Real Case Scenario and further insights from the REDUCE trial

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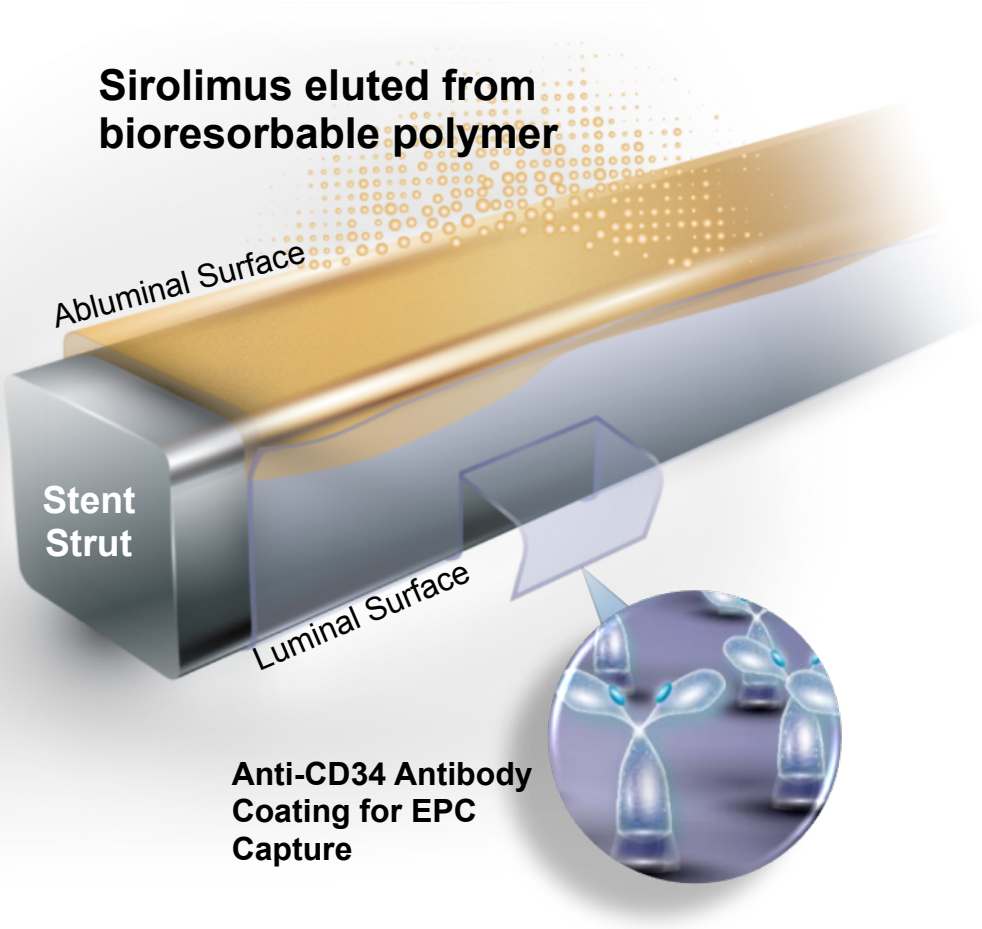
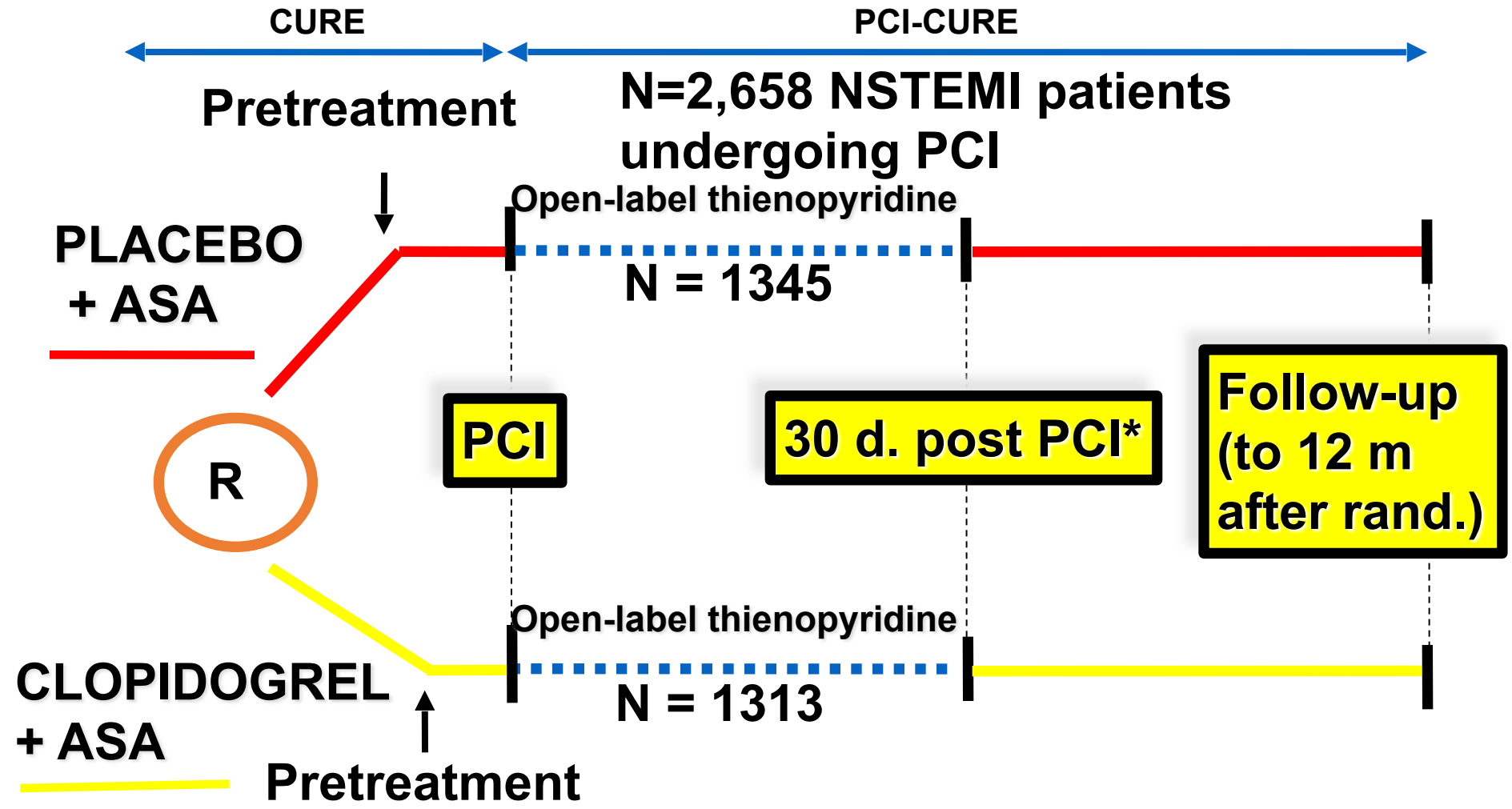
COMBO Dual Therapy Stent

- Sirolimus eluting stent with abluminal bioresorbable polymer
- EPC capture on luminal surface encourages fast, endothelial coverage
- Highly conformable stent platform with excellent radial strength and side branch accessibility



COMBO™
DUAL THERAPY STENT
REPAIR REGENERATE NATURALLY

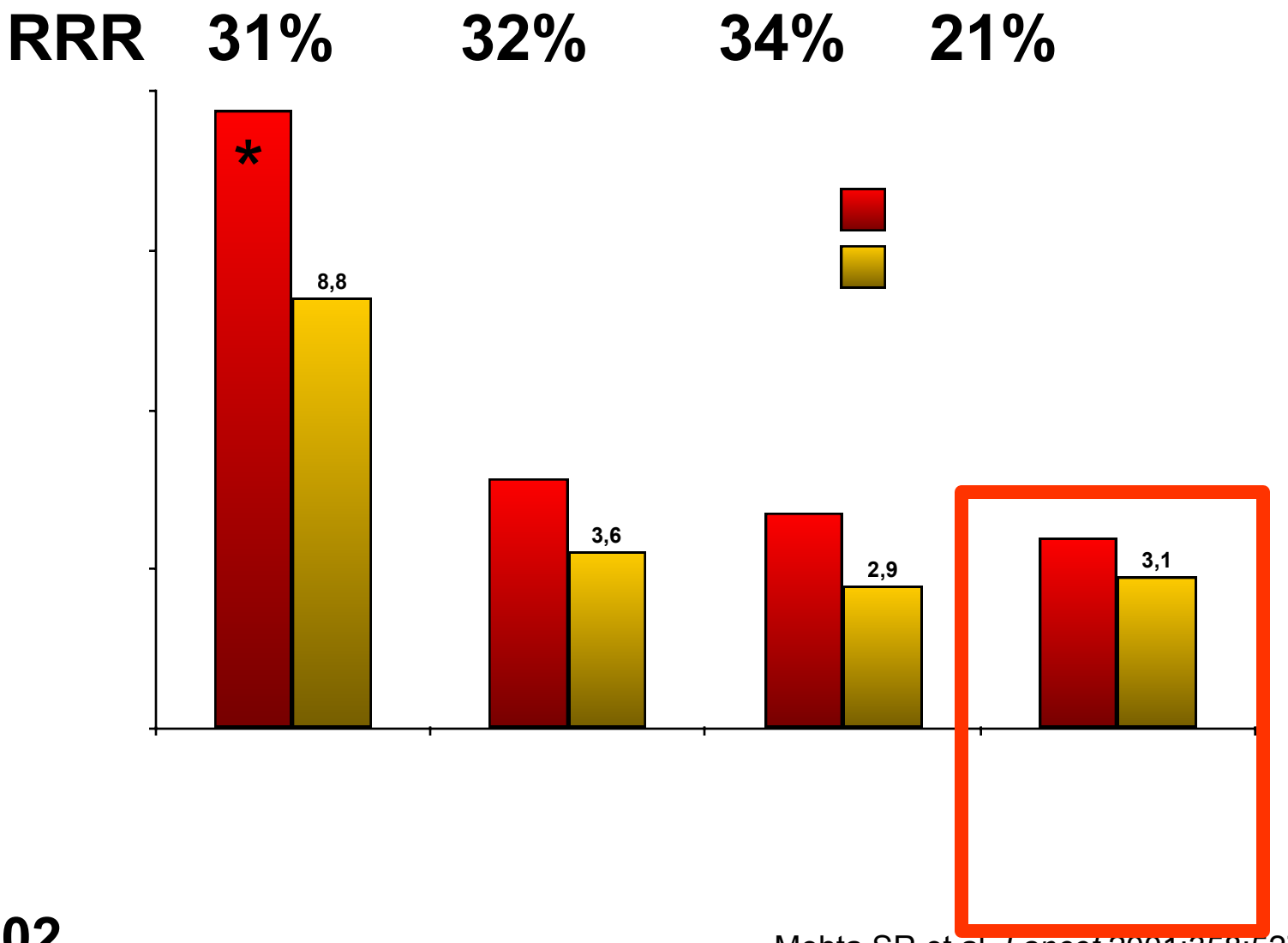
PCI-CURE: Study Design



*1º Outcome: CV Death, MI, Urg Revasc.

Mehta SR et al. *Lancet* 2001:358:527-33

CV Death or MI at Various Intervals



*P=0.002

Mehta SR et al. *Lancet* 2001:358:527-33

DIAGRAM • DIAGNOSTIC RESEARCH AND MANAGEMENT

REDUCE: A Randomized Trial of 3-Month vs 12-Month DAPT After Implantation of a Bioabsorbable Polymer-Based Metallic DES With a Luminal CD34+ Antibody Coating in Patients With ACS

12-Month Clinical Outcomes

Study Chairmen:
Prof. Giuseppe De Luca
Prof. Harry Suryapranata

ClinicalTrials.gov NCT02118870

Background

- Short-term DAPT reduces bleeding rates, without increasing thrombotic complications [1-2]. Therefore, recent guidelines recommend 6-12 months DAPT for patients with stable angina treated with new generation DES [3]
- The optimal duration of DAPT in ACS patients treated with DES is still unclear, especially in the era of new anticoagulants/antiplatelet agents
- The COMBO Dual Therapy Stent, which combines abluminal release of sirolimus *(to prevent neointima formation)* and capture of endothelial progenitor cells *(to enhance stent re-endothelialization)* [4] may be attractive in the context of ACS

1. Navarese et al. BMJ 2015;350:h1618
2. Palmerini et al. Lancet 2015; 385: 2371-82
3. Windecker et.al. Eurintervention 2015;10:1024-9
4. Granada et al. Circ Cardiovasc Interv 2010;3:257-266

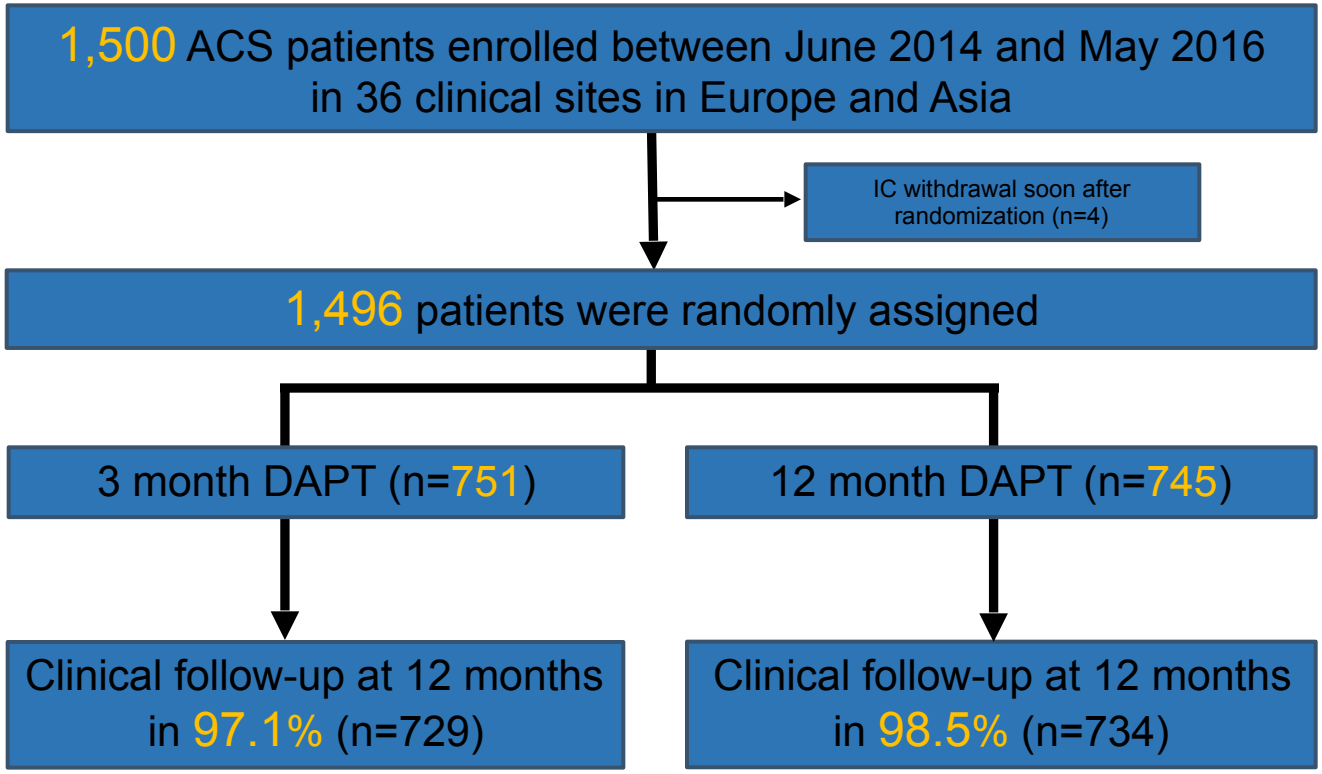
Methods

- Design: Investigator-initiated prospective, multicenter, randomized study with two randomization groups (3 versus 12 months DAPT) (NCT02118870)
- Objective: To evaluate the non-inferiority of a combined safety and efficacy endpoint of a short-term 3 months DAPT, compared to standard 12-month DAPT strategy, in ACS patients treated with the COMBO stent
- Key inclusion criteria:
  ACS patients undergoing successful COMBO stent implantation
- Key exclusion criteria:
  Recent major bleeding, contraindication to DAPT, revascularization with other stent type, need for permanent DAPT due to comorbidities

Methods

- Primary Endpoint:
  Composite of all cause death, MI, ST, stroke, TVR or bleeding (BARC II, III, V)
- Secondary Endpoints:
  - Pre-specified Landmark analysis of Primary Endpoint from 3 to 12 month
  - Individual components of the composite endpoint
- Sample Size: The calculation was based on a non-inferiority design, with a 1-sided test for differences in independent binomial proportions at the 2.5% significance level, a power of 80%, and a non-inferiority margin of 5% (assuming a counterbalance between thrombotic and bleeding complications)
- Principal Investigators:
  - Harry Suryapranata (Radboud University Medical Center, Nijmegen, Netherlands)
  - Giuseppe De Luca (Eastern Piedmont University, Novara, Italy)
- CRO: Diagram BV, Zwolle, Netherlands

Results: Flow Chart



Participating Centers & Co-Investigators

Hospital	Country	PI
Jessa Ziekenhuis (Hasselt)	BE	E. Benit
Radboud University Medical Center (Nijmegen)	NL	C. Camaro
Isala (Zwolle)	NL	E. Kedhi
Eastern Piedmont University (Novara)	IT	G. De Luca
Zuyderland Medical Center (Heerlen)	NL	S. Rasoul
Queen Elizabeth II Sabah (Sabah)	MY	H.B. Liew
Jeroen Bosch Ziekenhuis ('s Hertogenbosch)	NL	J. Polad
University Malaya (Kuala Lumpur)	MY	W.A.W. Ahmad
National Heart Institute (Kuala Lumpur)	MY	R. Zambahari
Centre Hospitalier Universitaire Charleroi (Charleroi)	BE	J. Lalmand
Onze Lieve Vrouwe Gasthuis (Amsterdam)	NL	R.J. Van der Schaaf
National Heart Center (Singapore)	SG	T.H. Koh
Queen Mary Hospital, University of Hong Kong	HK	F.C.C. Tan
Hospital du Sart-Tilman (Liège)	BE	V. Legrand
Hasan Sadikin Hospital (Bandung)	ID	A.F. Yahya
National University Heart Centre (Singapore)	SG	H.C. Tan
Kariadi General Hospital (Semarang)	ID	S. Rifqi
Hospital Besar Pulau Pinang (Penang)	MY	M.A.S.A. Kader

Hospital	Country	PI
Ospedale Generale Madre Giuseppina Vannini (Rome)	IT	B. Pironi
Academic Medical Center (Amsterdam)	NL	R.J. de Winter
Telogorejo Hospital (Semarang)	ID	S. Rifqi
Queen Elizabeth Hospital (Hong Kong)	HK	M.K.Y. Lee
Katholisches Krankenhaus St. Johann Nepomuk (Erfurt)	GE	H. Ebelt
Universitätsklinikum (Leipzig)	GE	M. Neef
Semmelweis Univ, Heart and Vascular Center (Budapest)	HU	B. Merkely
Medical University of Silezia (Katowice)	PL	W. Wojakowski
Ospedaliera Universitaria 'Paola Gaiccone' (Palermo)	IT	G. Andolina
University Hospital (Krakow)	PL	D. Dudeck
Tan Tock Seng Hospital (Singapore)	SG	J.K.B. Tan
Herz- und Diabeteszentrum NRW (Bad Oeynhausen)	GE	W. Scholtz
Pamela Youde Nethersole Eastern Hospital (Hong Kong)	HK	K.L. Tsui
Städtische Kliniken Lukaskrankenhaus (Neuss)	GE	M. Haude
Klinikum St.-Marien-Hospital Lünen GmbH (Lünen)	GE	C. Perings
San Bortolo Hospital (Vicenza)	IT	L. La Vecchia
Cliniques universitaires Saint-Luc (Brussels)	BE	J. Renkin
Princess Margaret Hospital (Hong Kong)	HK	P.T. Tsui

Results: Baseline

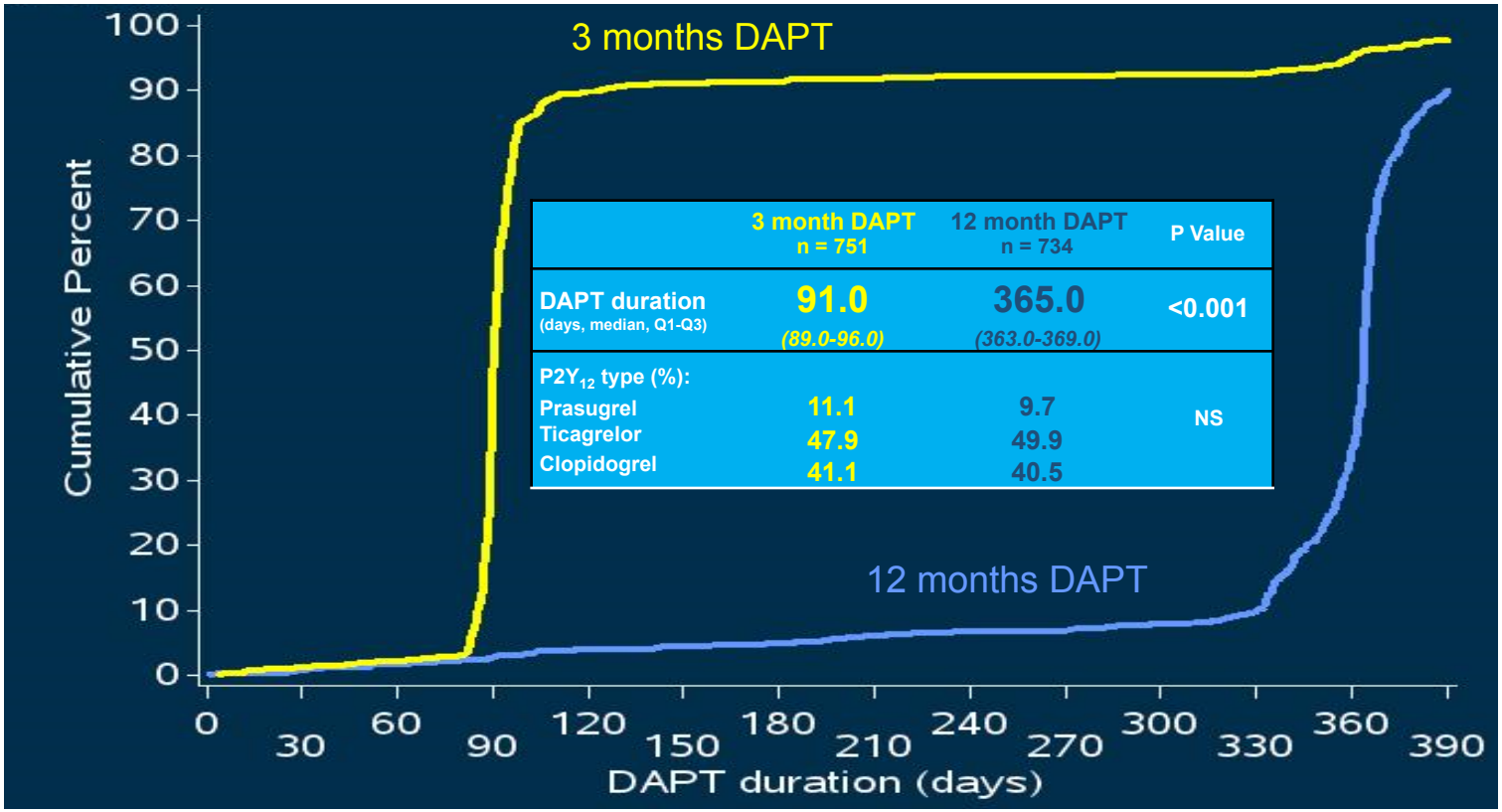
Baseline Characteristics

	3 month DAPT n = 751	12 month DAPT n = 734	P
Age (Mean ± SD)	61.2 ± 11.6	60.5 ± 12.0	NS
Female Gender (%)	17.4	22.7	0.01
STEMI diagnosis	49.3	45.2	NS
Diabetes Mellitus (%)	21.6	19.5	NS
Smoking (%)	42.1	42.7	NS
Hypercholesterolemia (%)	46.3	44.9	NS
Hypertension (%)	50.7	50.7	NS
Family history of CAD (%)	35.0	36.0	NS
Previous ACS (%)	12.5	11.8	NS
Previous PCI (%)	11.7	9.8	NS

Angiographic Characteristics

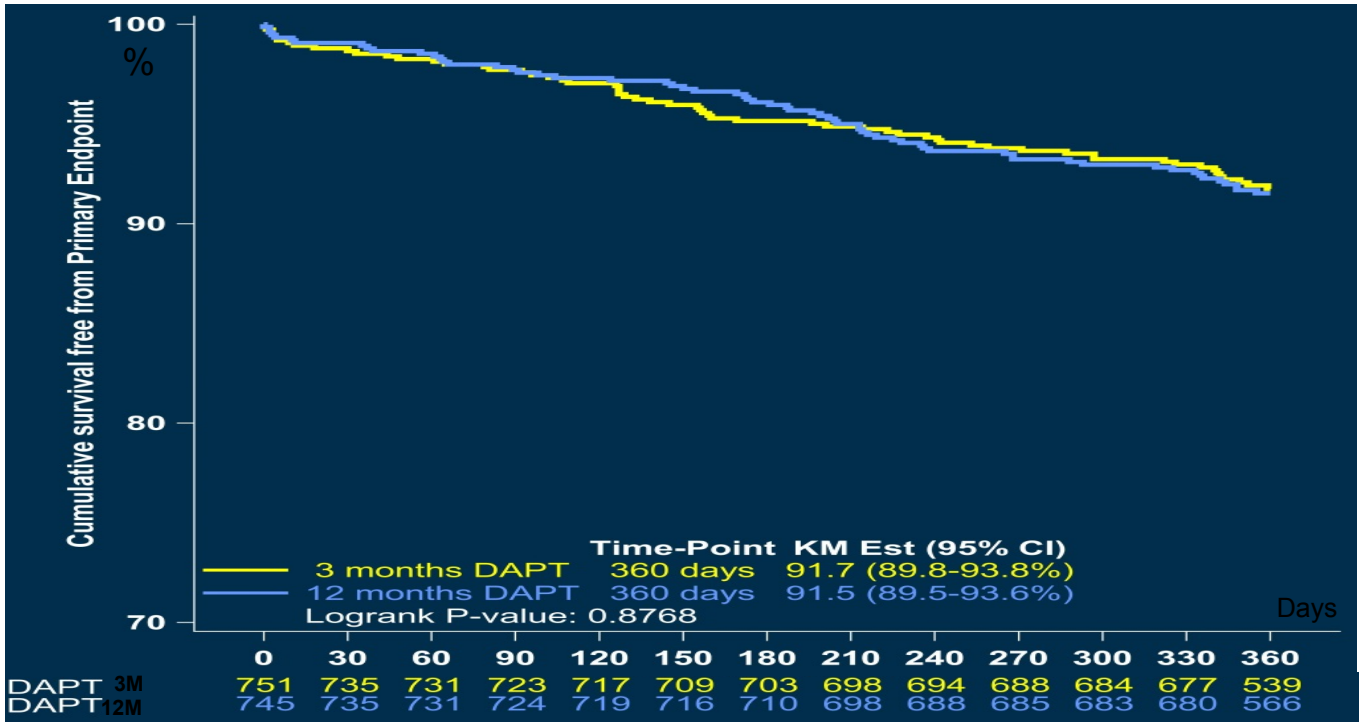
	3 month DAPT n = 751	12 month DAPT n = 734	P
Radial access (%)	76.1	76.9	NS
Multivessel disease (%)	36.1	33.8	NS
Target vessel (%): - LAD	48.0	44.2	NS
- RCA	31.2	33.0	NS
- RCX	19.5	22.0	NS
Initial TIMI flow 3 (%)	46.6	49.0	NS
Thrombosuction (%)	12.5	13.6	NS
Total stent length (mm, mean ± SD)	25.5 ± 12.8	25.2 ± 12.7	NS
Procedural success (%)	99.3	99.7	NS
PCI additional segments (%)	20.3	21.9	NS

Results: DAPT Duration



	3 month DAPT n = 751	12 month DAPT n = 734	P Value
DAPT duration (days, median, Q1-Q3)	91.0 *(89.0-96.0)*	365.0 *(363.0-369.0)*	<0.001
$P2Y_{12}$ type (%):			
Prasugrel	11.1	9.7	NS
Ticagrelor	47.9	49.9	
Clopidogrel	41.1	40.5	

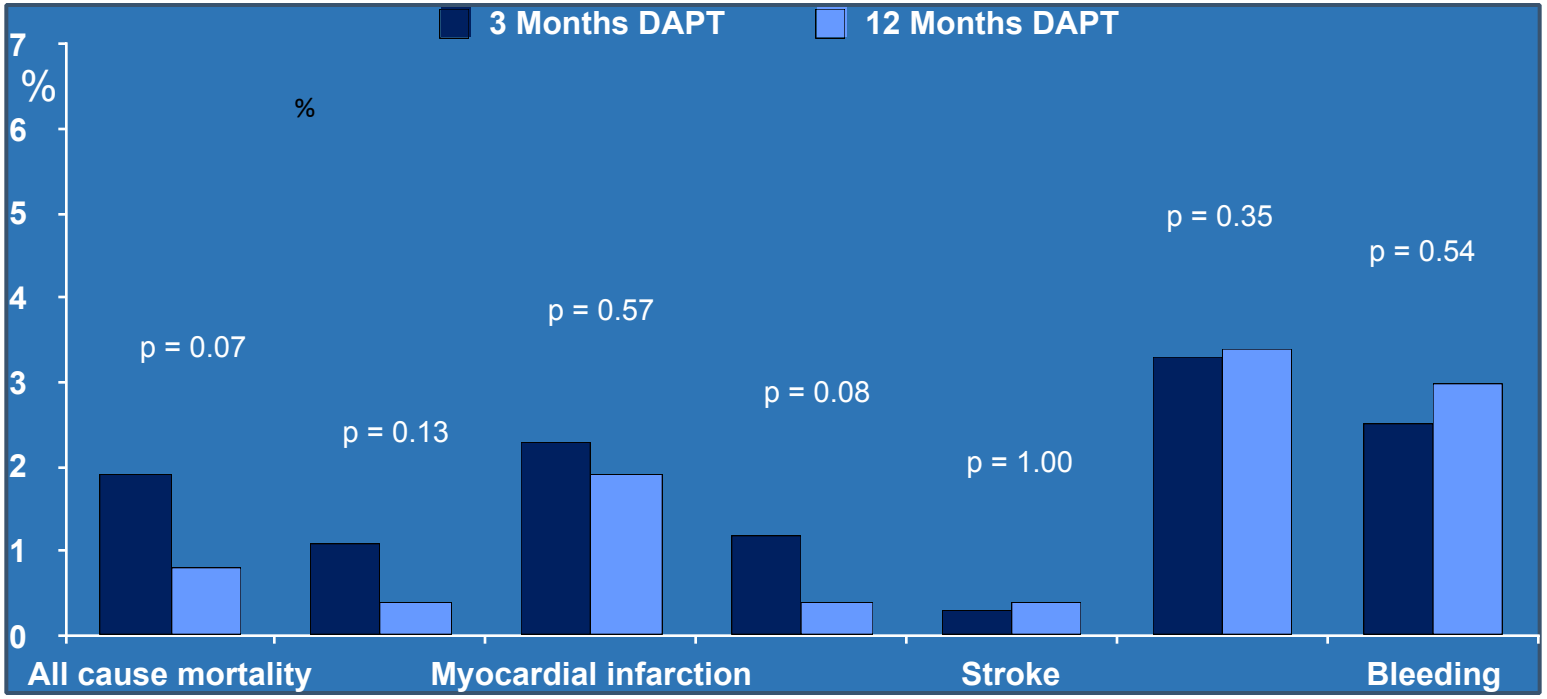
Results: Primary Study Endpoint



Analysis set	3 month DAPT n = 729	n = 734	Risk difference	Upper bound of 1 sided 97.5% CI	OR (95% CI)	P non-inferiority
Intention to treat	8.2		-0.002	0.027	0.97 (0.67-1.41)	<0.001

Confirmed by PP and AT analyses, and after adjustment for gender (adjusted OR (95% CI) = 0.95 (0.66–1.38), p=0.81)

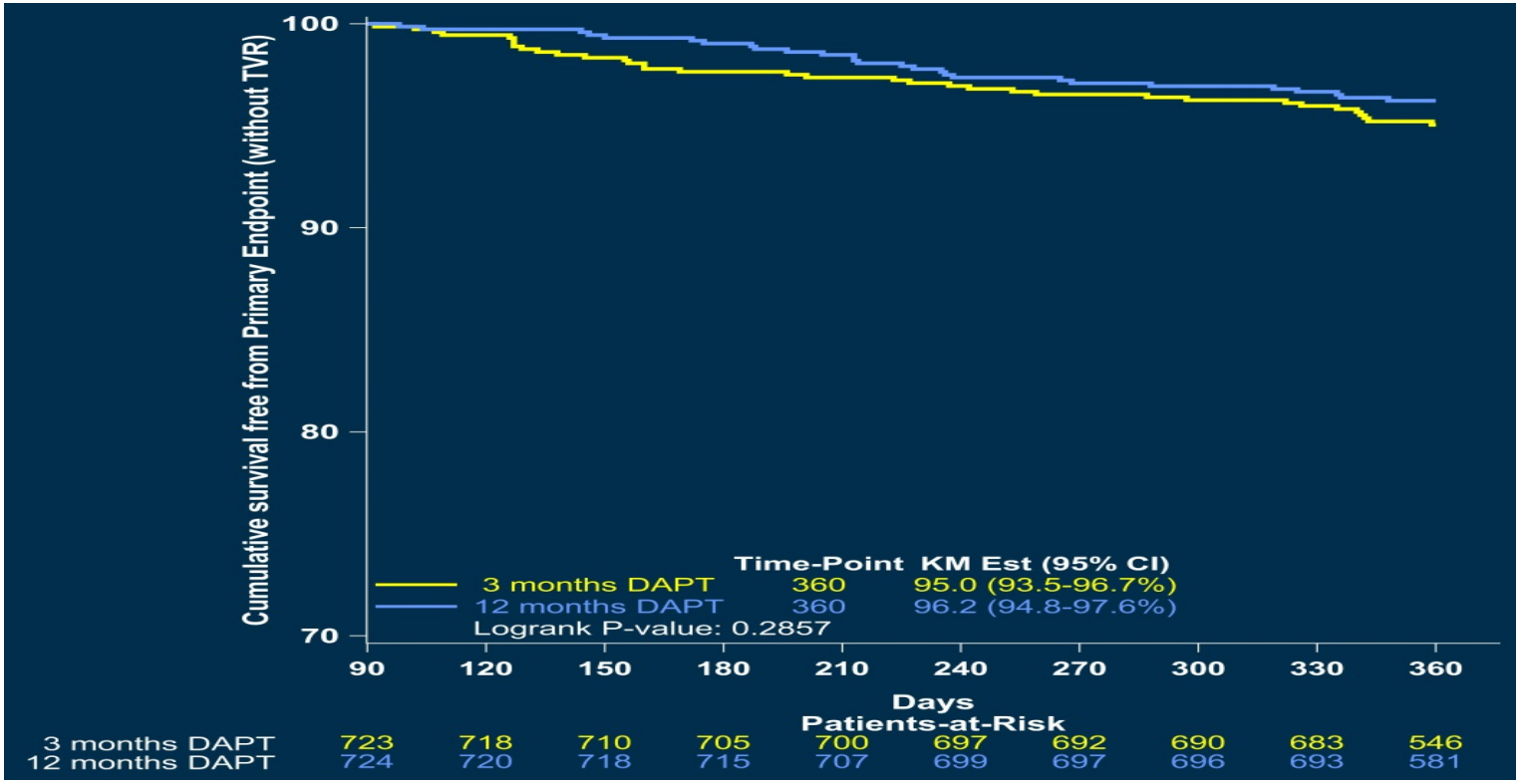
Results: Secondary Study Endpoints



No difference in any secondary endpoint

Results

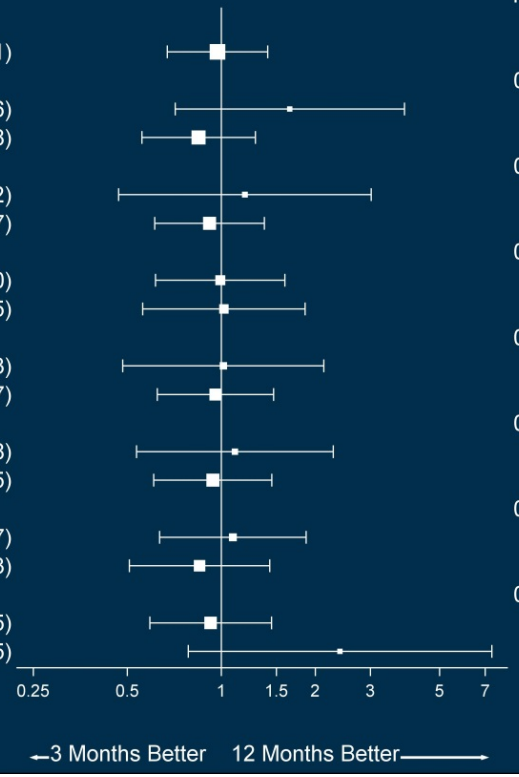
Secondary Endpoint: Pre-Specified Landmark Analysis



No difference in Pre-Specified Landmark Analysis of Composite Endpoint from 3 to 12 months follow-up

Results: Subgroup Analysis

Subgroup	3 Months DAPT Events/N (%)	12 Months DAPT Events/N (%)	OR (95% CI)	P Value*
All	60/ 729 (8.2)	62/ 734 (8.4)	0.97 (0.67 - 1.41)	
Age				0.16
≥ 75 (yrs)	16/ 100 (16.0)	10/ 97 (10.3)	1.66 (0.71 - 3.86)	
< 75 (yrs)	44/ 629 (7.0)	52/ 637 (8.2)	0.85 (0.56 - 1.28)	
Gender				0.61
Female	9/ 127 (7.1)	10/ 166 (6.0)	1.19 (0.47 - 3.02)	
Male	51/ 602 (8.5)	52/ 567 (9.2)	0.92 (0.61 - 1.37)	
Diagnosis				0.95
Non-STEMI	36/ 372 (9.7)	39/ 400 (9.8)	0.99 (0.62 - 1.60)	
STEMI	24/ 357 (6.7)	22/ 333 (6.6)	1.02 (0.56 - 1.85)	
Geographic region				0.89
Asian site	15/ 222 (6.8)	15/ 225 (6.7)	1.01 (0.48 - 2.13)	
European site	45/ 507 (8.9)	47/ 509 (9.2)	0.96 (0.62 - 1.47)	
Diabetes				0.70
Yes	18/ 158 (11.4)	15/ 144 (10.4)	1.11 (0.54 - 2.28)	
No	42/ 570 (7.4)	46/ 589 (7.8)	0.94 (0.61 - 1.45)	
Vessel Disease				0.52
Multi	32/ 264 (12.1)	28/ 249 (11.2)	1.09 (0.63 - 1.87)	
Single	28/ 464 (6.0)	34/ 485 (7.0)	0.85 (0.51 - 1.43)	
Zwolle Risk Score				0.12
≤ 3	40/ 527 (7.6)	43/ 527 (8.2)	0.92 (0.59 - 1.45)	
> 3	10/ 80 (12.5)	5/ 89 (5.6)	2.40 (0.78 - 7.35)	



* P-Value is the test of interaction between treatment and each subgroup unadjusted for multiplicity.

Consistent results across all subgroups, without any significant statistical interaction

Limitations

- Unblinded trial without placebo control - Use of heterogeneous $P2Y_{12}$ inhibitors
- Non-inferiority margin of 5% in our study might be relatively large, but consistent with other similar non-inferiority stent studies [1-2]
- Lower than expected event rates may be due to randomization after successful stenting *(freedom from in-hospital events)* – Potential selection of lower risk ACS pts
- Significant difference in gender between the groups, however the results were consistent in both male and female gender, without any significant interaction
- Although 3 Months DAPT showed numerically higher rates of ST and all cause mortality, and lower rates of major bleeding, these were not statistically significant. In fact, the overall event rates were very low, and this study has not been designed to detect any differences in each individual component of the composite endpoint

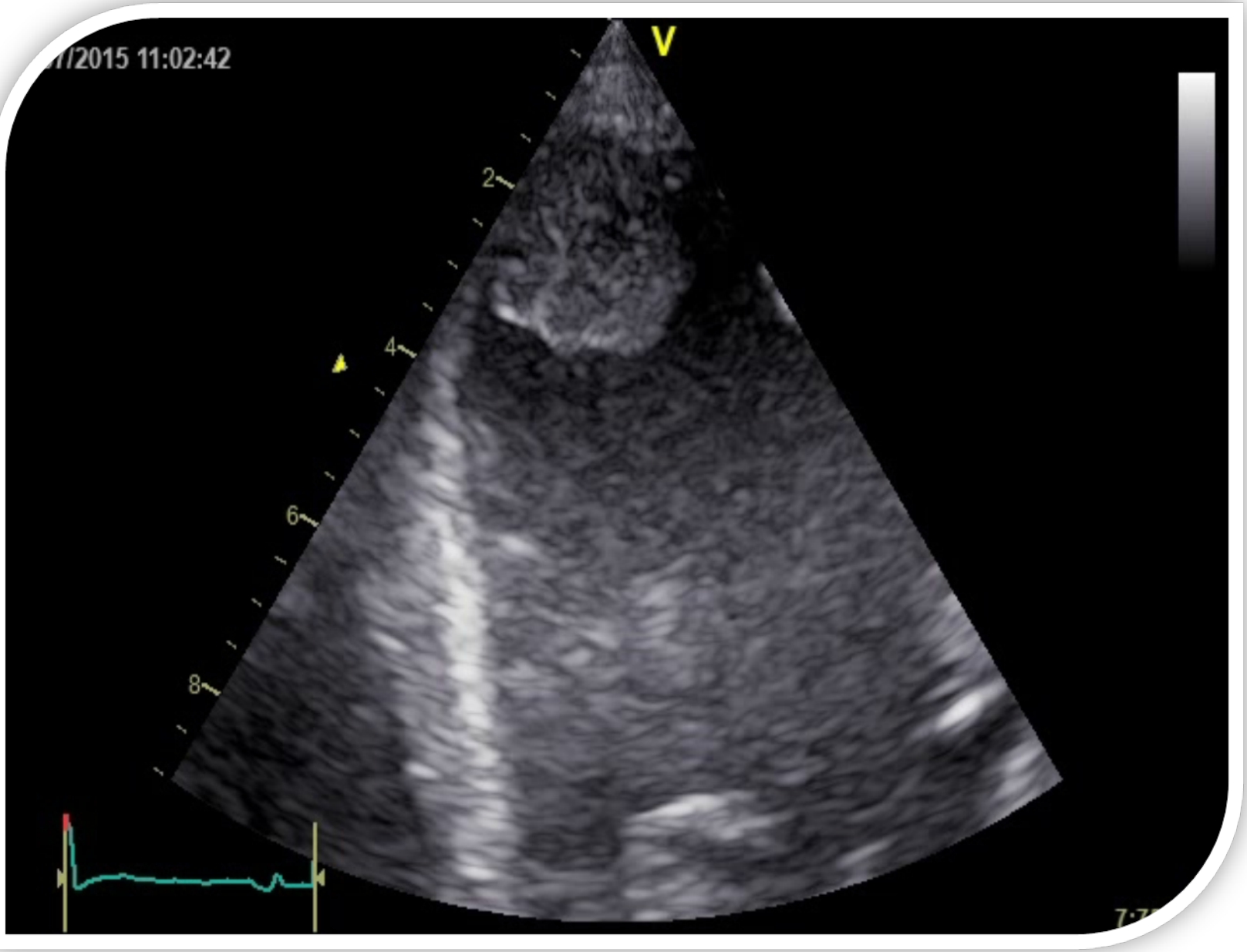
1. Smits et al. Lancet 2013; 381: 651-660
2. Stone et al. J Am Coll Cardiol 2011; 57: 1700-1708

Conclusion

- The REDUCE trial is the first study restricted to ACS patients, comparing a short 3-month *vs* a standard 12-month DAPT
- The main finding of the present study is that, among ACS patients treated with the COMBO stent, 3-month DAPT is not inferior to 12-month DAPT
- This finding is consistent for all pre-specified subgroups
- Therefore, a shorter DAPT strategy could be considered, if necessary, even in ACS population
- Future large trials are needed to further investigate and confirm the safety of short-term DAPT regimen in ACS patients in the era of new ADP antagonists and new generation DES

Case 1

- 70 years male
- Risk factors: Diabetes mellitus (HbA1c 10% at admission).
- Medication at admission: None
- Hospital admission: Chest pain with dyspnea (Troponin I 2,5ng/ml).
- Chest x-ray showed bilateral pleural effusion.
- ECG: LBBB.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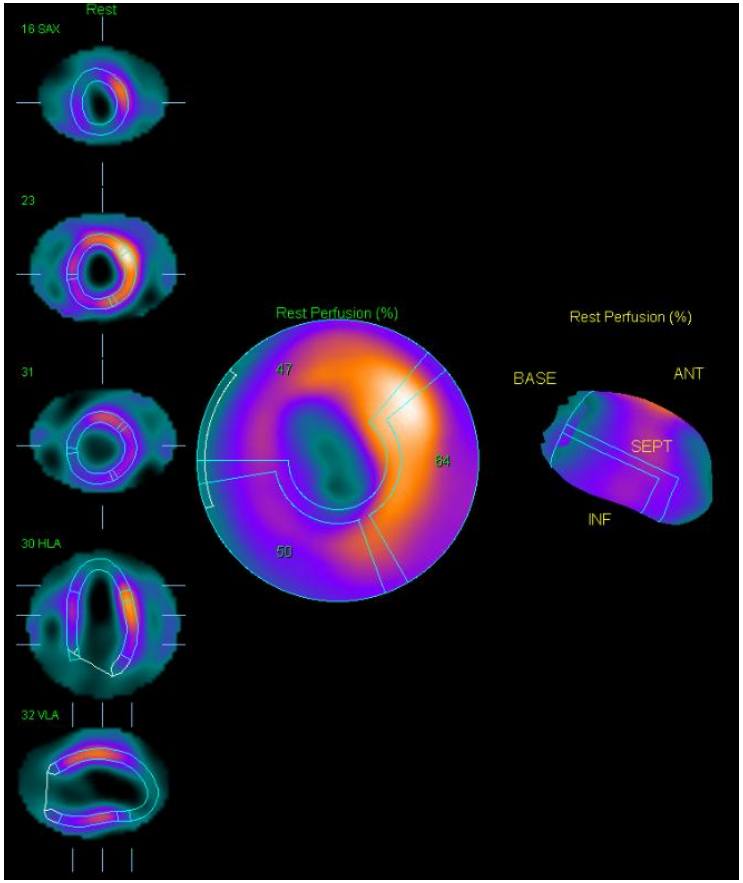
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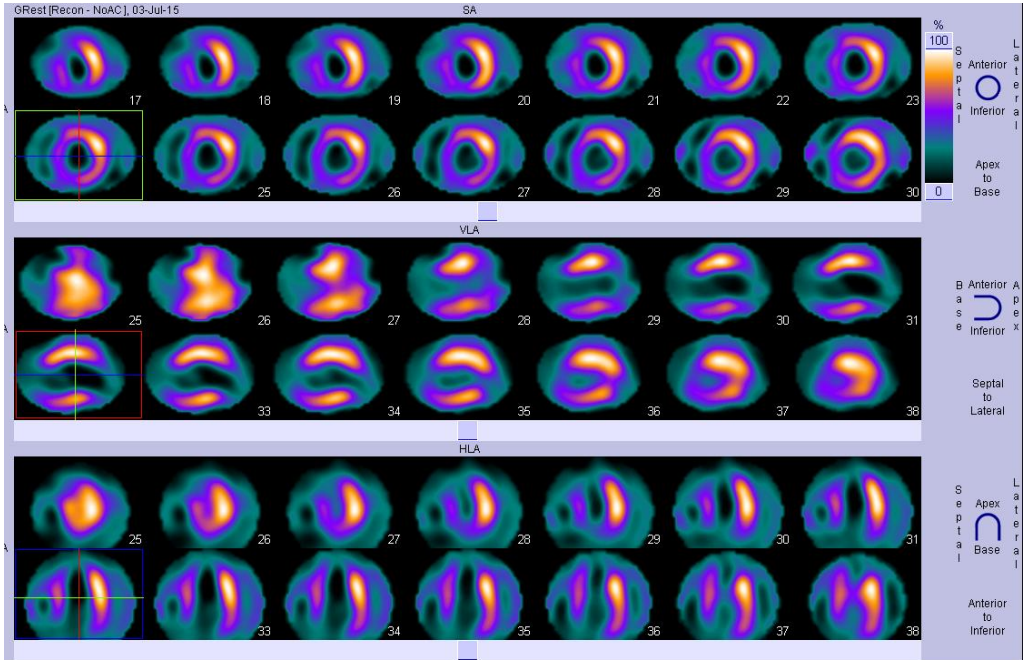
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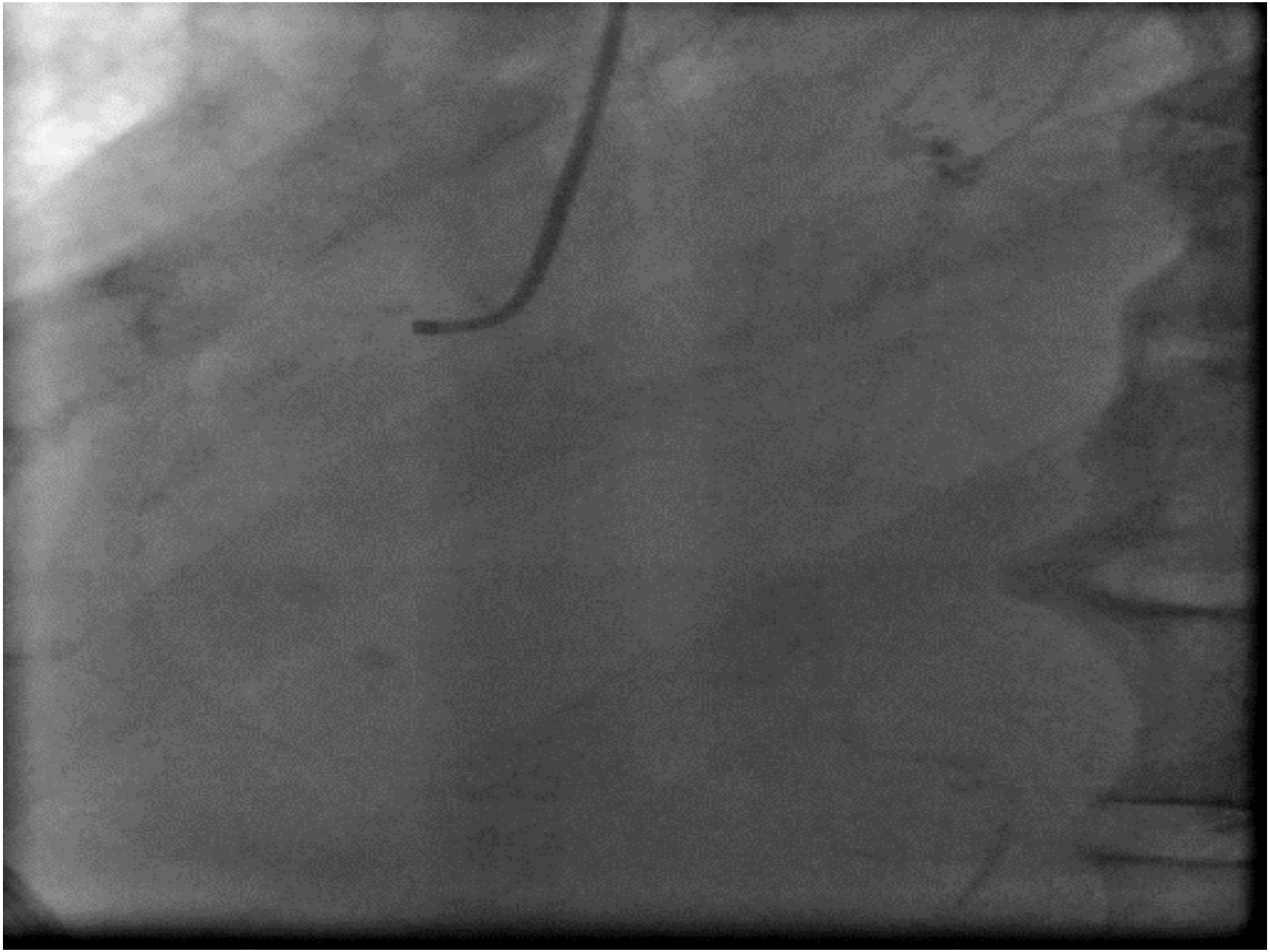

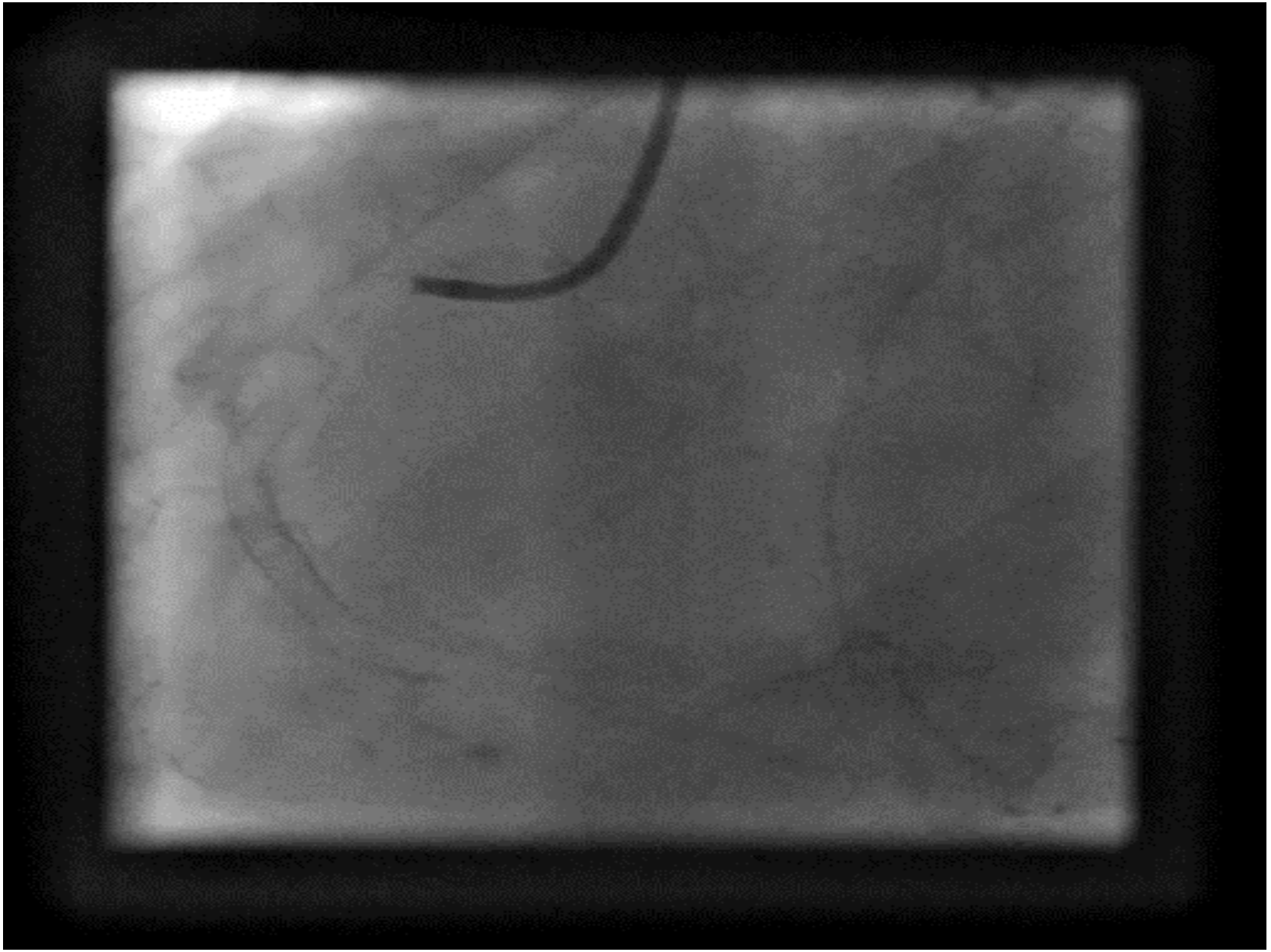

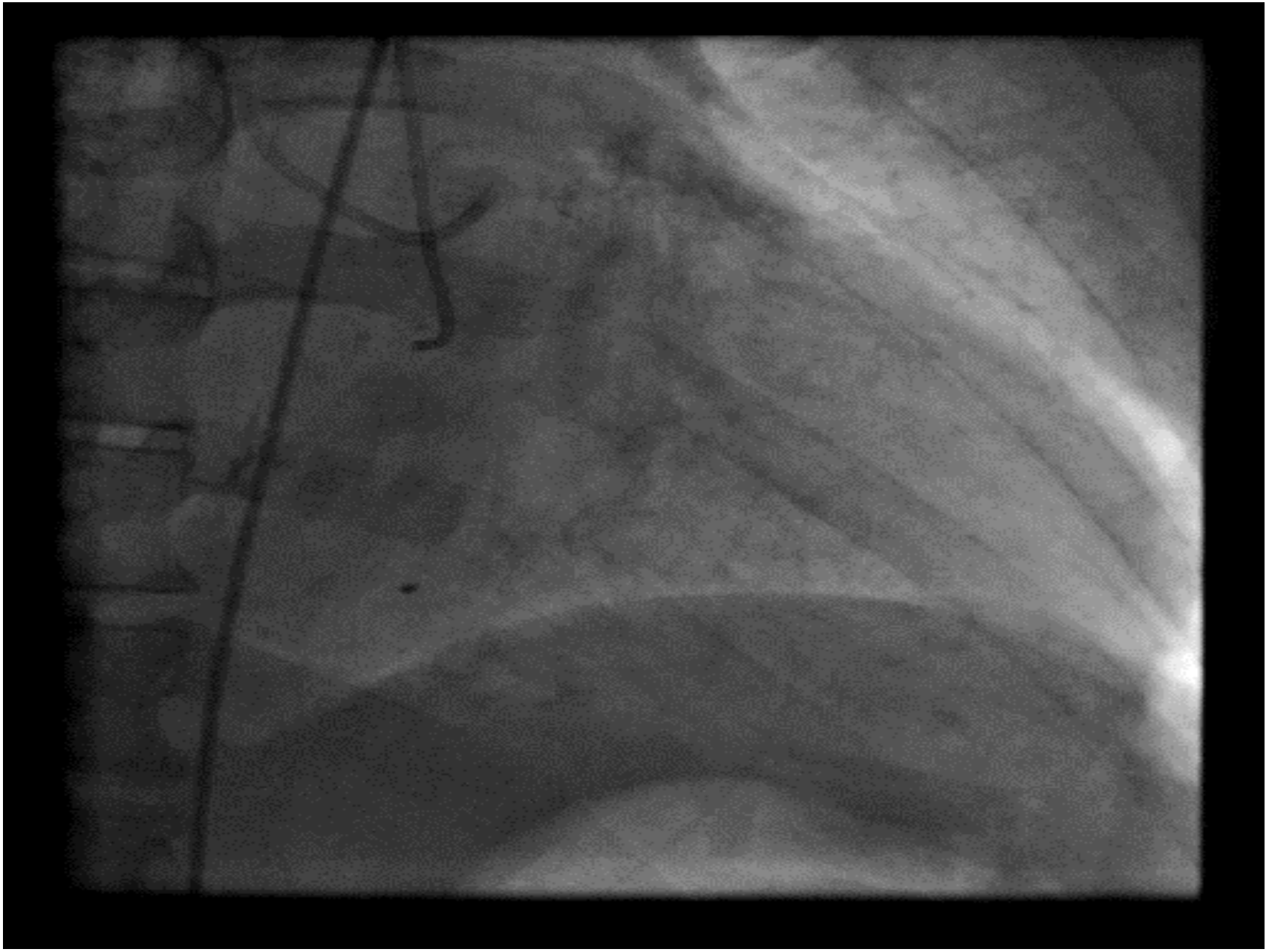

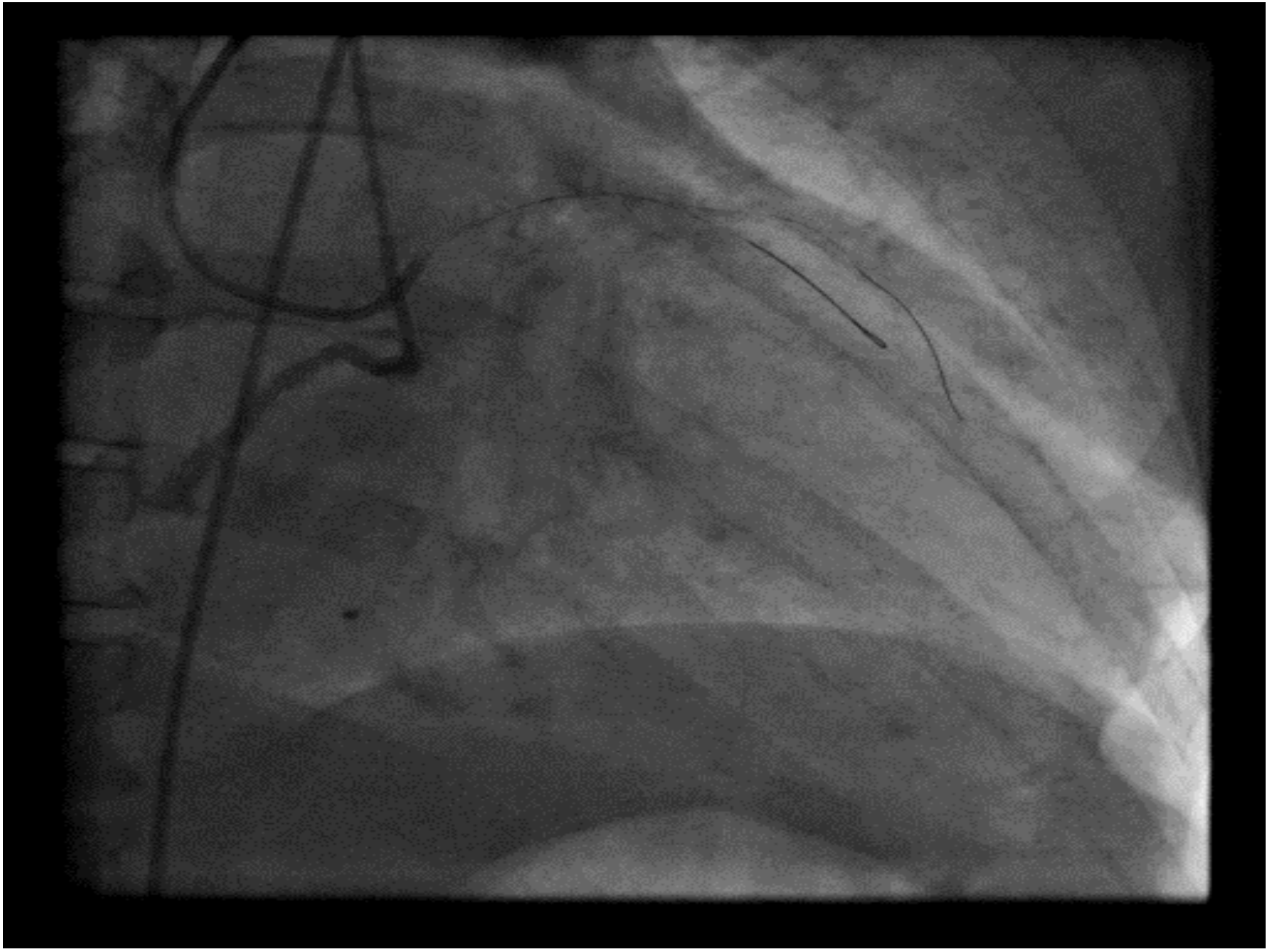

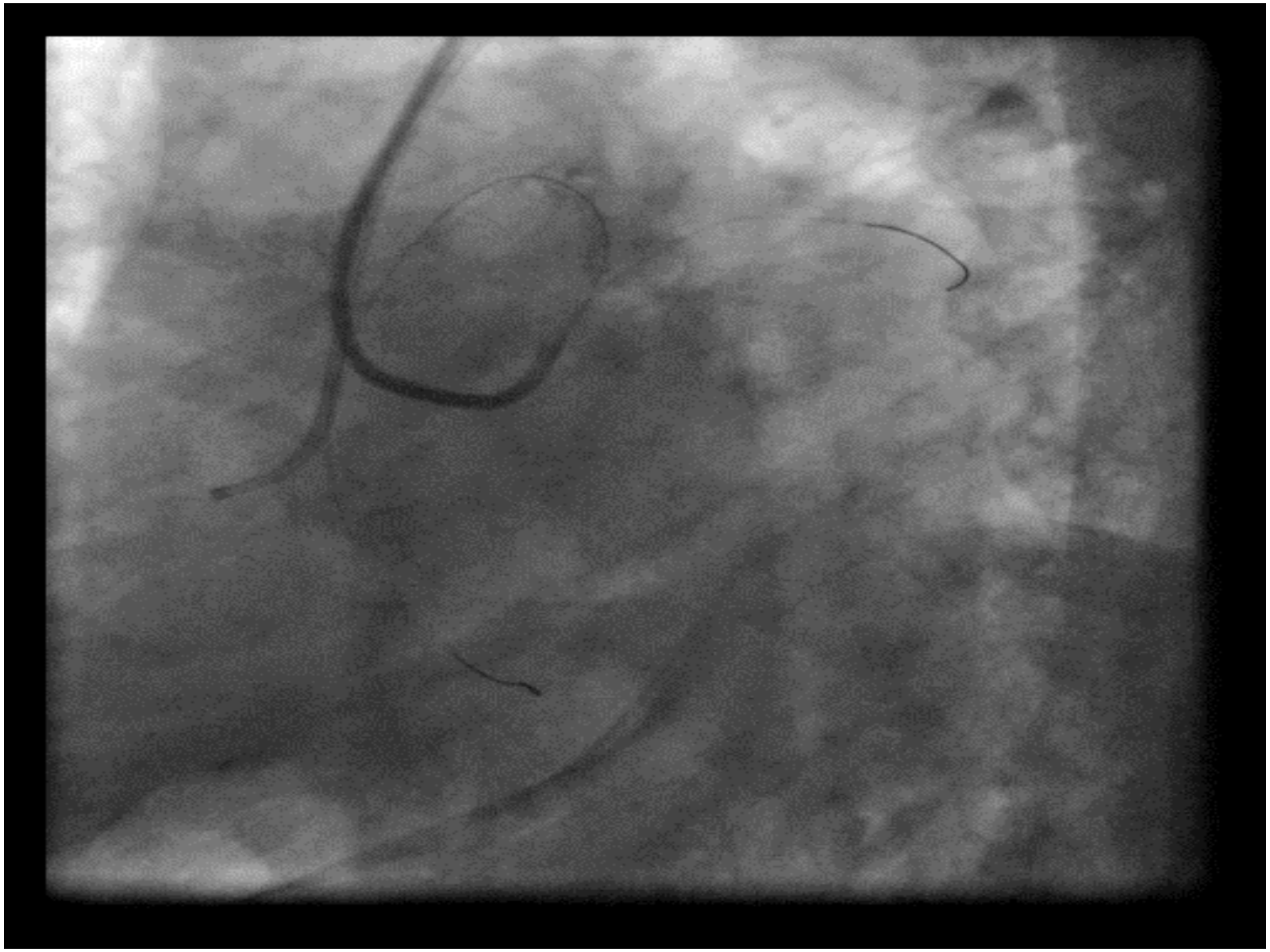

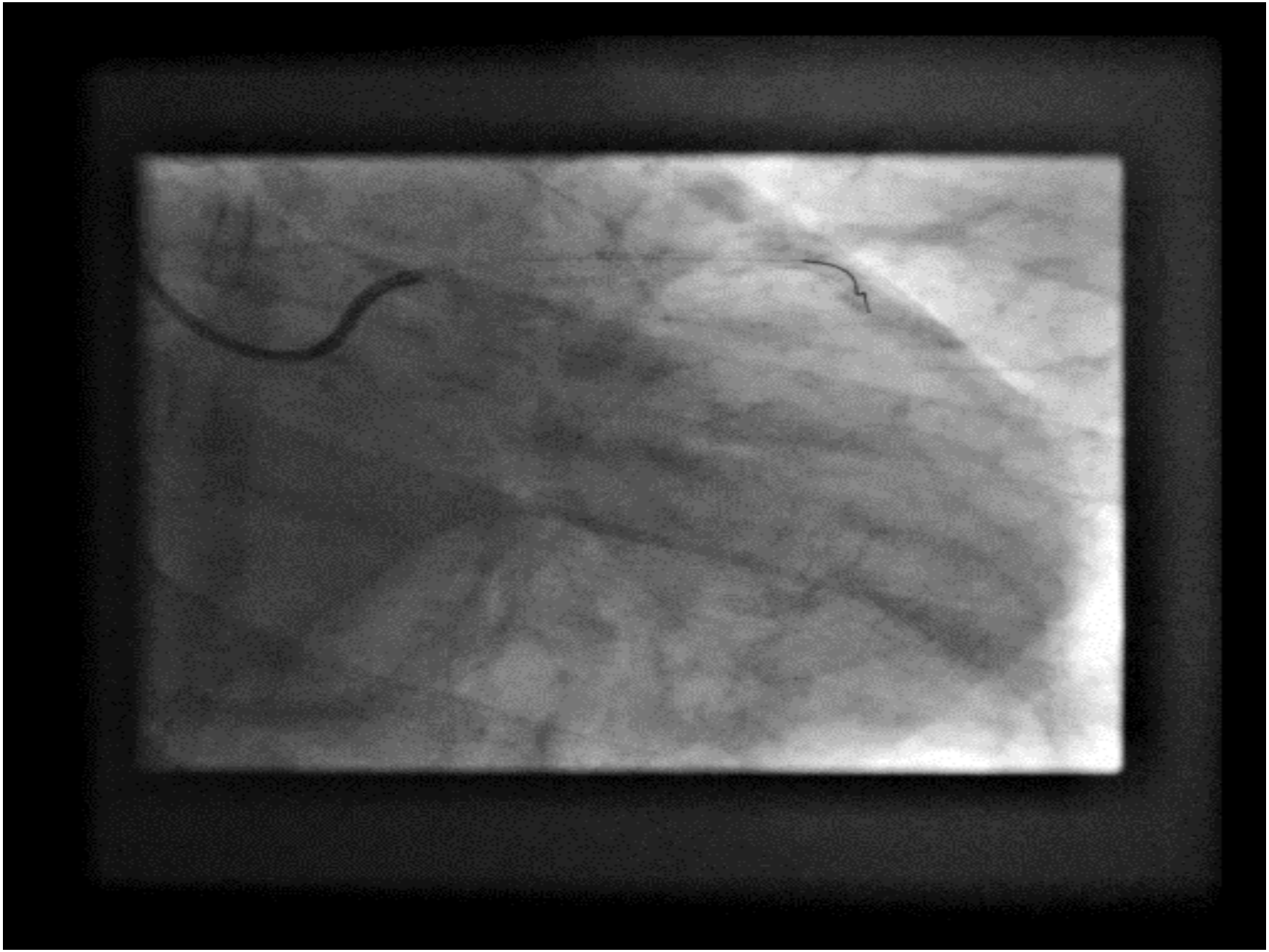

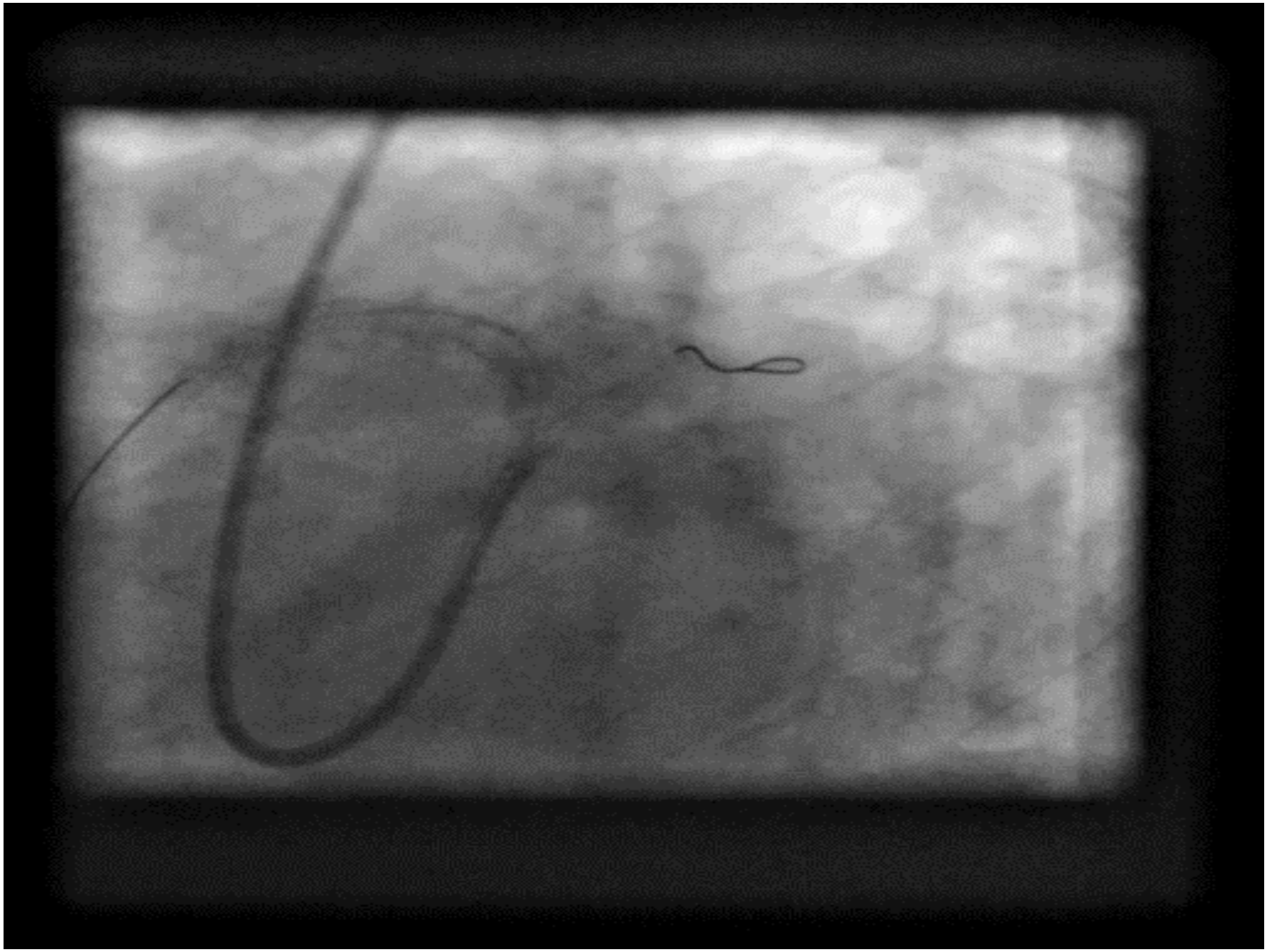

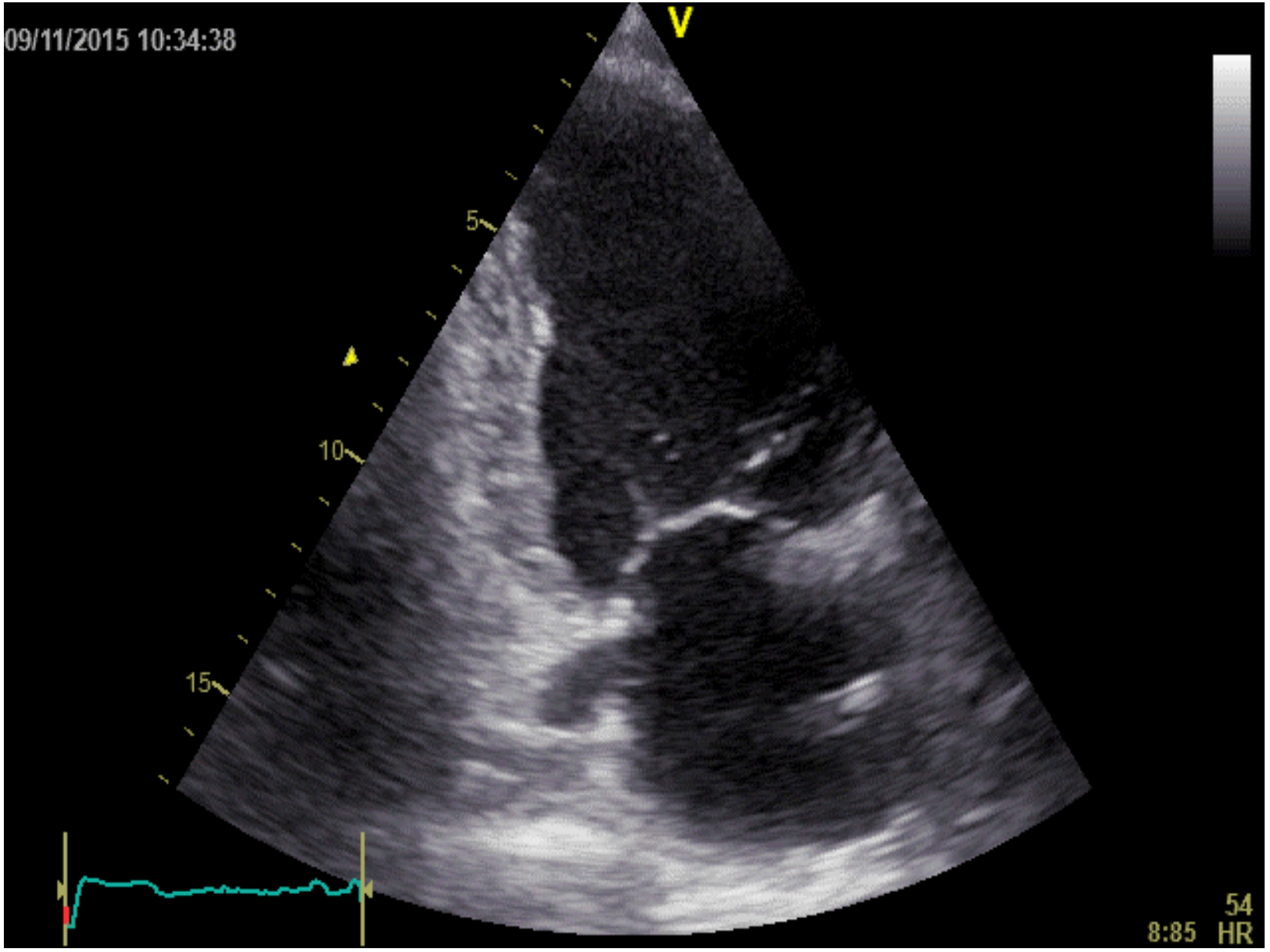
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8:85 HR

Randomized to 3 months DAPT

Received NOAc – ASA- Clopidogrel

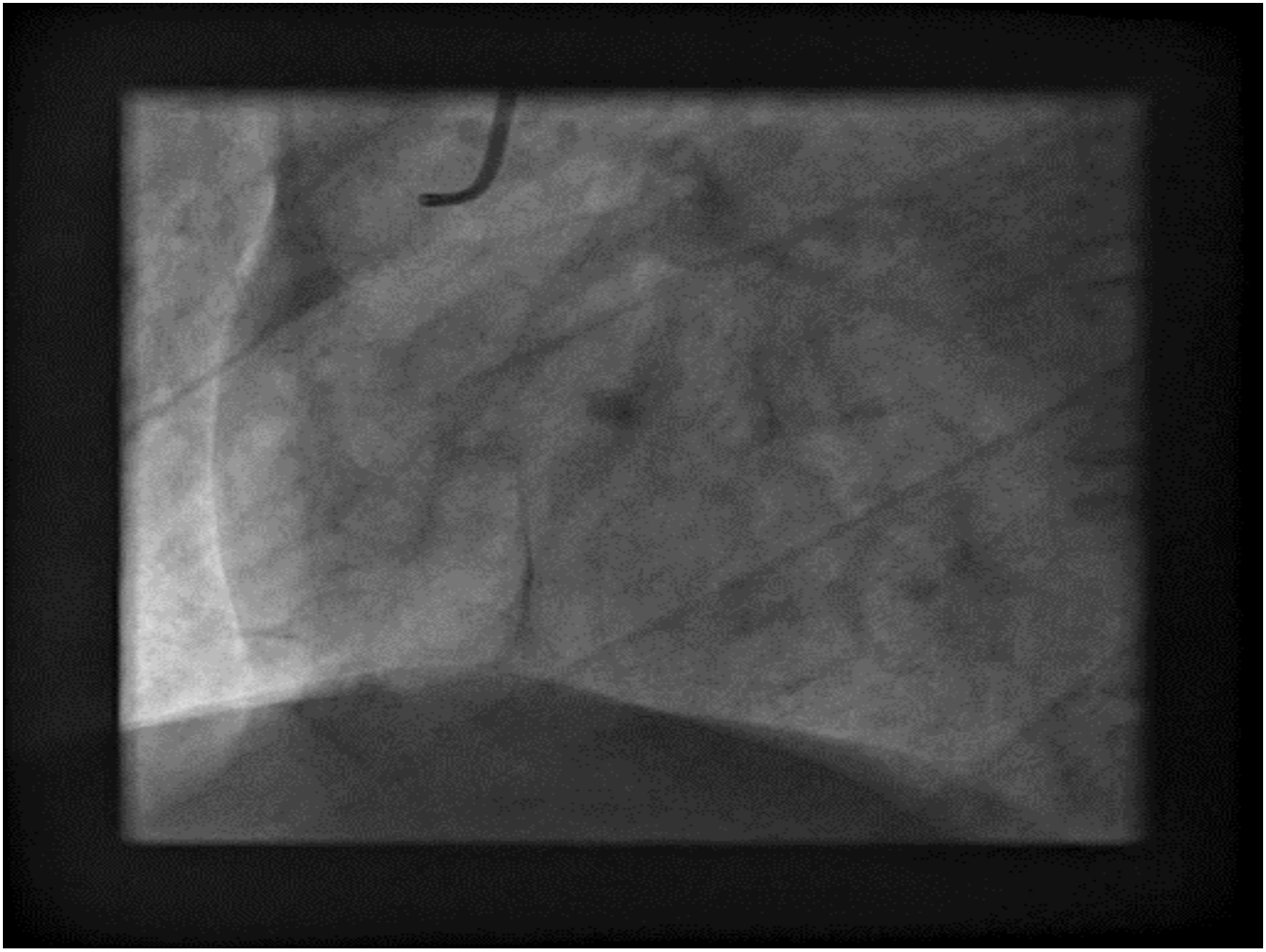
At 1 year FU

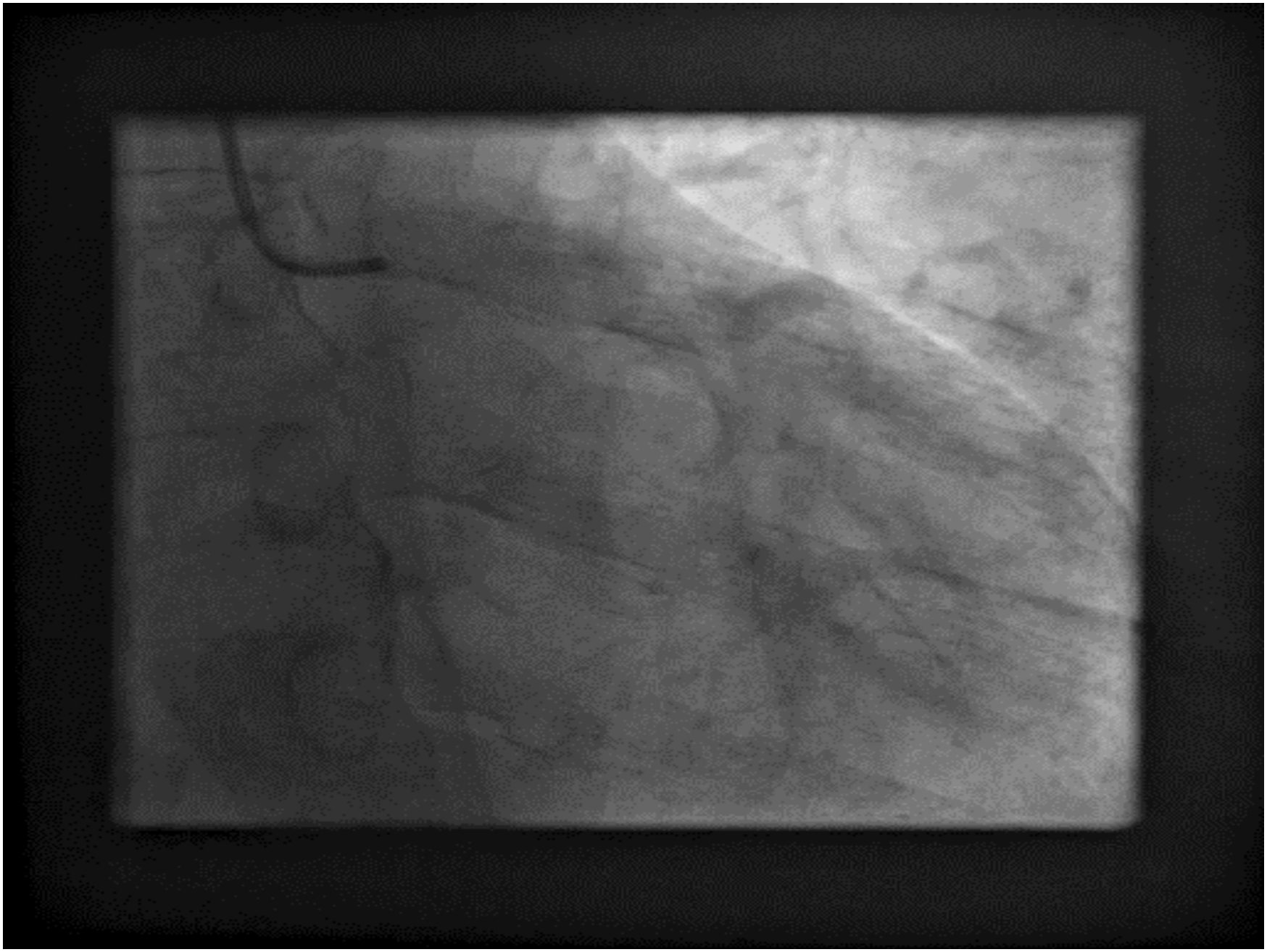
He was asymptomatic (no event)

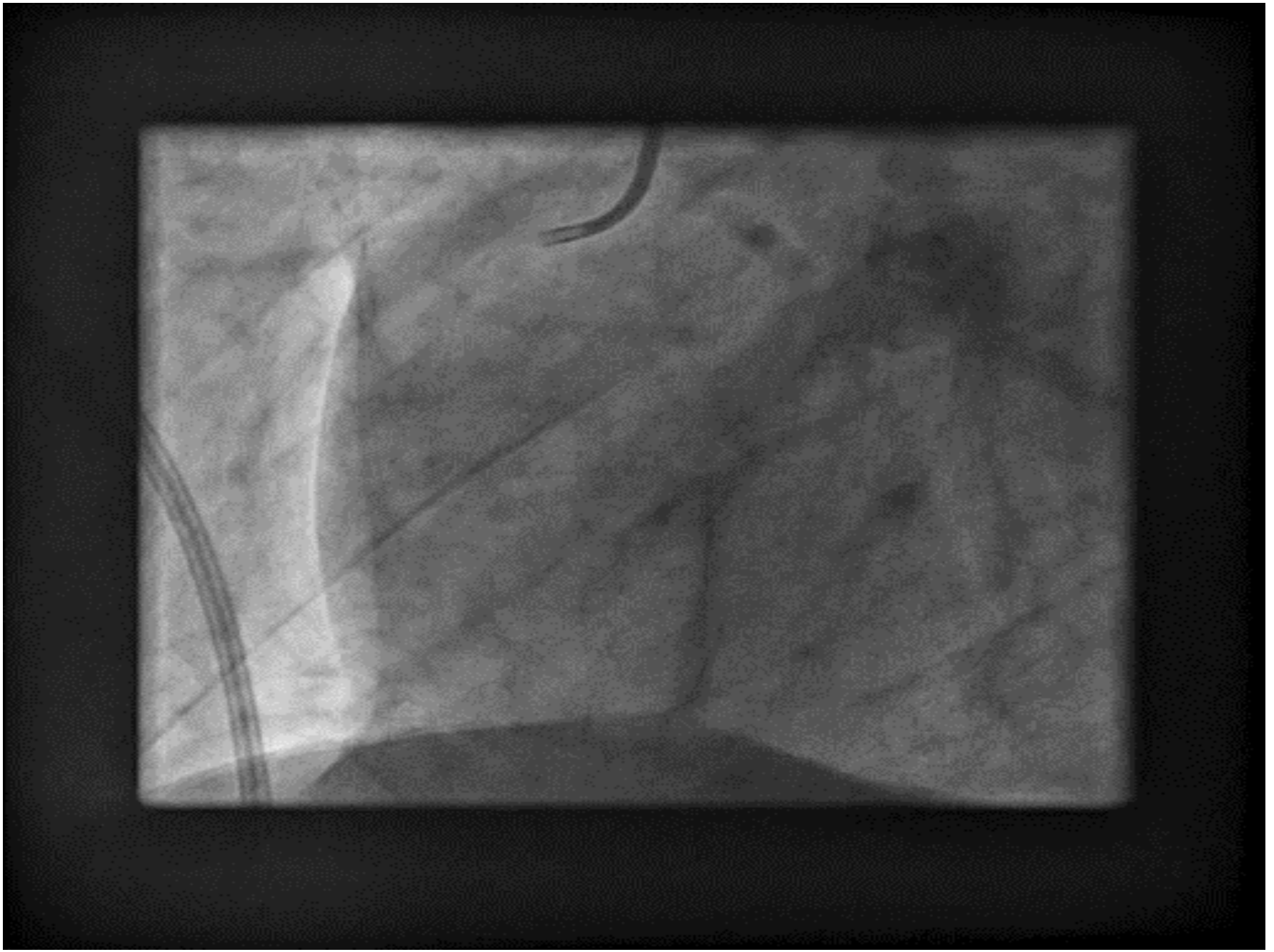
Improvement in ejection fraction (from 15% to 40%

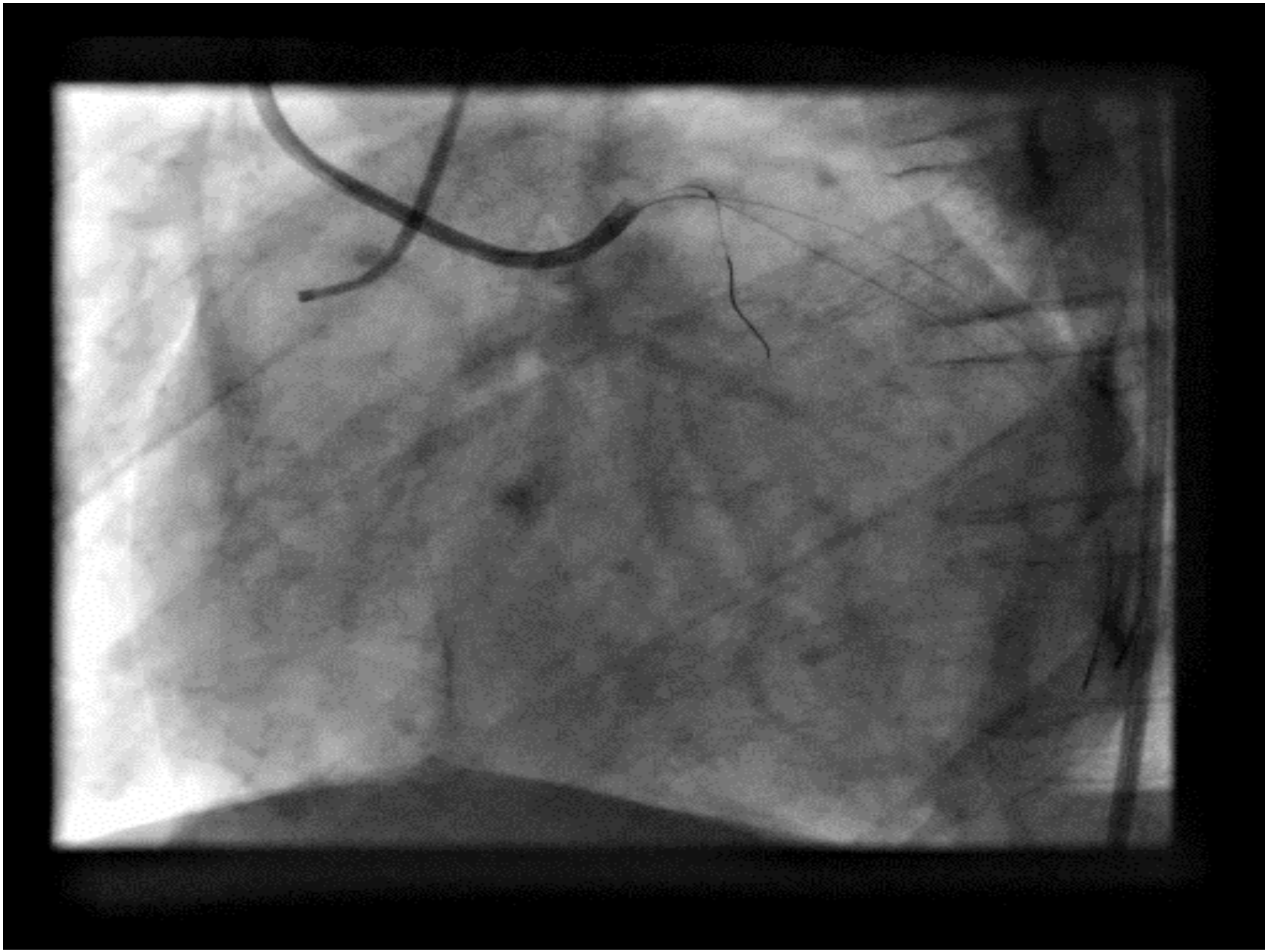
Case 2

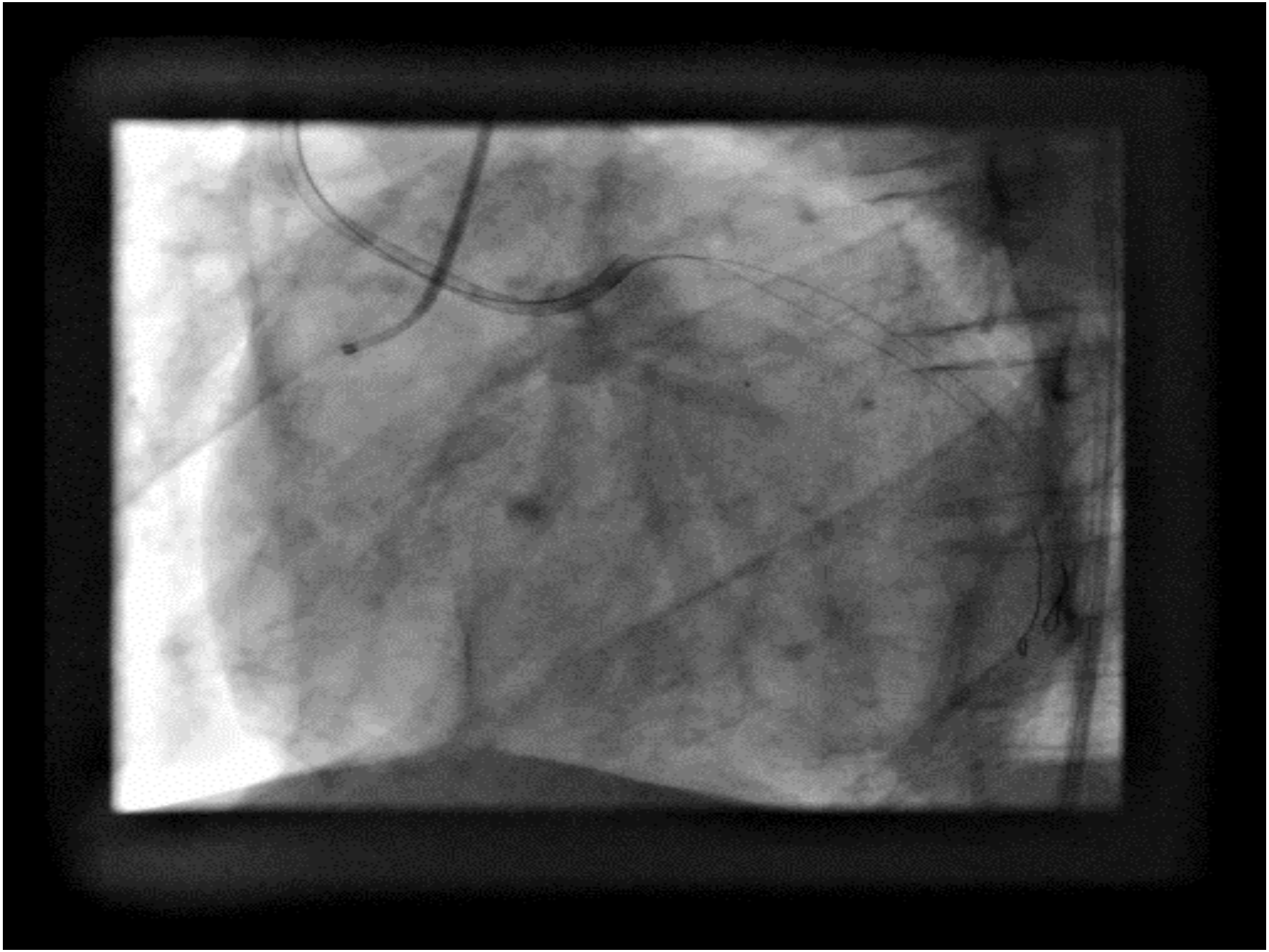
- 45 years male.
- Risk factors: Diabetes mellitus , Hypertension, Smoker (3 packs/day).
- Medications: Atenolol, Isosorbide, Glibenclamide, Metformin.
- Hospital admission: Chest pain at rest
- ECG: Anterior STEMI (V3-V5) with spontaneous complete ST segment regression.

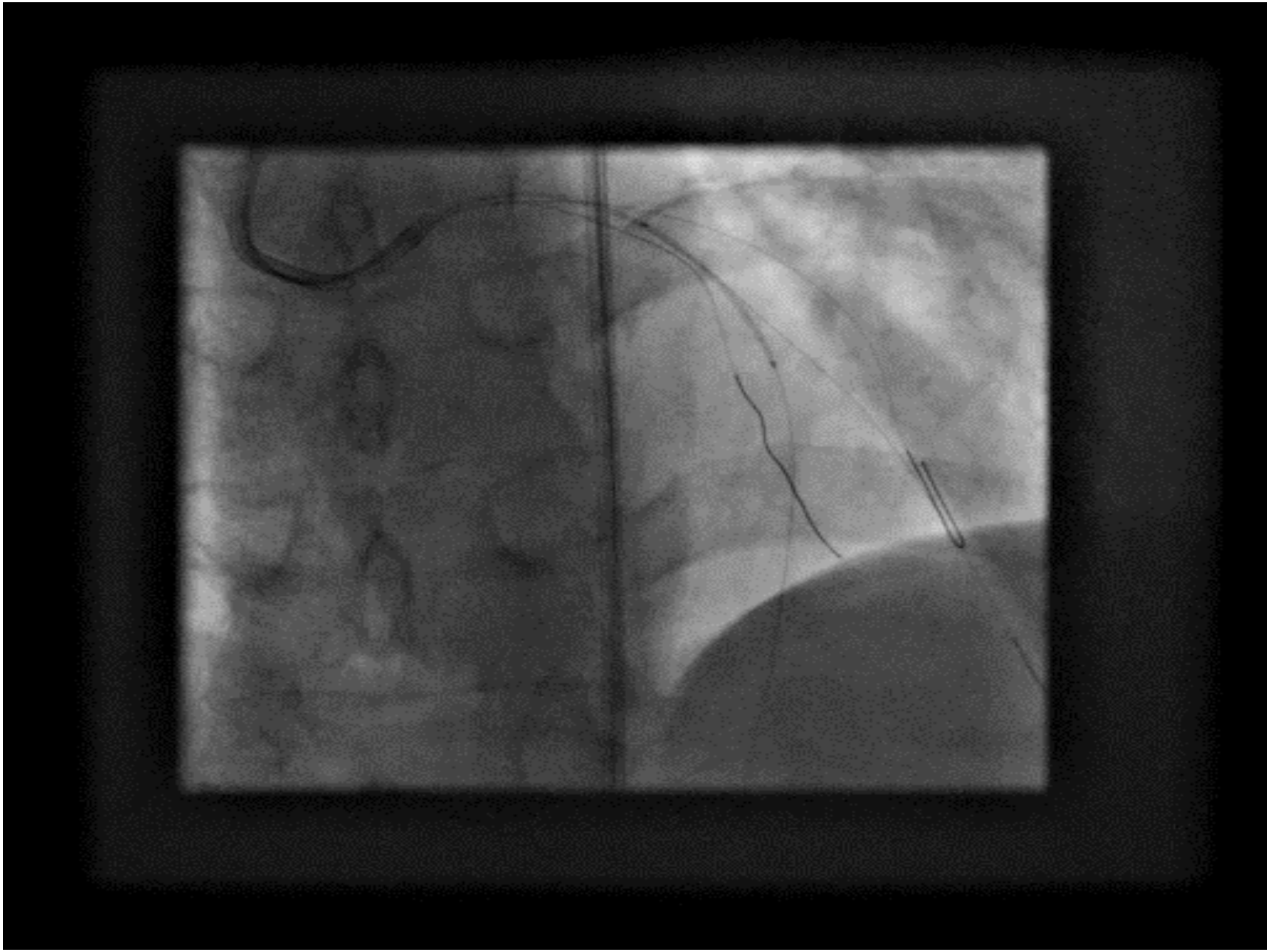


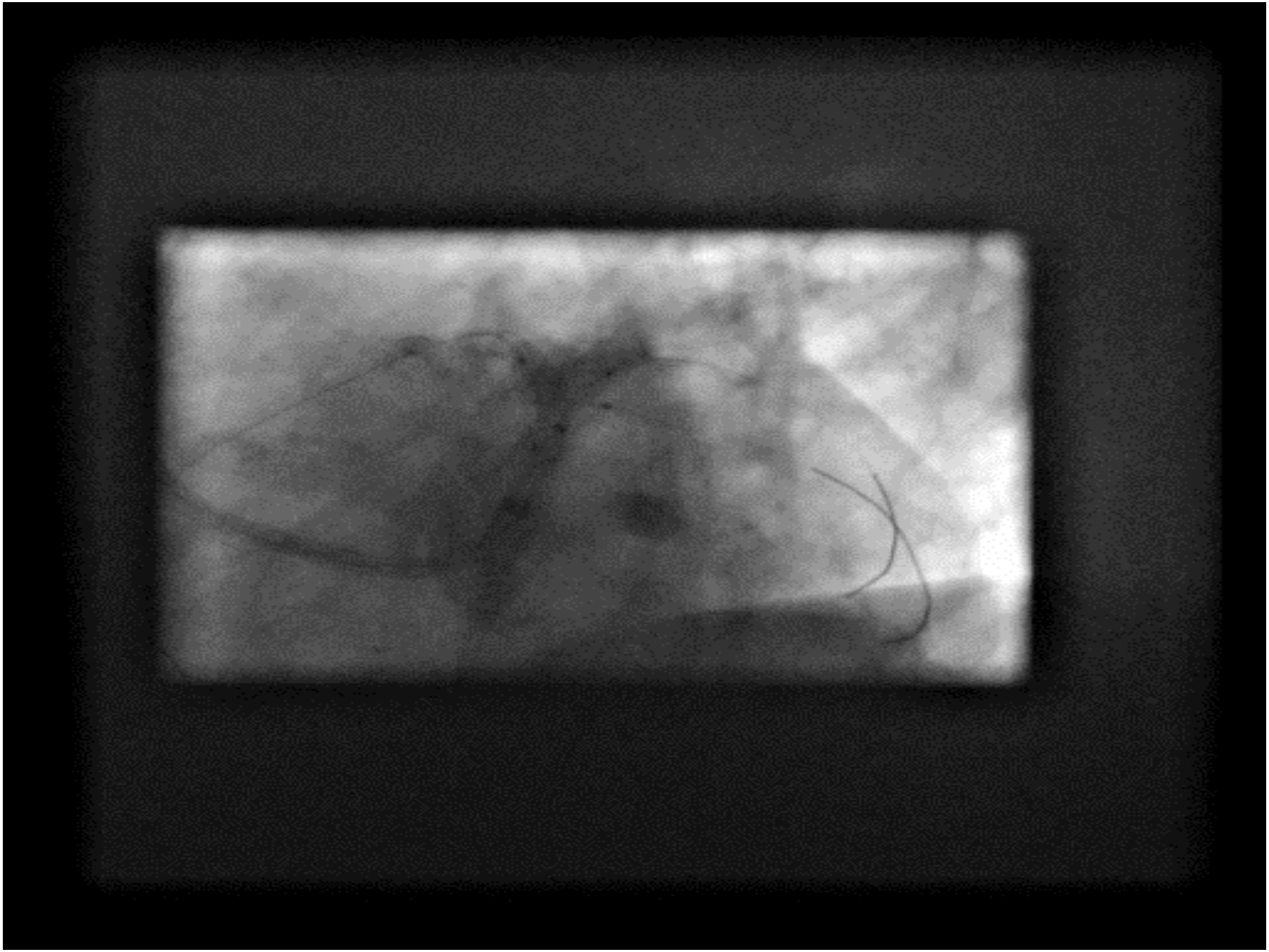


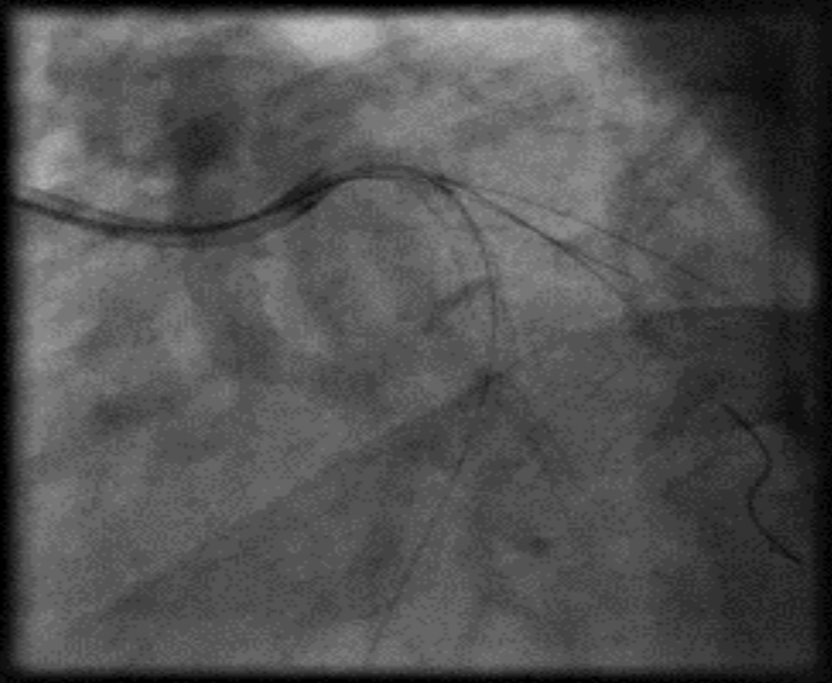


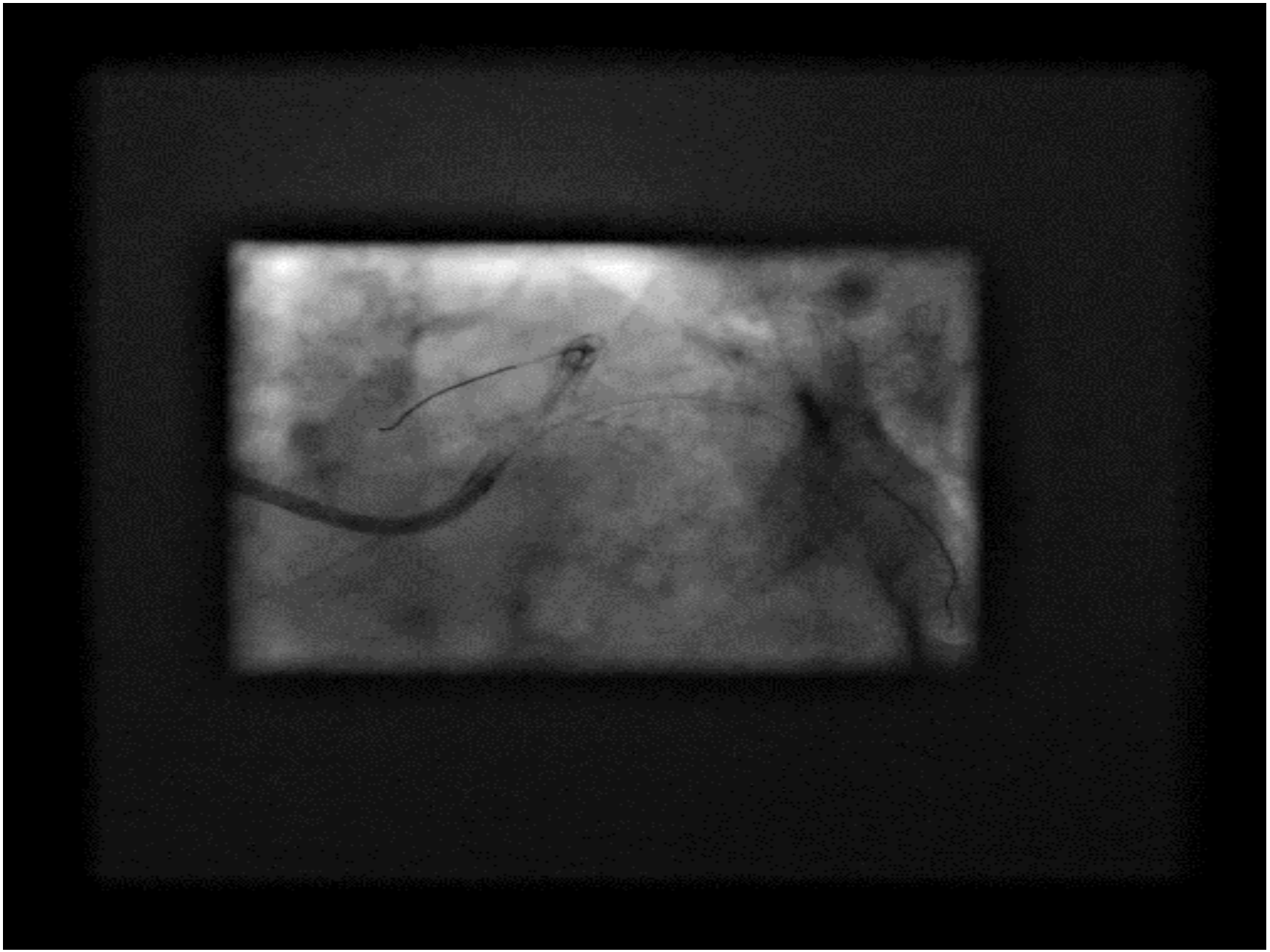












Randomized to 3 months DAPT

Received – ASA- Ticagrelor

At 1 year FU

He was asymptomatic (no event)

Normal ECHO


THANK YOU