Penumbra ENGINE and Penumbra Pump MAX were both used during study.
The clinical results presented herein are for informational purposes only, and may not be predictive for all patients. Individual results may vary depending on patient-specific attributes and other factors.

CHEETAH Study

Low Distal Embolization Rate

Core lab adjudicated



Improved Myocardial Perfusion

Core lab adjudicated

Achieving high myocardial blush grade (MBG 3) during PCI has been associated with improved outcomes in acute MI[2]

99.8% of patients with MBG 3 at final angiography

1. Henriques JPS, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J. 2002 Jul;23(14):1112–1117. doi: 10.1053/euhj.2001.3035.
2. Rehman AU, Malik J, Javed N, et al. Myocardial blush grade: a determinant of left ventricular ejection fraction and adverse outcomes in STEMI. Scott Med J. 2021 Feb;66(1):34–39. doi: 10.1177/0036933020941260. Epub 2020 Jul 6.
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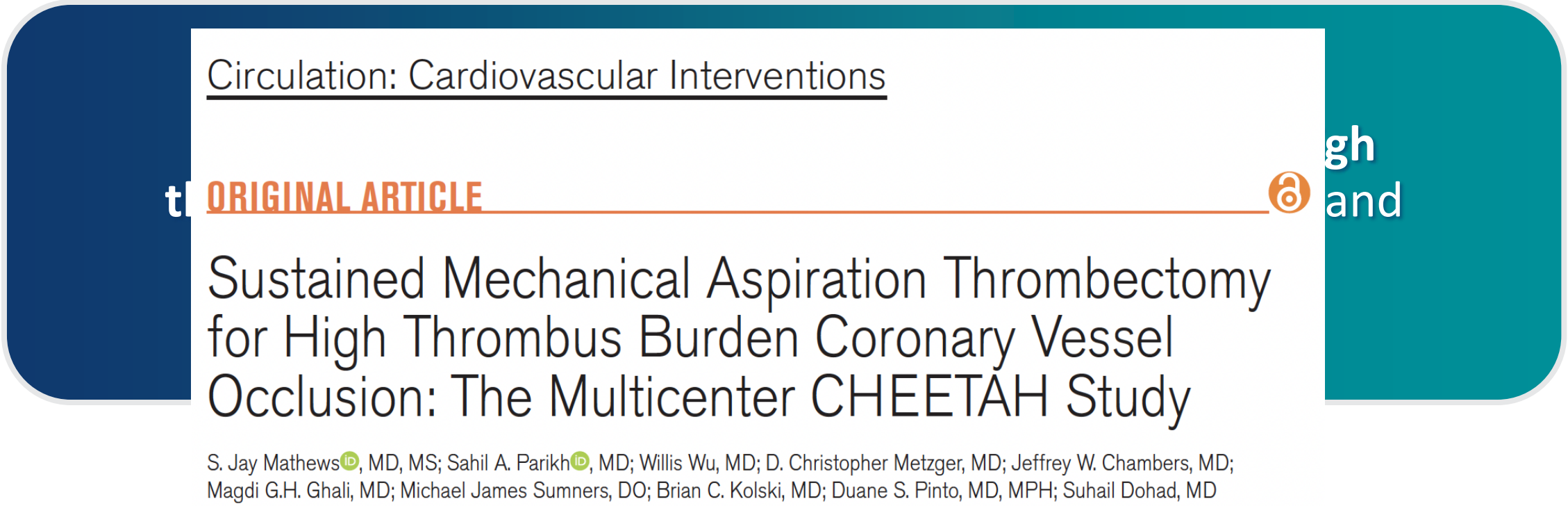
CHEETAH Study



Cases

HSR

- 68-year-old man with hypertension and diabetes mellitus type 2 who presented to the Emergency Department with one hour of chest pain.

Presentation

One hour prior to presentation the patient noted acute onset of left-sided chest pain with radiation to the jaw while watching television. He endorsed associated nausea and diaphoresis. He took Motrin without significant improvement. On presentation he was uncomfortable-appearing without other significant physical exam findings.

CASE

Cardiac medications

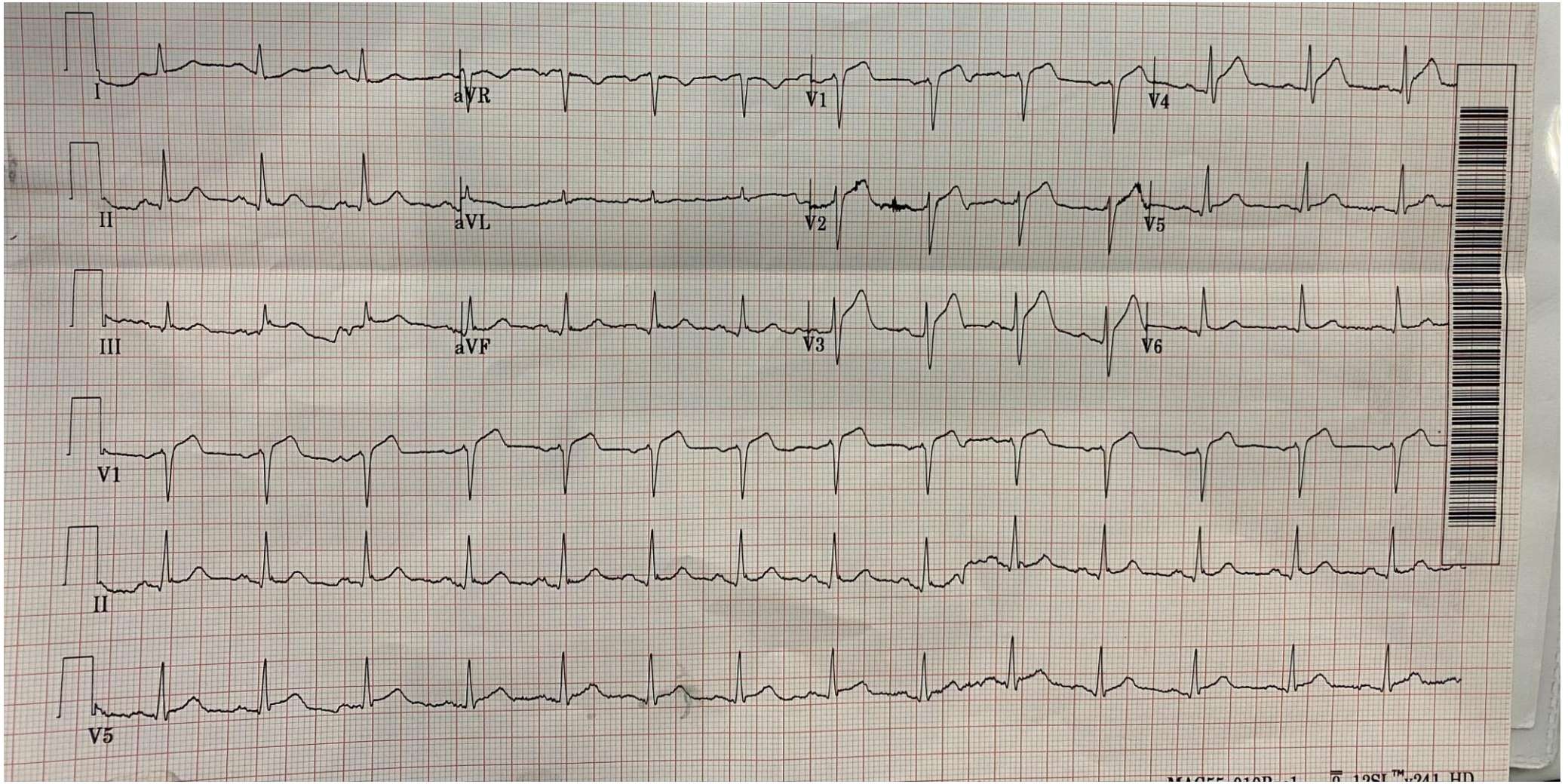
Metformin 850 once daily

Laboratory studies

WBC 6.2
Hgb 15.2 g/dL
Plt 281
Cr 0.98 mg/dL (GFR >90 mL/min/m^2)
HgbA1c 6.8%
Troponin I POCT 0.04 ng/mL
High-sensitivity troponin-T 12 ng/L
Total cholesterol 182 mg/dL
HDL cholesterol 47 mg/dL
LDL cholesterol 77 mg/dL
Triglycerides 291 mg/dL
Hepatic panel within normal limits

Diagnostic studies

EKG


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5

- Notably, the patient did not receive aspirin 325, a second dual antiplatelet agent, or heparin in the Emergency Department

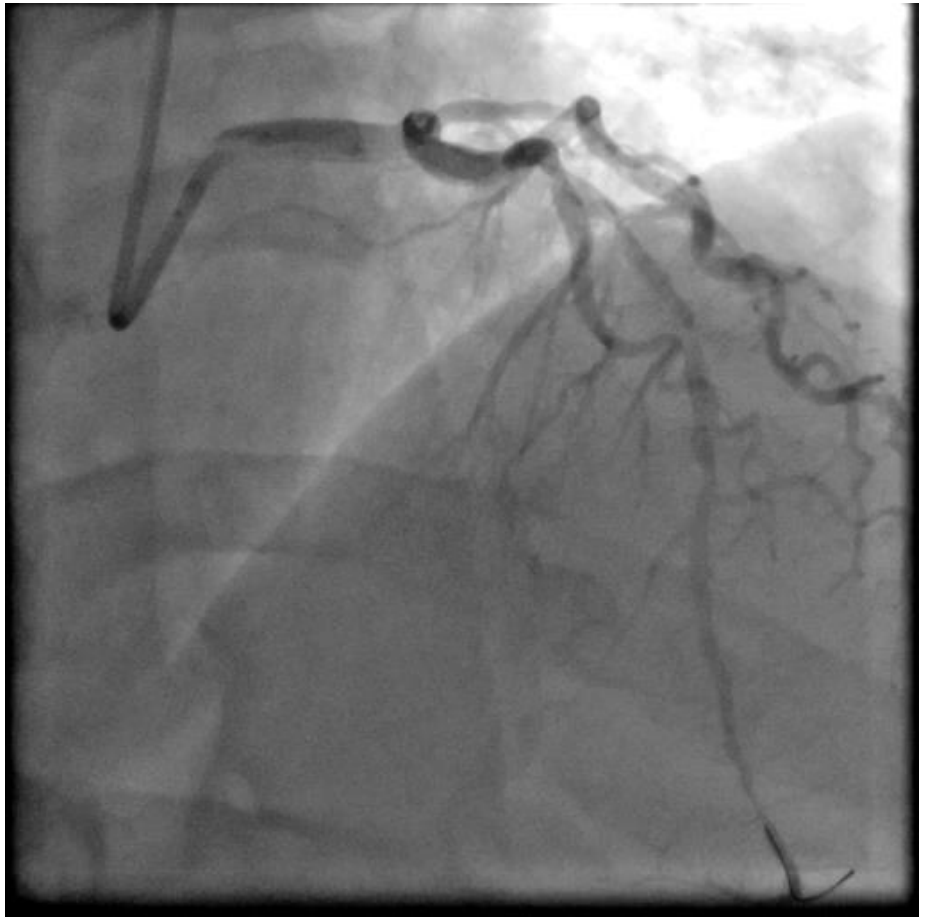
- Vital signs on arrival to room N: HR 93, BP 173/107, SpO2 99%
- Right radial access achieved with a 6Fr slender sheath
- Nicardipine 100 mcg & nitroglycerin 100 mcg given through radial sheath
- Images of the RCA using diagnostic 5Fr JR4 catheter
- Left main coronary artery engaged using EBU3.5 guide catheter
- Patient given aspirin 325 and cangrelor infusion initiated during the case

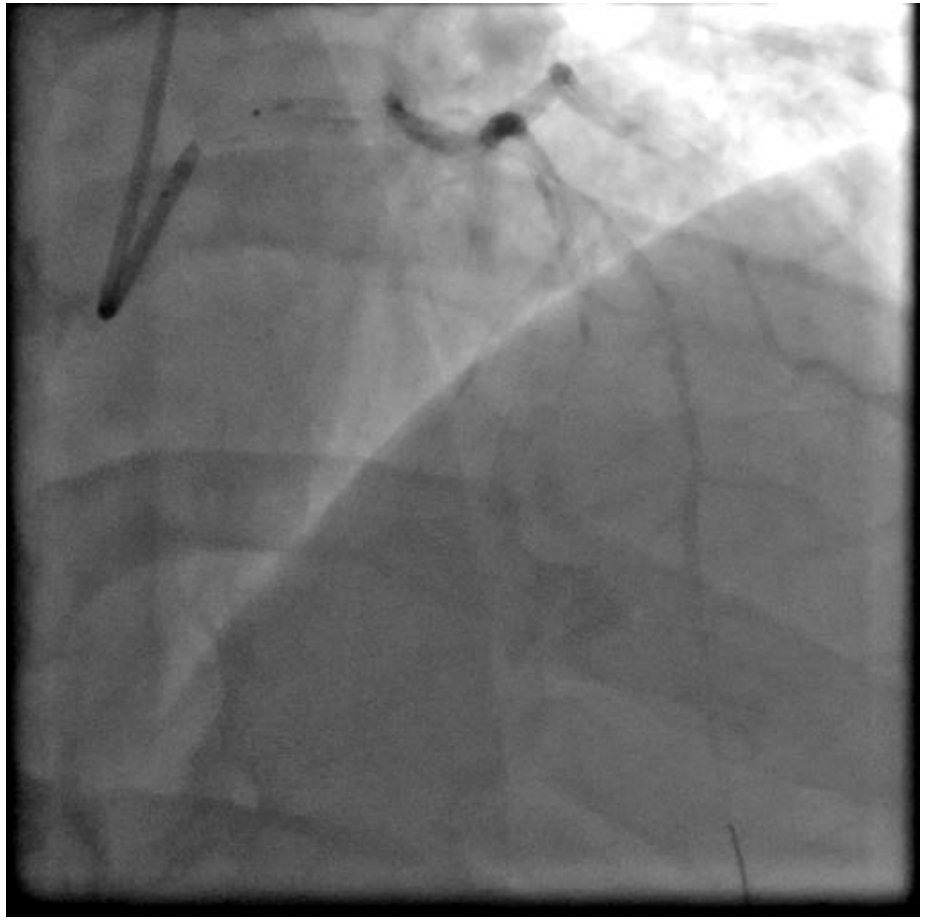
Initial images – RCA

Initial images – LAD, LCx

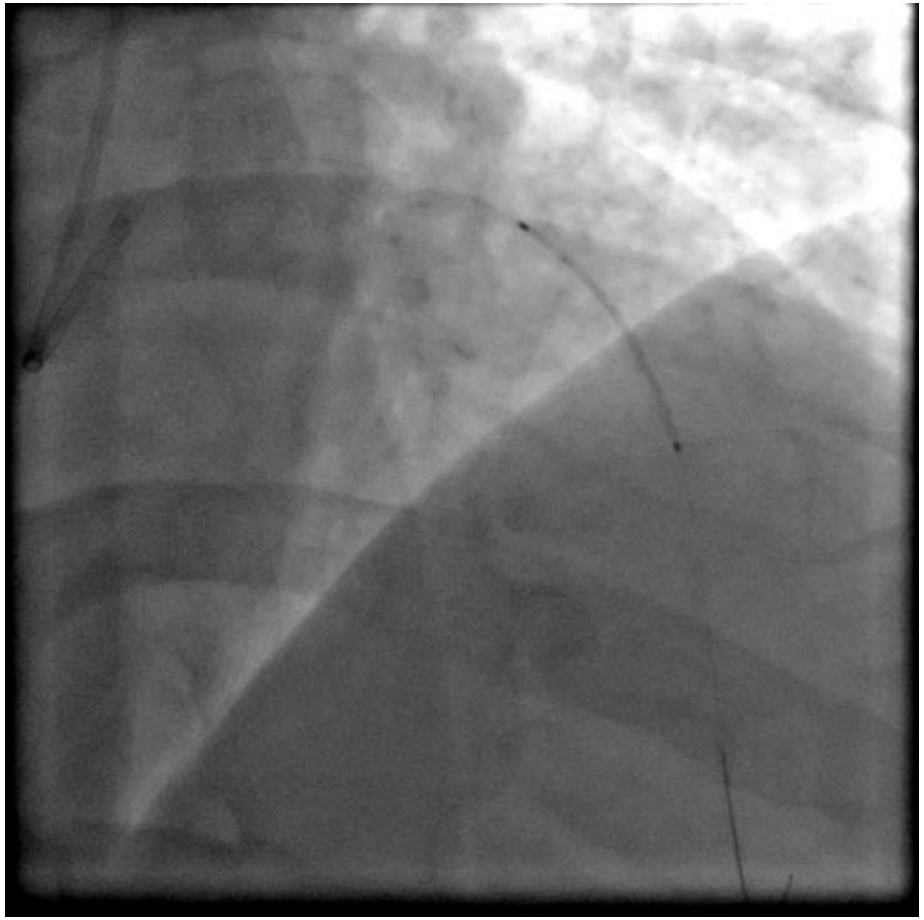
Initial images – LAD, LCx

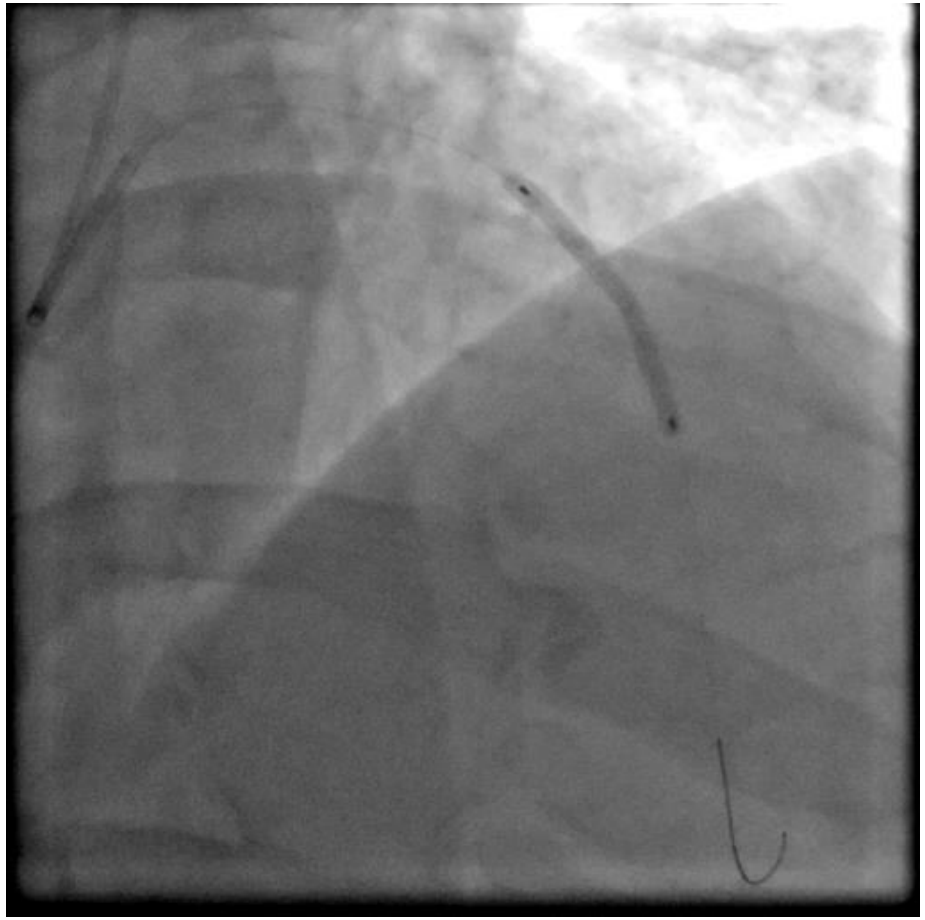
Intervention





Intervention





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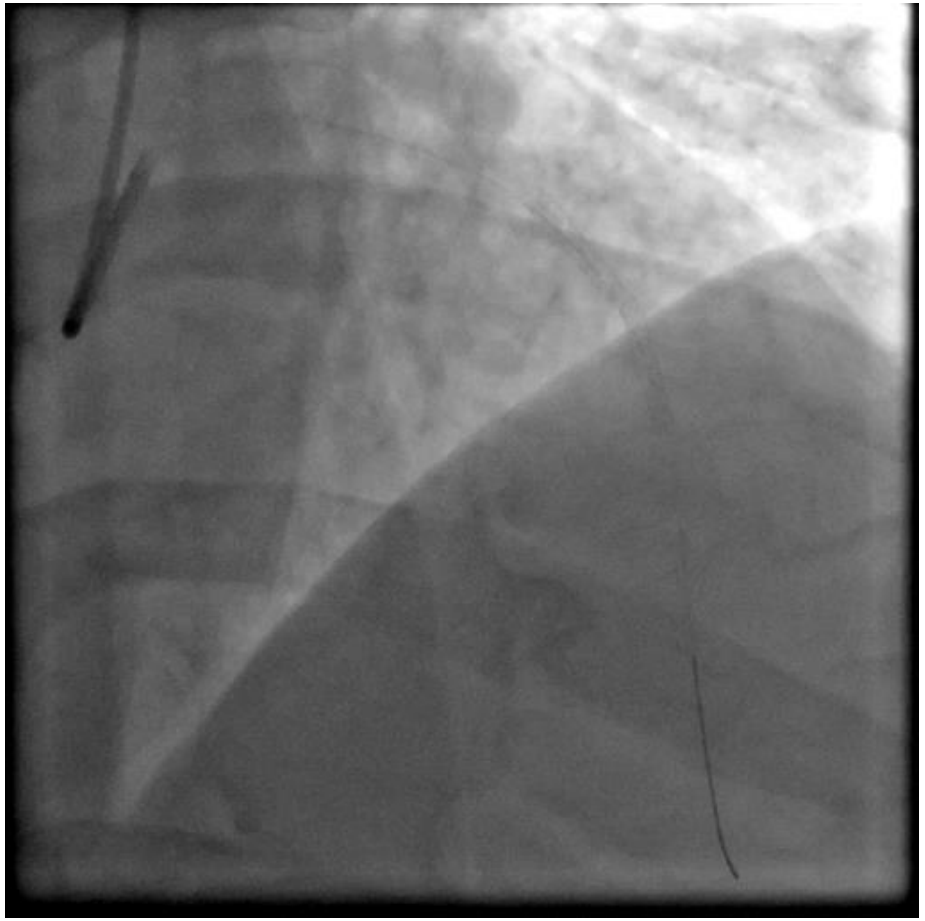

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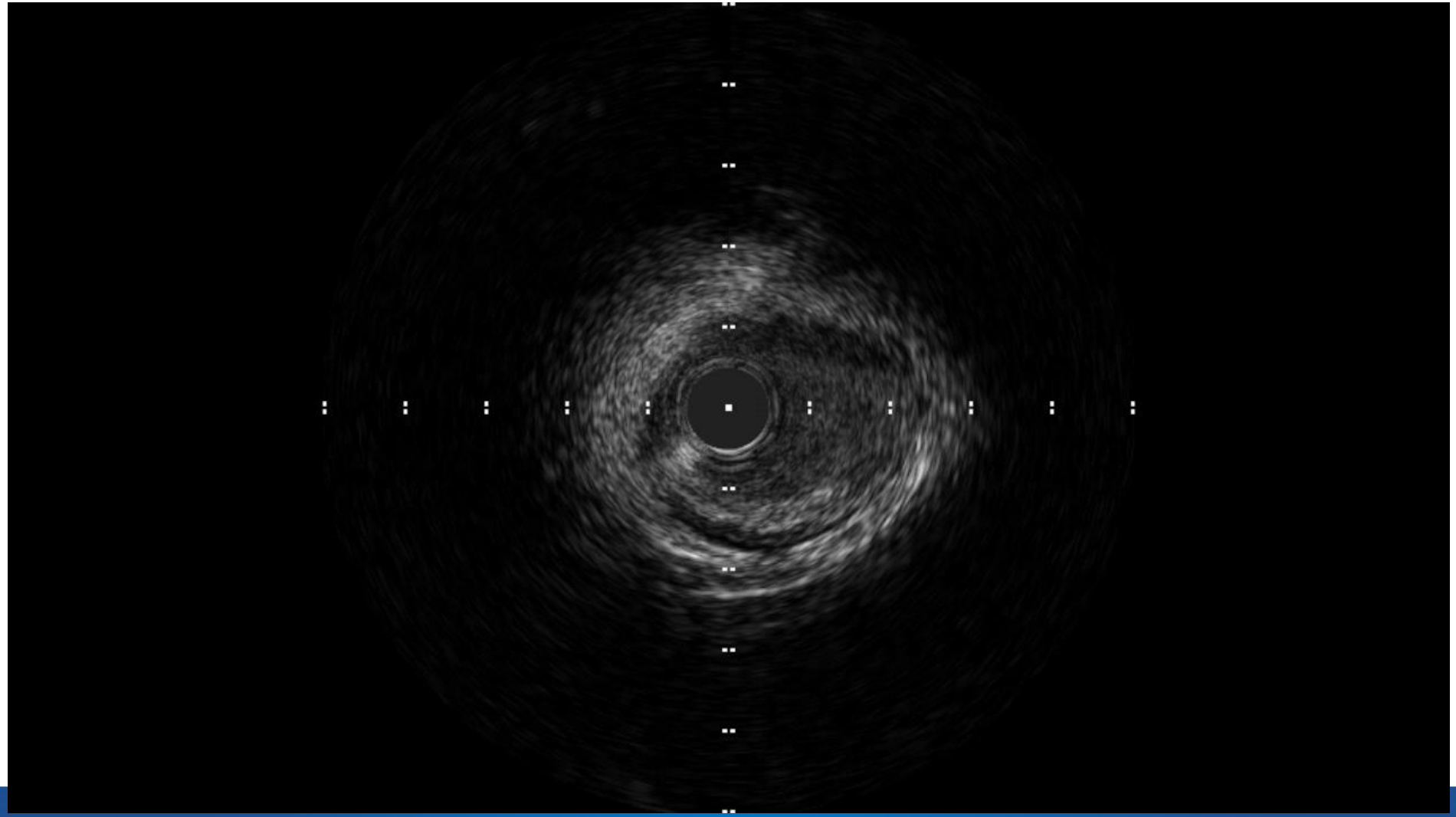

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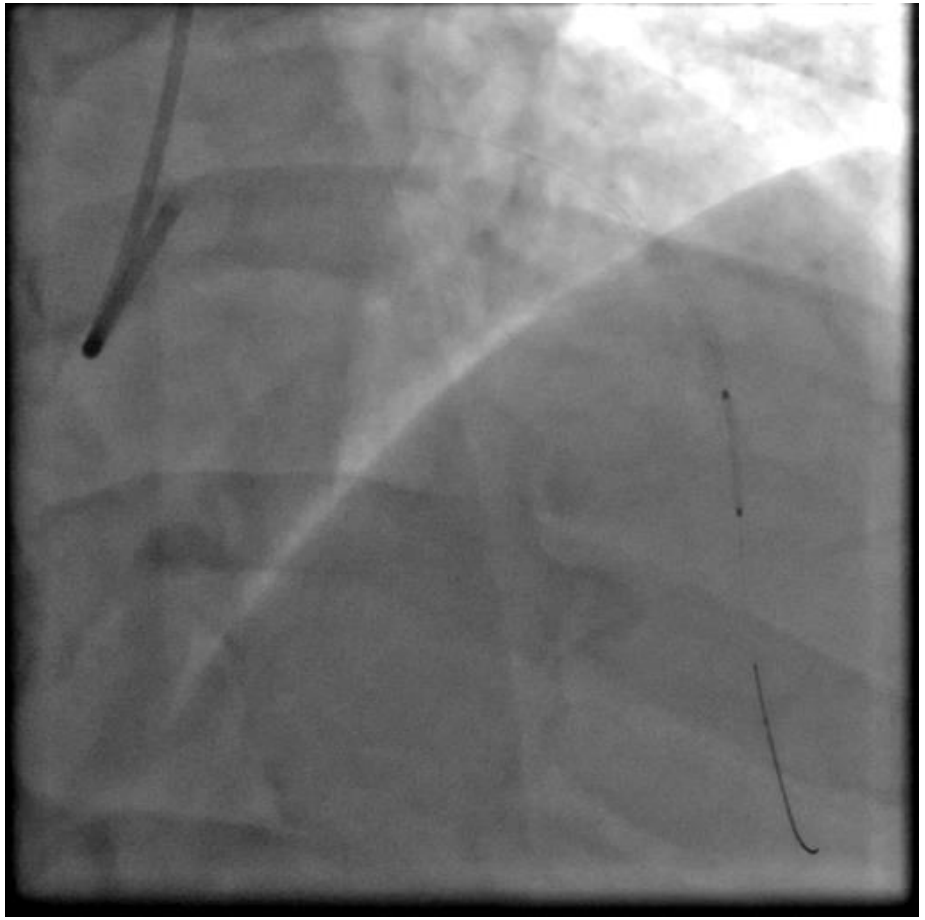
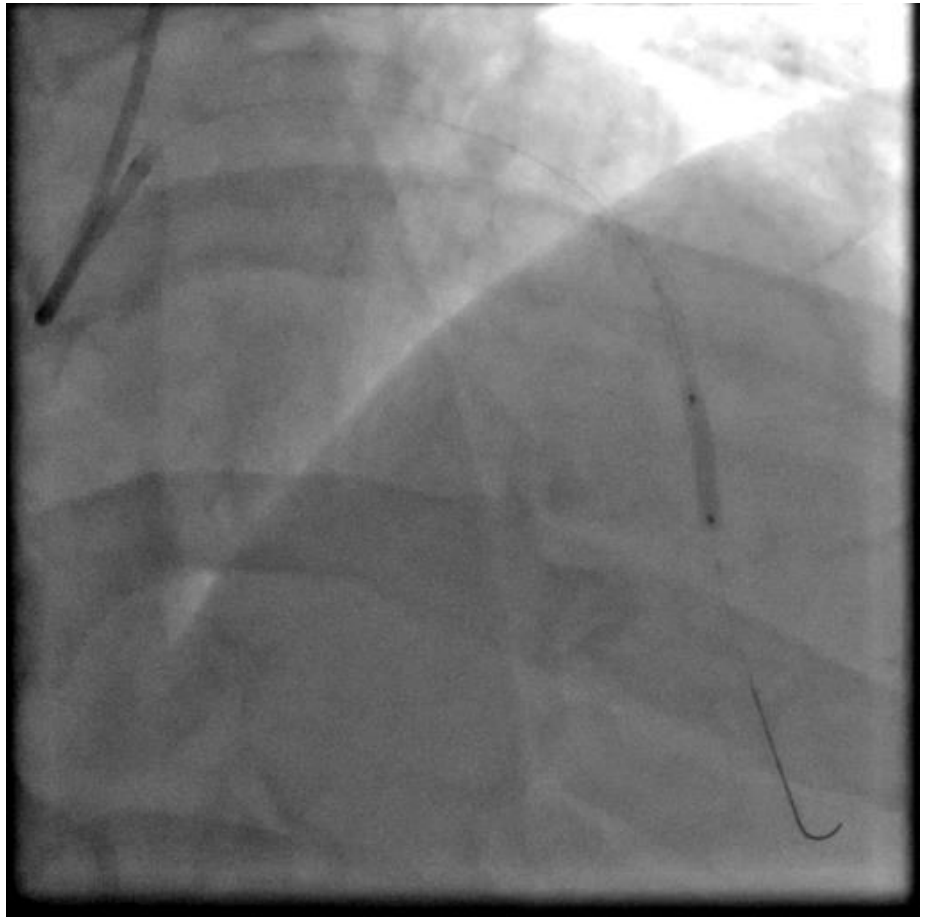
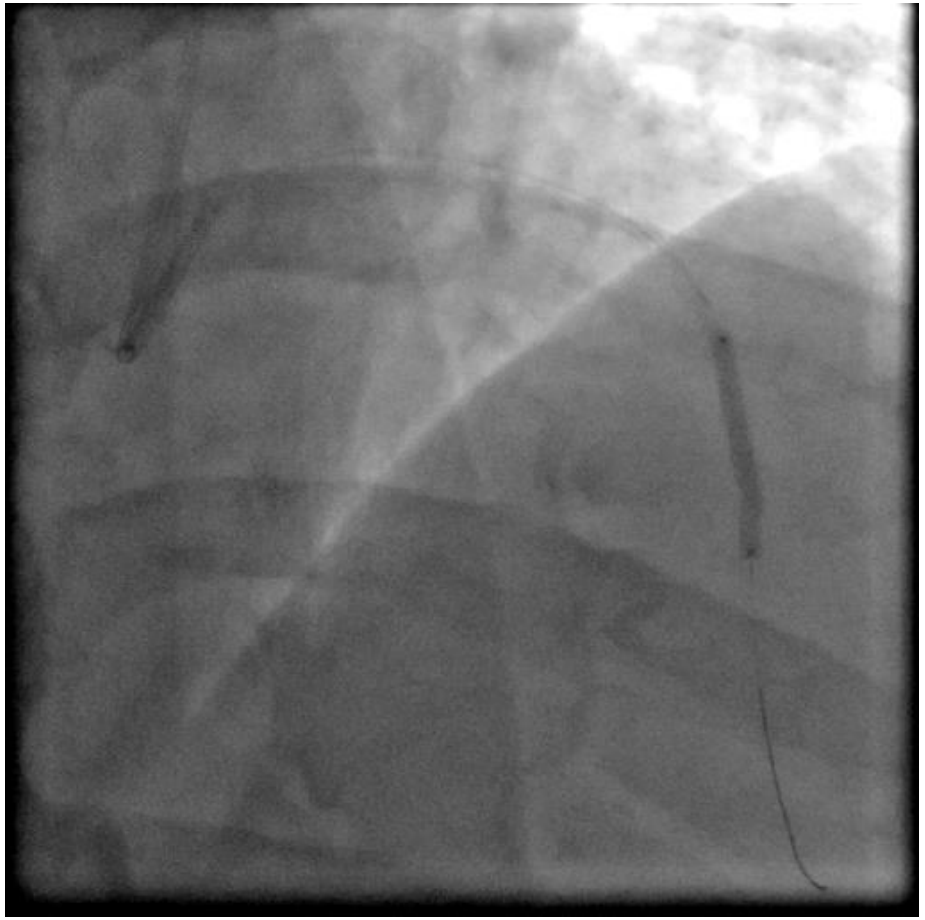
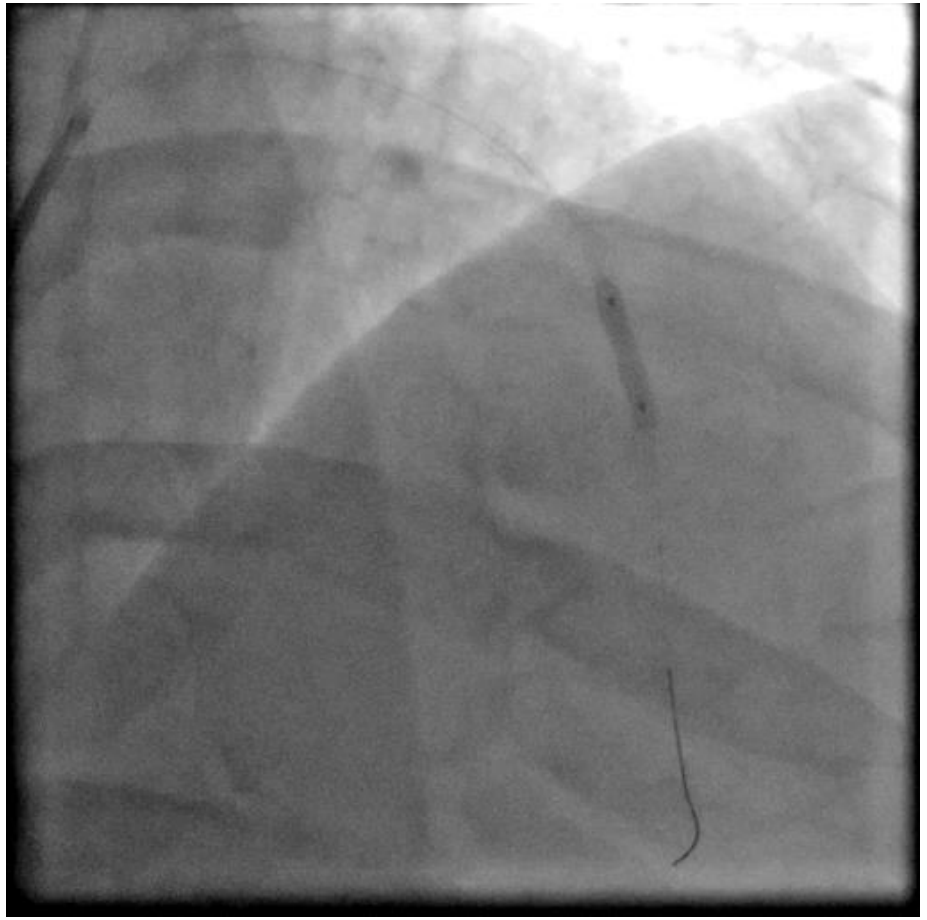
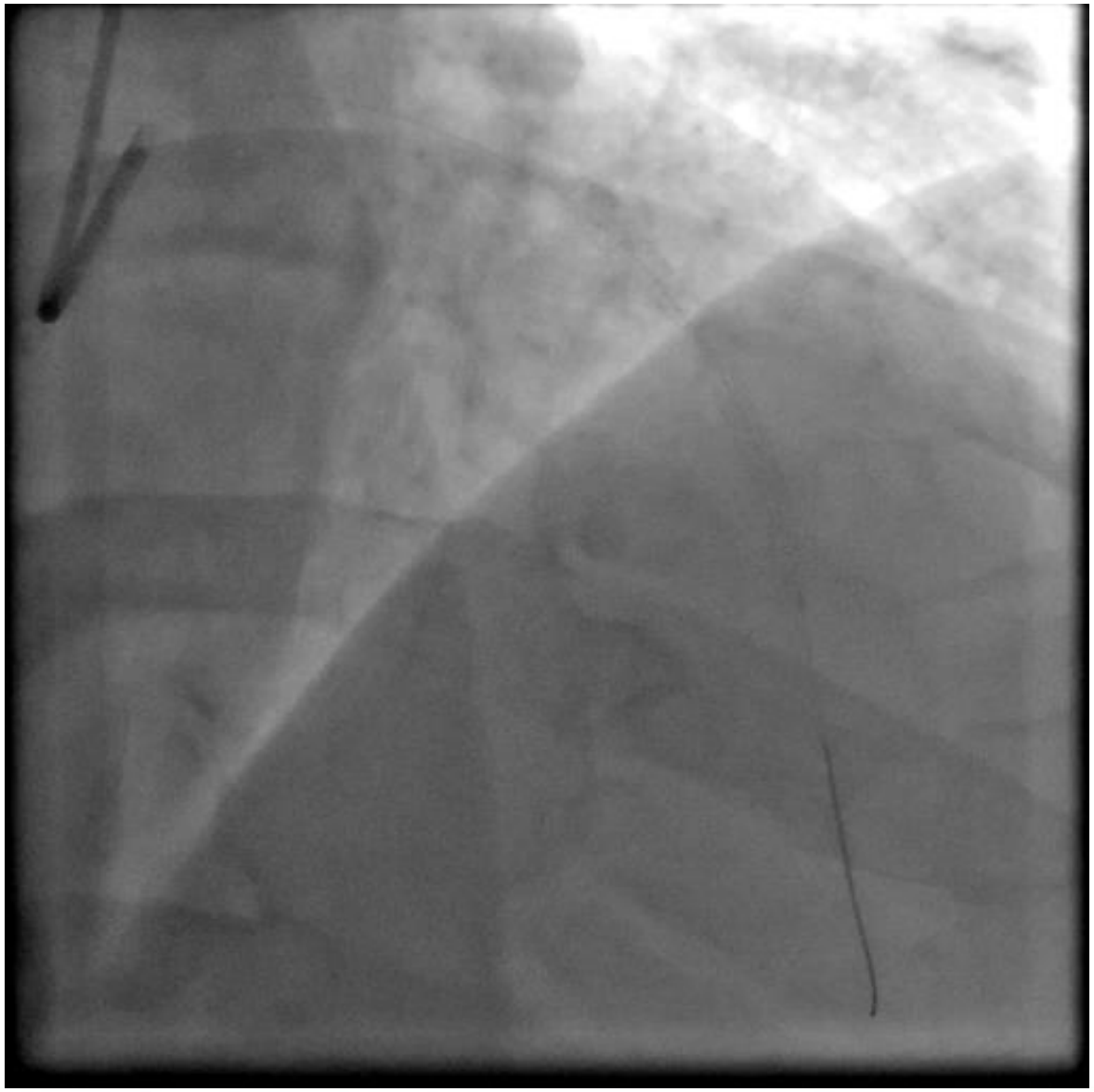




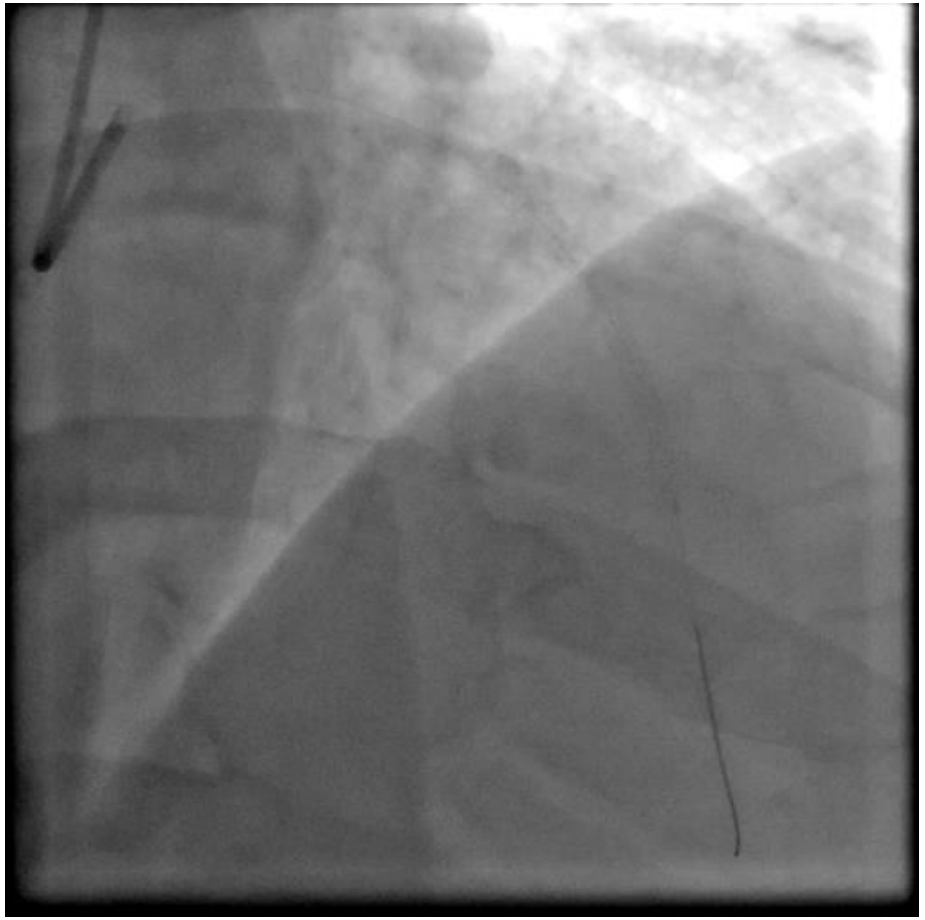
Intervention



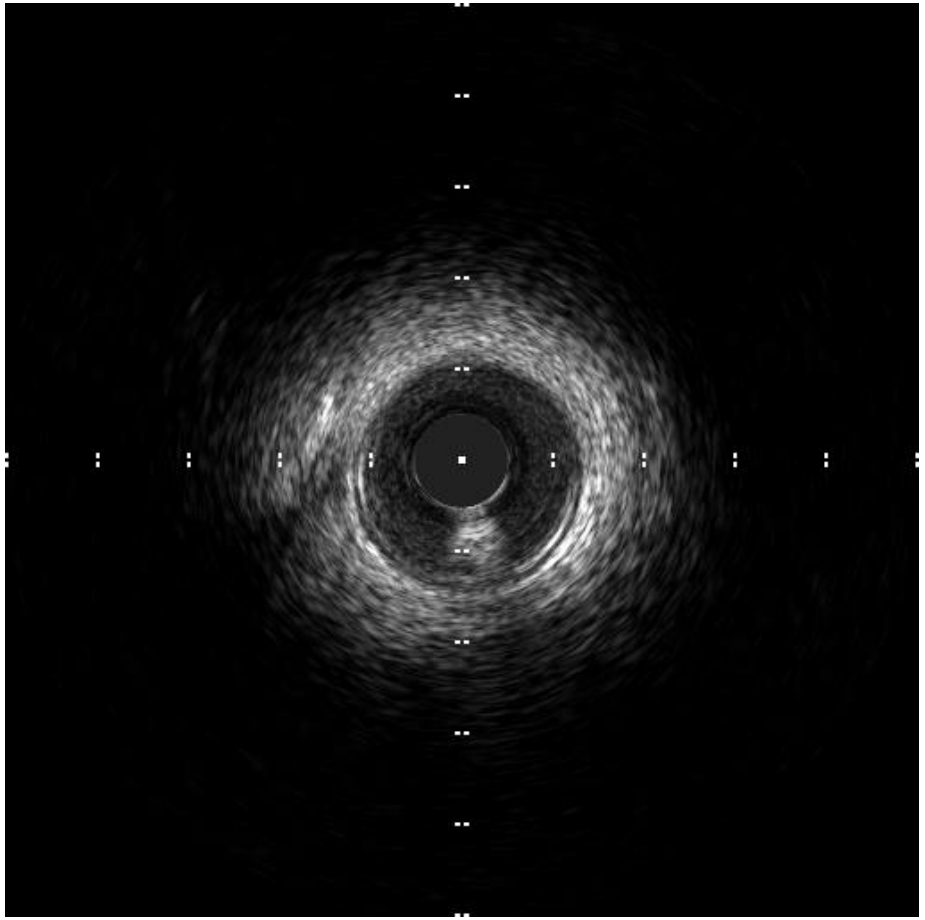




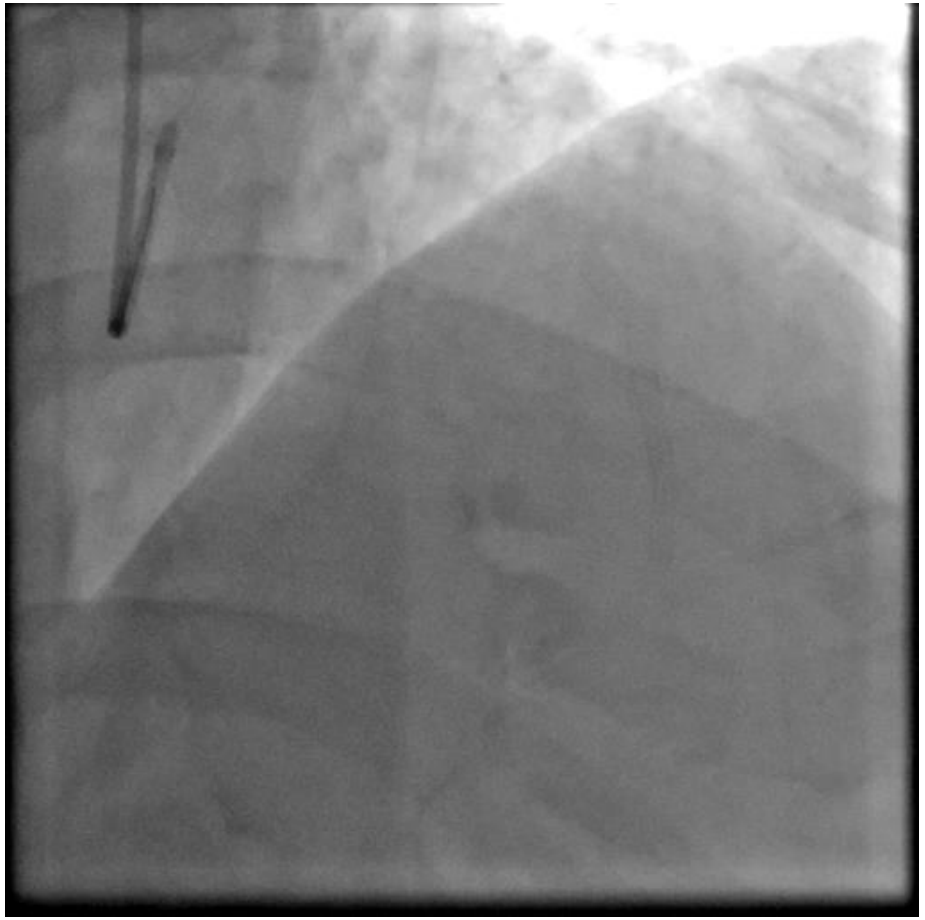
Intervention

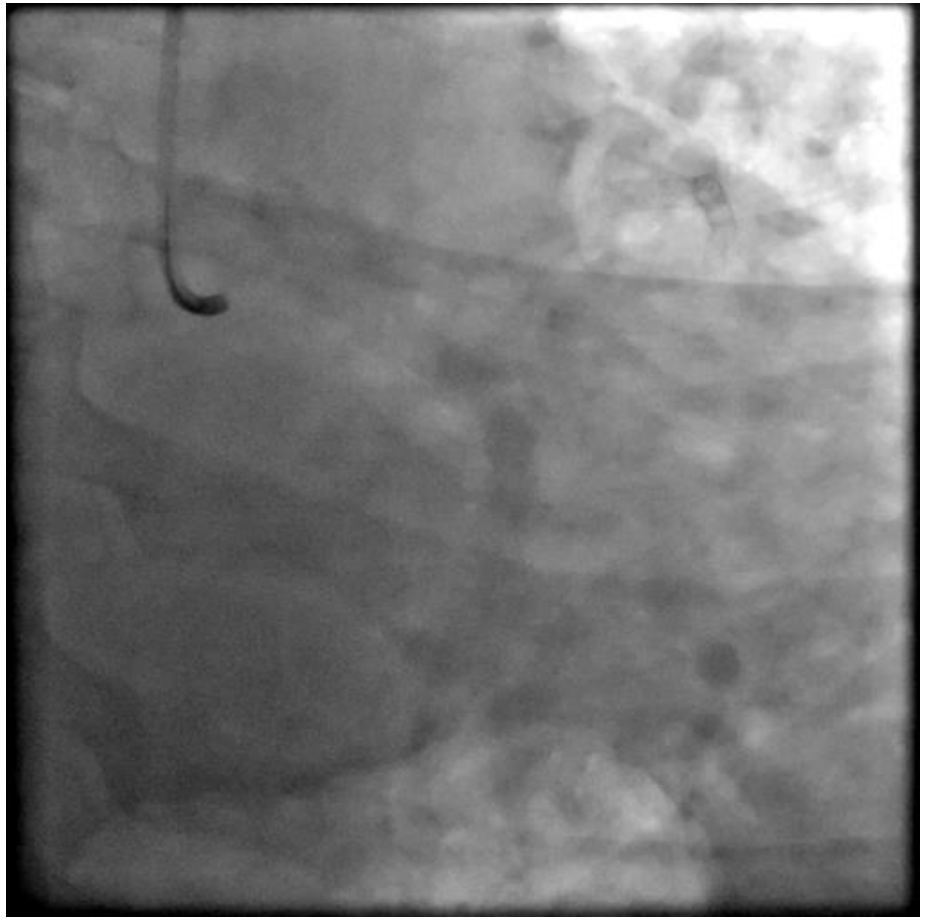


IVUS images



Final images – LAD, LCx





Discharge

- Post-intervention transthoracic echocardiogram (8/10/2021)
  - EF 0.35-0.40
  - Akinesis of the apical septum, apex, and apical inferior wall
  - Normal RV size and function
  - No significant valvular disease
- Repeat TTE (8/12/2021)
  - EF 0.40-0.45
- Medications on discharge:
  - ASA 81, Plavix 75, Atorvastatin 80, Losartan 25, Metoprolol XL 50, Metformin 500 BID

Case 2

- 82-year-old female with:
  - Hypertension
  - Hyperlipidemia
  - Diabetes mellitus type 2
  - COVID-19 infection in June 2021 (hospitalized for 22 days)
  - Symptoms
    - Chest pain & weakness for 3 days with new left bundle branch block on EKG

Case 2

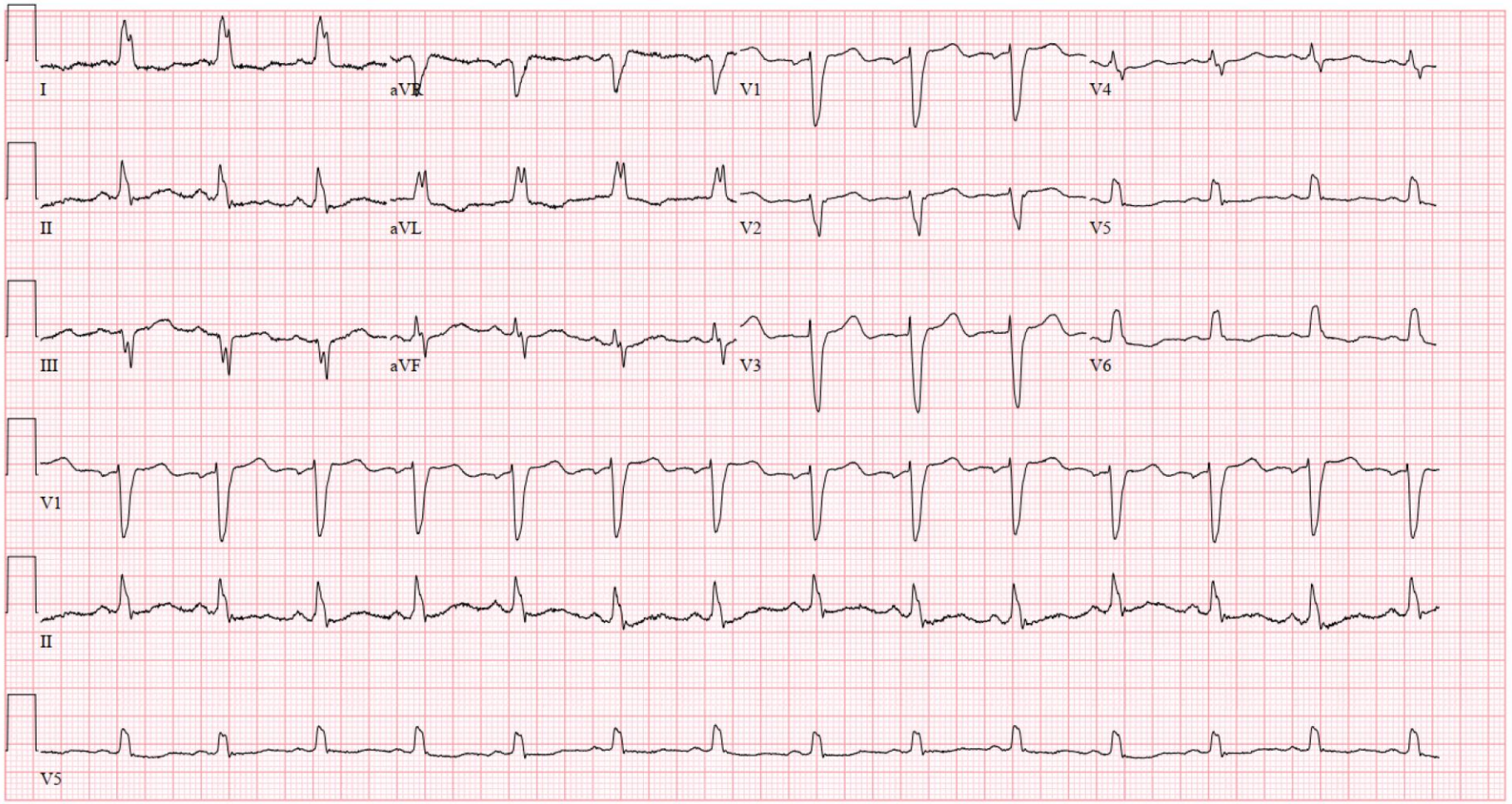
- Relevant medications:
  - Aspirin 81 daily
  - Clopidogrel 75 daily
  - Atorvastatin 40 daily
  - Carvedilol 6.25 BID
  - Amlodipine 10 daily
  - Lisinopril 20 daily
  - Hydrochlorothiazide 25 daily
  - Furosemide 40 daily
  - Metformin 500 BID

- Relevant laboratory studies (10/24/2021):
  - WBC 8.4
  - Hgb 12.4
  - Platelets 174
  - Cr 1.19
  - NT-proBNP 1221
  - hsTroponin-T 395 -> 528 -> 471

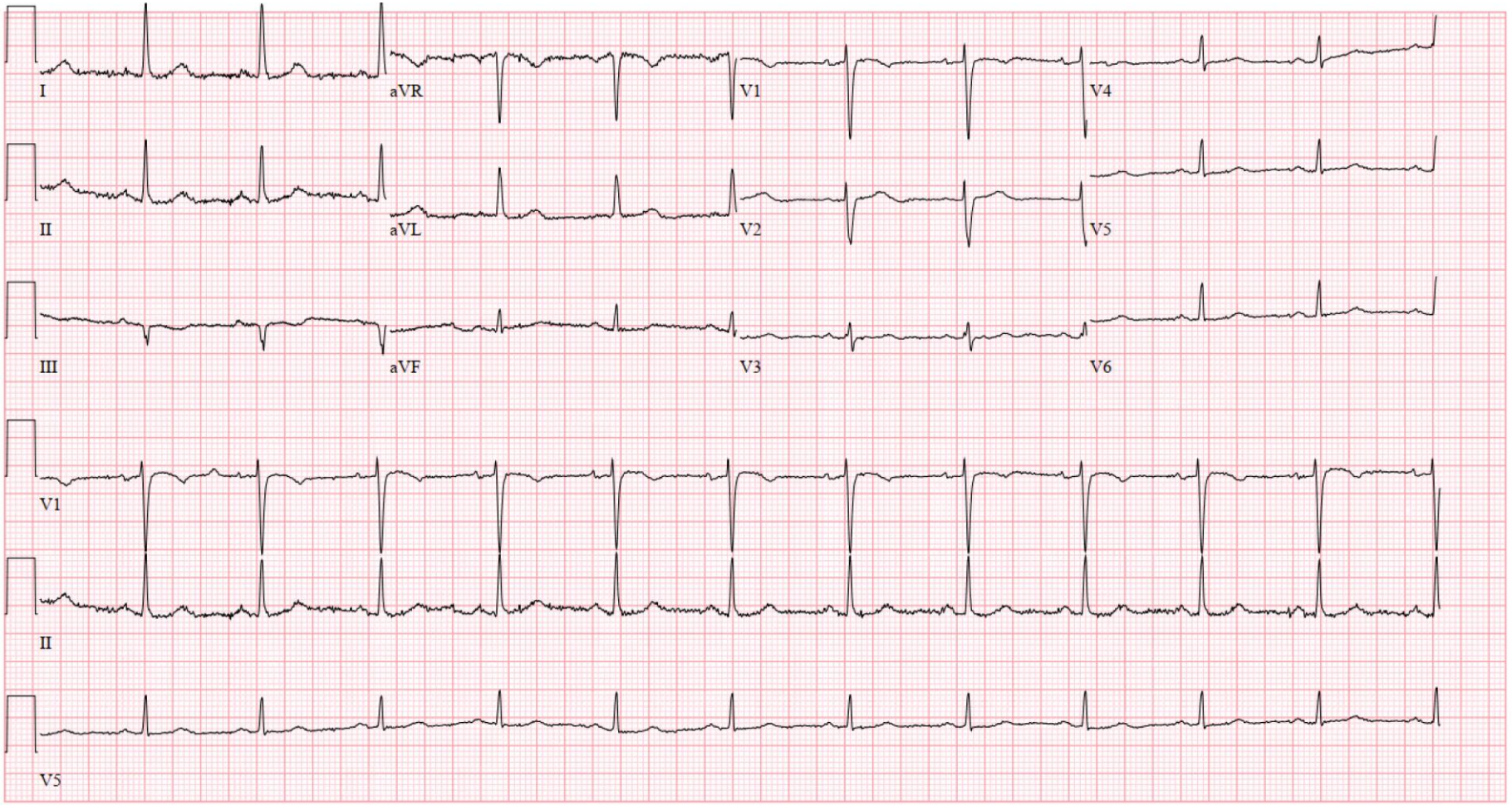
Case 2

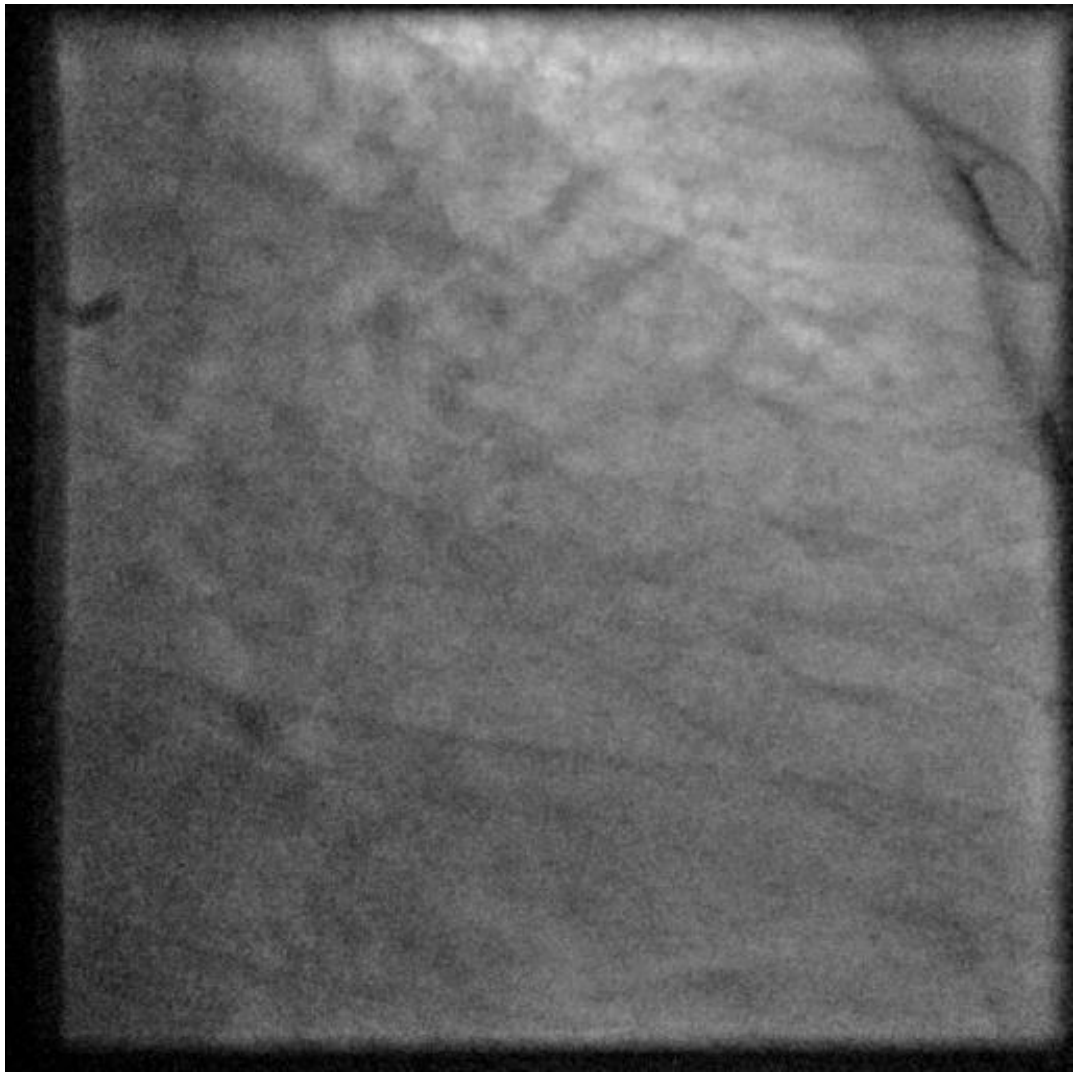
- Relevant diagnostic studies:
  - TTE (10/25/2021): LVEDd 4.2, IVS 0.6, LVPW 04, LVEF 0.55-0.60. Basal inferior and inferolateral walls are hypokinetic. Normal right ventricular size and function. Mild tricuspid regurgitation.

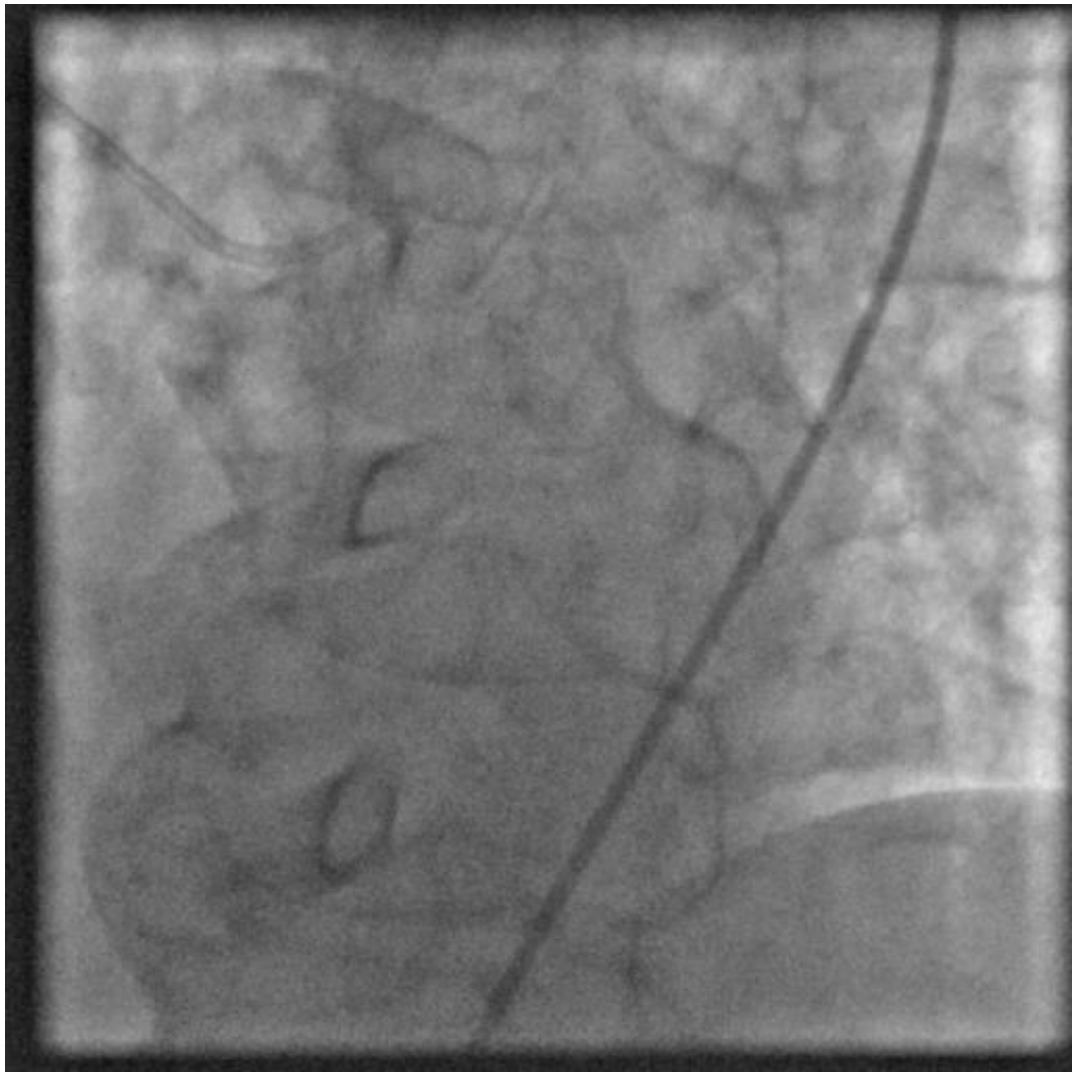
Initial EKG

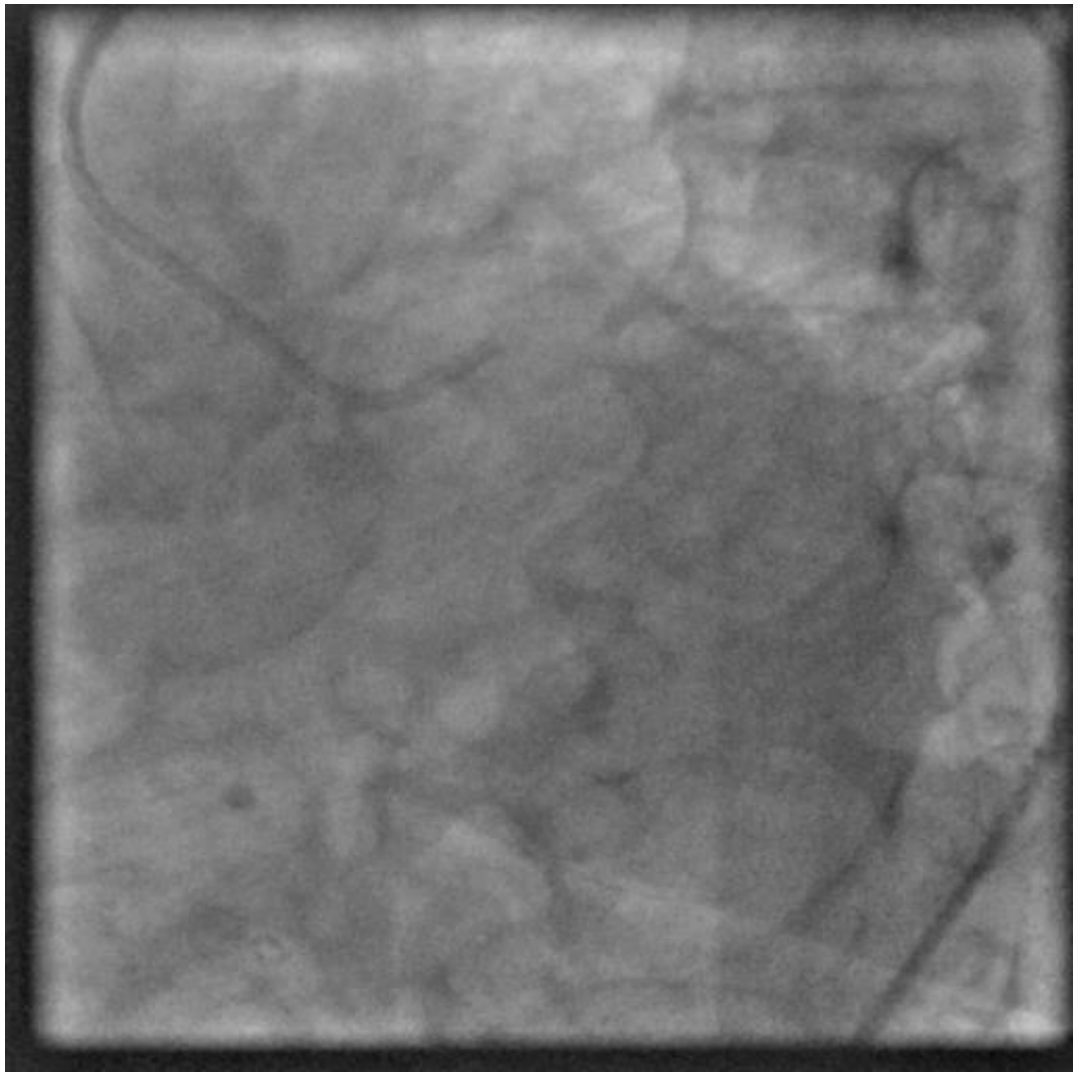


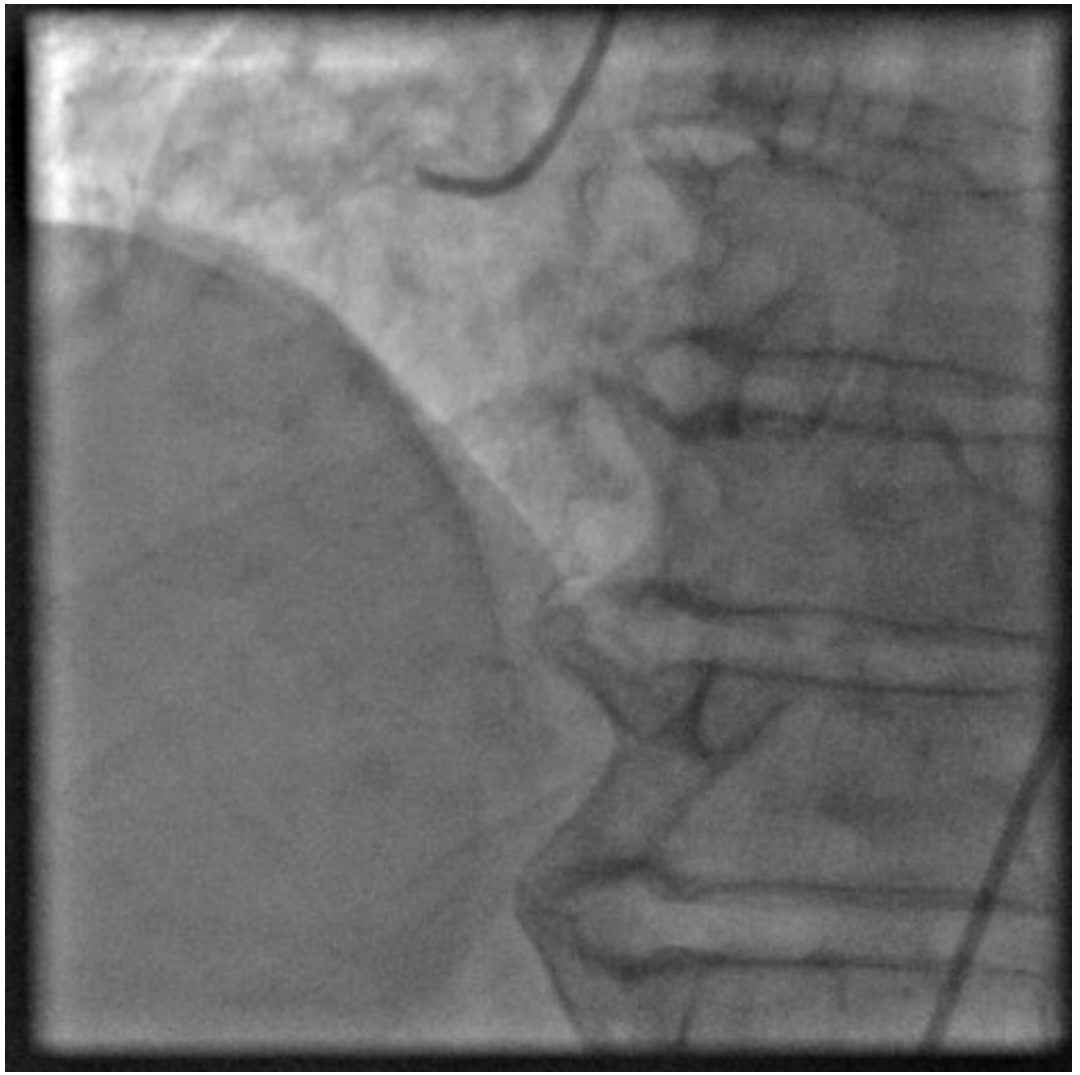
Prior EKG

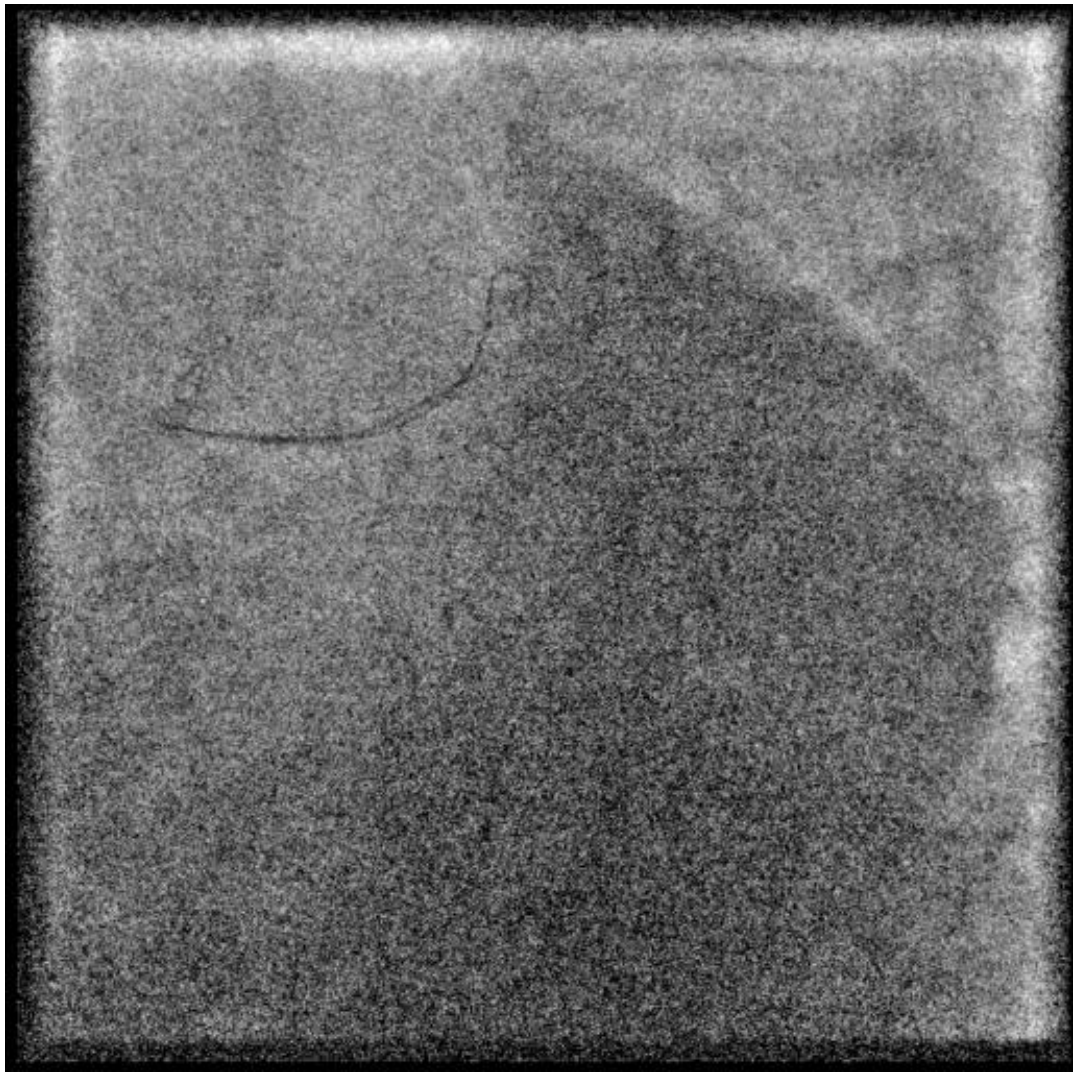


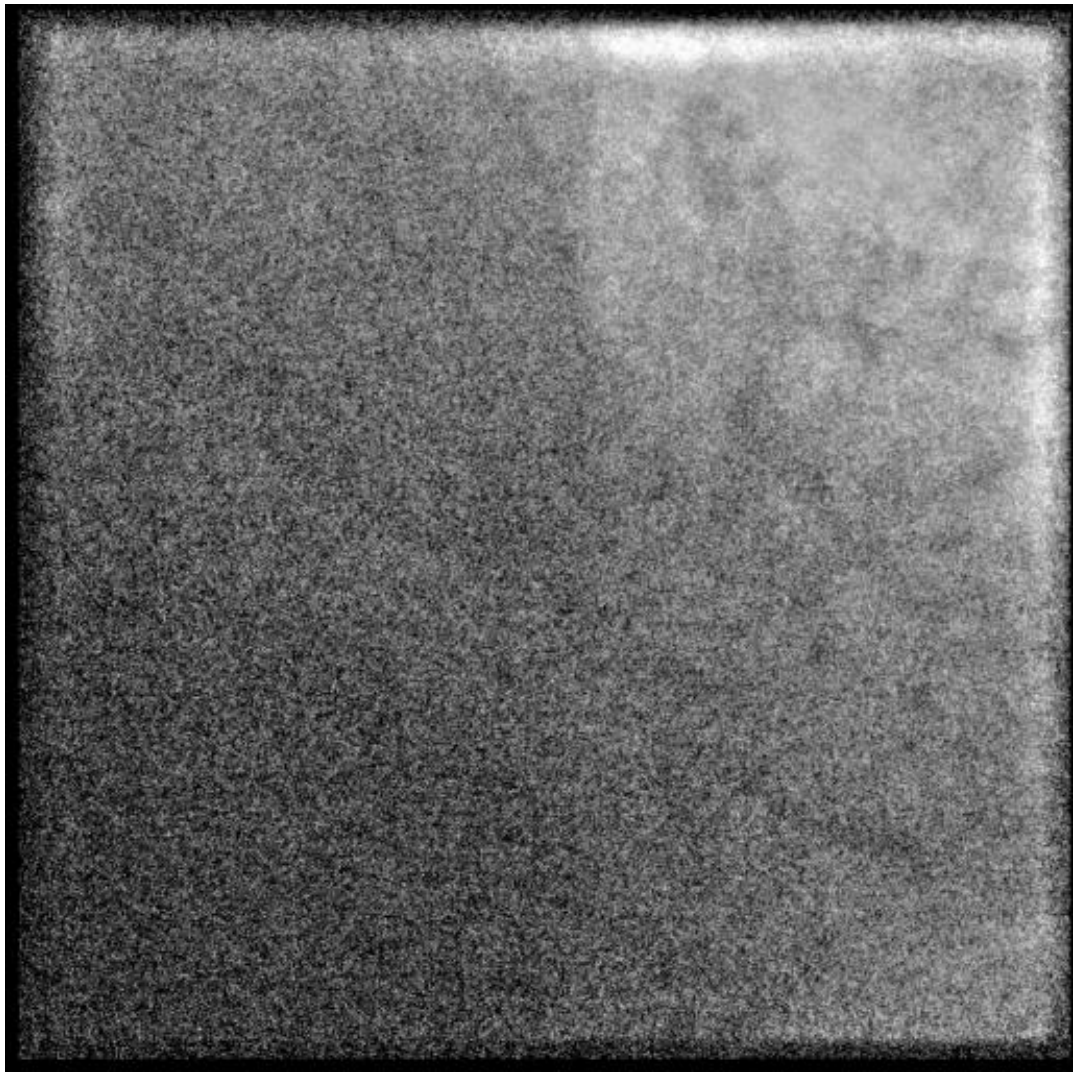




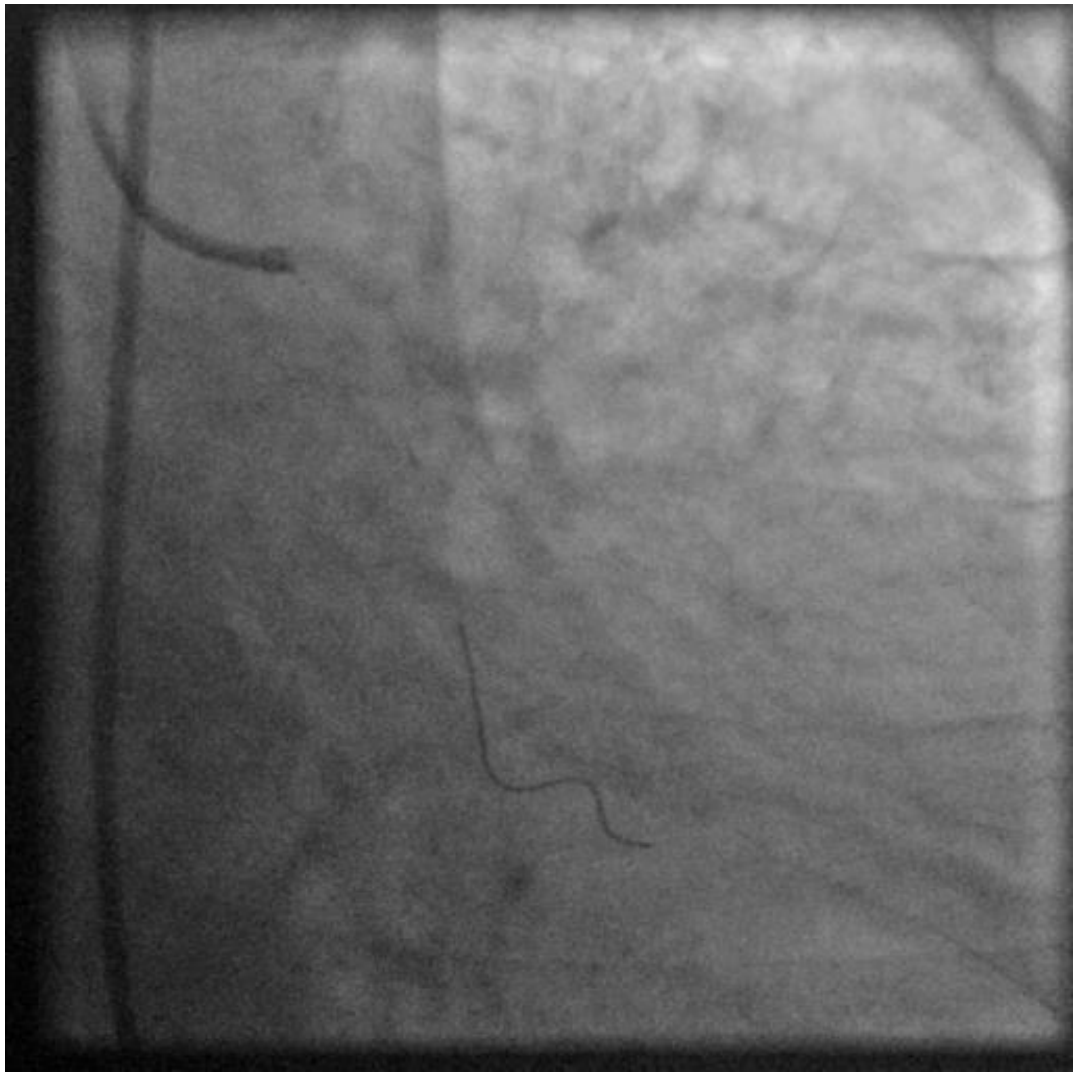


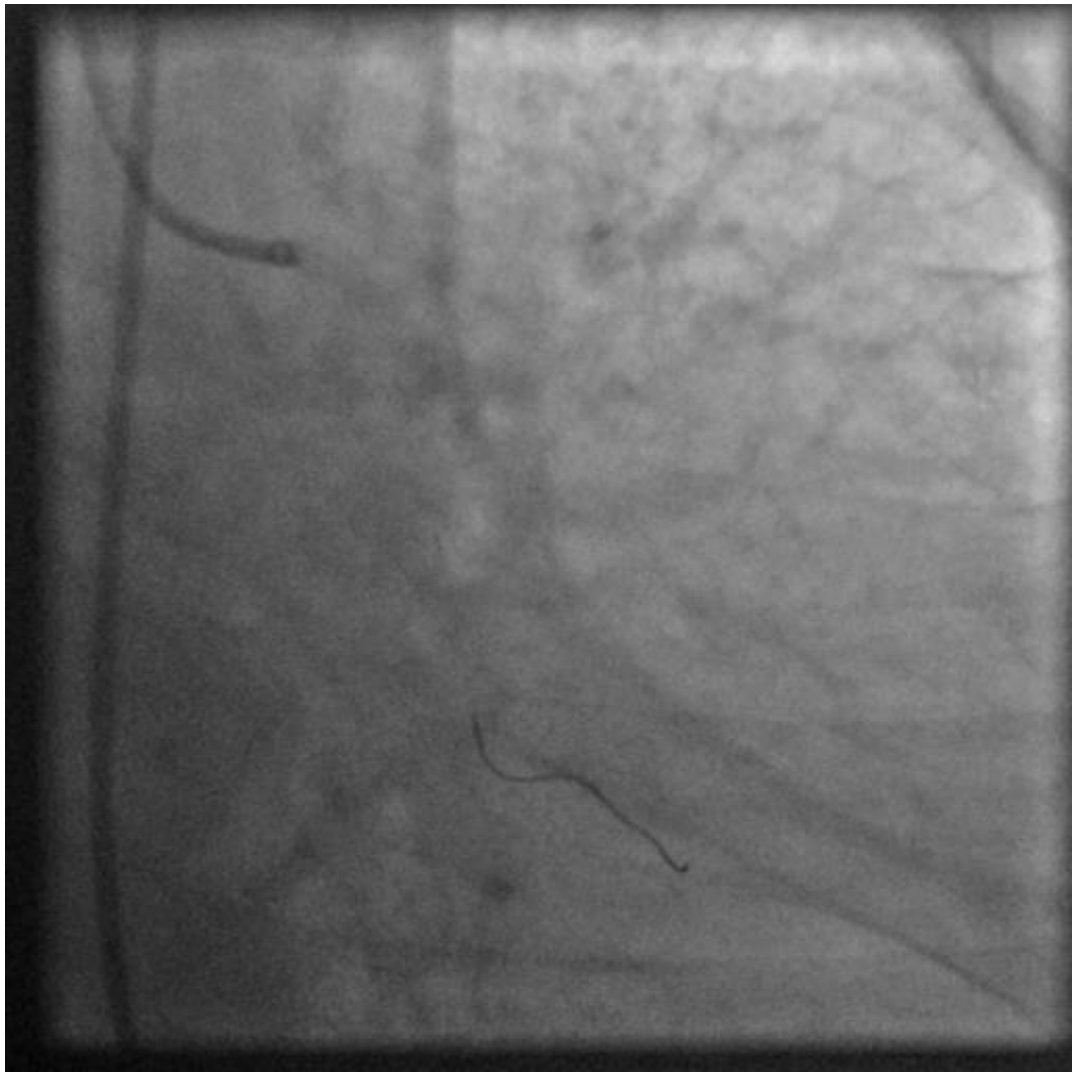


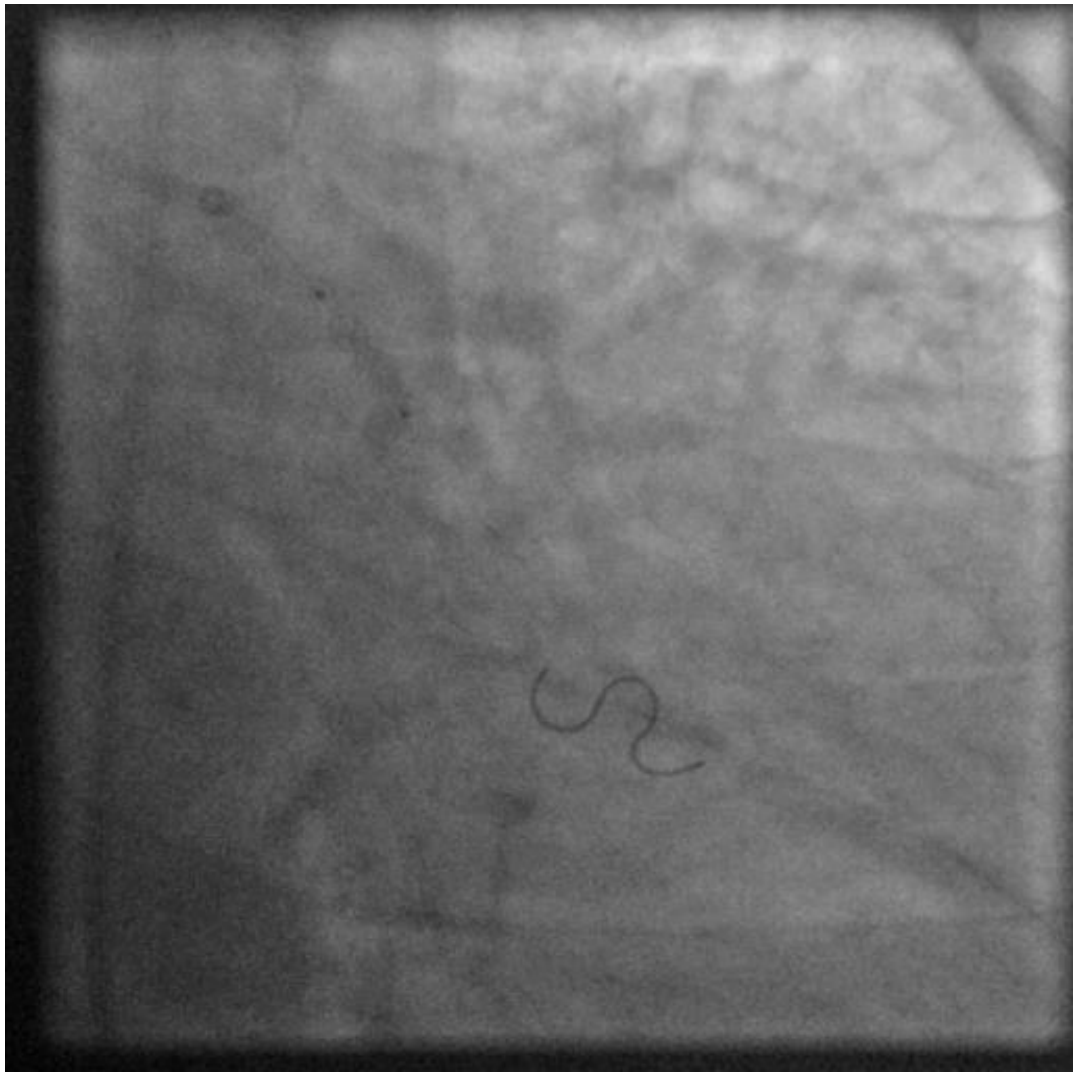


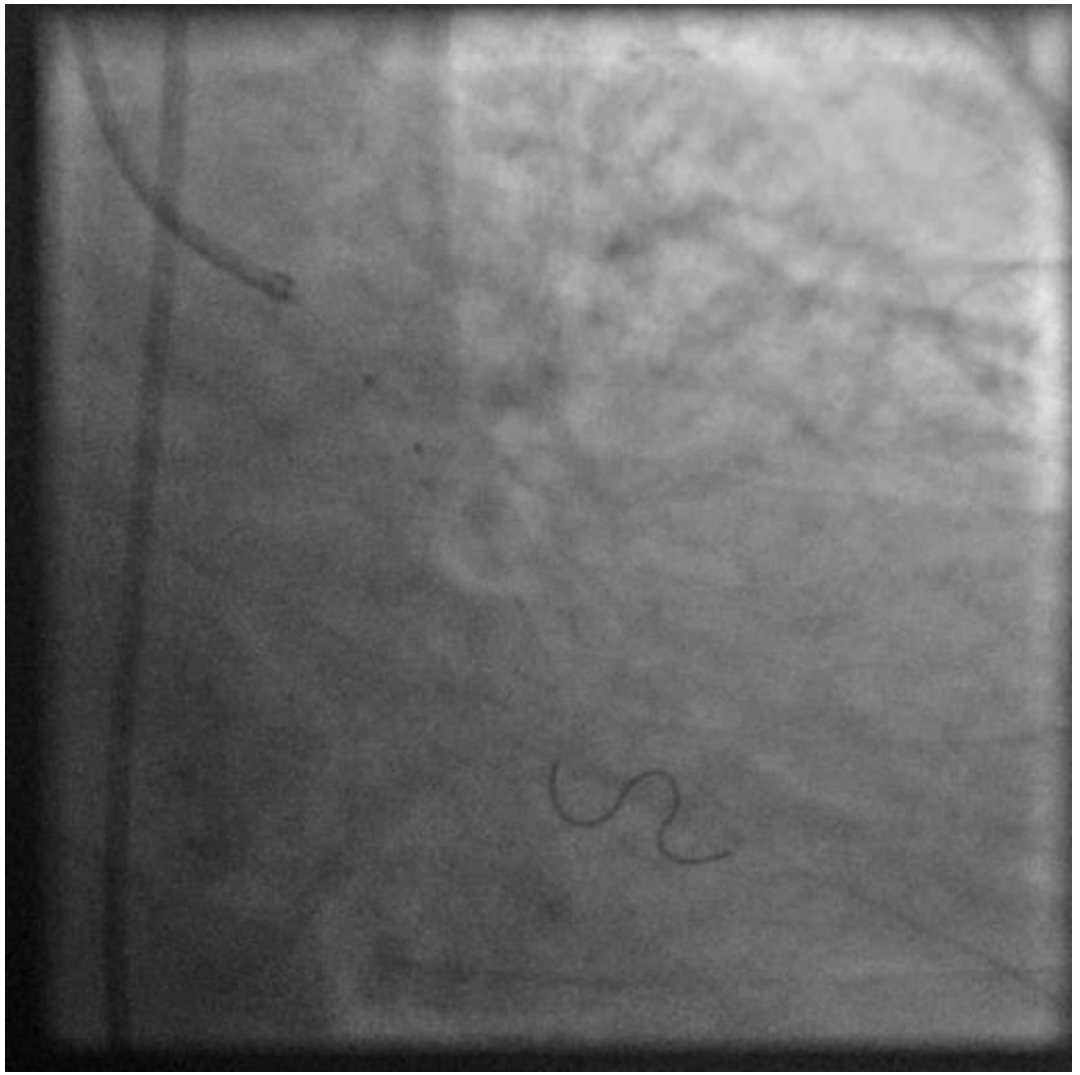


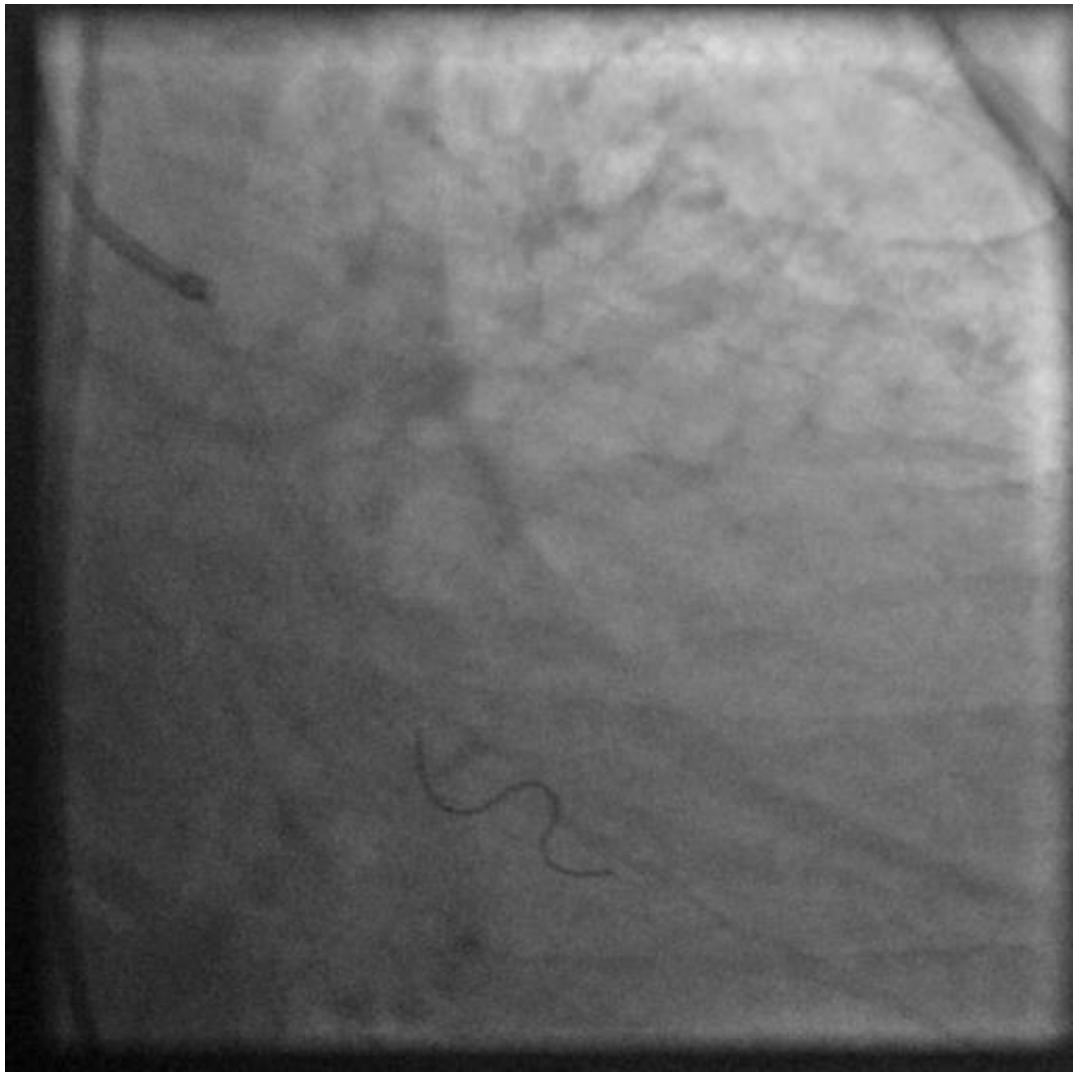
CAT Rx

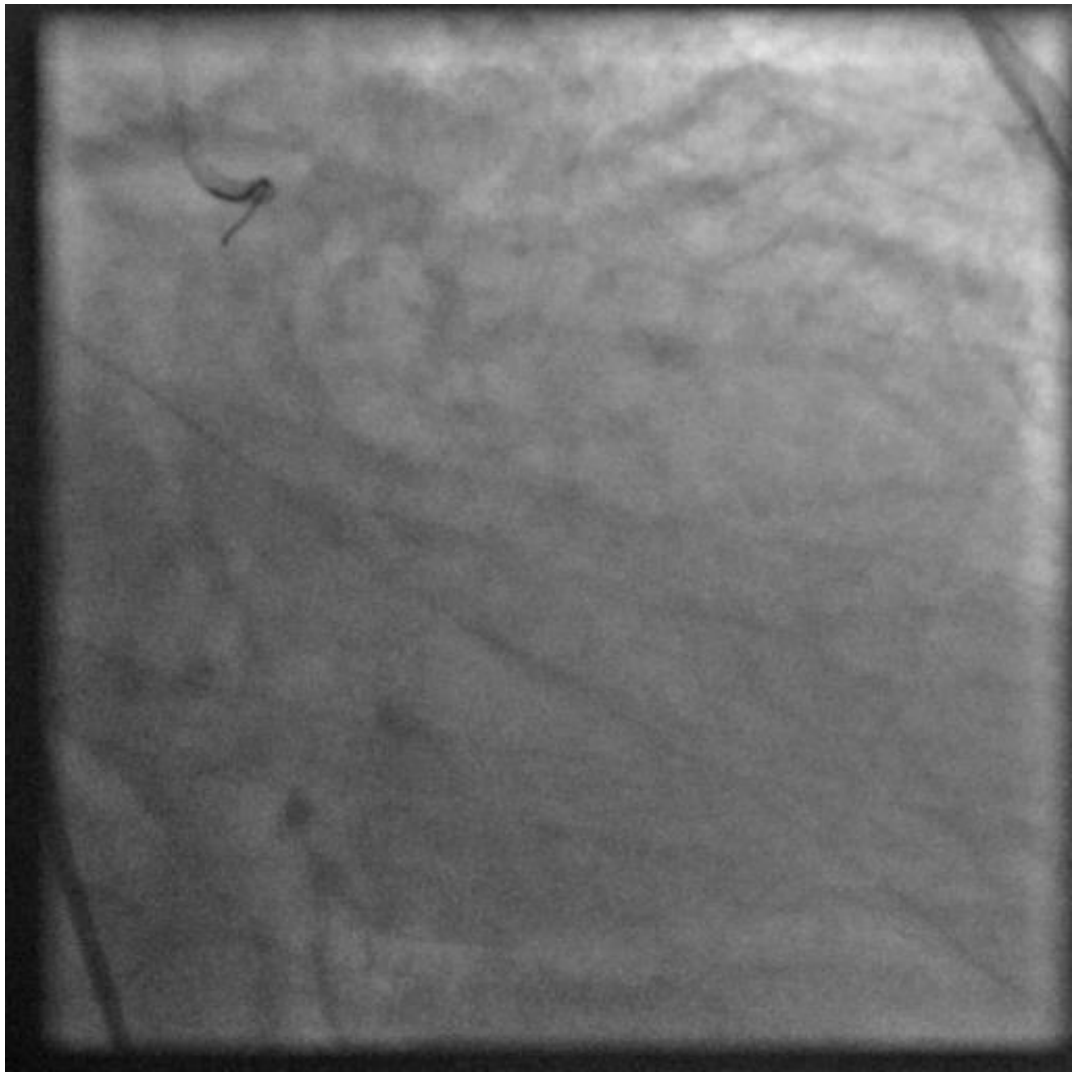












Summary

- Achieving high myocardial perfusion has been associated with improved long-term outcomes
- No-reflow has adverse long-term outcomes and strategies should be employed to prevent no-reflow from occurring
- Continuous power aspiration with CAT RX can minimize distal embolization and improve myocardial perfusion normalization