

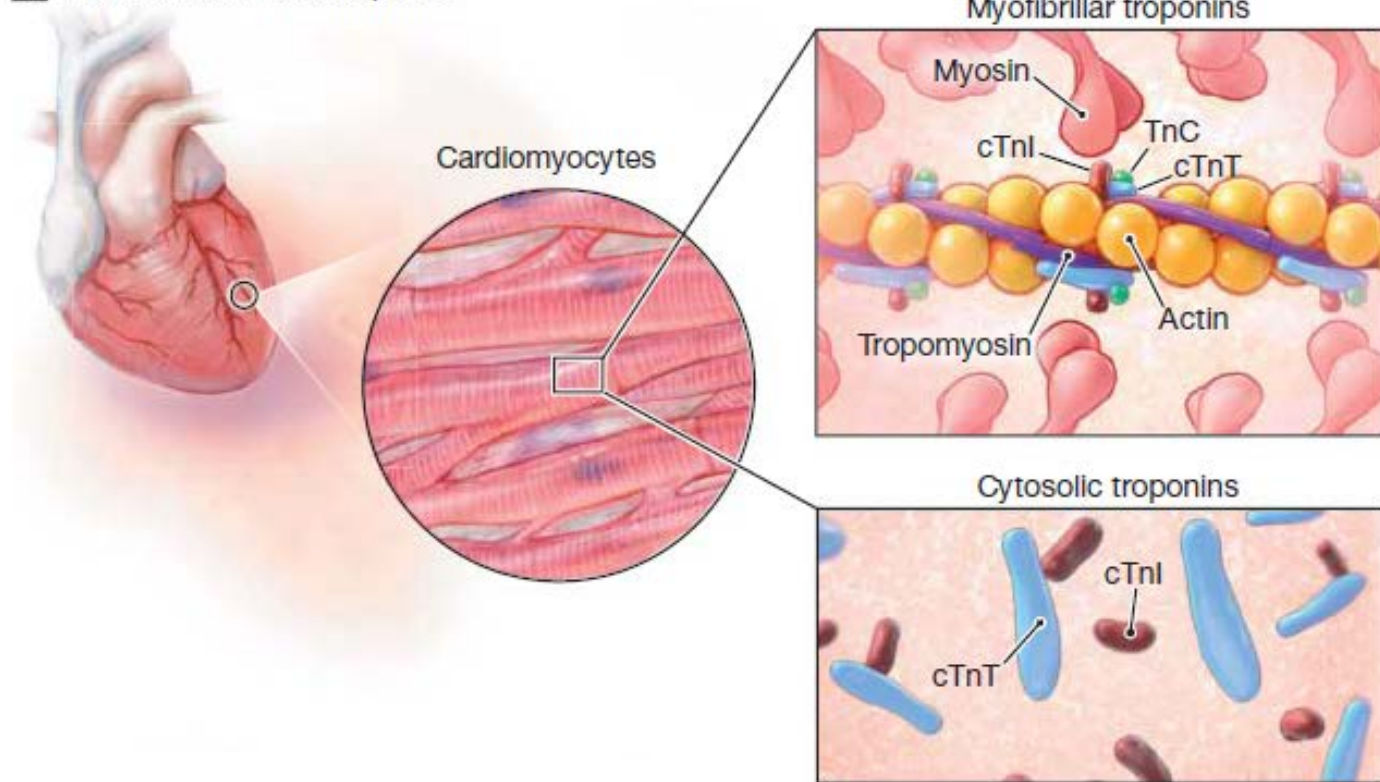
Increasingly Sensitive Assays for Cardiac Troponins

A Review

James A. de Lemos, MD

JAMA. 2013;309(21):2262-2269

A Structure of cardiac troponins



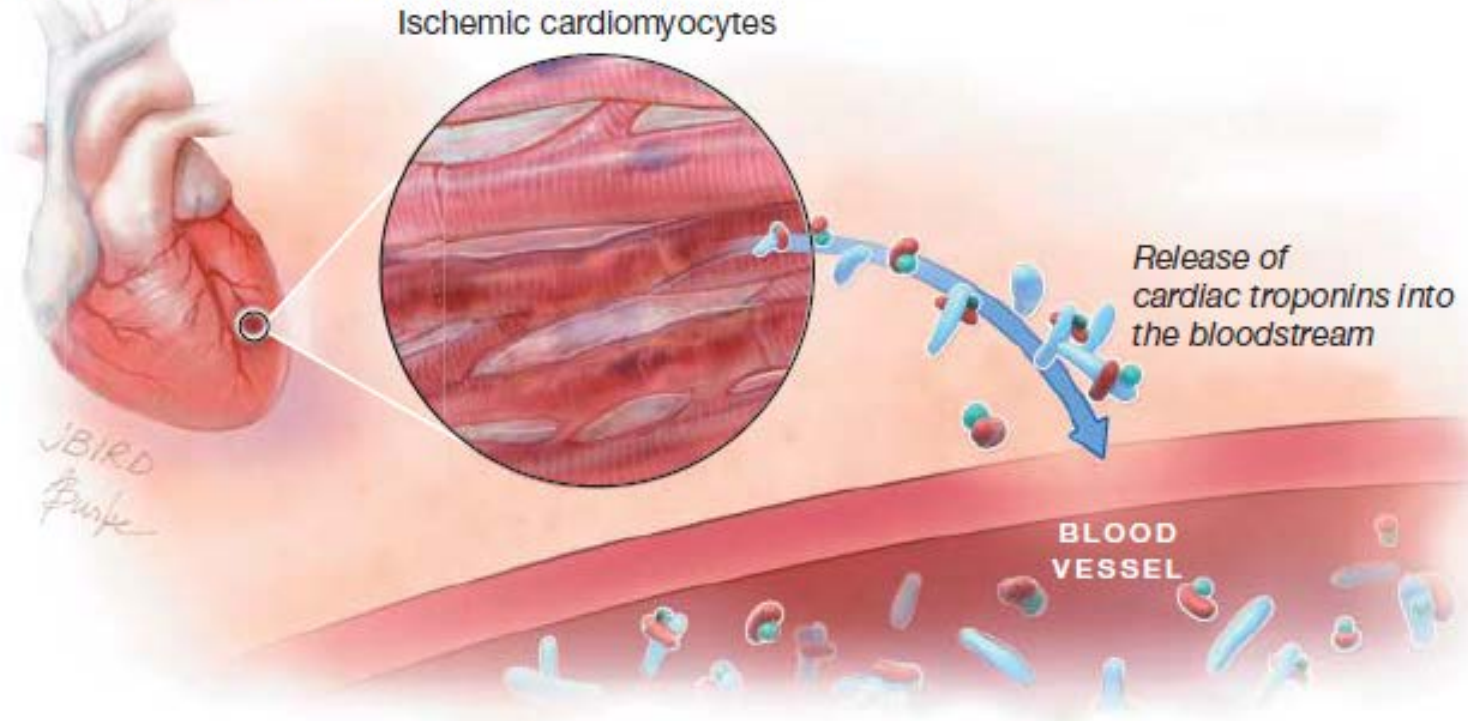
Increasingly Sensitive Assays for Cardiac Troponins

A Review

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JAMA. 2013;309(21):2262-2269

[B] Ischemia-induced cardiomyocyte damage



How to Interpret Elevated Cardiac Troponin Levels

Vinay S. Mahajan, MD, PhD; Petr Jarolim, MD, PhD

Circulation November 22, 2011

high-sensitivity cTn assays are among the greatest, most useful assays in clinical chemistry laboratories.

Increasingly Sensitive Assays for Cardiac Troponins

A Review

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JAMA. 2013;309(21):2262-2269

The new highly sensitive troponin assays will present myriad challenges for clinicians evaluating patients with chest pain.

Case 1 Mr B. U. *16.08.1962

- *Presentation:* Since that morning (>6 hours ago) dyspnea and chest pain, no radiation, not aggravated by breathing
- *History:* Stopped antihypertensive therapy years ago, no other medical history
- *cvRF:* Hypertension, former smoking (20 py)
- *Medication:* None

Geb: 16.08.1962
Alter: 45 Jahre
Geschl: M
Grösse: -/- cm
Gewicht: -/- kg
BD: -/- mmHg

HF 82 /min
Achsen
P 17°
QRS -12°
T -16°

Intervalle
RR 730 ms
P 106 ms
PQ 156 ms
QRS 78 ms
QT 356 ms
QTc 416 ms

Interpretation

Med:
Bem:

Validiert von



Case Mr B.U. *16.08.1962

- Lab results:

	0 h
TnT4 [<0.01mcg/L)	<0.01
CK	136 U/L
CK-MB	4.4

6 h
<0.01
107 U/L
4.2

- Same patient presenting 4 (!) days later
- Acute chest pain radiating in his left arm and back

Geb: 16.08.1962
Alter: 45 Jahre
Geschl: M
Grösse: -- cm
Gewicht: -- kg
BD: -- / -- mmHg

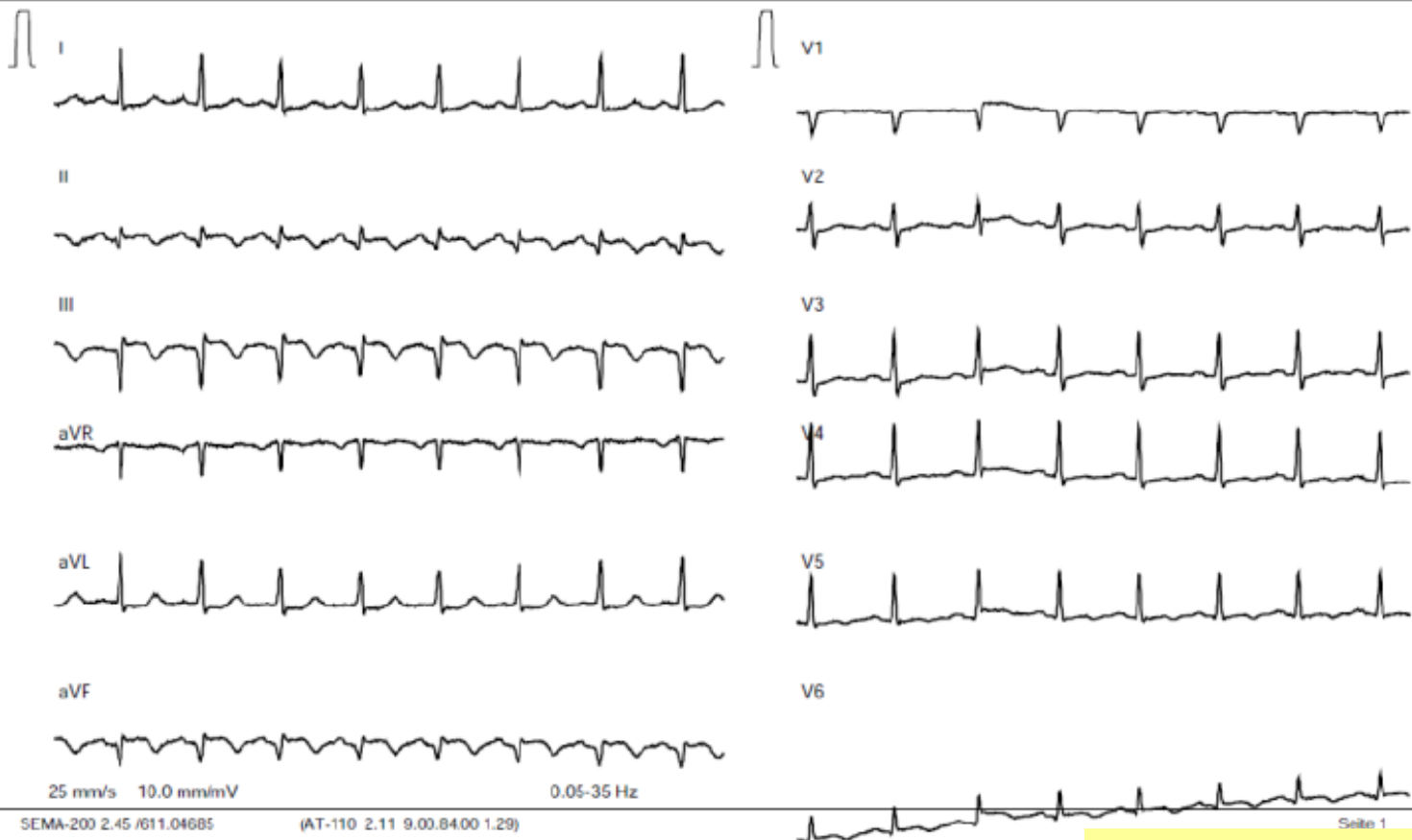
HF	103 /min
Achsen	
P	39 °
QRS	-14 °
T	-33 °

Intervalle	
RR	579 ms
P	114 ms
PQ	158 ms
QRS	94 ms
QT	288 ms
QTc	377 ms

Interpretation

Med:
Bern:

Validiert von



How About hs-cTn at Initial Presentation 4 Days Ago?

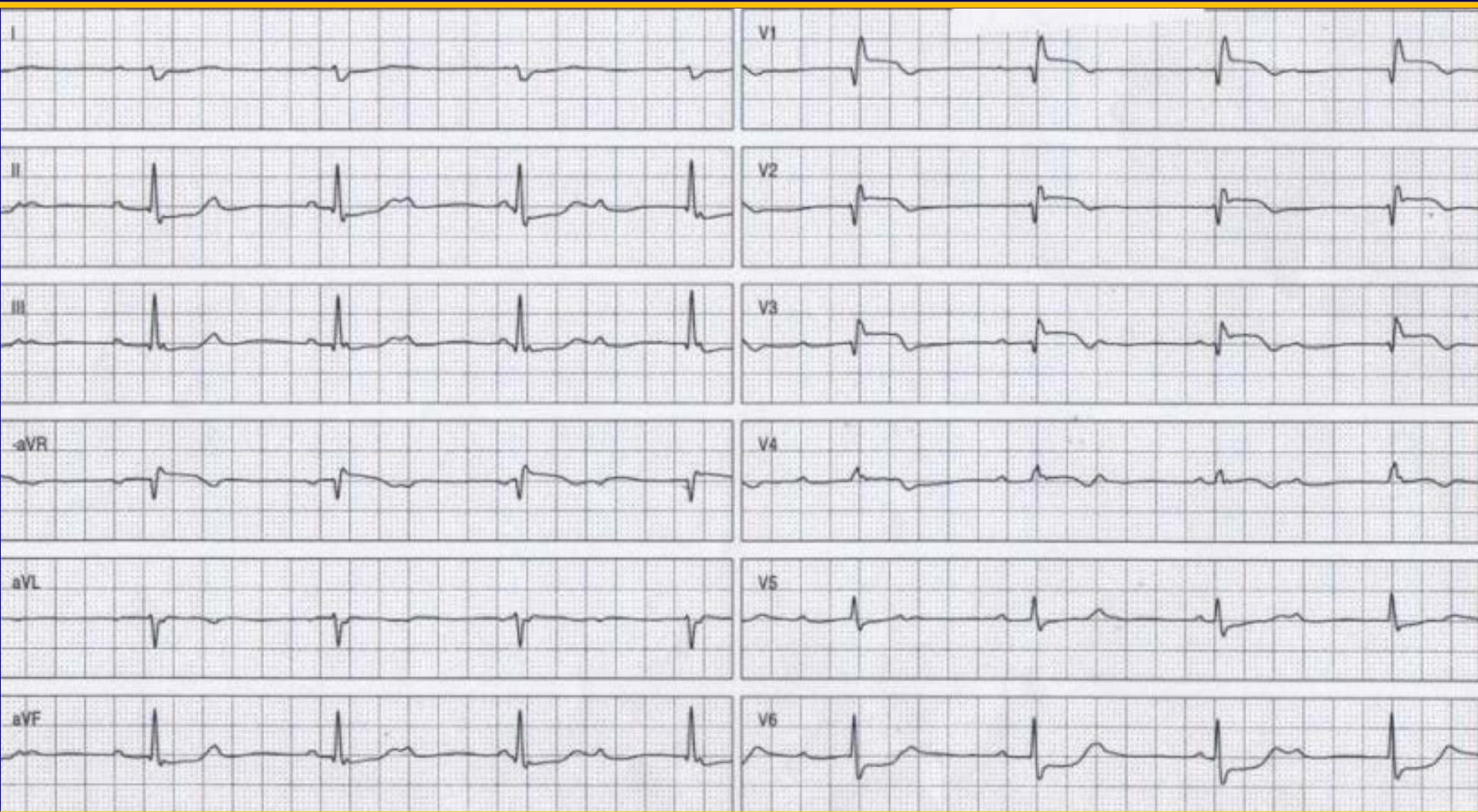
	Study blood examination				
	0 h	1 h	2 h	3 h	6 h
TnT4 [<0.01 mcg/L]	<0.01	<0.01	<0.01	<0.01	<0.01
CK	136 U/L			120 U/L	107 U/L
CK-MB	4.4			4.4	4.2
Siemens TnI – Ultra [Ref. 0.04 mcg/L]	0.016 mcg/L	0.039 mcg/L	0.088 mcg/L	0.102 mcg/L	
Siemens hs-cTnI [Ref. 9 ng/L]	18.2 ng/L	44.8 ng/L	66.7 ng/L	100.0 ng/L	
Roche hs-cTnT [Ref. 14 ng/L]	11.2 ng/L	22.4 ng/L	31.0 ng/L	32.0 ng/L	

(H)s-cTn improve the early rule-in of AMI

Case 2

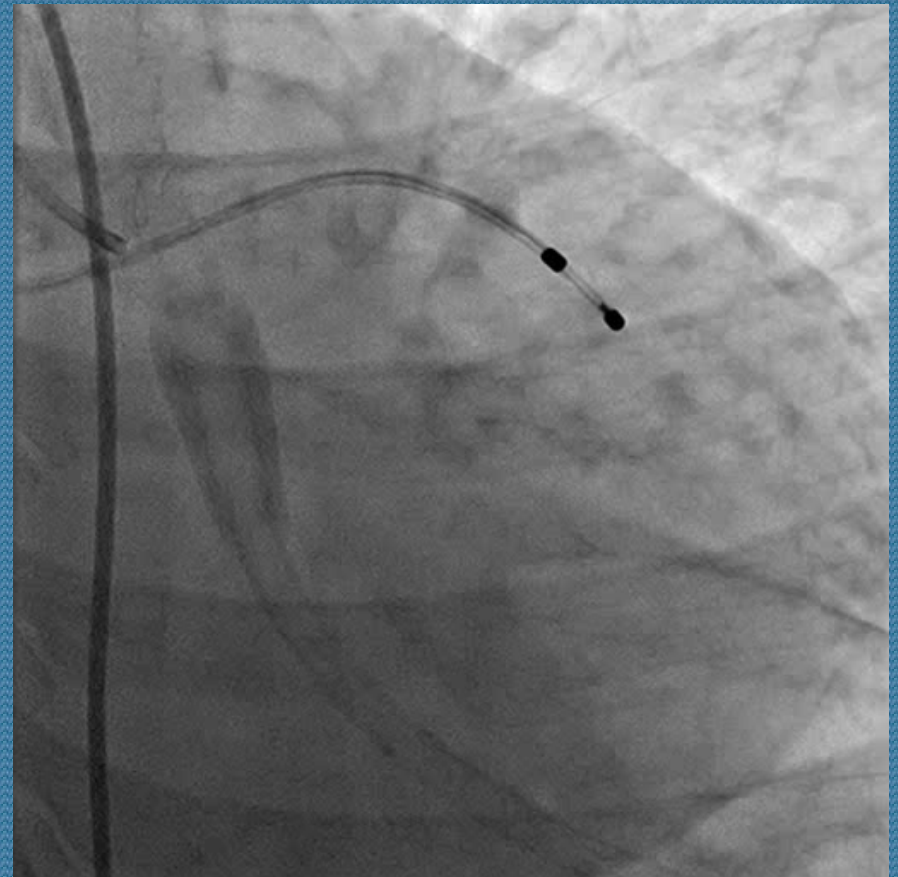
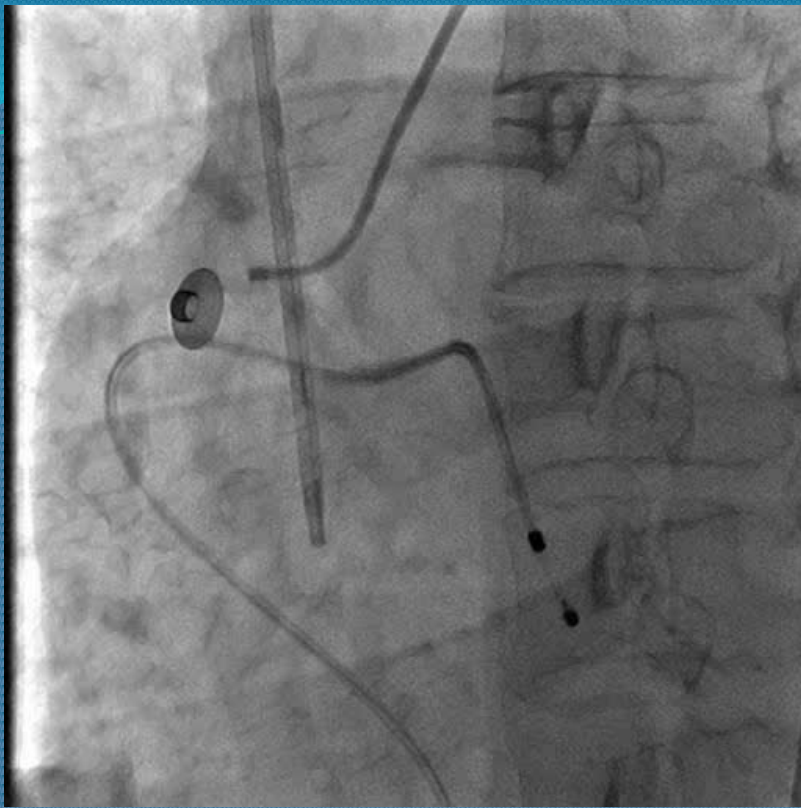
- **35-years old woman without risk factors for IHD.**
- **She had complained of fever and headache for three days. The evening before admission she had chest pain that increased on deep breaths.**
- **On admission : temperature 38,5 °C. No heart murmurs. No signs of CHF. AP 85/50 HR 50 bpm**

Case 2 : ECG on admission



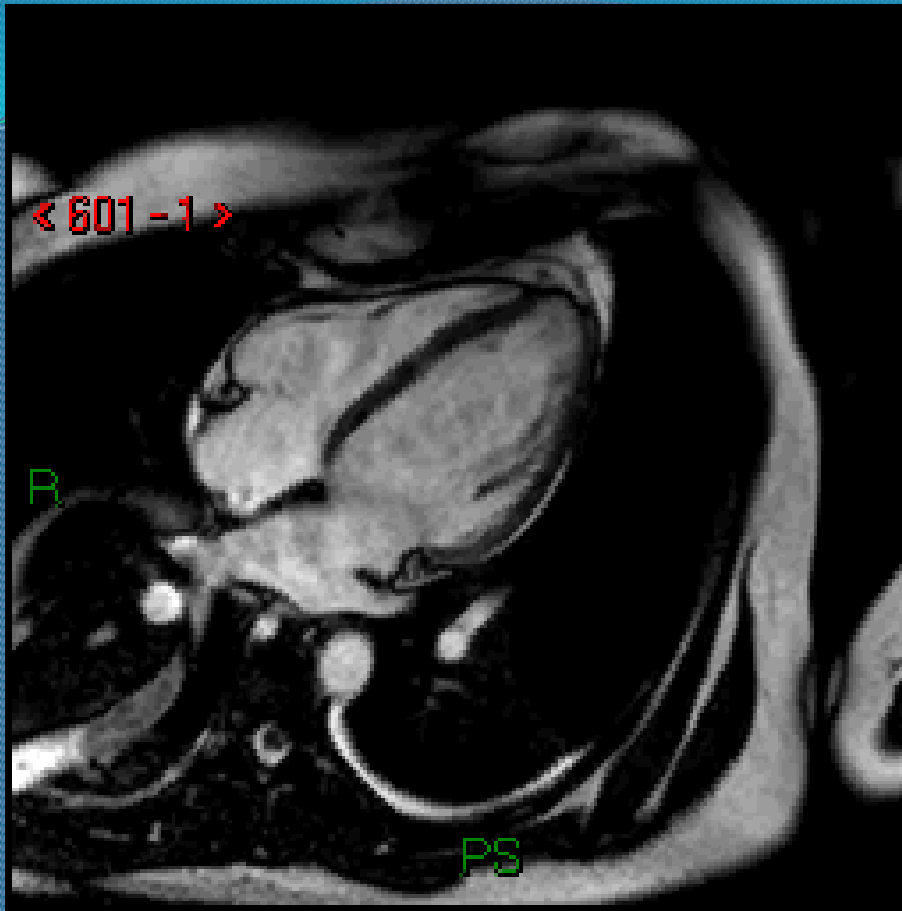
Case 2 : Lab results

	0 h		
Roche Hs-cTnT (pg/ml)	2748		
CK total (U/L)	507		
CK MB (U/L)	32		

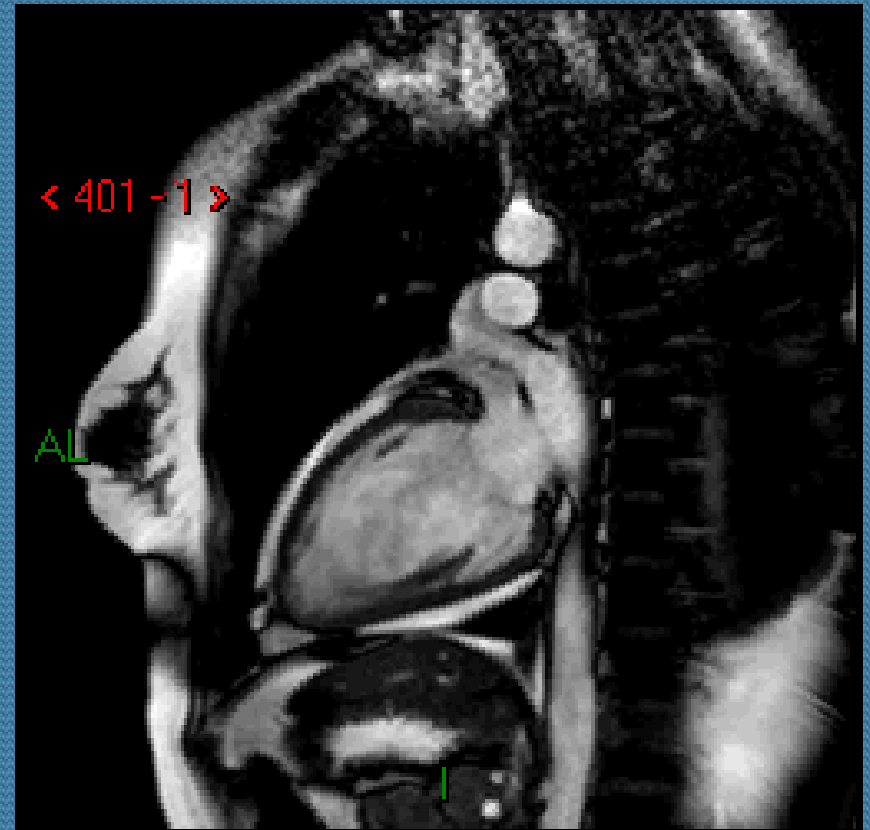


Coronary arteriography

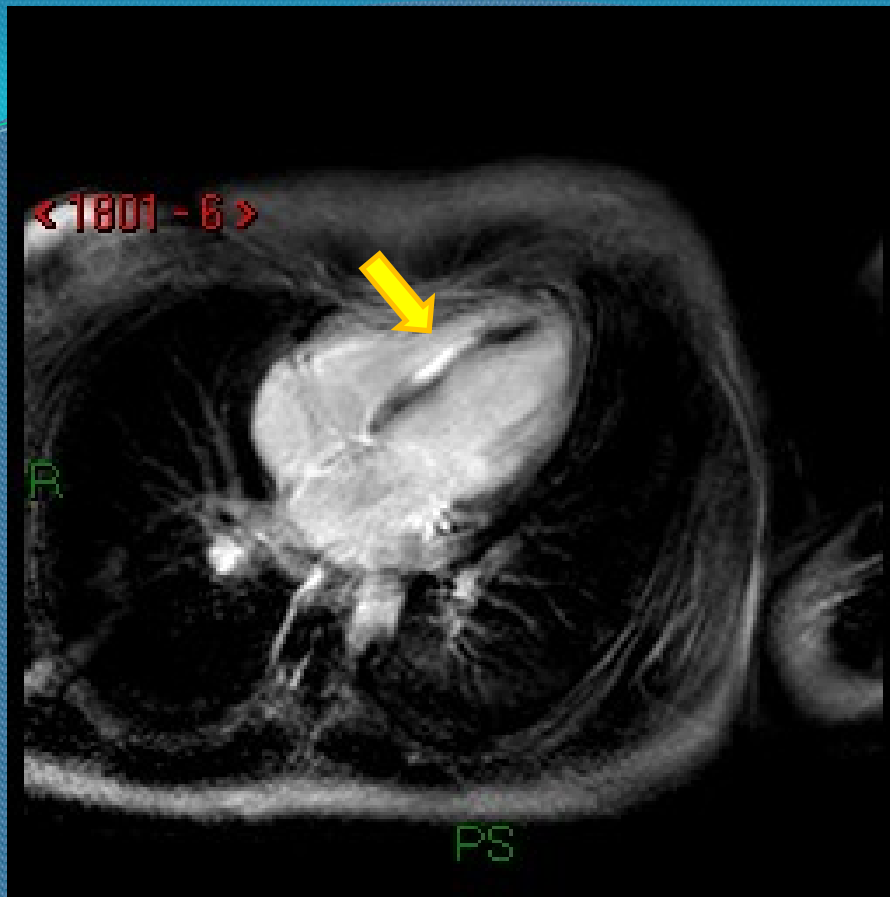
cine MRI (day 5)



4-chamber view :
Septal akinesia , small pericardial effusion

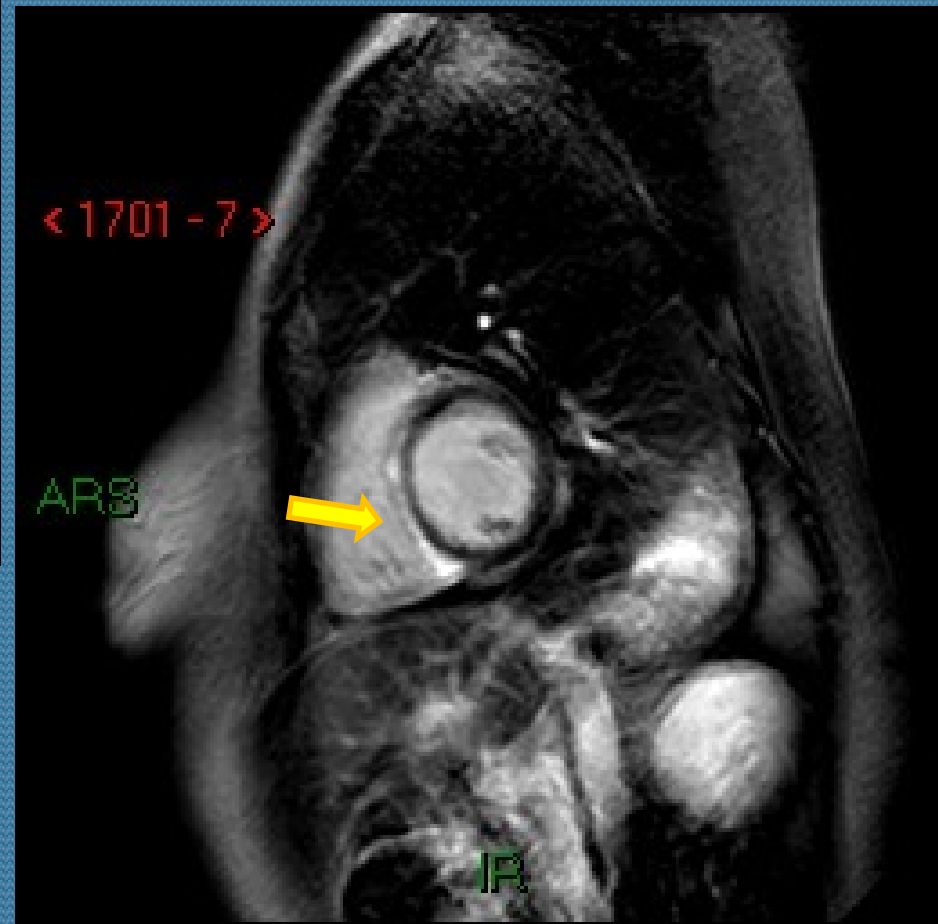


2-chamber view:
Hypokinesia anterior wall



T1 sequences:
Late Gadolinium enhancement of
the subepicardium in mid-septal
wall

cine MRI (day 5)



Case 3

- **62-year old man presenting to the E.R. with intermittent pressure in his chest .**
- **Clinical history: type-2 diabetes , hypertension, stage 3 CKD. Coronary arteriography one year before: no significant CAD, reduced LVEF (42%).**
- **Clinical examination: HR 52 bpm, AP 144/85. No signs of heart failure .**



Velocità: 25mm/s Amp.: 10mm/mV Filtro: Monitoraggio

Case 2 : Lab results

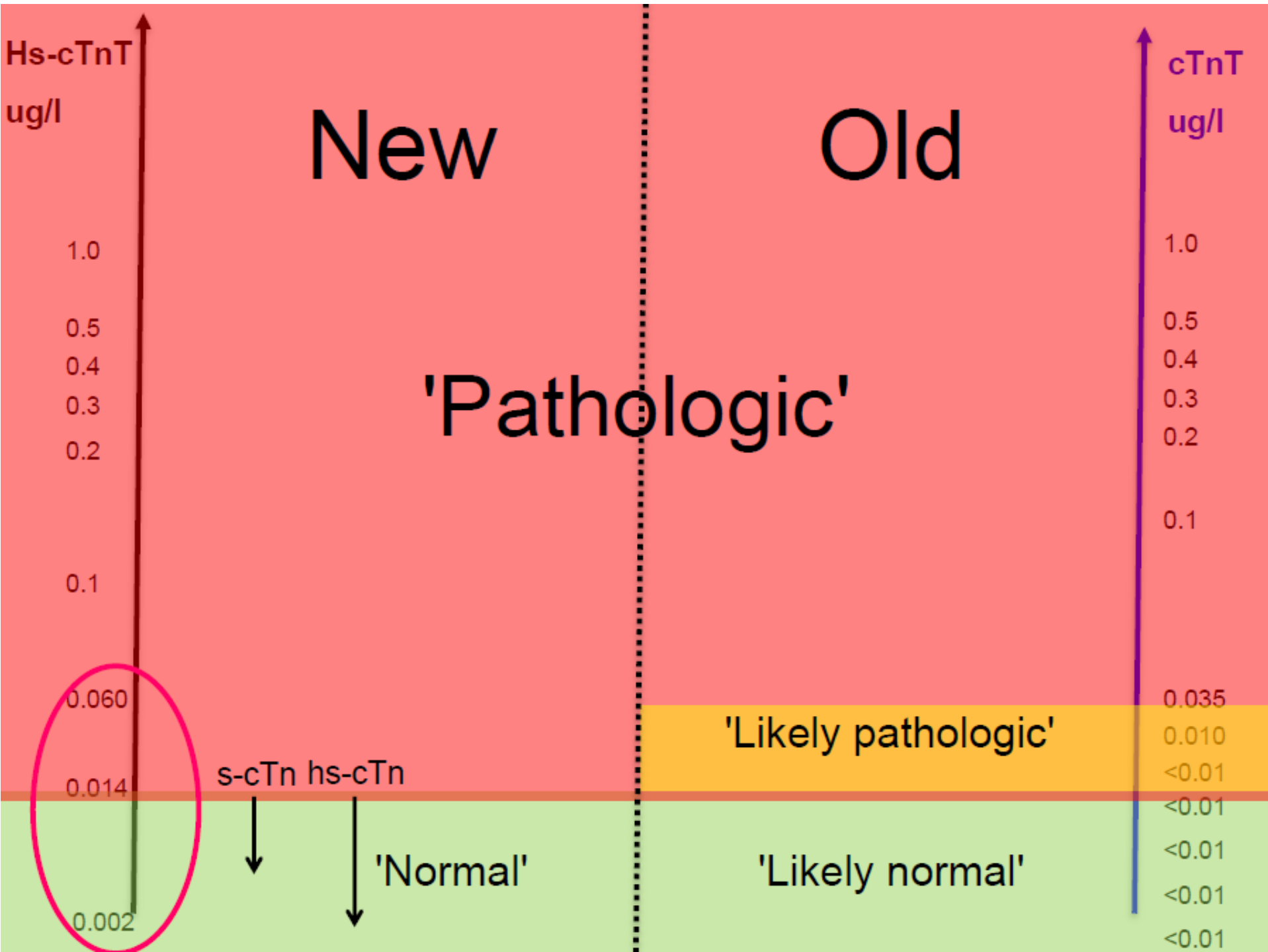
	0 h	3 h	6 h
Roche Hs-cTnT (pg/ml)	24	22	25
CK total (U/L)	118		112
CK MB (U/L)	4.6		4.8

Case 3

- **An echocardiogram was repeated in the E.R. showing data similar to a prior test (LV hypertrophy , diffuse hypokinesia with an EF of 40%).**
- **Serum creatinine and glycemia were not different from prior lab tests .**
- **The patient was discharged from E.R. with a diagnosis of chest pain of non-ischemic origin .**

Clinical cases

- **Increased sensitivity for ACS diagnosis with hs-troponin assays (case 1)**
- Other causes for acute troponin increases than ACS (case 2)
- Patients with chronic elevations of hs-troponins (case 3)



Clinical cases

- Increased sensitivity for ACS diagnosis with hs-troponin assays (case 1)
- **Other causes different from ACS for acute troponin increases (case 2)**
- Patients with chronic elevations of hs-troponins (case 3)

Most common **Non- ACS causes** for acute
Troponin increases

- ***Infection or Sepsis***
- ***Myocarditis***
- ***Stroke***
- ***Subarachnoid hemorrhage***
- ***Pulmonary embolism***

Clinical cases

- Increased sensitivity for ACS diagnosis with hs-troponin assays (case 1)
- Other causes for acute troponin increases than ACS (case 2)
- **Patients with chronic elevations of hs-troponins (case 3)**

**Most common non-ischemic causes for chronic
Troponin increases**

- **Renal failure**
- **Congestive heart failure**
- **Infiltrative diseases**
- **Cancer chemotherapy**

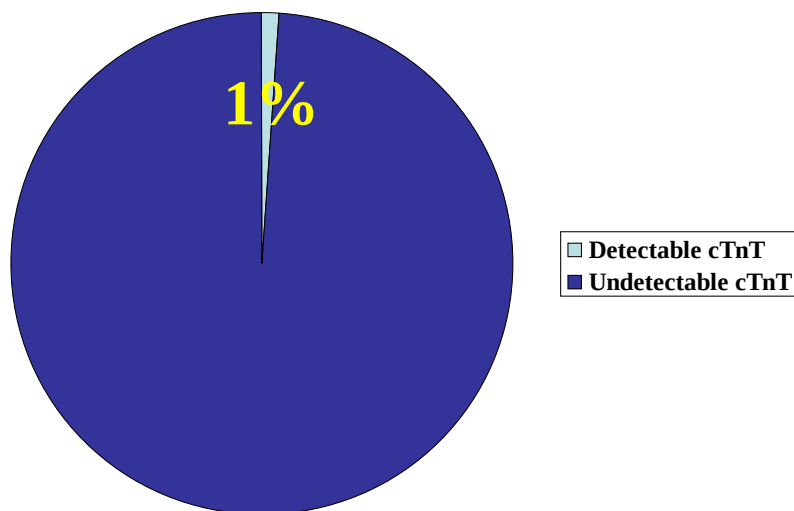
Association of Troponin T Detected With a Highly Sensitive Assay and Cardiac Structure and Mortality Risk in the General Population

James A. de Lemos, MD

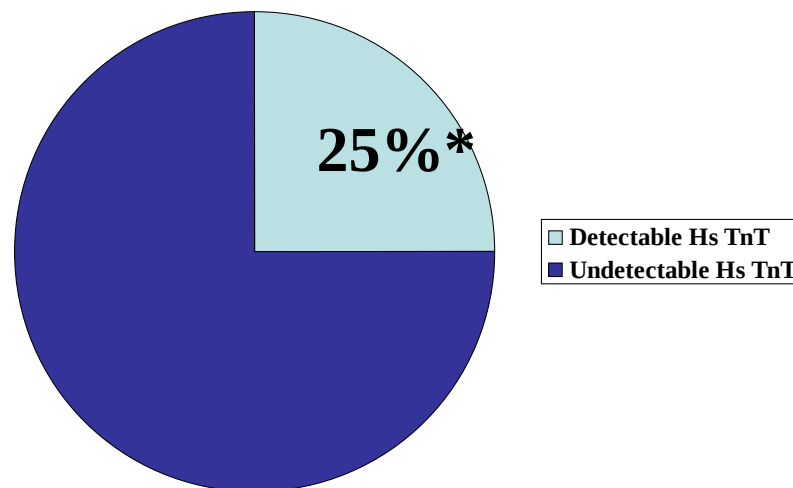
JAMA. 2010;304(22):2503-2512

The Dallas Heart Study

3546 individuals, aged 30 to 65 years



Standard assay



Highly Sensitive Assay

* 3.4% above URL

Association of Troponin T Detected With a Highly Sensitive Assay and Cardiac Structure and Mortality Risk in the General Population

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JAMA. 2010;304(22):2503-2512

Variables associated with chronic elevations of hs/Troponins

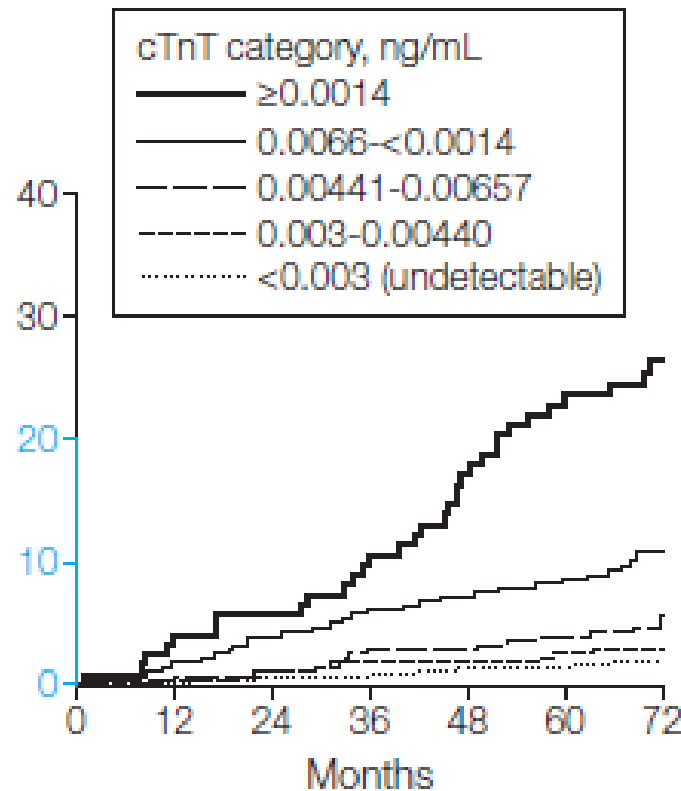
Variable	cTnT Category, ng/mL ^a					P for Trend
	<0.003 (n = 2589)	0.003-0.00440 (n = 278)	0.00441-0.00657 (n = 279)	0.0066-<0.0014 (n = 278)	≥0.0014 (n = 122)	
cTnT ≥0.01 ng/mL with standard assay, No./total (%)	0/2589	0/278	0/279	1/277 (0.4)	40/120 (33.3)	<.001
Age (median)	41 (35-49)	47 (39-55)	49 (41-55)	52 (45-58)	53 (44-58)	<.001
Hypertension (%)	694/2554 (27.2)	116/277 (41.9)	125/271 (46.1)	170/274 (62.0)	83/117 (70.9)	<.001
Diabetes (%)	200/2588 (7.7)	38/278 (13.7)	43/279 (15.4)	79/278 (28.4)	50/122 (41.0)	<.001
CKD stage (%)						
1	1804/2588 (69.7)	158/278 (56.8)	161/279 (57.7)	124/278 (44.6)	58/122 (47.5)	<.001
2	767/2588 (29.6)	113/278 (40.6)	110/279 (39.4)	135/278 (48.6)	33/122 (27.0)	<.001
3	15/2588 (0.6)	6/278 (2.2)	6/279 (2.2)	18/278 (6.5)	16/122 (13.1)	<.001
4	0/2588	1/278 (0.4)	0/279	0/278	1/122 (0.8)	.02
5	2/2588 (0.1)	0/278	2/279 (0.7)	1/278 (0.4)	14/122 (11.5)	<.001
LV Hypertrophy	154/2043 (7.5)	22/213 (10.3)	40/232 (17.2)	60/232 (25.9)	38/79 (48.1)	<.001
NT-proBNP (ng/L)	28.2 (13.2-55)	27.4 (10.6-61.2)	24.3 (12.8-56.5)	39.2 (15.7-104.4)	104.9 (42.9-557.4)	<.001

Association of Troponin T Detected With a Highly Sensitive Assay and Cardiac Structure and Mortality Risk in the General Population

James A. de Lemos, MD

JAMA. 2010;304(22):2503-2512

All-cause mortality



Thus, although clinicians frequently trivialize elevated troponin levels not attributable to ACS using terms such as “troponinemia” or “troponinosis,” these elevations are of important prognostic significance.

Third Universal Definition of Myocardial Infarction

Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman and Harvey D. White: the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction

Definition of Myocardial Infarction

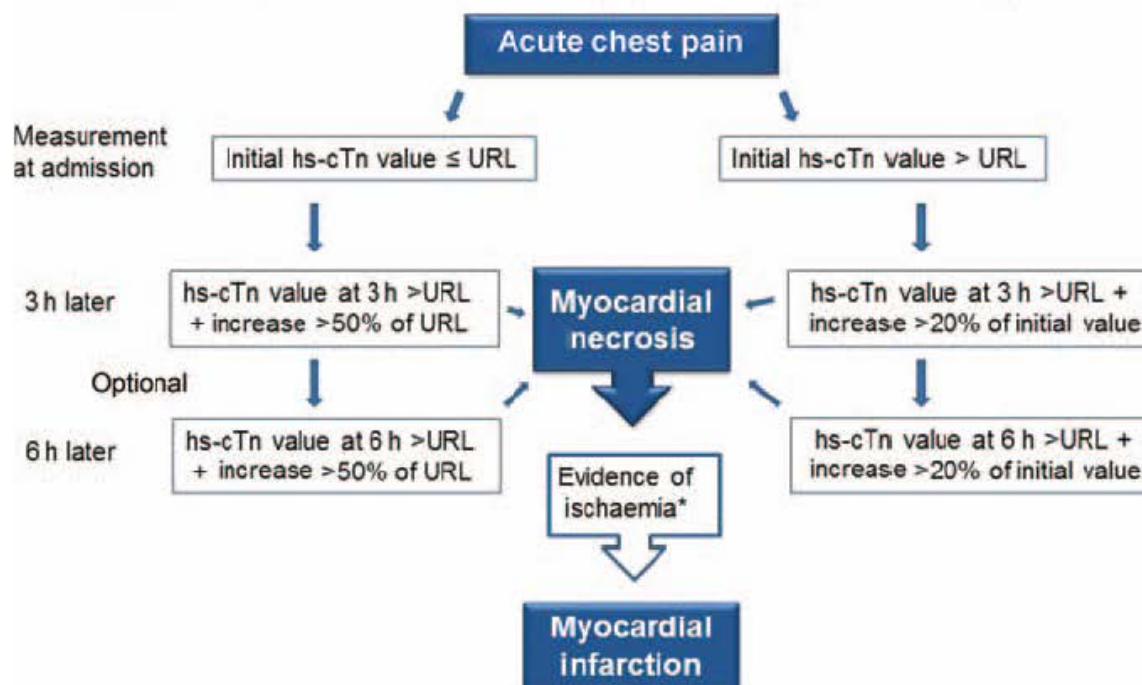
Criteria for acute myocardial infarction

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
 - Symptoms of ischemia.
 - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
 - Development of pathological Q waves in the ECG.
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
 - Identification of an intracoronary thrombus by angiography or autopsy.

How to use high-sensitivity cardiac troponins in acute cardiac care[†]

Kristian Thygesen*, Johannes Mair, Evangelos Giannitsis, Christian Mueller, Bertil Lindahl, Stefan Blankenberg, Kurt Huber, Mario Plebani, Luigi M. Biasucci, Marco Tubaro, Paul Collinson, Per Venge, Yonathan Hasin, Marcello Galvani, Wolfgang Koenig, Christian Hamm, Joseph S. Alpert, Hugo Katus, and Allan S. Jaffe, the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care

Rapid early rule-in of AMI with high-sensitivity cardiac troponin



it is important to note that an increased hs-cTn concentration alone is not sufficient to make the diagnosis of AMI.

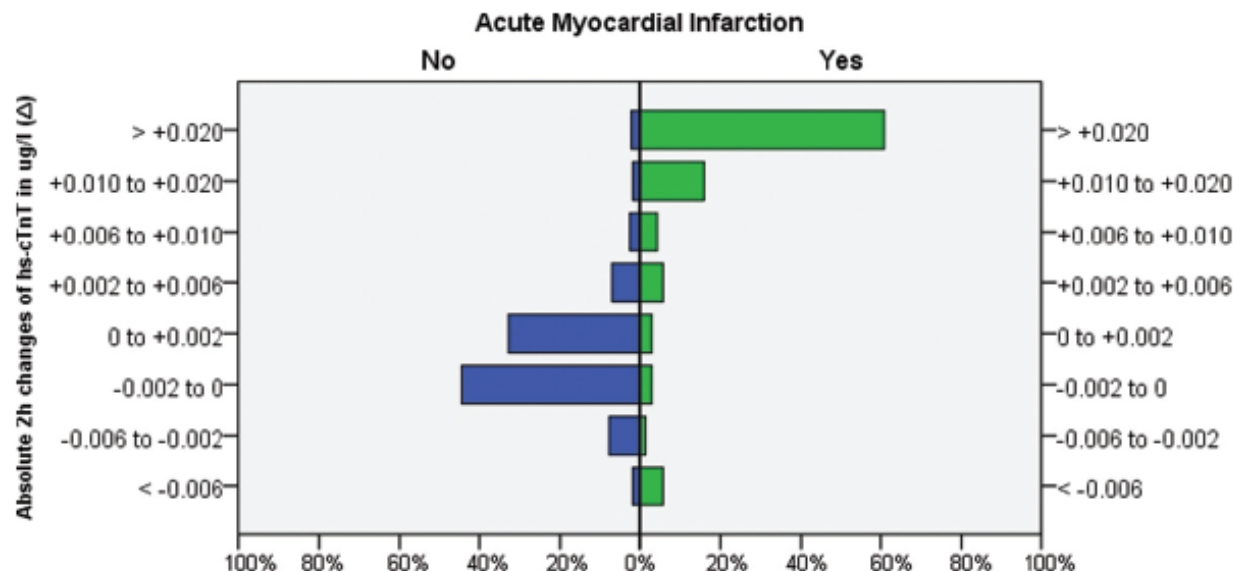
Utility of Absolute and Relative Changes in Cardiac Troponin Concentrations in the Early Diagnosis of Acute Myocardial Infarction

Circulation

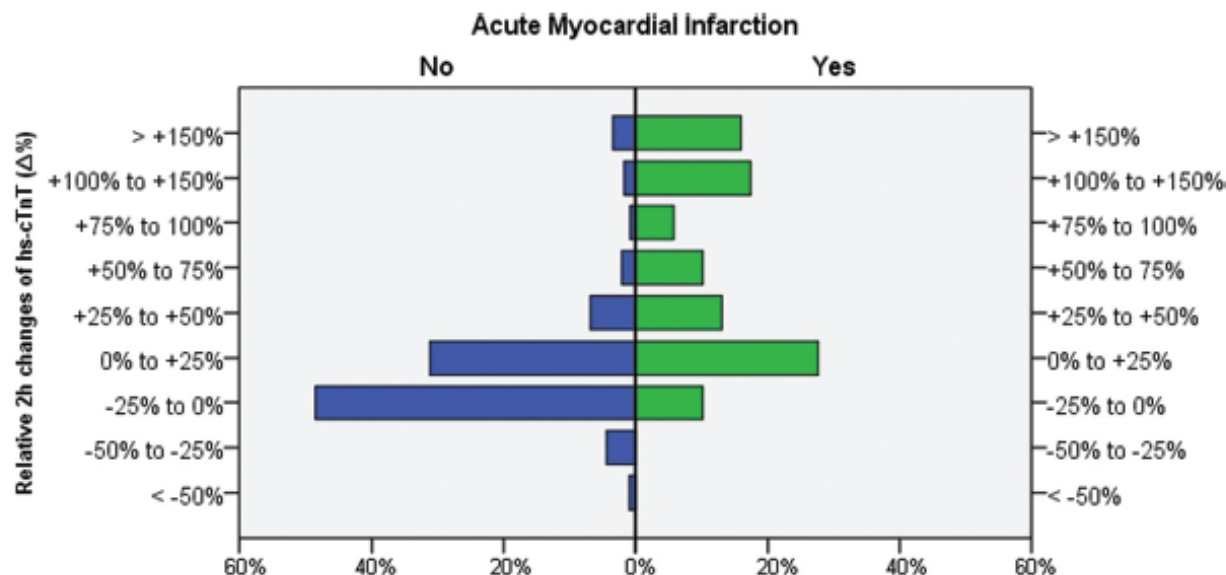
July 12, 2011

Tobias Reichlin, MD*; Affan Irfan, MD*; Raphael Twerenbold, MD; Miriam Reiter, MD; Willibald Hochholzer, MD; Hanna Burkhalter, MD; Stefano Bassetti, MD; Stephan Steuer, MD; Katrin Winkler, MD; Federico Peter, MD; Julia Meissner, MD; Philip Haaf, MD; Mihael Potocki, MD; Beatrice Drexler, MD; Stefan Osswald, MD; Christian Mueller, MD, FESC

Absolute changes



Relative changes



Utility of Absolute and Relative Changes in Cardiac
Troponin Concentrations in the Early Diagnosis of Acute
Myocardial Infarction

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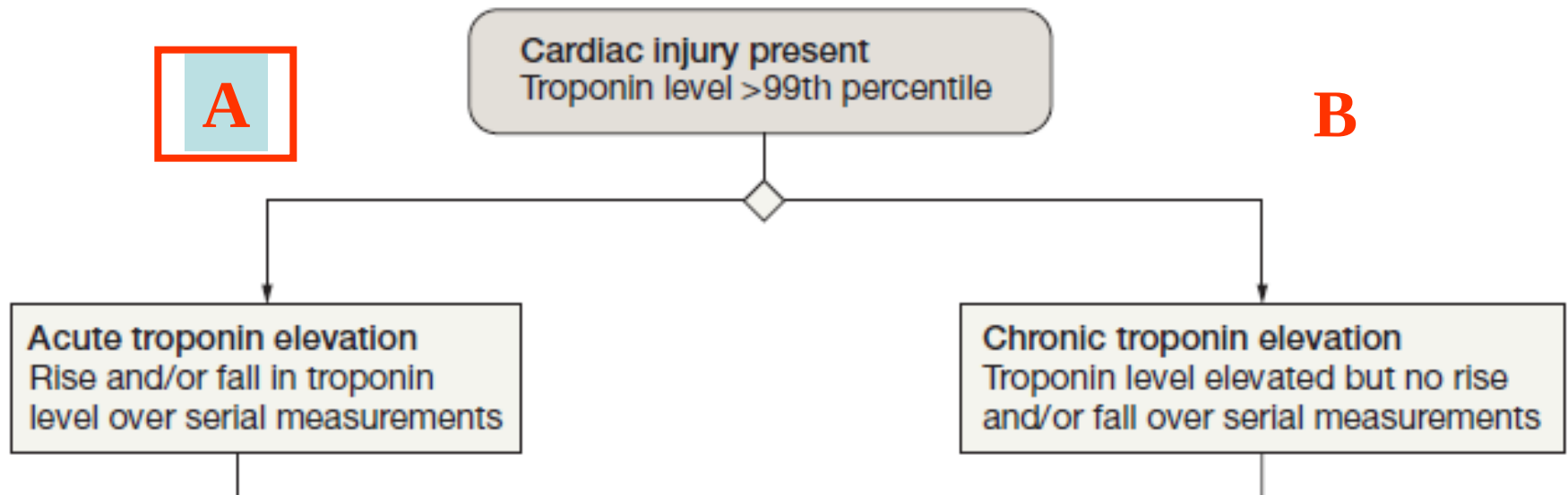
Circulation

July 12, 2011

	AUC (95% CI)	<i>P</i>	ROC Cutoff	Patients Above Cutoff, %	Sensitivity	Specificity
Absolute changes	0.95 (0.92–0.98)	<0.001	0.007	16	89	93
Relative changes	0.76 (0.70–0.83)		30	21	64	84

ROC curve–derived optimal cutoff values for absolute
changes within 2 hours were 0.007 $\mu\text{g/L}$ for hs-cTnT

INCREASED LEVELS OF hs-TROPONINS: Diagnostic algorithm



James A. de Lemos, MD

JAMA. 2013;309(21):2262-2269

A

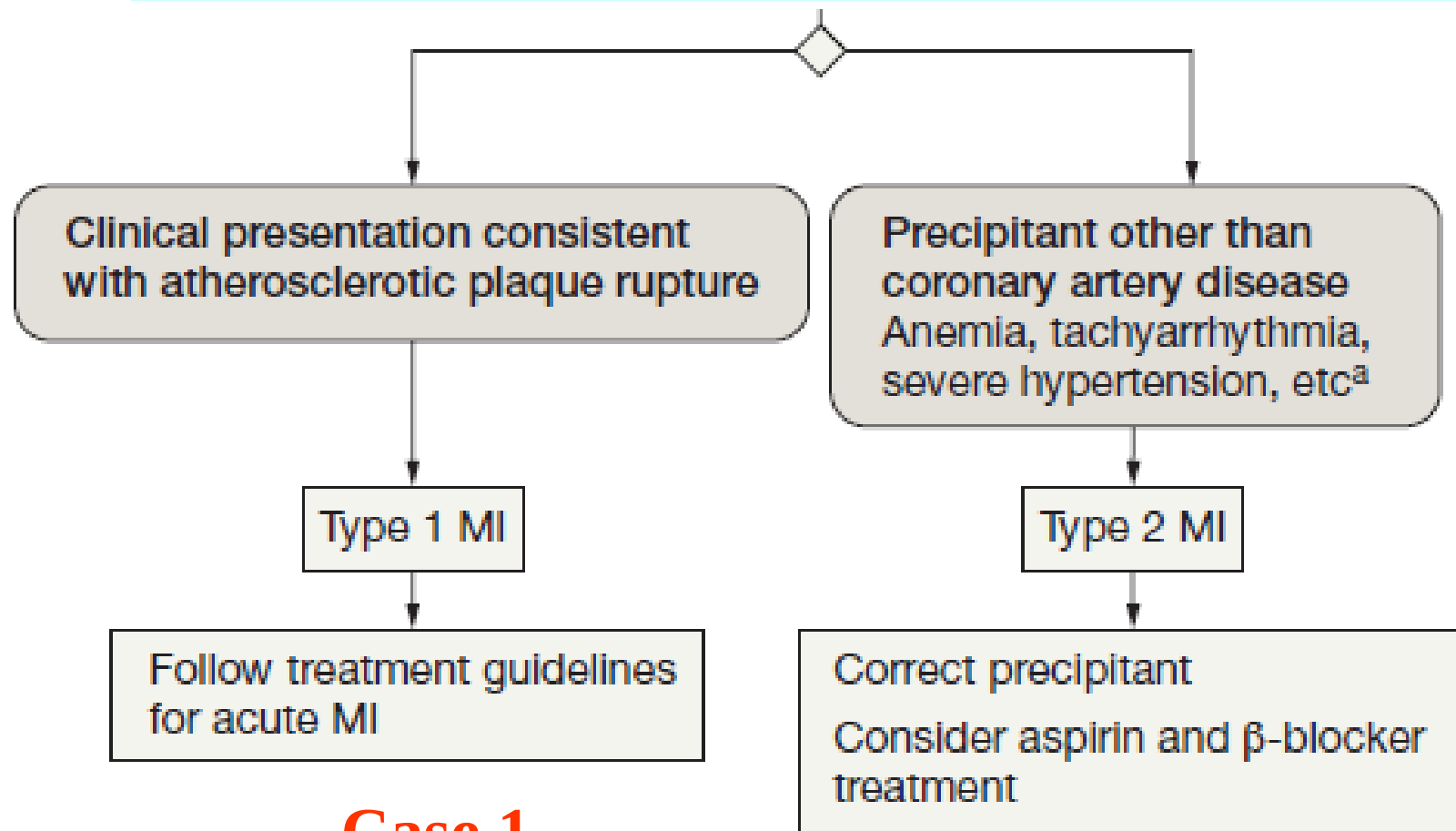
Acute troponin elevation
Rise and/or fall in troponin
level over serial measurements

Yes

Are the patient history, ECG,
or cardiac imaging consistent
with acute coronary syndrome ?

No

RULED-IN ACUTE MYOCARDIAL INFARCTION



ACUTE TROPONINS INCREASE
but...

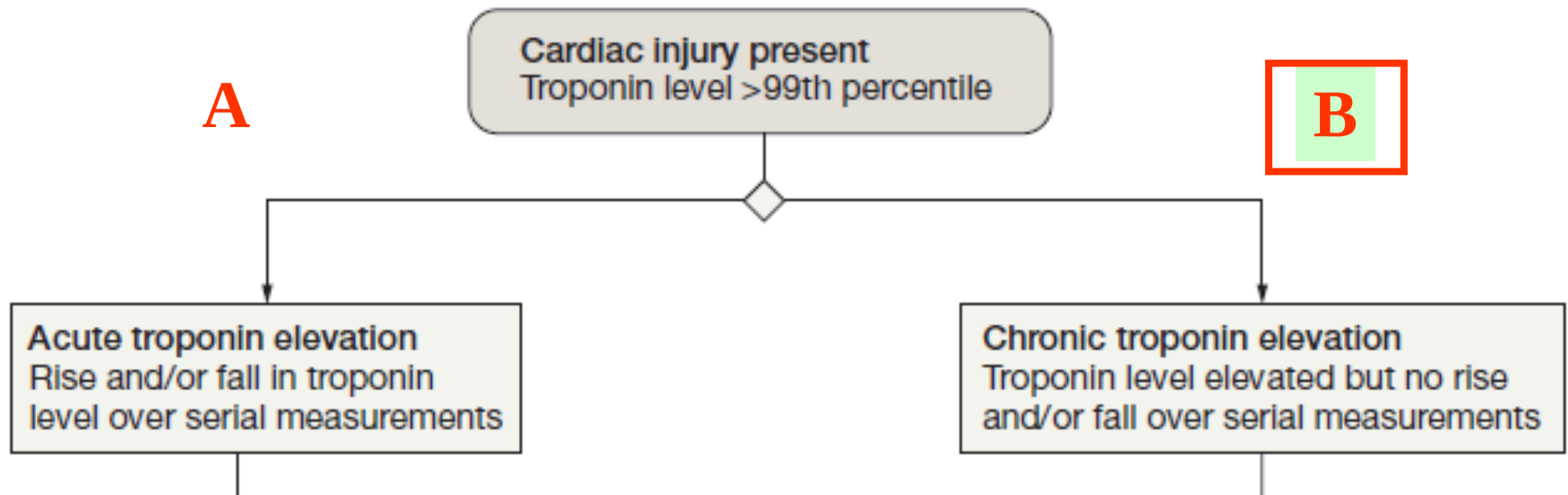
RULED-OUT ACUTE MYOCARDIAL INFARCTION

Non-ACS acute
myocardial injury
Pulmonary embolism,
acute heart failure, myocarditis

Case 2

Treat underlying disease
Recognize elevated troponin
level as poor prognostic marker

INCREASED LEVELS OF hs-TROPONINS: Diagnostic algorithm



James A. de Lemos, MD

JAMA. 2013;309(21):2262-2269

B

Chronic troponin elevation
Troponin level elevated but no rise
and/or fall over serial measurements

Case 3

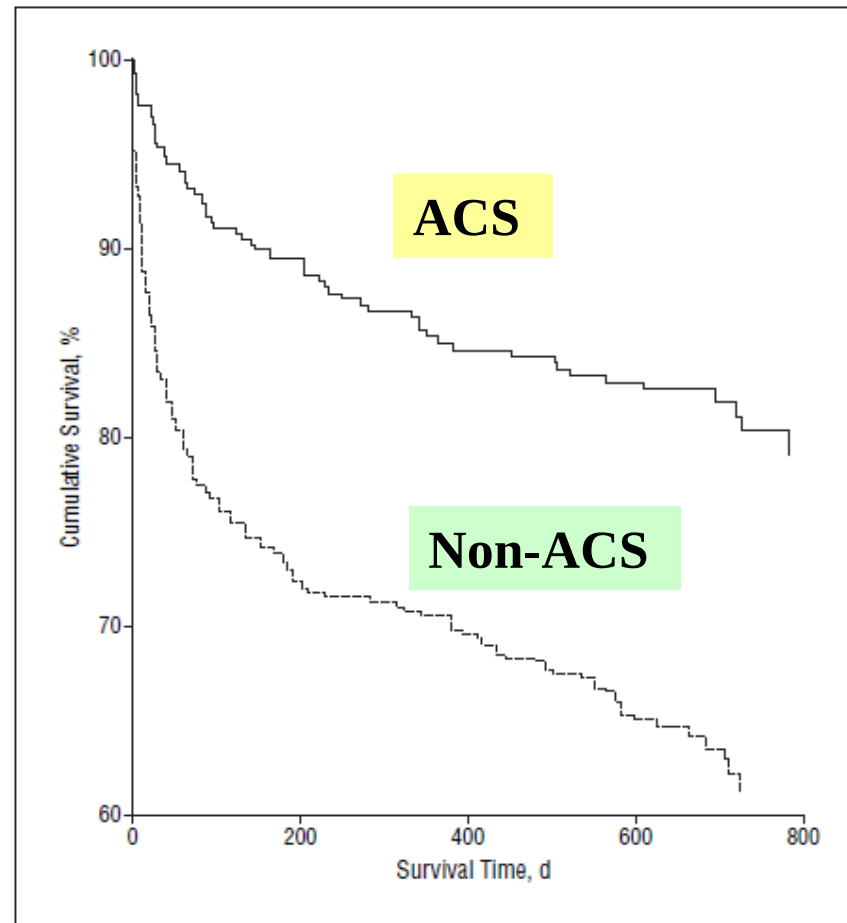
Possible structural heart
disease, chronic renal disease

Acute Coronary Syndrome vs Nonspecific Troponin Elevation

Clinical Predictors and Survival Analysis

Arch Intern Med. 2007;167:276-281

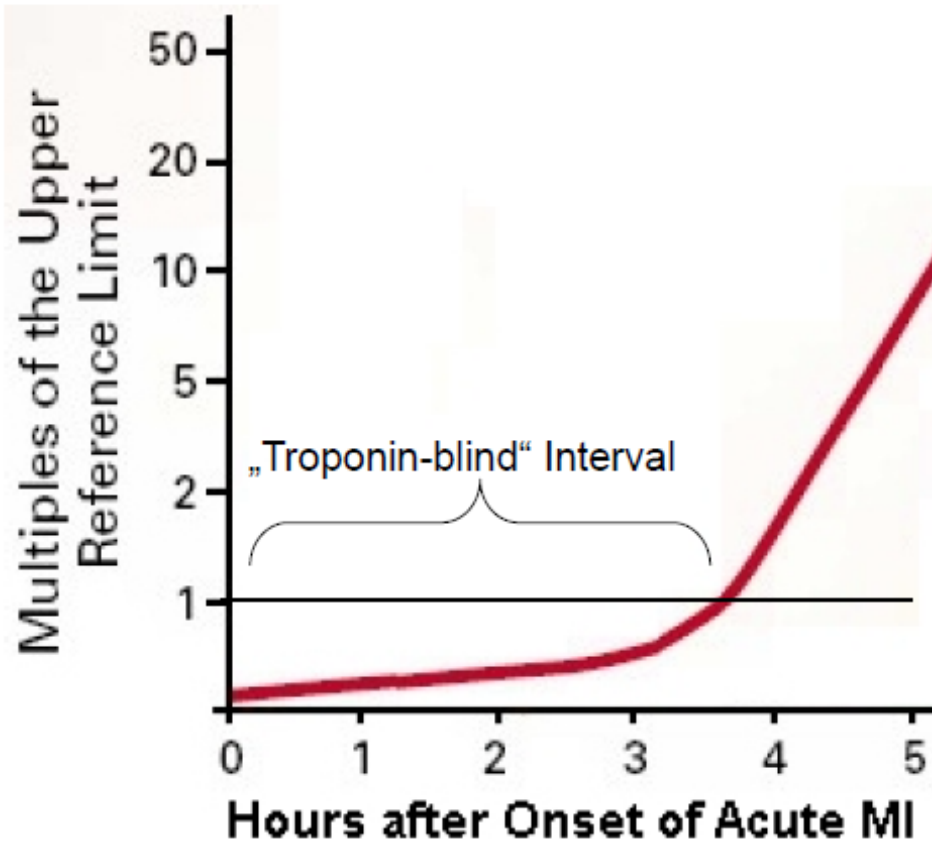
*Ronny Alcalai, MD; David Planer, MD; Afsin Culhaoglu, MD;
Aydin Osman, MD; Arthur Pollak, MD; Chaim Lotan, MD*



He described pressure in his chest and shoulders that was not worsened by exertion and had no obvious precipitating cause. The patient had a history of diabetes, hypertension, stage 2 chronic kidney disease (CKD), gastroesophageal reflux disease, chronic heart failure with a left ventricular ejection fraction of 30%, and paroxysmal atrial flutter. The results of coronary angiography, performed 3 years previously at an outside hospital, were reported by the patient to have been “normal.”

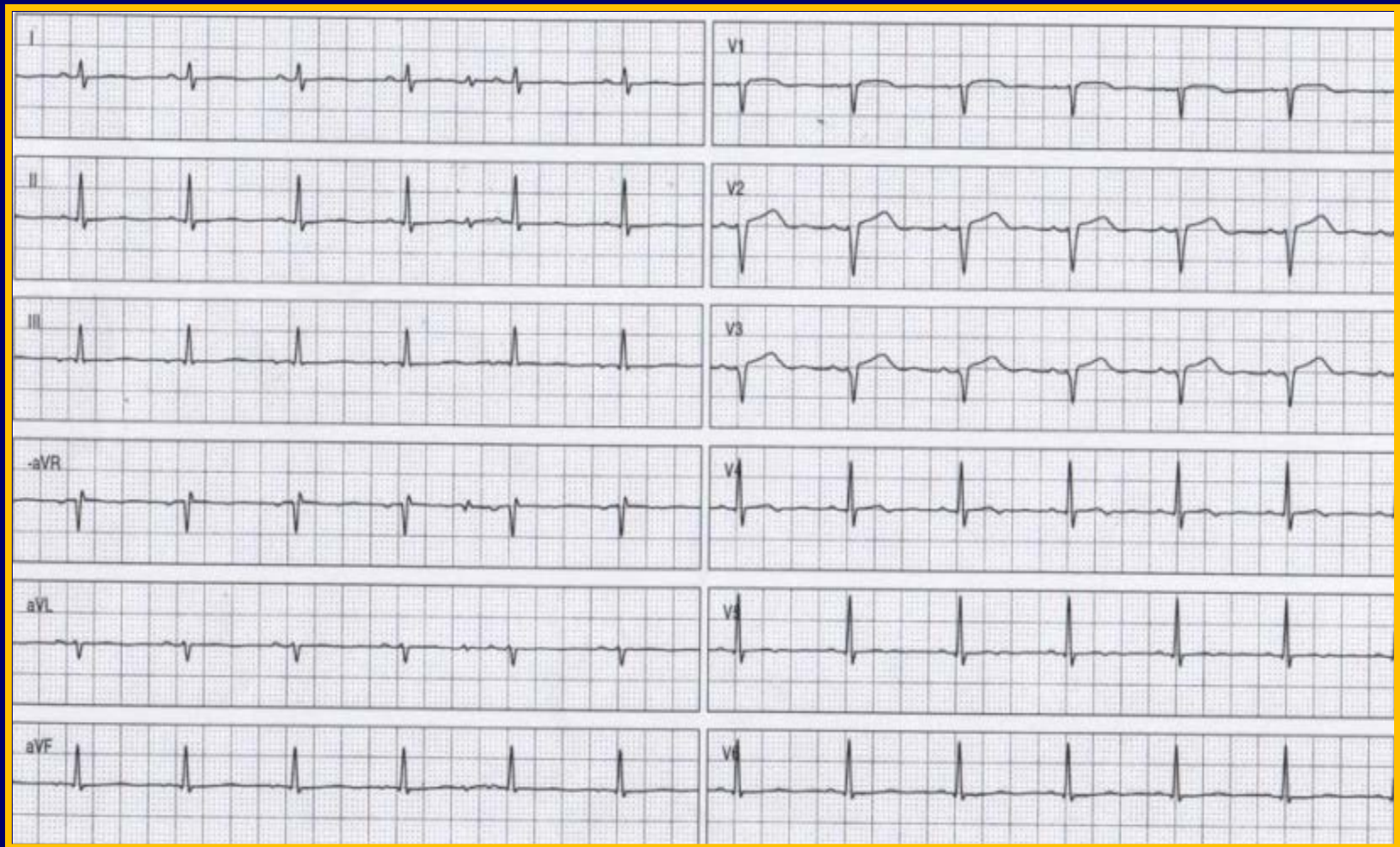
On examination, his heart rate was 60 beats/min; his blood pressure was 118/70 mm Hg. Pulses were equal in all extremities and no edema, ascites, or jugular venous distension was noted. His 12-lead electrocardiogram (ECG) showed sinus rhythm with low

Cardiac Troponin



- cTn 0h + cTn 6h
- ECG monitoring 6-8h
- Time and resources

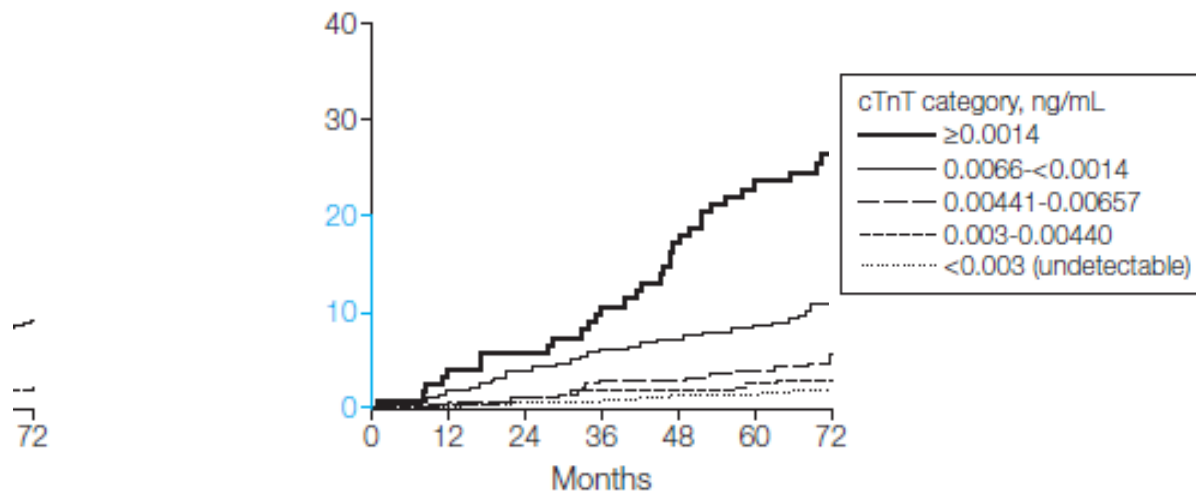
ECG on discharge



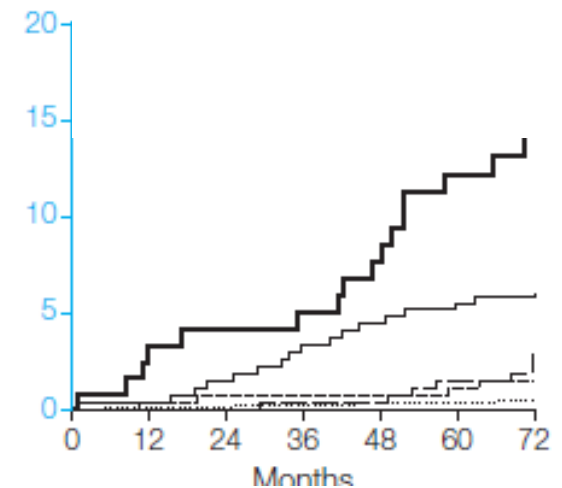
Association of Troponin T Detected With a Highly Sensitive Assay and Cardiac Structure and Mortality Risk in the General Population

The Dallas Heart Study : 3557 subjects 30-65 yrs old*

All-cause mortality



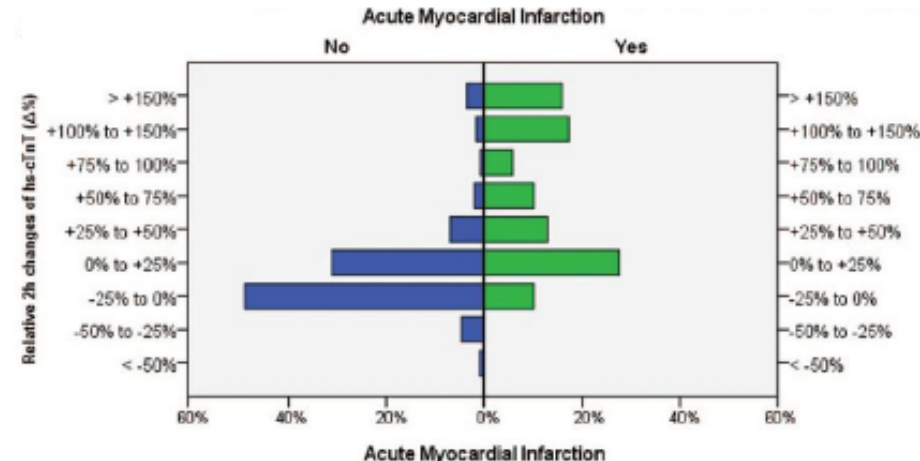
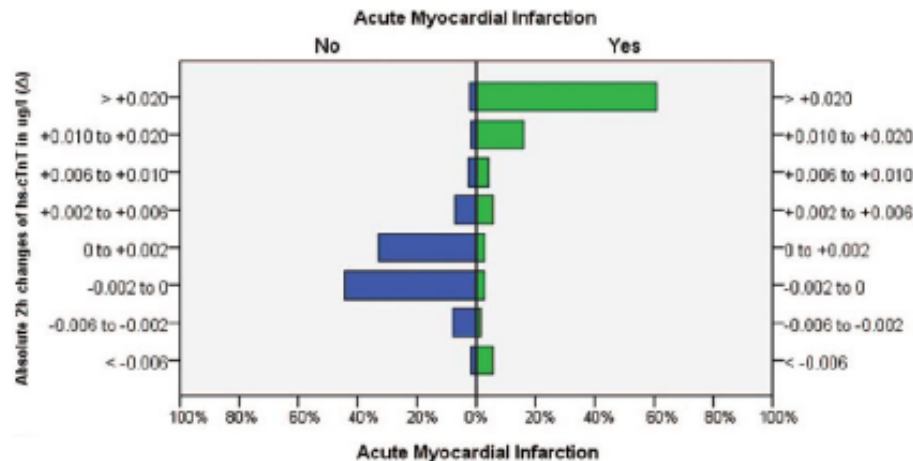
Cardiovascular disease mortality



***25% with detectable hs-troponin levels**

Delta: Absolute or Relative?

AHF, Myocarditis, TTC, Hypertension, Afib, Severe Sepsis
also
show a RISE



IL GIORNO SUCCESSIVO TORNA IN PS...

Persistenza di febbre

Dolore toracico accentuato dagli atti respiratori

Dolore epigastrico

PA 85/50 mmHg, FC 50 bpm

EO

torace e cuore: nulla da rilevare

Addome: Murphy positivo → ecoscopia addome : colecisti distesa con pareti ispessite e immagine iperecogena riferibile a calcolo : colecistite?

Esami ematochimici:

AST 563 U/l

ALT 256 U/l

GGT 227 U/l

LDH 1452 U/l

Impostata terapia con

ASA alte dosi, gastroprotettore,

Noradrenalina

Piperacillina/tazobactam nel sospetto di colecistite (poi sospesa perché non confermata)

Intanto arrivano i risultati di altri esami ematochimici:

TNT HS 2748 pg/ml

CK MBm 32 ng/ml

CK tot 507 U/l

Emocromo:

- all'ingresso in GB 6400 $\times 10^3$ (Neu 80% Linf 14% Eos <1%)
- la mattina dopo GB 13400 $\times 10^3$ (Neu 94% Linf 4% Eos <1%)

PCR 2 mg/l

VES 39 mm/h

Un caso di STE...Miocardite

- ✓ M. V.
- ✓ F, 35 anni
- ✓ ACR muta
- ✓ Da circa 6 giorni cefalea intensa , malessere generale e da 3 giorni febbre anche $>38^{\circ}\text{C}$
- ✓ La sera prima del ricovero comparsa di dolore epigastrico e toracico variabile con il respiro per cui si reca in PS:
 - TC $38,5^{\circ}\text{C}$
 - Iniziale rialzo enzimi epatici con ALT e AST >50 U/l
 - Non eseguito ECG



Somministrati liquidi e dimessa
con consiglio di ripetere dopo
qualche giorno gli esami
ematochimici

IL GIORNO SUCCESSIVO TORNA IN PS...

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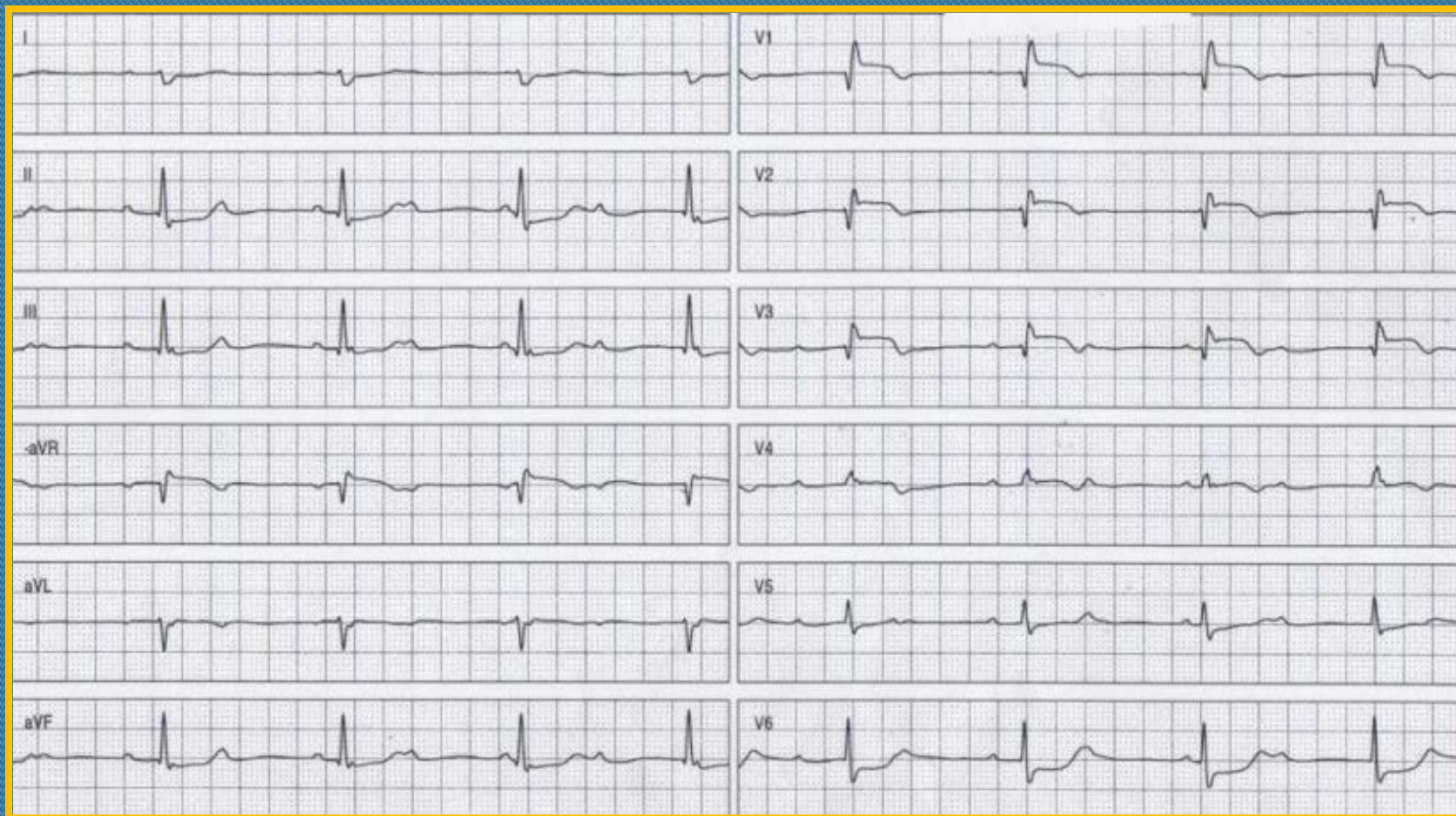
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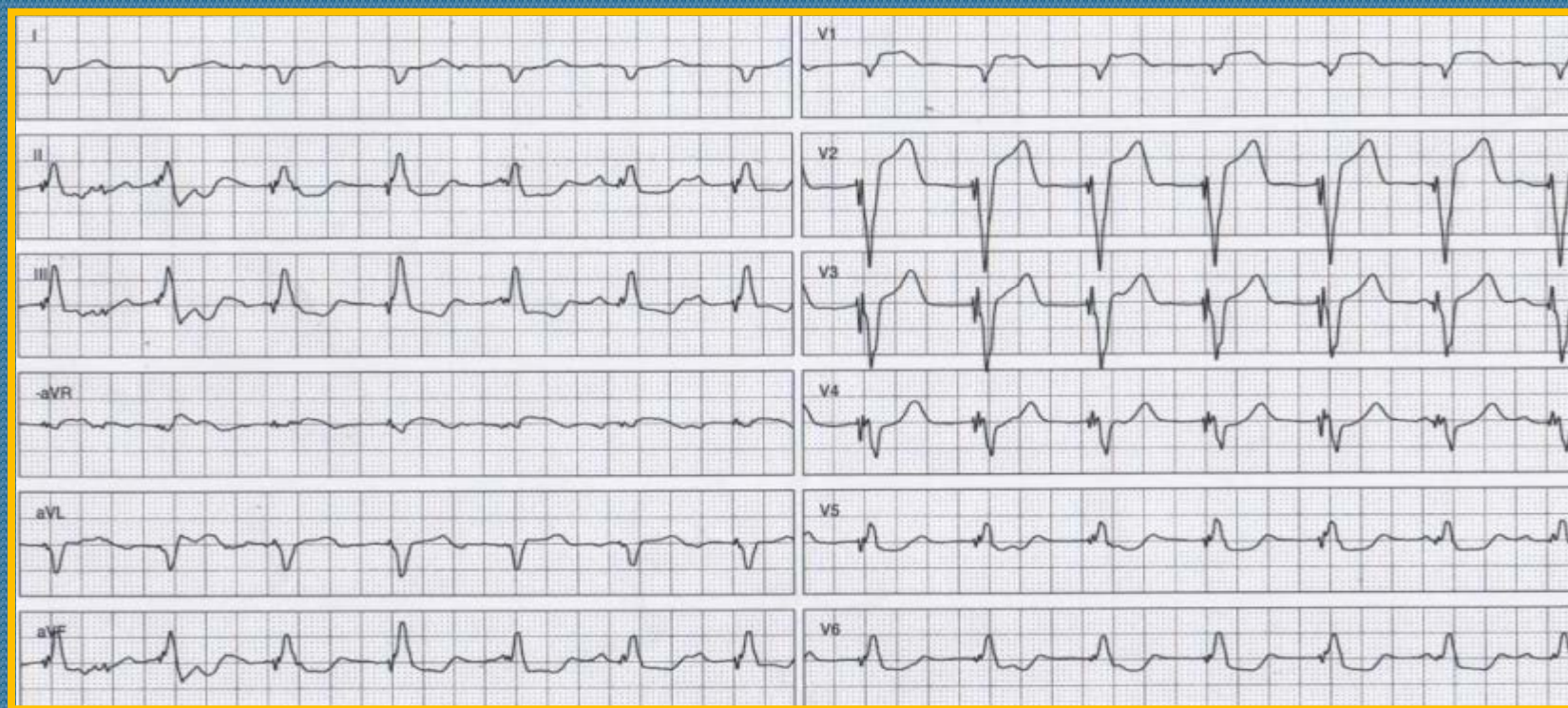
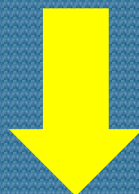
ECG in PS



....Ricovero in Utic

Nel frattempo ...

Ulteriore ipotensione improvvisa 60/40 mmHg associata al BAV di III grado non responsiva a liquidi e atropina



Posizionato PM temporaneo ; in corso noradrenalina 0,05 μ /Kg/min

Impostata terapia con

ASA alte dosi, gastroprotettore,

Noradrenalina

Piperacillina/tazobactam nel sospetto di colecistite (poi sospesa perché non confermata)

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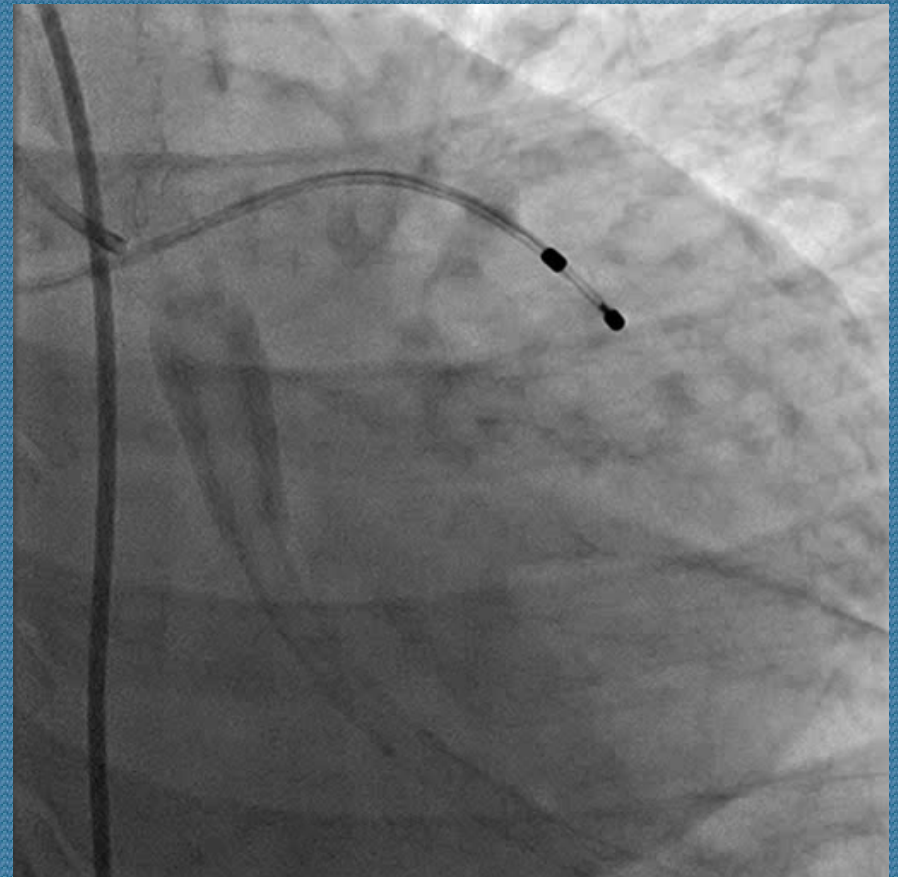
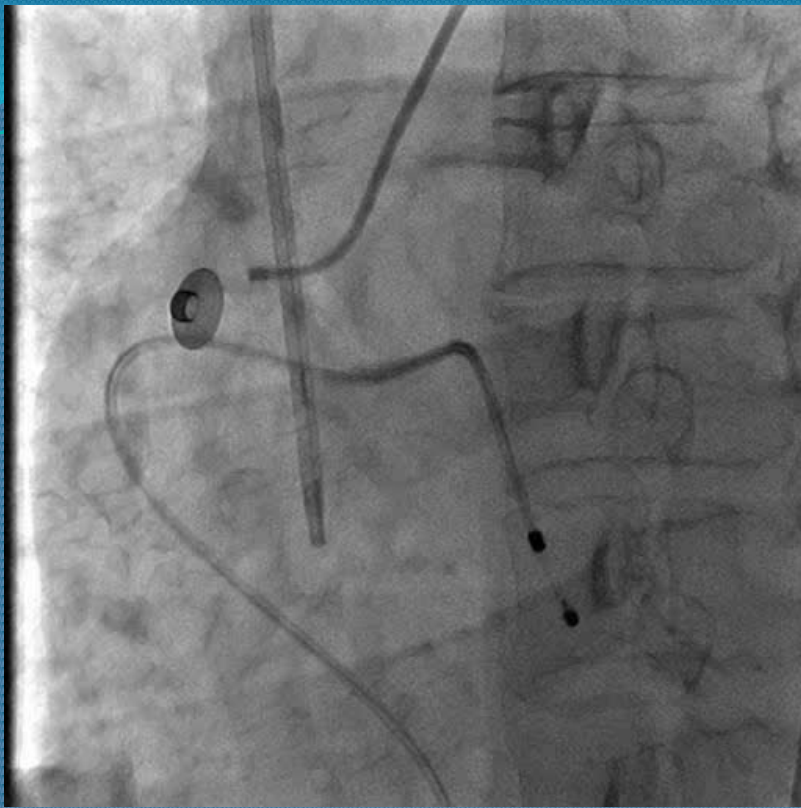
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Emocromo:

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- la mattina dopo GB 13400 $\times 10^3$ (Neu 94% Linf 4% Eos <1%)

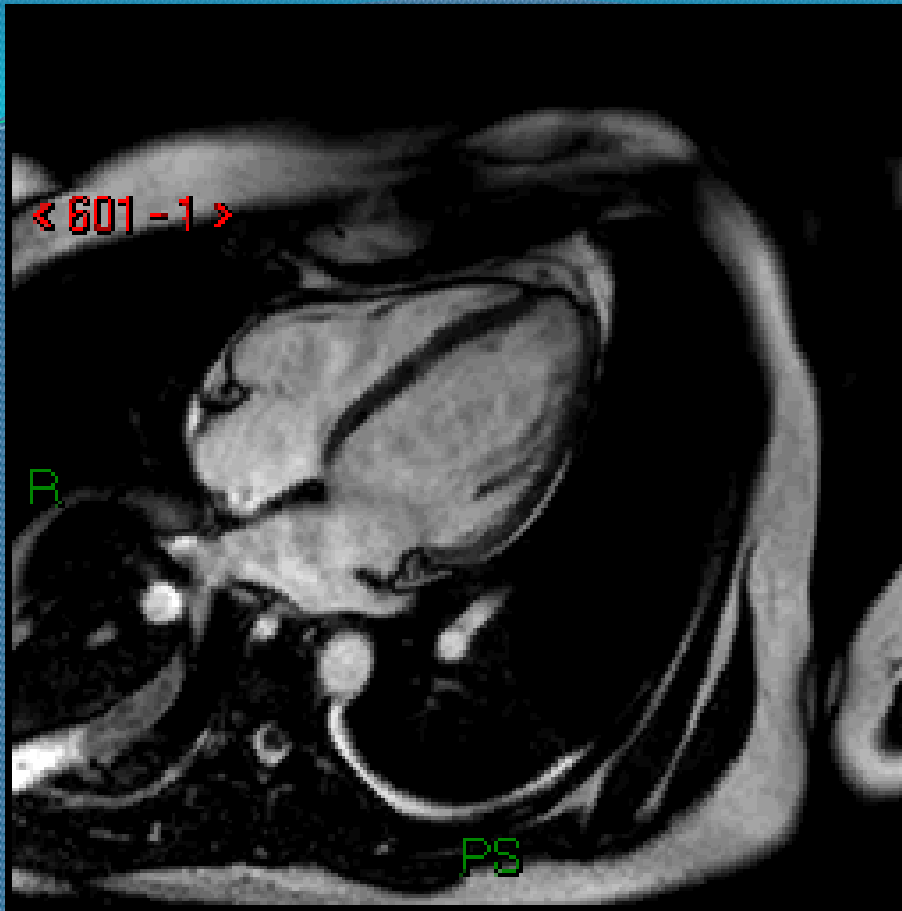
PCR 2 mg/l

VES 39 mm/h

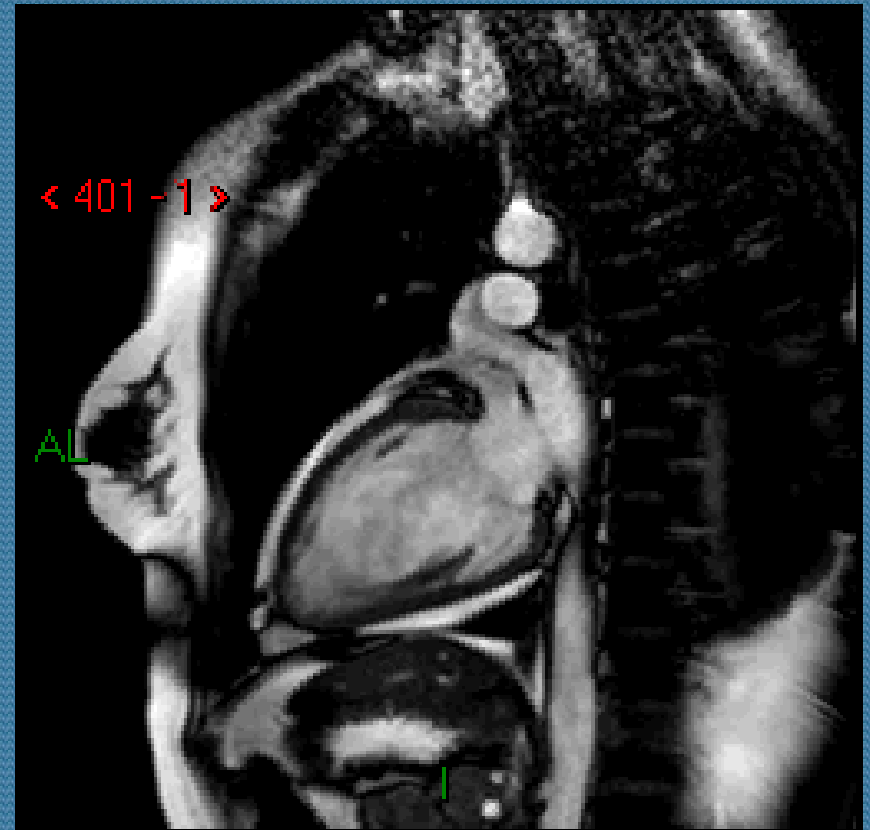


Coronarografia

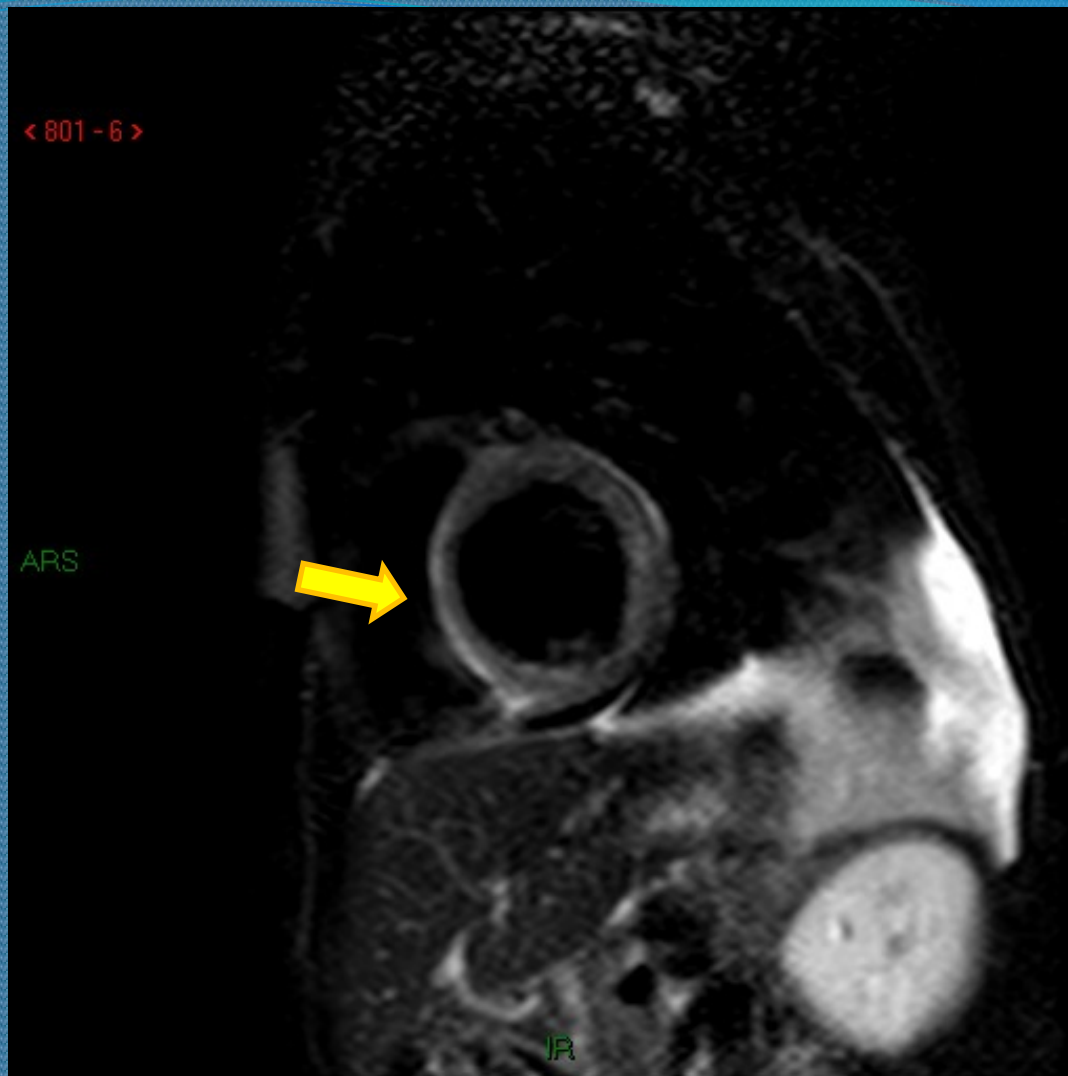
cine RMN CUORE



Sequenze cine 4 camere:
acinesia del setto e
sottile falda di versamento pericardico



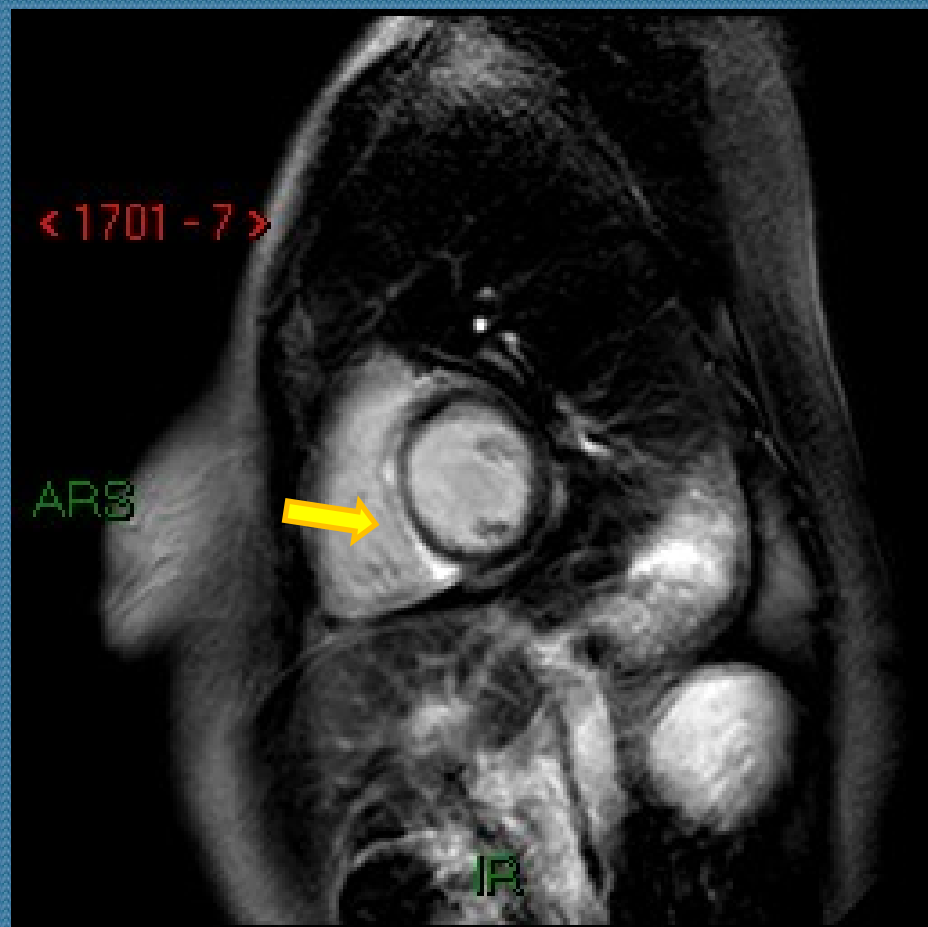
Sequenze cine 2 camere: ipocinesia
della parete anteriore e versamento
pericardico



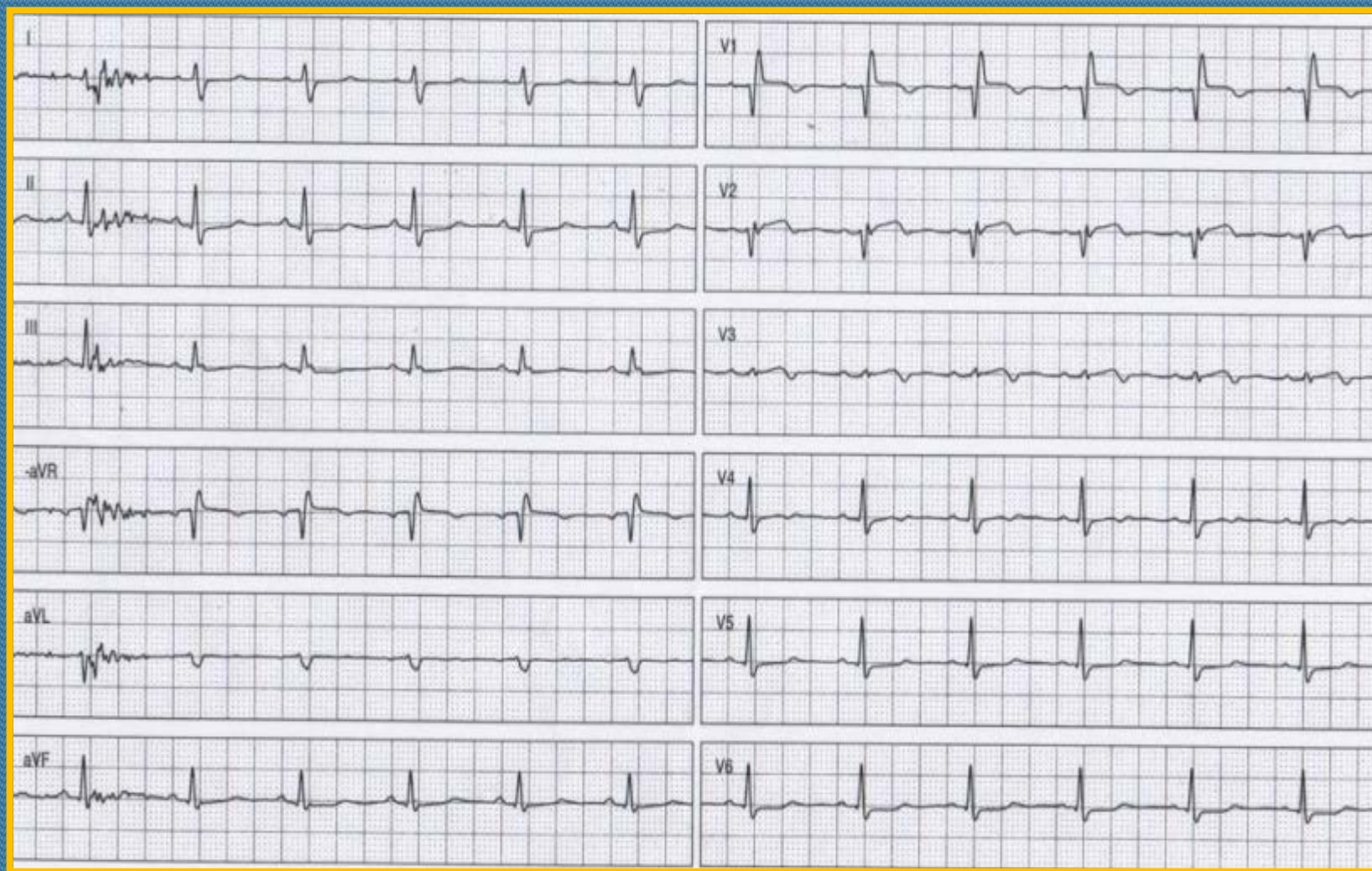
Sequenze Black blood T2 pesate: iperintensità del segnale compatibile con edema del setto e giunzione posteriore e parete anteriore



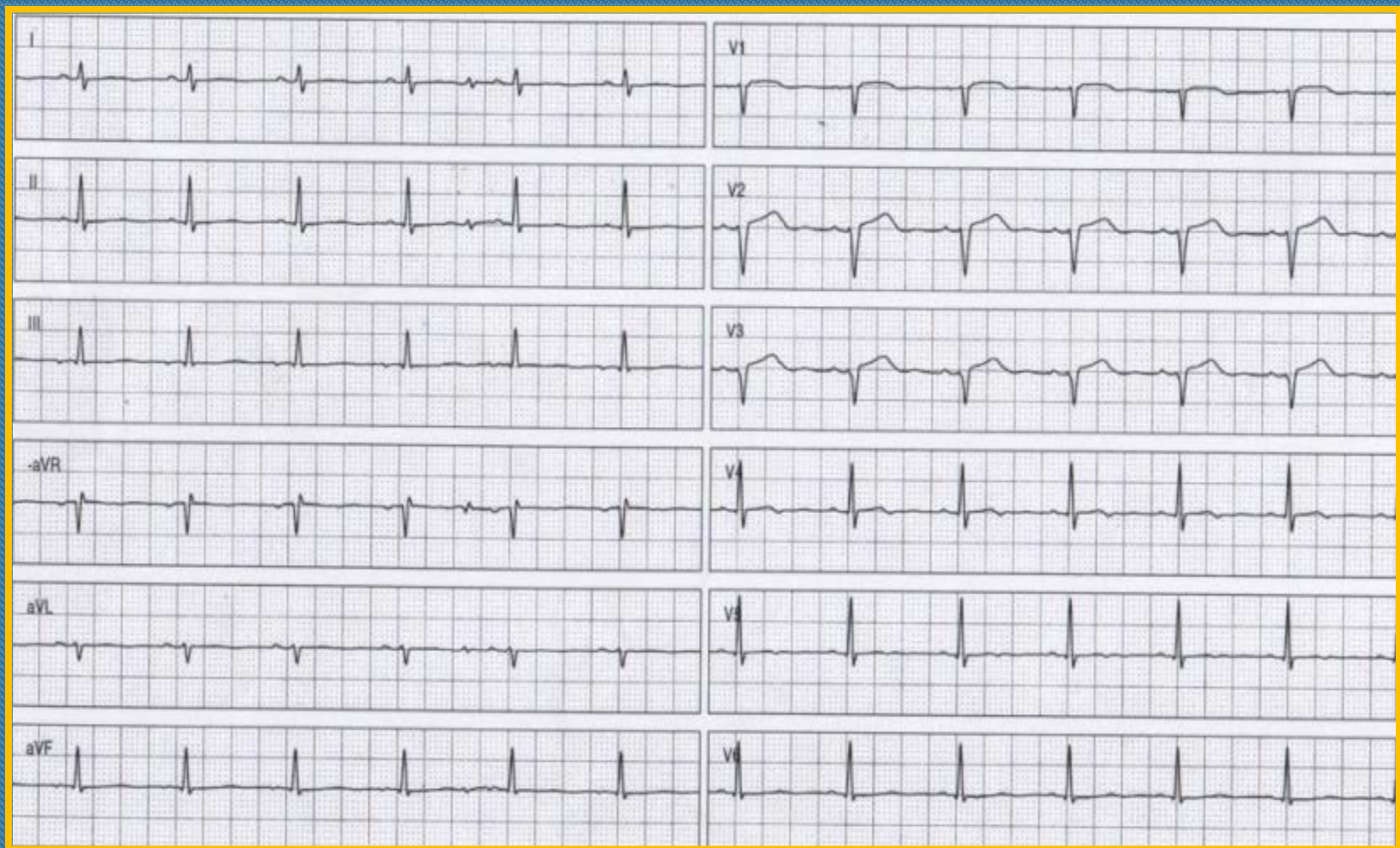
Sequenze inversion recovery:
late enhancement subepicardico
del setto medio compatibile con
necrosi cellulare associata a
miocardite



ECG in V giornata dopo ripresa di ritmo spontaneo e svezzamento da amine e scomparsa del dolore toracico



ECG in VIII giornata



Increasingly Sensitive Assays for Cardiac Troponins

A Review

James A. de Lemos, MD

JAMA. 2013;309(21):2262-2269

Characteristic	cTnT ^a		cTnI ^b	
	Fourth-Generation	Highly Sensitive	Contemporary Sensitive	Highly Sensitive
AUC	0.90 (0.86-0.94)	0.96 (0.94-0.98)	0.92 (0.90-0.94)	0.96 (0.95-0.97)
99th Percentile cut point, ng/L	10	14	32	30
10% CV threshold, ng/L	35	13	32	5.2
Sensitivity, %	83 (76-90)	95 (90-98)	79 (75-84)	82 (77-87)
Specificity, %	93 (91-95)	80 (77-83)	95 (93-96)	92 (90-94)
Positive predictive value, %	72 (64-79)	50 (43-56)	81 (76-85)	75 (70-80)
Negative predictive value, %	97 (95-98)	99 (97-100)	94 (92-95)	95 (93-96)

