AKUT KORONER SENDROMLAR

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Akdeniz Üniversitesi Acil Tıp Anabilim Dalı

Hedef

- AKS'ların patofizyolojik süreç ve tanımlarına hakim olmak
- Göğüs ağrılı bir hastanın AKS tanısını koyabilmek
- AKS'larda en uygun tedavisel yaklaşımı kavramak

Plan

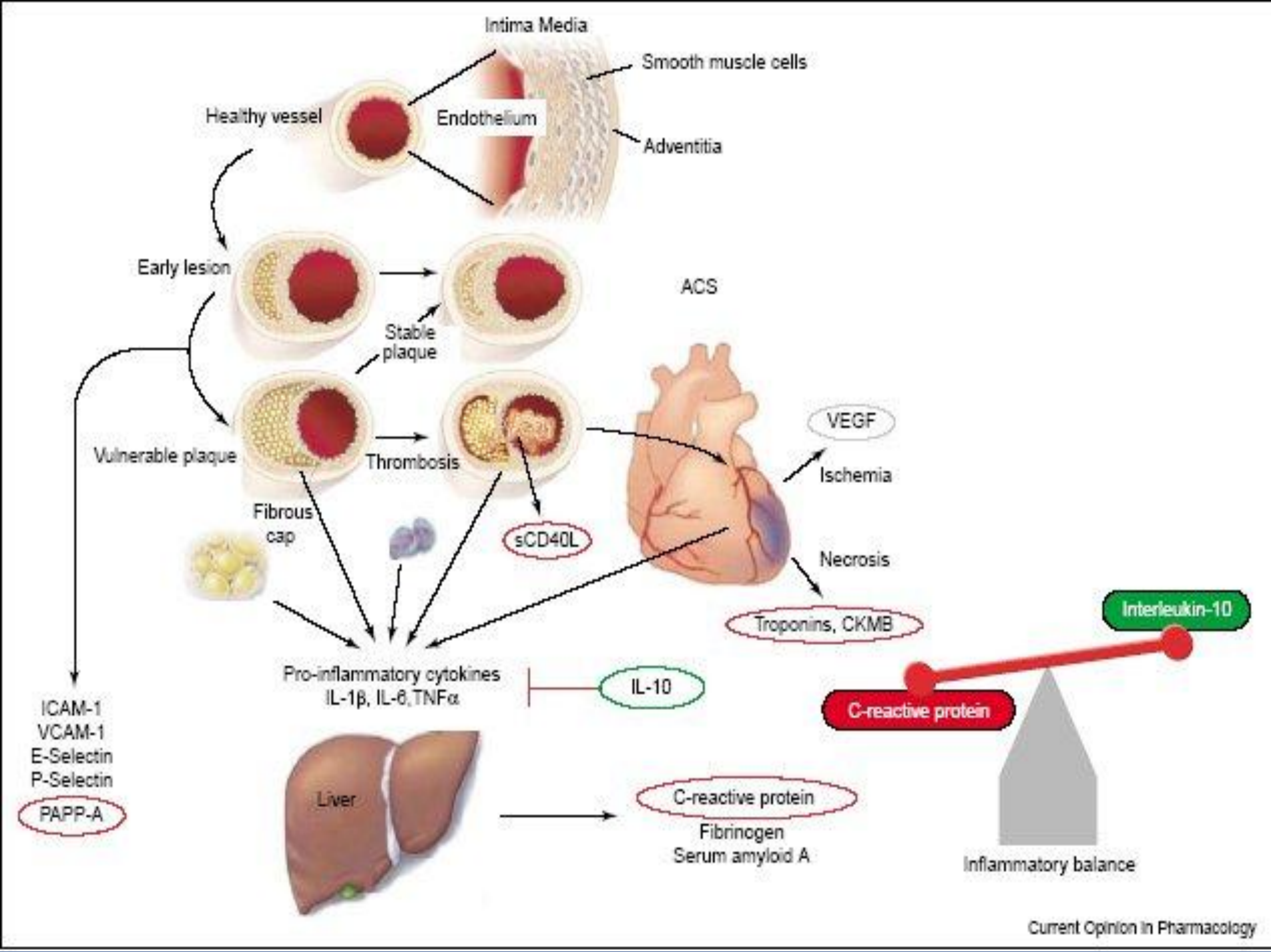
- Koroner arter hastalığı patofizyolojisi
- Akut koroner sendrom patofizyolojisi
- Risk ve olasılık belirlemede kullanılan ajanlar
- Risk ve olasılık sınıflamaları
- Tedavi

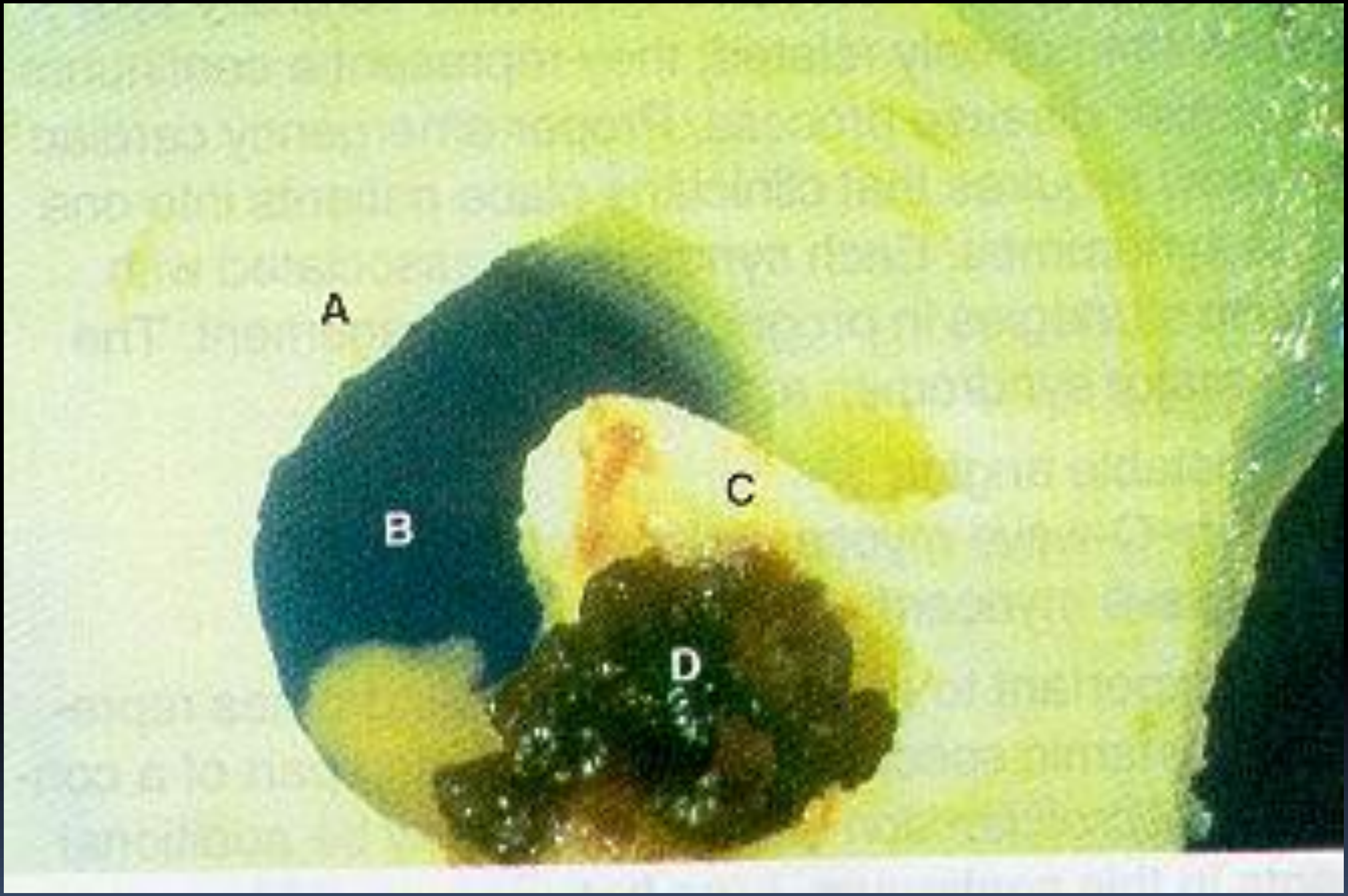
Koroner Arter Hastalığı Patofizyolojisi

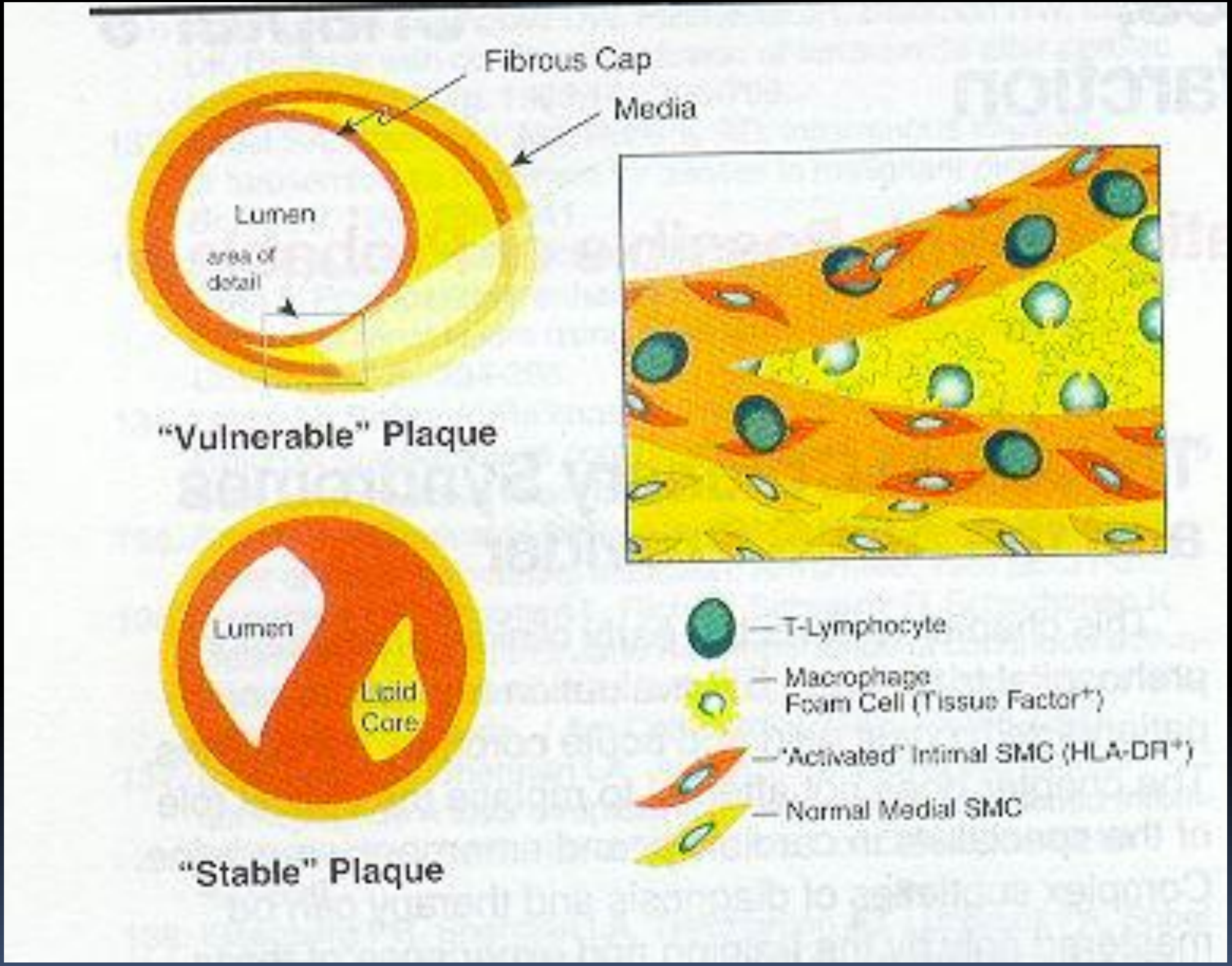
- Aterogenez zemini
- Plak oluşumu
- Rüptür
- Trombüs
- İskemi
- İnfarkt

Aterogenez

- Aterojenik diyet
- Selektif adezyon molekülleri
- VCAM-1 (monosit ve T lenfosit)
- M-CSF, makrofajlar
- Köpük hücreler
- Düz kas hipertorifisi
- Kompleks inflamatuar süreç


Intima Media
Smooth muscle cells
Healthy vessel
Endothelium
Adventitia
Early lesion
ACS
Stable plaque
Vulnerable plaque
Thrombosis
VEGF
Ischemia
Fibrous cap
sCD40L
Necrosis
Troponins, CKMB
Interleukin-10
Pro-inflammatory cytokines
IL-1β, IL-6,TNFα
IL-10
C-reactive protein
ICAM-1
VCAM-1
E-Selectin
P-Selectin
PAPP-A
Liver
C-reactive protein
Fibrinogen
Serum amyloid A
Inflammatory balance
Current Opinion in Pharmacology


A
B
C
D

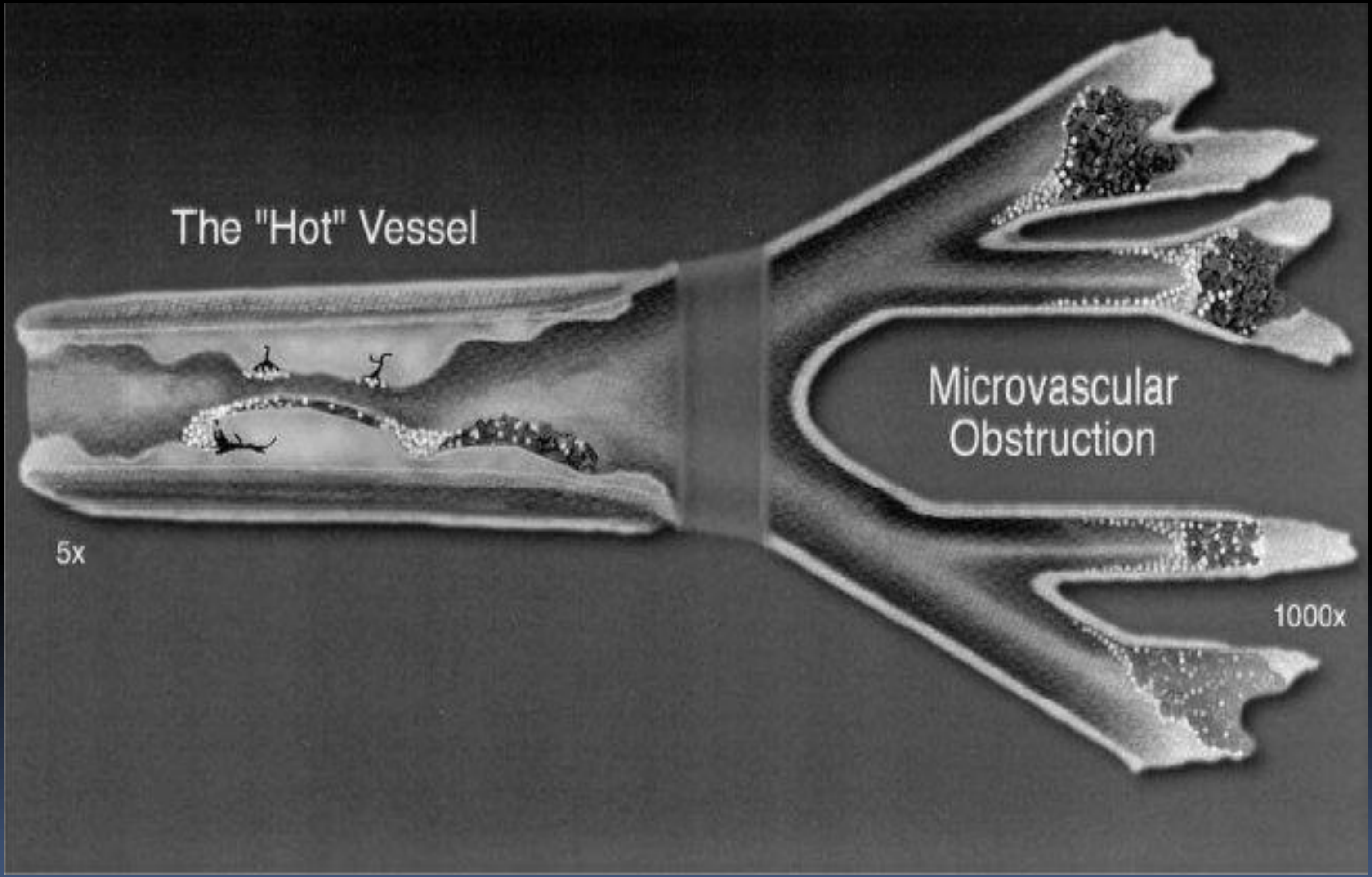

Fibrous Cap
Media
Lumen
area of detail
"Vulnerable" Plaque
Lumen
Lipid Core
"Stable" Plaque
T-Lymphocyte
Macrophage Foam Cell (Tissue Factor+)
'Activated' Intimal SMC (HLA-DR+)
Normal Medial SMC

Akut Koroner Sendrom Nedir?

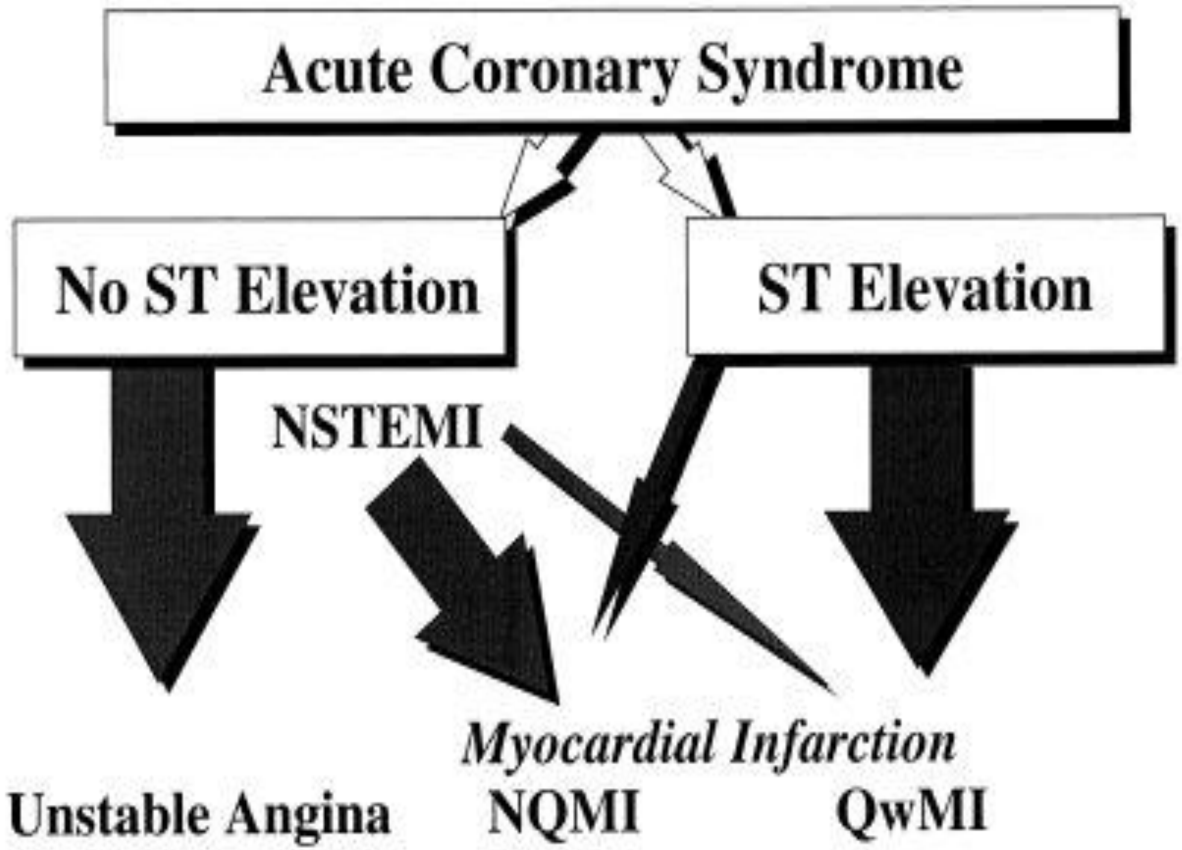
- İlk kullanımı tıbbi teknisyen ve triyaj hemşireleri
- ACS hemen her zaman aterosklerotik KAH′na bağlı gelişir.
- Aterosklerotik plağın rüptürüne bağlı gelişen bir takım patolojik süreci takiben koroner kan akımının azalması sonucu meydana gelir.

Akut Koroner Sendrom Nedir?

- Kararsız anjina (UAP)
- ST yükseklikli MI
- ST yükselmesi olmayan MI


The "Hot" Vessel
Microvascular
Obstruction
5x
1000x

JACC Vol. 36, No. 3, 2000
September 2000:970–1062



Kararsız Anjina

- İstirahatte gelen ve 20 dakikayı geçmeyen anjina
- Kreşendo tipte anjina
- Yeni başlangıçlı Sınıf III ve IV anjina

Göğüs Ağrısının Sınıflanmasında Kullanılan Araçlar

- Hikaye
  - Anjinal semptomların karakteri
  - KAH öyküsü
  - Cinsiyet
  - Yaş
  - Geleneksel risk faktörleri
- Fizik muayene
- EKG
- Biyokimyasal testler
  - Kreatinin kinaz
  - Miyoglobin
  - Troponin
  - Diğer

Anjina eşdeğerleri

- İzole, açıklanamamayan, yeni başlayan ya da artmış egzersiz dispnesi
- Bulantı, kusma
- Soğuk terleme
- Açıklanamamayan yorgunluk

Anginal Semptomlar

	Ana semptom göğüs ağrısı		Ana semptom karın ağrısı		Ana semptom nefes darlığı	
	Evet	Hayır	Evet	Hayır	Evet	Hayır
AMI 889 hasta	728	161	84	803	103	786
USAP 966 hasta	896	70	58	907	50	916

J. Hector Pope. Missed Diagnosis of Acute Cardiac Ischemia In The Emergency Department.
N Eng J Med 2000;342:1163-70

Anginal Semptomalar

- Lee TH. Acute chest pain in the emergency room: idenfication and examination of low risk patients. Arch Intern Med 1985;145:65-9
  - %22′si bıçak saplanır tarzda ağrı
  - %13′ü ploretik
  - %7′si palpasyonla ağrı

Diğer

- Kokain kullanımı
- Anemi veya GİS kanaması
- KOAH
- Hipertiroidi
- Ateş
- AV fistüller

EKG

EKG

- Yeni başlangıçlı ağrıda en iyi tanı yöntemidir
- Trombolitik tedavi endikasyonu için kullanılan tek yöntemdir
- Non-invaziv
- Kolay ulaşılabilir
- Ucuz

EKG

- EKG AMİ olan hastaların sadece %40-50′sinde tanısaldır
- AMİ olan hastaların %1-6′unun ilk EKG′si normaldir
- Tanısı konamayan AMİ′lerinin %25′inin EKG′leri yanlış yorumlanmaktadır.

Biyokimyasal Testler

- Miyokartta maksimum
- Diğer dokularda olmayacak
- Erken saptanabilecek
- Ucuz olacak
- Hızlı ölçülebilecek
  - KREATİN KİNAZ
  - MİYOGLOBİN
  - TROPONİN
  - FABP

Kreatin kinaz

- Hücre içi enzim
- B (brain) ve M (muscle) tipi var
- CK-BB, CK-MM, CK-MB
- İskelet kasında da bir miktar var
- 4-6 saatte yükselir, 18-24 saatte pik yapar.
- 3-4 günde normale dönüş

Acil serviste tek ölçümün duyarlılığı %36, 6-9 saatte %90, 24. saatte %100' dür.

Miyoglobin

- Düşük molekül ağırlıklı bir hem proteinidir
- Çizgili kaslarda ve kalpte bulunur.
- Renal fonksiyonlar normalse; AMI′da:
- 2. saatte yükselir
- 4-9 saatte pik yapar
- 24. saatte başlangıç düzeyine iner

Miyoglobin

- Başvuru sırasında
  - Miyoglobin %62, CK-MB %14
- 2. saatte
  - Miyoglobin %100, CK-MB %82
- 3. saatte
  - Miyoglobin %100, CK-MB %90

İlk 4-8 saatte infarktüsü dışlamada bir belirteç olarak kullanılabilir

Troponin I ve T:

Troponin 3 bileşenden meydana gelir.

Troponin I: İnhibitör (iskelet kasında yok)

Troponin T: Tropomyozin bağlar

Troponin C: Kalsiyum bağlar.

<u>AMI' da troponin I ve T :</u>

4-6 Saatte yükselir,

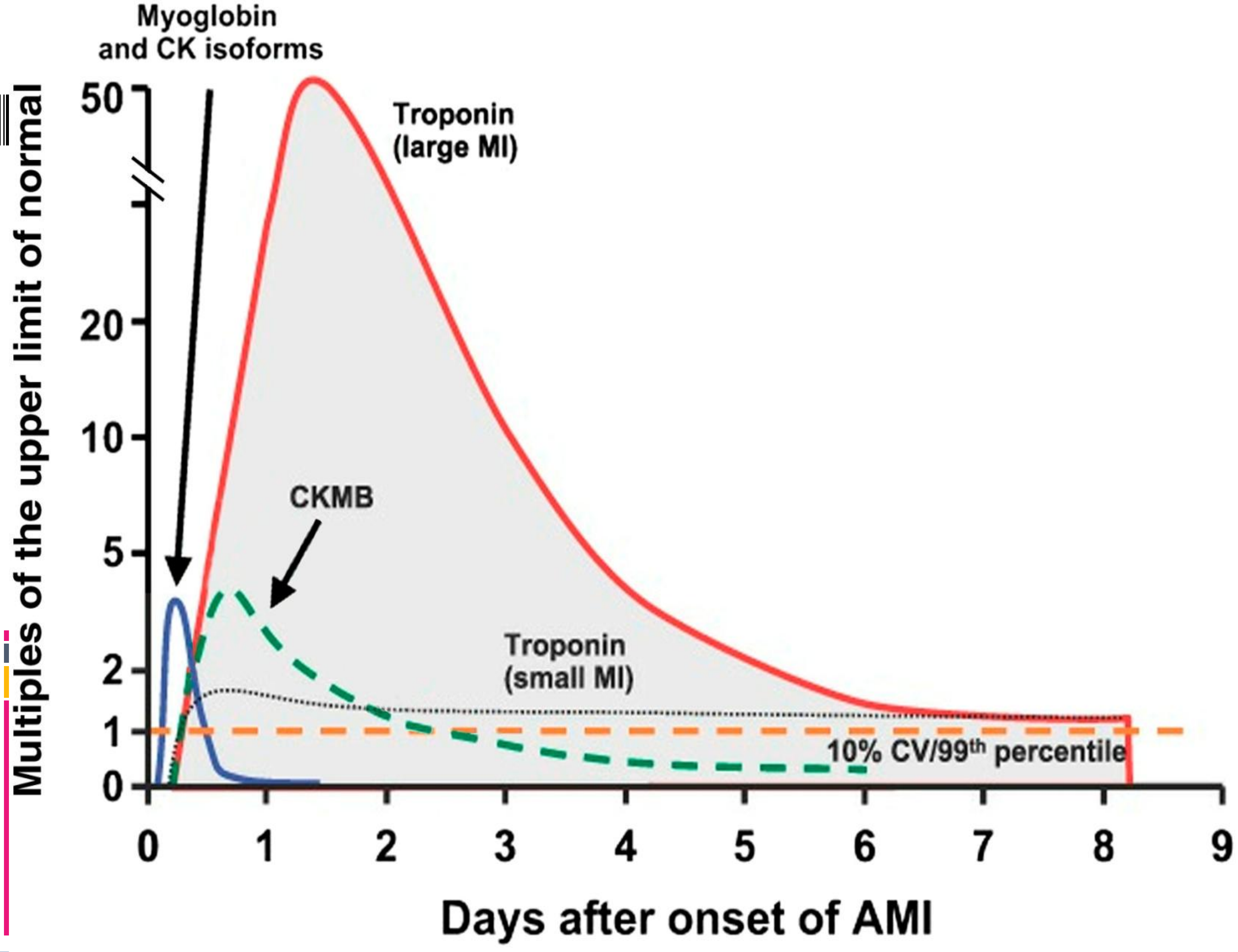
12-24 saatte pik yapar,

7-10 gün yüksek kalır

Sensitivite ve spesitivitesi CK-mb 'den yüksektir.

Troponinler

- cTnT ve cTnI normal insanların kanında saptanamaz.
- cTnT ve cTnI miktarları ile prognoz arasında kantitatif bir ilişki vardır.
- TnT′nin duyarlılığı %100, seçiciliği ise %95'dir.
- Kötü prognoz ve mortalite ile yakından ilgilidir ve tüm skorlamalarda kullanılır


Myoglobin
and CK isoforms
Troponin
(large MI)
CKMB
Troponin
(small MI)
10% CV/99th percentile
Multiples of the upper limit of normal
50
20
10
5
2
1
0
0
1
2
3
4
5
6
7
8
9
Days after onset of AMI

Hastaların Sınıflandırılması

1. Olasılık Sınıflaması
2. Risk Sınıflaması

Skorlamada Kullanılan Kılavuzlar

- Goldman göğüs ağrısı protokolü
- ACI-TIPI
- Medical Collage of Virginia
- ACC/AHA kılavuzu

ACC/AHA kılavuzu

e680 *Circulation* **June 11, 2013**

Table 6. Likelihood That Signs and Symptoms Represent an ACS Secondary to CAD

Feature	High Likelihood *Any of the following:*	Intermediate Likelihood *Absence of high-likelihood features and presence of any of the following:*	Low Likelihood *Absence of high- or intermediate-likelihood features but may have:*
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age greater than 70 years Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (1 mm or greater) or T-wave inversion in multiple precordial leads	Fixed waves ST depression 0.5 to 1 mm or T-wave inversion greater than 1 mm	T-wave flattening or inversion less than 1 mm in leads with dominant waves Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

Modified with permission from Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, U.S. Public Health Service, U.S. Department of Health and Human Service, 1994. AHCPR publication no. 94-0602.[124]

ACS = acute coronary syndrome; CAD = coronary artery disease; CK-MB = MB fraction of creatine kinase; ECG = electrocardiogram; MI = myocardial infarction; MR = mitral regurgitation; TnI = troponin I; TnT = troponin T.

TIMI Risk Skorlaması

- TIMI 11B ve ESSENCE çalışmalarından elde verilerden oluşturulmuştur
  - *65 yaş ve üstü olmak*
  - *KAH için en az 3 risk faktörüne sahip olmak*
  - *Önceden bilinen %50 veya daha fazla koroner darlık*
  - *Giriş EKG'sinde ST segment deviasyonu*
  - *Son 24 saat içinde en az iki anjinal episod olması*
  - *Son 7 gün içinde aspirin kullanımı*
  - *Artmış kardiyak enzim*

TIMI risk skorlaması

- Her bir faktörün olup olmamasına göre 1 veya 0 olarak puanlar verilir
  - 0/1 puan için %4,7 Düşük Risk
  - 2 puan için %8,3 Düşük Risk
  - 3 puan için %13.2 Orta Risk
  - 4 puan için %19.9 Orta Risk
  - 5 puan için %26.2 Yüksek Risk
  - 6/7 puan için %40.9 Yüksek Risk

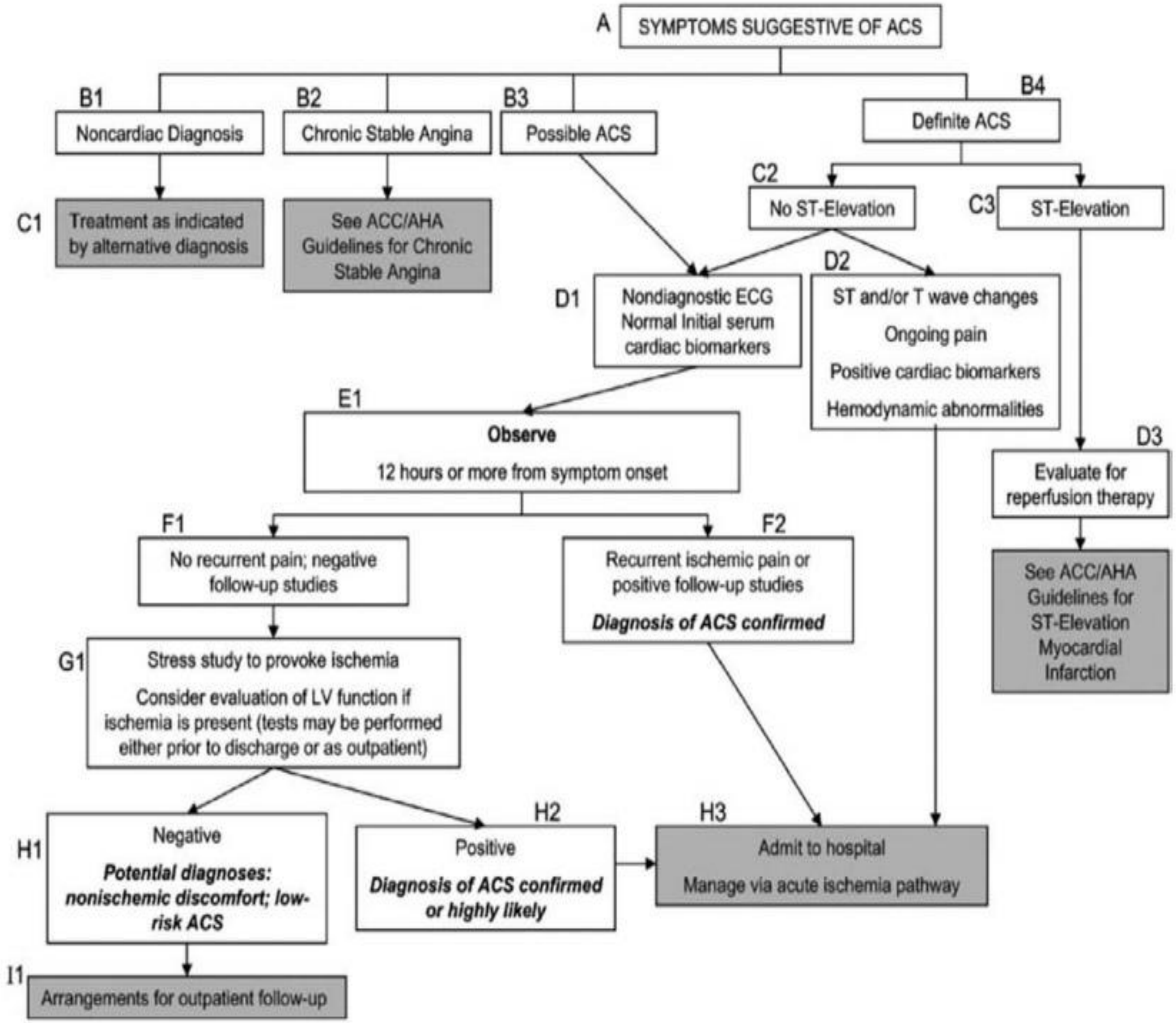


Figure 2. Algorithm for Evaluation and Management of Patients Suspected of Having ACS. To facilitate interpretation of this algorithm and a more detailed discussion in the text, each box is assigned a letter code that reflects its level in the algorithm and a number that is allocated from left to right across the diagram on a given level. ACC/AHA = American College of Cardiology/American Heart Association; ACS = acute coronary syndrome; ECG = electrocardiogram; LV = left ventricular.

TEDAVİ

Class

- Class I: Kesin yararlı
  (definetely helpful)
- Class IIa: Kabul edilebilir, büyük olasılıkla yararlı
  (acceptable, probably helpful)
- Class IIb: Kabul edilebilir, muhtemelen yararlı
  (acceptable, possibly helpful)
- Class III: Endike değil, zararlı olabilir
  (not indicated, may be harmful)

UAP ve NSTEMI

Class I Öneriler

Class I

- Oksijen saturasyonu %90'nın altında olan, solunum sıkıntısı olan tüm hastalara oksijen verilmesi
- Devam eden göğüs ağrısı olan hastalara beş dakika aralarla üç doz sublingual nitrogliserin (0.4 mg)
- Devam eden iskemi, kalp yetmezliği ve hipertansiyon varlığında IV ntg.

Class I

- İlk 24 saatte oral beta-blokör başlanır
- Beta blokör kontrendikasyonları:
  - Kalp yetmezliği bulguları
  - Düşük output bulguları
  - Kardiyojenik şok açısından artmış risk
  - Göreceli kontrendikasyonlar
    - PR interval 0.24 sn'den daha uzun olması
    - İki ve üçüncü derece AV blok
    - Aktif astma, reaktif havayolu hastalığı

Class IIa

Class IIa

- İlk altı saatte tüm hastalara oksijen başlamak
- NTG ile kontrol altına alınamayan hastalara morfin sülfat verilmesi
- Kontrendikasyonu yoksa başvuru sırasında hipertansiyon olan hastalara IV Beta-blokör verilmesi

Class III

- NSAID ilaç kullanımı
- Son 24 saatte sindenafil, son 48 saatte tadalafil alanlarda NTG kullanımı
  - RV MI dikkat !
  - Hipotansiyon dikkat !
  - Sistolik kan basıncı <90 mmHg
  - Bazal kan basıncında ≥30 mmHg
  - Kalp hızı <50 veya >100 atım/dk

UAP/NSTEMI'da Antiagregan ve Antikoagülan Tedavi

Class I

- Aspirin
  - 162-325 mg çiğneterek
- Aspirin allerjisi yada GIS intoleransı durumunda clopidogrel , prasugrel yada ticagrelor
- Erken invaziv tedavi yapılacak acil serviste ikinci anti-agregan
  - Klopidogrel, ticagrelor, GP IIb/IIIa inh

Class I (Anti-koagülan Tedavi)

- Erken invaziv tedavi tercih edilen hastalarda enoxiparin, UFH, bivaluridin veya fondaparinux
- Konservatif tedavi tercih edilenlerde enoxiparin, UFH veya fondaparinux
  - Kanama riski varsa fondaparinux.
  - İlk tercih enoxiparin yada fondaparinux Class IIa öneri

STEMI

Reperfüzyon için amaçlanan zaman

- Fibrinolitik ajan: door-to needle < 30 dk
- Primer PCI: EMS to balon zamanı < 90 dk

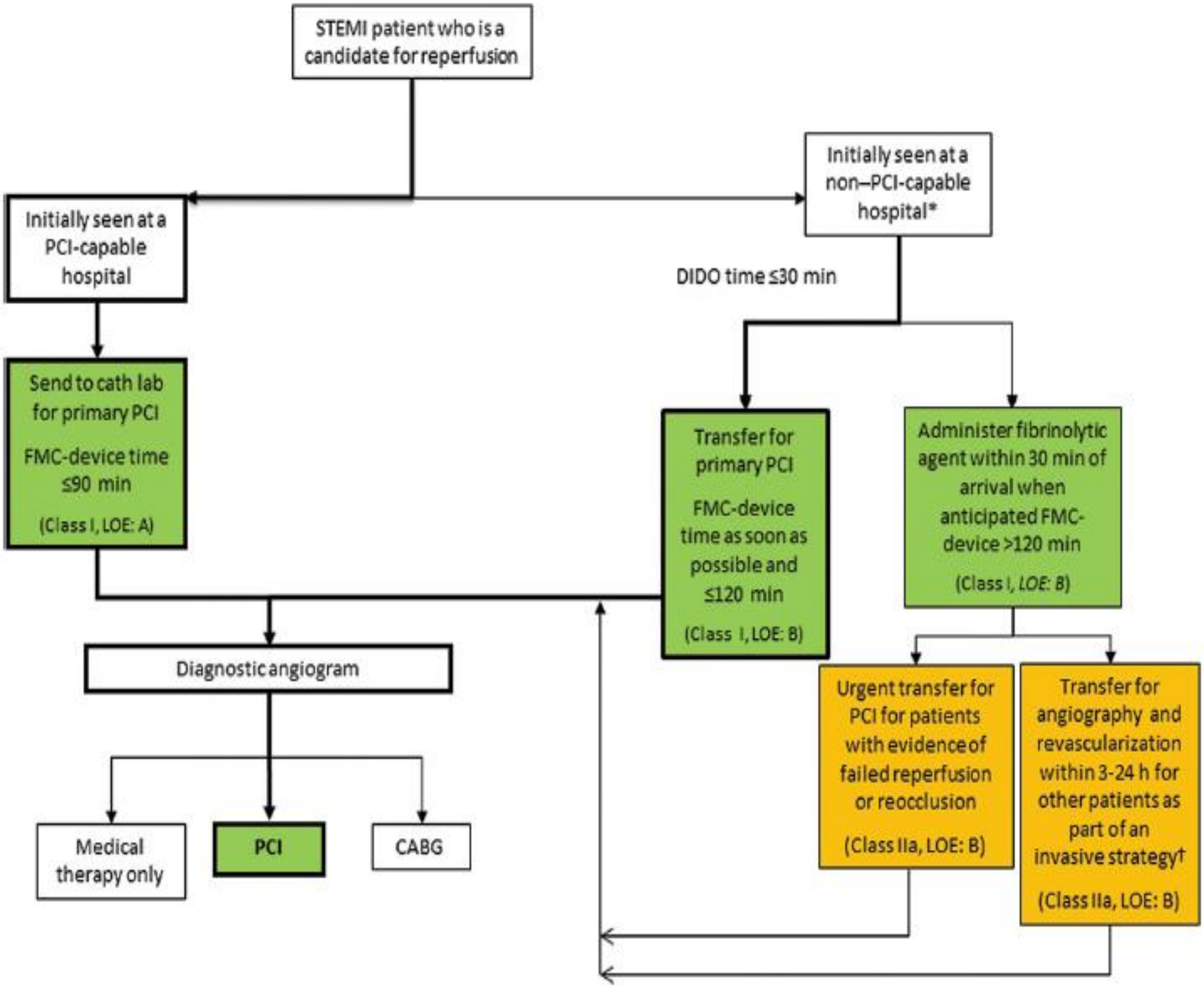

STEMI patient who is a candidate for reperfusion
Initially seen at a PCI-capable hospital
Initially seen at a non–PCI-capable hospital*
DIDO time ≤30 min
Send to cath lab for primary PCI
FMC-device time ≤90 min
(Class I, LOE: A)
Transfer for primary PCI
FMC-device time as soon as possible and ≤120 min
(Class I, LOE: B)
Administer fibrinolytic agent within 30 min of arrival when anticipated FMC-device >120 min
(Class I, LOE: B)
Diagnostic angiogram
Urgent transfer for PCI for patients with evidence of failed reperfusion or reocclusion
(Class IIa, LOE: B)
Transfer for angiography and revascularization within 3-24 h for other patients as part of an invasive strategy†
(Class IIa, LOE: B)
Medical therapy only
PCI
CABG

Table 2. Primary PCI in STEMI

	COR	LOE	References
Ischemic symptoms <12 h	I	A	82, 208, 209
Ischemic symptoms <12 h and contraindications to fibrinolytic therapy irrespective of time delay from FMC	I	B	210, 211
Cardiogenic shock or acute severe HF irrespective of time delay from MI onset	I	B	212–215
Evidence of ongoing ischemia 12 to 24 h after symptom onset	IIa	B	94, 95
PCI of a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise	III: Harm	B	216–218

COR indicates Class of Recommendation; FMC, first medical contact; HF, heart failure; LOE, Level of Evidence; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Table 3. Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg load before procedure	I	B
• 81- to 325-mg daily maintenance dose (indefinite)*	I	A
• 81 mg daily is the preferred maintenance dose*	IIa	B
$P2Y_{12}$ inhibitors		
Loading doses		
• Clopidogrel: 600 mg as early as possible or at time of PCI	I	B
• Prasugrel: 60 mg as early as possible or at time of PCI	I	B
• Ticagrelor: 180 mg as early as possible or at time of PCI	I	B
Anticoagulant therapy		
• UFH: • With GP IIb/IIIa receptor antagonist planned: 50- to 70-U/kg IV bolus to achieve therapeutic ACT‡	I	C
• With no GP IIb/IIIa receptor antagonist planned: 70- to 100-U/kg bolus to achieve therapeutic ACT§	I	C
• Bivalirudin: 0.75-mg/kg IV bolus, then 1.75-mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg can be given if needed. • Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min	I	B
• Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding	IIa	B
• Fondaparinux: Not recommended as sole anticoagulant for primary PCI	III: Harm	B

Table 4. Indications for Fibrinolytic Therapy When There Is a >120-Minute Delay From FMC to Primary PCI (Figure 2)

	COR	LOE	References
Ischemic symptoms <12 h	I	A	81, 306–311
Evidence of ongoing ischemia 12 to 24 h after symptom onset, and a large area of myocardium at risk or hemodynamic instability	IIa	C	N/A
ST depression except if true posterior (inferobasal) MI suspected or when associated with ST-elevation in lead aVR	III: Harm	B	10, 11, 81, 312, 313

Table 5. Fibrinolytic Agents

Fibrinolytic Agent	Dose	Fibrin Specificity*	Antigenic	Patency Rate (90-min TIMI 2 or 3 flow)
Fibrin-specific:				
Tenecteplase (TNK-tPA)	Single IV weight-based bolus†	++++	No	85%[328]
Reteplase (rPA)	10 U + 10-U IV boluses given 30 min apart	++	No	84%[314]
Alteplase (tPA)	90-min weight-based infusion‡	++	No	73% to 84%[314, 324, 326]
Non–fibrin-specific:				
Streptokinase§	1.5 million units IV given over 30–60 min	No	Yes‖	60% to 68%[324, 329]

Table 7. Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg loading dose	I	A
• 81- to 325-mg daily maintenance dose (indefinite)	I	A
• 81 mg daily is the preferred maintenance dose	IIa	B
$P2Y_{12}$ receptor inhibitors		
• Clopidogrel:	I	A
• Age ≤75 y: 300-mg loading dose		
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d) C (up to 1 y)
• Age >75 y: no loading dose, give 75 mg	I	A
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d) C (up to 1 y)
Anticoagulant therapy		
• UFH:	I	C
• Weight-based IV bolus and infusion adjusted to obtain aPTT of 1.5 to 2.0 times control for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48 h or until revascularization.		
• Enoxaparin:	I	A
• If age <75 y: 30-mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12 h (maximum 100 mg for the first 2 doses)		
• If age ≥75 y: no bolus, 0.75 mg/kg subcutaneously every 12 h (maximum 75 mg for the first 2 doses)		
• Regardless of age, if CrCl <30 mL/min: 1 mg/kg subcutaneously every 24 h		
• Duration: For the index hospitalization, up to 8 d or until revascularization		
• Fondaparinux:	I	B
• Initial dose 2.5 mg IV, then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 d or until revascularization		
• Contraindicated if CrCl <30 mL/min		

Percutaneous Coronary Intervention

- Hasta mortalite veya LV disfonksiyonu yönünden yüksek riskli ise
  - Şok
  - Hipotansiyon, taşikardi
  - Pulmoner konjesyon

PCI = Class I

Heparin

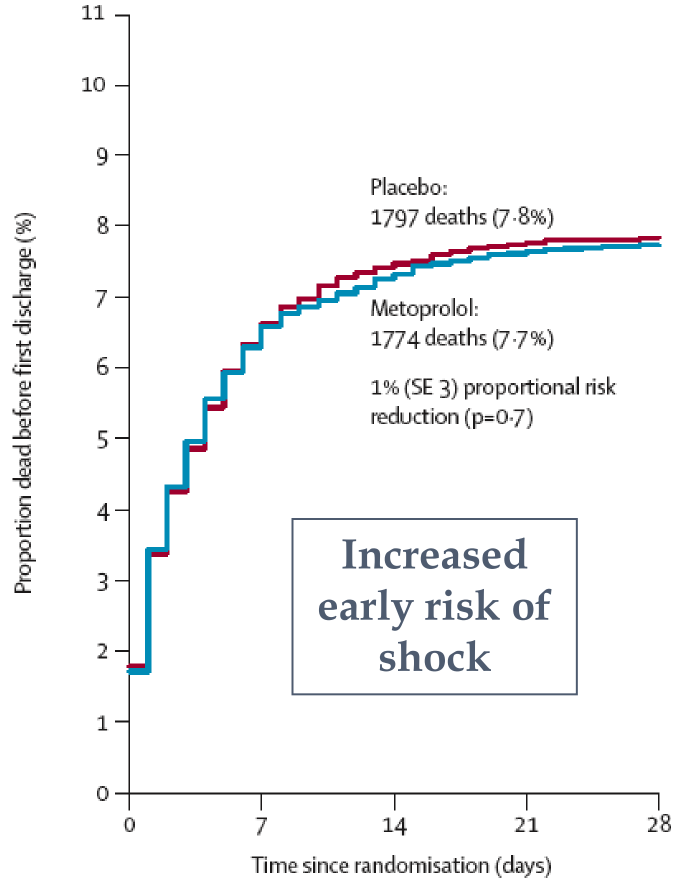
- 60 Ü/kg bolus, 12 Ü/kg/saat infüzyon (> 70 kg hasta için Max 4000 bolus, 1000 Ü saat)
- aPTT 50-70 saniye

Enoksiparin

- 1 mg/kg sc, 12 saatte bir
- GFR <30 mL/dk ise günde bir kez

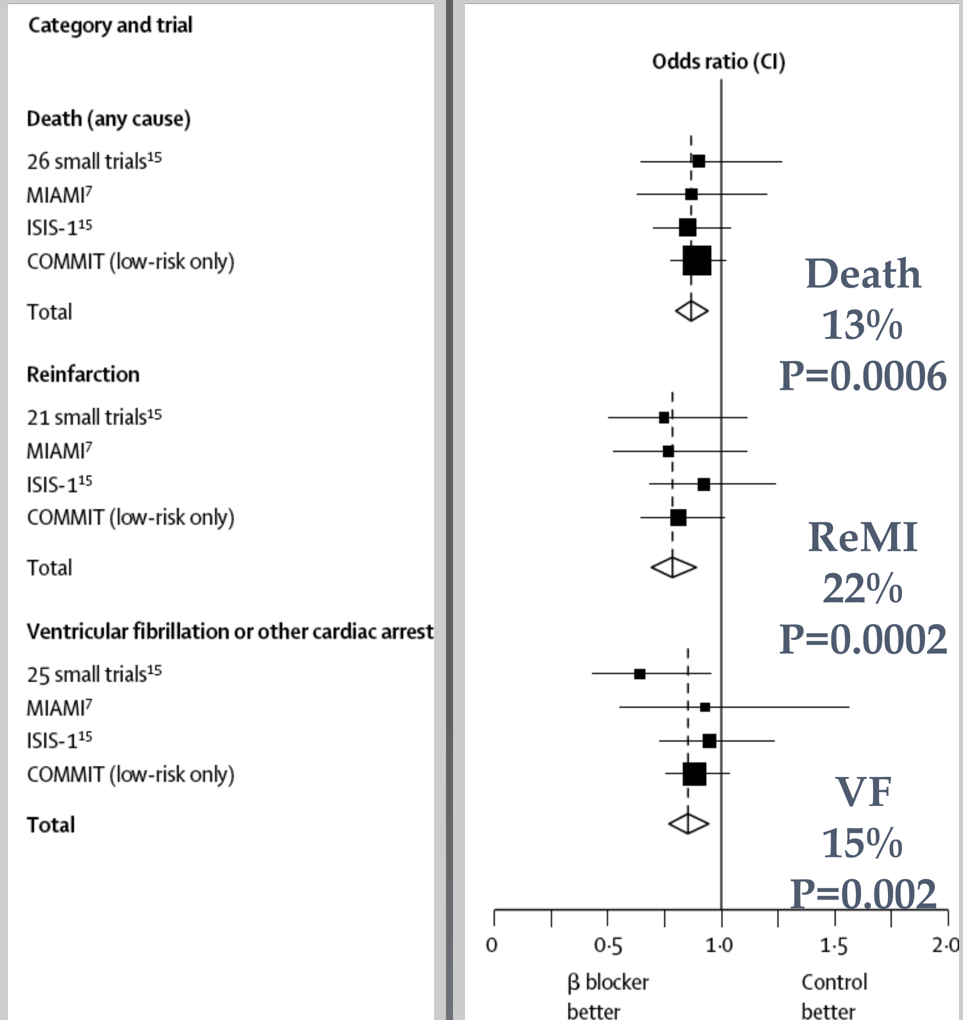
Metoprololün Etkileri

COMMIT (N = 45,852)



Days	0–6	7–13	14–20	21–28
Number of events				
Metoprolol	1441	220	83	30
Placebo	1449	249	75	24

Totality of Evidence (N = 52,411)



Risk factors for cardiogenic shock :heart failure, age > 70 , systolic blood pressure < 120, sinus tachycardia > 110 or heart rate < 60, increased time since onset of STEMI symptoms

Lancet. 2005;366:1622.

Fatty Acid Binding Protein

Heart-type fatty acid binding protein as an early marker for myocardial infarction: systematic review and meta-analysis

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ABSTRACT

Background Heart-type fatty acid binding protein (H-FABP) has been proposed as an early biomarker of myocardial infarction (MI). The authors aimed to undertake a systematic review and meta-analysis to estimate the early sensitivity and specificity of quantitative and qualitative H-FABP assays.

Methods The authors undertook a systematic search using electronic databases, citation lists and expert contacts to identify all diagnostic cohort studies of patients presenting with suspected acute coronary syndrome that compared H-FABP at presentation to a reference standard based on the Universal definition of MI. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool. Meta-analysis was conducted using Bayesian Markov chain Monte Carlo simulation.

Results The authors included eight studies of

developing alternative or additional early markers of myocardial necrosis.

Heart-type fatty acid binding protein (H-FABP) is a relatively small (15 kDa) protein found in the cytoplasm, which because of its small molecular size would be released very early in myocardial ischaemia or infarction. The pharmacokinetic properties of H-FABP that involve early release and detectability in the peripheral circulation have led to interest in its use as an early diagnostic tool for MI. It has been developed as a quantitative and qualitative assay and evaluated in a substantial number of diagnostic cohort studies. Our objective in this meta-analysis was to estimate the diagnostic accuracy of H-FABP for MI when used at patient presentation to hospital.

METHODS

Taranan Veri Tabanları

- MEDLINE (1950), MEDLINE In-Process & Other Non-Indexed Citations (1950),
- Cumulative Index of Nursing and Allied Health Literature (CINAHL) (1981),
- EMBASE (1980),
- Web of Science (WoS) (includes Science Citation Index and Conference Proceedings Citation Index) (1899),
- Cochrane Central Database of Controlled Trials (CENTRAL),
- Cochrane Database of Systematic Reviews (CDSR),
- NHS Database of Abstracts of Reviews of Effectiveness (DARE) and the Health Technology Assessment (HTA) database.

- Anahtar Kelimeler
    - Göğüs ağrısı
    - Akut Koroner Sendrom
    - Myocardial Infarction
    - H-FABP
- Altın standard troponin olarak kabul edilmiş.

Dahil Edilme Kriterleri

1. Design: diagnostic cohort study
2. Population: adults presenting with suspected ACS. Studies were excluded if patients were selected on the basis of having a clinical diagnosis of ACS (rather than a clinical suspicion of ACS) or positive diagnostic test for ACS, such as ST deviation on the ECG or an elevated biomarker. Studies of patients selected on the basis of a negative diagnostic test were included (eg, studies that excluded patients with ST-elevation MI).
3. Index test: H-FABP
4. Reference standard test: acute MI defined according to the universal definition[2] using troponin I or T measurement for a minimum of 80% of the population at least 6 h after symptom onset.

Dahil Edilen Çalışmalar

Table 1 Population characteristics of studies of heart-type fatty acid-binding protein

Study	Study type	Population: age (mean in years, unless stated); number (%) Male	Inclusion criteria	Exclusion criteria*	Time from symptoms (hours)	Number of patients
Body 2011[12]	Single-centre, UK	59; 430 (61%) Male	Suspected cardiac chest pain within 24 h	Chest trauma, renal failure, hospital admission, pregnancy	3.5 (Median)	705
Cete 2010[13]	Single centre, Turkey	57; 163 (73%) Male	Age >18 years with typical chest pain	Atypical chest pain, trauma, electrical cardioversion, musculoskeletal disease, renal failure, liver disease	Not reported	224
Charpentier 2010[14]	Single-centre, France	57; 454 (67%) Male	Chest pain due to suspected ACS within 12 h	ST elevation, traumatic cause, renal impairment	2.9 (Median)	677
Di Serio 2005[15]	Single centre, Italy	79 (women), 65 (men); 23 (77%) Male	Not specified	ST elevation	3.4 (Mean)	30
Ecollan 2007[16]	Mobile units, France	68; 68 (63%) Male	Consecutive emergencies with chest pain	Cardiogenic shock, recent chest trauma	2.3 (Median)	108
Garcia-Valdecasas 2011[17]	Single-centre, France	67; 114 (69%) Male	Chest pain >20 min duration within 6 h	Chest trauma	Not reported	165
Haltern 2010[18]	Single-centre, Germany	69; 27 (55%) Male	Ischaemic-type chest pain	Interhospital transfer	4 (Median)	94
Hjortshoj 2010[19]	Single centre, UK	61 (Median); 70 (65%) Male	Chest pain and suspected of ACS	None reported	Not reported	107
Ilva 2009[20]	Single-centre, Finland	67; 181 (62%) Male	Chest pain suggesting MI	Uncertain or >24 h delay from symptom onset	4.7 (Median)	293
Lefevre 2007[21]	Multi-centre, France	61; 71 (71%) Male	Not specified	None reported	5.9 (Median)	75
Li 2010[22]	Multi-centre, China	64; 163 (72%) Male	Chest pain more than 30 min within 12 h suspected of AMI	None reported	4 (Median)	227
Liao, 2009[23]	Single centre, China	69; 54 (73%) Male	Acute chest pain and/or dyspnoea lasting >20 min within the last 3 h	None reported	2.2 (Median)	74
Mad 2007[24]	Single centre, Austria	58; 213 (76%) Male	Onset of acute chest pain and/or dyspnoea lasting >20 min within the last 24 h	None reported	3 (Median)	280
McCann 2008[25]	Multi centre, Northern Ireland	63; 281 (68%) Male	Ischaemic type chest pain within 24 h	Interhospital transfer	5.3 (Median)	415
Mion 2007[26]	Single centre, Italy	63; 88 (67%) Males	Non-consecutive patients with chest pain	None reported	3.8 (Median)	132
Naroo 2009[27]	Single centre, UAE	Age not reported, 627 (79%) male	Onset of typical cardiac pain 20 min to 12 h	ST elevation MI, renal disease	Not reported	791
Valle 2007[28]	Multi-centre, Spain	65; 287 (68%) Male	Suspected ACS with symptoms between 20 min and 180 min of presentation	None reported	1.2 (Mean)	419

Bulgular

- Çalışmalarda ki MI prevalansı %15 lie %73 arasında saptanmış.
- Semptom başlangıcı ve örneğin alınması arasında geçen süre 1.2 (ortalama) lie 5.9 (ortanca) saat arasında.

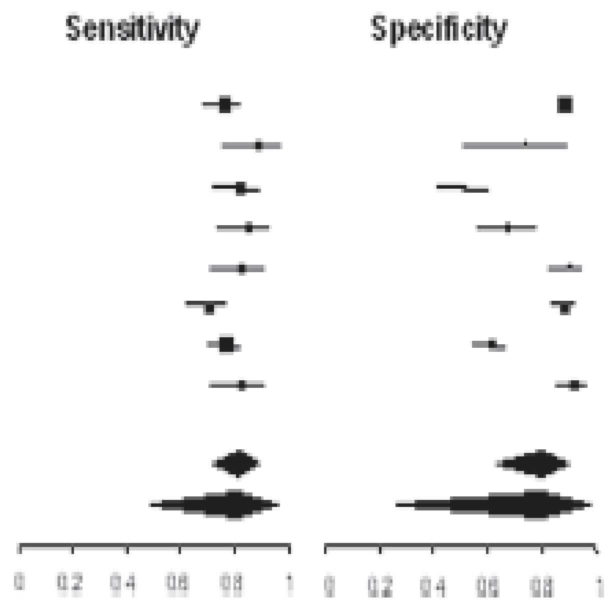
Çalışma Kaliteleri

	Representative spectrum?	Acceptable reference standard?	Acceptable delay between tests?	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Reference standard results blinded?	Index test results blinded?
Body 2011 a[12]	+	+	+	+	+	+	−	+
Cete 2010[13]	+	+	+	+	+	+	?	?
Charpentier 2010[14]	+	+	+	+	+	+	+	+
Di Serio 2005[15]	?	?	+	?	+	+	?	?
Ecollan 2007[16]	+	+	+	+	+	+	?	?
Garcia-Valdecasas 2011[17]	+	+	?	+	+	+	+	+
Haltern 2010[18]	+	+	+	+	+	+	?	?
Hjortshoj 2010[19]	+	+	+	+	+	+	?	?
Ilva 2009[20]	+	+	+	+	+	+	?	?
LeFevre 2007[21]	?	?	+	+	+	+	+	+
Li 2010[22]	+	+	+	+	+	+	+	+
Liao 2009[23]	+	?	?	+	+	?	−	−
Mad 2007[24]	+	?	?	+	+	?	+	+
McCann 2008[25]	+	+	+	+	+	?	+	+
Mion 2007[26]	−	+	+	+	?	+	?	?
Naroo 2009[27]	+	+	+	+	+	+	+	+
Valle 2007[28]	+	?	+	+	+	+	+	?

Figure 1 Quality assessment of diagnostic studies of heart-type fatty acid-binding protein. A green+ circle indicates a positive answer to the criterion listed, red— indicates negative and yellow? indicates unclear.

Kantitatif FABP Çalışmalarının Meta-Analizi

Study	TP	FP	FN	TN	Sensitivity	Specificity
Body 2011a[12]	97	63	32	513	0.76 (0.68, 0.82)	0.89 (0.86, 0.91)
Di Serio 2005[15]	16	4	0	10	0.89 (0.76, 0.97)	0.74 (0.51, 0.90)
Garcia-Valdecasas 2011[17]	53	50	12	50	0.82 (0.72, 0.89)	0.52 (0.42, 0.61)
Haltern, 2010[18]	27	21	4	42	0.85 (0.73, 0.93)	0.68 (0.56, 0.78)
Hjortshoj 2010[19]	31	6	6	64	0.82 (0.71, 0.91)	0.90 (0.82, 0.96)
Ilva 2009[20]	84	19	39	151	0.70 (0.62, 0.77)	0.89 (0.83, 0.93)
McCann 2008[25]	150	85	48	132	0.76 (0.70, 0.82)	0.62 (0.55, 0.68)
Mion 2007[26]	35	6	7	84	0.82 (0.71, 0.91)	0.92 (0.86, 0.96)
Pooled effect					**0.81 (0.72, 0.89)**	**0.80 (0.64, 0.90)**
Predictive effect					**0.81 (0.50, 0.95)**	**0.80 (0.26, 0.98)**



Kalitatif FABP Çalışmalarının Meta-Analizi

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cete 2010[13]	30	0	43	151	0.41 (0.30, 0.53)	0.99 (0.98, 1.00)
Charpentier 2010[14]	21	20	78	558	0.23 (0.15, 0.32)	0.97 (0.95, 0.98)
Ecollan 2007[16]	48	3	7	50	0.86 (0.75, 0.93)	0.94 (0.86, 0.98)
LeFevre 2007[21]	19	5	17	34	0.55 (0.39, 0.70)	0.89 (0.77, 0.96)
Li 2010[22]	106	10	8	103	0.92 (0.86, 0.96)	0.91 (0.85, 0.95)
Liao 2009[23]	45	14	9	6	0.84 (0.73, 0.92)	0.36 (0.17, 0.58)
Mad 2007[24]	34	12	18	43	0.66 (0.53, 0.78)	0.80 (0.68, 0.88)
Naroo 2009[27]	75	21	24	671	0.75 (0.66, 0.83)	0.97 (0.95, 0.98)
Valle 2007[28]	89	33	59	238	0.61 (0.53, 0.68)	0.88 (0.84, 0.92)
Pooled effect					**0.68 (0.46, 0.84)**	**0.92 (0.77, 0.98)**
Predictive effect					**0.68 (0.11, 0.97)**	**0.92 (0.20, 1.00)**

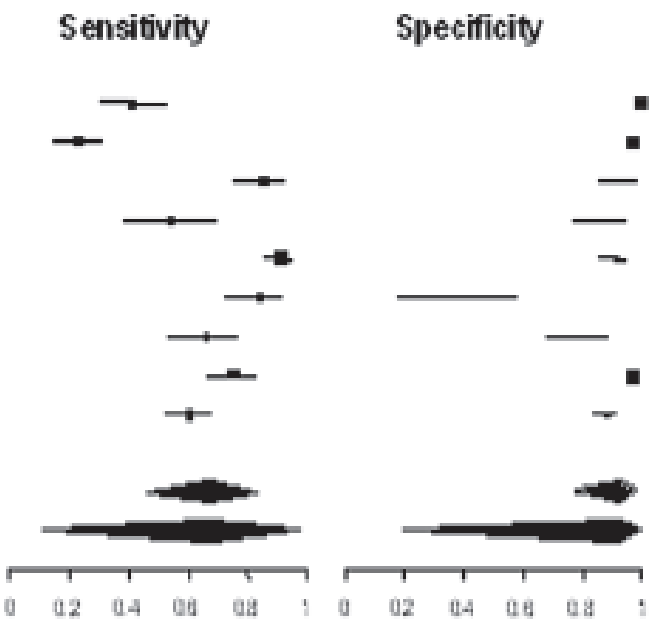


Table 3 Sensitivity and specificity of combinations of biomarkers with troponin versus troponin alone

		Troponin alone		Combination	
Study	Combination	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Body 2011[12]	TnI or H-FABP	0.42 (0.33 to 0.51)	0.96 (0.94 to 0.97)	0.82 (0.74 to 0.88)	0.88 (0.83 to 0.88)
Haltem 2010[18]	TnT or H-FABP	0.74 (0.66 to 0.74)	1.0 (0.96 to 1.0)	0.97 (0.86 to 0.99)	0.65 (0.6 to 0.66)
McCann 2008[25]	TnT or H-FABP	0.75 (0.69 to 0.81)	0.94 (0.9 to 0.96)	0.93 (0.89 to 0.96)	0.93 (0.89 to 0.96)
Mion 2007[26]	TnI or H-FABP	0.55 (0.39 to 0.7)	0.98 (0.92 to 1.0)	0.76 (0.6 to 0.87)	0.93 (0.86 to 0.97)

Tn I, troponin I; H-FABP, heart-type fatty acid-binding protein.

ORIGINAL ARTICLE

Heart-type fatty acid-binding protein in the early diagnosis of acute myocardial infarction

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▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2012-303325).

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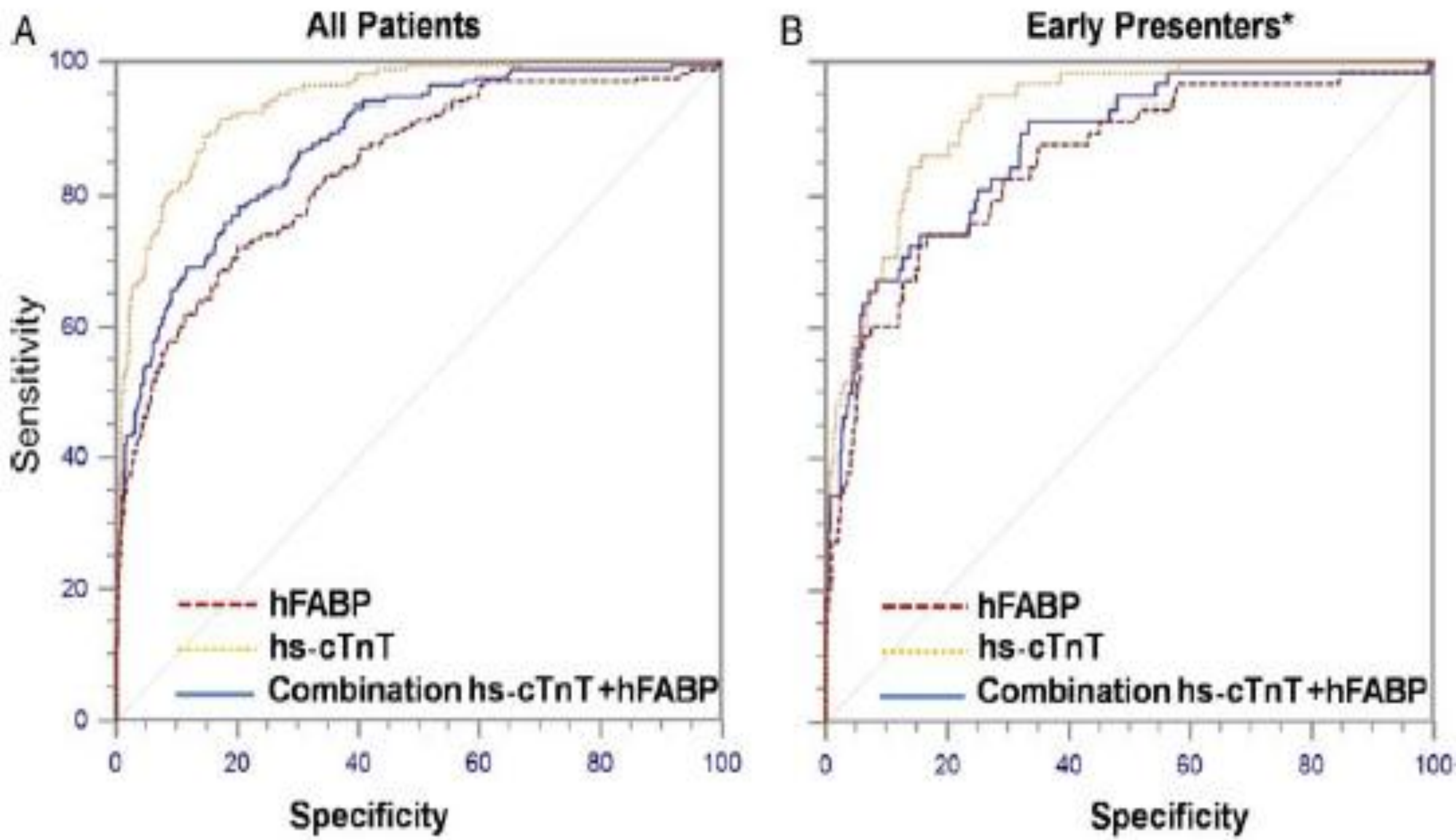
ABSTRACT

Objective To investigate the diagnostic and prognostic role of heart-type fatty acid-binding protein (hFABP) compared with copeptin and in addition to high-sensitivity cardiac troponin T (hs-cTnT) in patients with chest pain suspected of acute myocardial infarction (AMI).

assessment.[2 3] But particularly in patients without ST-segment elevation in the ECG, diagnosis of non-ST-elevation myocardial infarction (non-STEMI) often requires serial blood sampling and causes prolonged time spent in the emergency department (ED), increasing patients' uncertainty and anxiety, and costs for the healthcare system.[4 5] Furthermore,

- Dahil Etme Kriterleri:
  - Son 12 saatte AMI düşündüren göğüs ağrısı nedeniyle başvuran hastalar
- Dışlama Kriterleri:
  - Böbrek yetmezliği
  - STEMI



*Patients presenting within three hours from chest pain onset

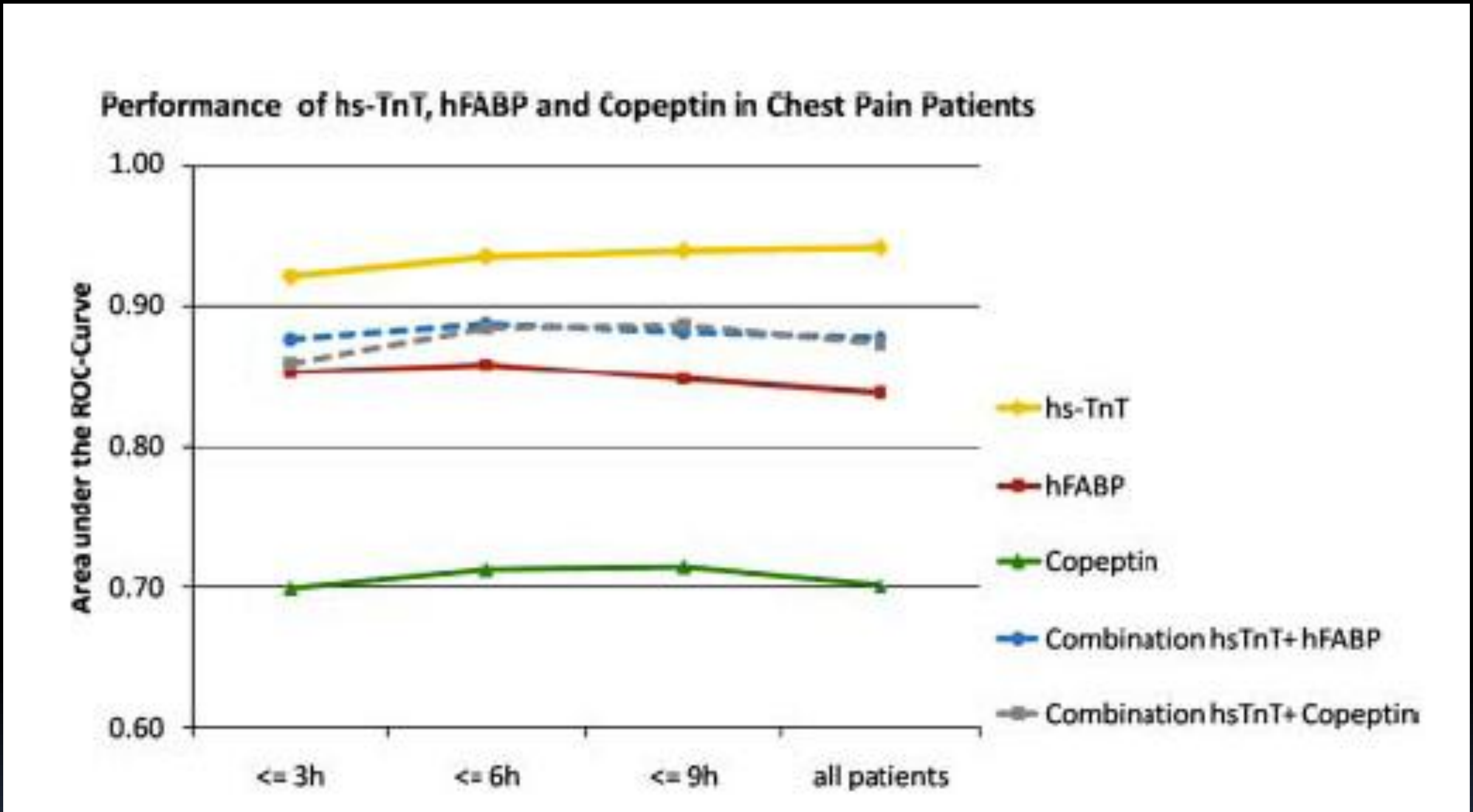

Performance of hs-TnT, hFABP and Copeptin in Chest Pain Patients
Area under the ROC-Curve
1.00
0.90
0.80
0.70
0.60
<= 3h
<= 6h
<= 9h
all patients
hs-TnT
hFABP
Copeptin
Combination hsTnT+ hFABP
Combination hsTnT+ Copeptin

Table 2 Diagnostic performance of hFABP and cardiac troponin (95% CI)

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Negative predictive value, % (95% CI)	Positive predictive value, % (95% CI)
Heart type, FABP ROC-derived optimal cut-off (4.2 ng/ml)	72 (65 to 89)	80 (77 to 82)	94 (92 to 95)	41 (35 to 47)
Heart type, FABP median (2.7 ng/ml)	87 (81 to 92)	59 (56 to 63)	96 (94 to 98)	29 (25 to 33)
Roche high-sensitive troponin T 99th percentile (0.014 μg/l)	93 (88 to 96)	77 (74 to 80)	98 (97 to 99)	42 (37 to 47)
Roche high-sensitive troponin T ≥0.014 μg/l + heart type, FABP ≥4.2 ng/ml	70 (63 to 77)	89 (86 to 91)	94 (92 to 96)	55 (48 to 61)
Roche High-Sensitive troponin T ≥0.014 μg/l + heart type, FABP ≥2.7 ng/ml	83 (77 to 88)	83 (80 to 85)	96 (95 to 97)	48 (42 to 54)

hFABP, heart-type fatty acid-binding protein; ROC, receiver operating characteristic.

Yüksek Duyarlılıklı Troponin ile Ortaya Çıkan Problem

- Standart troponin kitin referans aralığı 10-100 pg/ml (ng/L)
- HsTn kitin referans aralığı 0-14 pg/ml (ng/L)

1. 14-100 pg/ml aralığında kalan hastaların tanısı nedir?
2. Gereksiz yatış ve acilde kalış?

Yüksek Duyarlılıklı Troponin Pratikte Nasıl Kullanılabilir?

1. Erken dışlama?
2. İlk altı saatte HsTn düzeylerinde meydana minör artışlar AKS tanısı koydurabilir mi?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sensitive Troponin I Assay in Early Diagnosis of Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

Cardiac troponin testing is central to the diagnosis of acute myocardial infarction. We evaluated a sensitive troponin I assay for the early diagnosis and risk stratification of myocardial infarction.

cine II
C.R.S.,
Z., F.P.,
Clinical

Metod

- Çok merkezli çalışma
- Yeni başlangıçlı göğüs ağrısı ile başvuran 1818 hasta ardışık olarak çalışmaya alınmış.
- MI tanısı enzim, EKG, klinik ve anjiografi, EKO sonuçlarına göre bağımsız iki kardiyolog tarafından konulmuş.
- 0.04 ng/ml üst sınır olarak kabul edilmiş, ayrıca ilk altı saatteki %30'luk artış yada düşüş anlamlı kabul edilmiş.

Table 1. Baseline Characteristics of the Patients, According to the Final Diagnosis.*

Variable	Noncoronary Chest Pain†	Unstable Angina Pectoris	Acute Myocardial Infarction‡	All Patients
Patients — no. (%)	1165 (64.1)	240 (13.2)	413 (22.7)	1818 (100)
Age — yr	59.7±14.3	65.2±10.6	64.0±11.8	61.4±13.5
Male sex — no./total no. (%)	729/1165 (62.6)	165/240 (68.8)	314/413 (76.0)	1208/1818 (66.4)

Table 2. Discriminatory Value of Biomarkers for the Diagnosis of Acute Myocardial Infarction.*

Variable	Sensitive Troponin I Assay*	Troponin T, Standard Assay†		Myoglobin‡	Myoglobin or Troponin T	
		99th Percentile	10% CV		99th Percentile	10% CV
	value (95% confidence interval)					
Presentation <3 hr after chest-pain onset						
Sensitivity	84.0 (77.5–89.3)	55.2 (47.2–62.9)	43.6 (35.9–51.6)	61.9 (52.5–70.6)	79.6 (72.2–85.8)	77.6 (69.9–84.2)
Specificity	93.2 (90.4–95.3)	95.7 (93.4–97.4)	98.0 (96.2–99.1)	88.0 (84.1–91.3)	83.5 (79.2–87.2)	86.2 (82.1–89.6)
Positive predictive value	82.0 (75.4–87.5)	82.7 (74.3–89.3)	88.9 (80.0–94.8)	64.0 (54.5–72.8)	66.9 (59.4–73.8)	69.8 (62.0–76.8)
Negative predictive value	94.0 (91.3–96.0)	85.2 (81.7–88.2)	82.4 (78.9–85.5)	87.0 (83.0–90.4)	90.7 (87.0–93.6)	90.3 (86.6–93.3)
Presentation <6 hr after chest-pain onset						
Sensitivity	86.8 (81.7–90.8)	62.1 (55.6–68.4)	50.6 (44.1–57.2)	62.4 (54.6–69.7)	83.8 (78.2–88.4)	80.0 (73.9–85.2)
Specificity	92.2 (90.0–94.1)	94.9 (93.0–96.4)	97.8 (96.4–98.8)	86.9 (83.7–89.6)	82.0 (78.6–85.2)	84.8 (81.5–87.7)
Positive predictive value	79.3 (73.8–84.1)	80.7 (74.1–86.1)	88.8 (82.2–93.6)	59.9 (52.3–67.2)	64.6 (58.7–70.2)	66.9 (60.7–72.7)
Negative predictive value	95.3 (93.4–96.8)	88.0 (85.5–90.3)	85.3 (82.7–87.7)	88.0 (84.9–90.6)	92.8 (90.1–94.9)	91.7 (88.9–93.9)
Presentation <12 hr after chest-pain onset						
Sensitivity	88.1 (83.7–91.6)	64.1 (58.3–69.7)	54.0 (48.1–59.9)	61.2 (54.1–67.9)	83.4 (78.4–87.7)	80.3 (74.9–85.0)
Specificity	92.1 (90.1–93.8)	95.4 (93.8–96.7)	97.9 (96.8–98.8)	86.9 (84.1–89.3)	82.6 (79.6–85.3)	85.0 (82.2–87.6)
Positive predictive value	78.7 (73.8–83.0)	82.1 (76.5–86.9)	89.6 (84.1–93.7)	58.3 (51.5–65.0)	64.4 (59.1–69.5)	66.7 (61.1–71.9)
Negative predictive value	95.9 (94.3–97.1)	89.0 (86.8–90.9)	86.6 (84.3–88.7)	88.2 (85.5–90.5)	92.9 (90.6–94.8)	92.1 (89.7–94.0)
All patients						
Sensitivity	90.7 (87.4–93.3)	72.7 (68.1–76.9)	63.7 (58.8–68.3)	61.3 (55.6–66.9)	87.1 (83.3–90.3)	84.1 (80.0–87.7)
Specificity	90.2 (88.3–91.9)	94.1 (92.6–95.4)	97.2 (96.0–98.0)	86.9 (84.6–89.0)	81.9 (79.3–84.4)	84.6 (82.1–86.9)
Positive predictive value	76.7 (72.7–80.4)	81.4 (77.1–85.3)	88.8 (84.6–92.1)	60.5 (54.8–66.1)	66.6 (62.3–70.7)	69.0 (64.5–73.2)
Negative predictive value	96.4 (95.2–97.5)	90.7 (88.9–92.3)	88.3 (86.4–90.0)	87.3 (85.0–89.4)	93.9 (92.0–95.4)	92.9 (91.0–94.5)

* A cutoff value of 0.04 ng per milliliter for the sensitive troponin I assay was determined to be the 99th percentile on the basis of analysis of samples obtained from 5000 subjects in the Gutenberg Heart Study. The 10% coefficient of variation (CV) was lower than the 99th percentile, so only the 99th percentile is presented.

† A troponin T level of 0.01 ng per milliliter represents the 99th percentile in the reference population. A troponin T level of 0.03 ng per milliliter represents the 10% coefficient of variation.

‡ The cutoff value for myoglobin was 107 ng per milliliter.

Table 3. Correct Diagnosis of Acute Myocardial Infarction, According to the Time of a Single Sensitive Troponin I Assay.*

Time of Testing	Detection of Myocardial Infarction
	% of patients
On admission	
0 to <6 hr after chest-pain onset	87.7
6 to 12 hr after chest-pain onset	94.5
>12 hr after chest-pain onset	100
After admission	
At 3 hr	100
At 6 hr	100

* The diagnostic criteria for acute myocardial infarction were a troponin I level (as measured by sensitive assay) above the 99th percentile of 0.04 ng per milliliter in at least one measurement and a rise or fall in the level of at least 30%.

Serial Changes in Highly Sensitive Troponin I Assay and Early Diagnosis of Myocardial Infarction

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Ascan Warnholtz, MD
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Stefan Blankenberg, MD

Context Introduction of highly sensitive troponin assays into clinical practice has substantially improved the evaluation of patients with chest pain.

Objective To evaluate the diagnostic performance of a highly sensitive troponin I (hsTnI) assay compared with a contemporary troponin I (cTnI) assay and their serial changes in the diagnosis of acute myocardial infarction (AMI).

Design, Setting, and Patients A total of 1818 patients with suspected acute coronary syndrome were consecutively enrolled at the chest pain units of the University Heart Center Hamburg, the University Medical Center Mainz, and the Federal Armed Forces Hospital Koblenz, all in Germany, from 2007 to 2008. Twelve biomarkers including hsTnI (level of detection, 3.4 pg/mL) and cTnI (level of detection, 10 pg/mL) were measured on admission and after 3 and 6 hours.

Main Outcome Measures Diagnostic performance for AMI of baseline and serial changes in hsTnI and cTnI results at 3 hours after admission to the emergency department.

Results Of the 1818 patients, 413 (22.7%) were diagnosed as having AMI. For discrimination of AMI, the area under the receiver operating characteristic (ROC) curve was 0.96 (95% CI, 0.95-0.97) for hsTnI on admission and 0.92 (95% CI, 0.90-0.94) for cTnI on admission. Both were superior to the other evaluated diagnostic biomarkers. The use of hsTnI at admission (with the diagnostic cutoff value at the 99th percentile of 30 pg/mL) had a sensitivity of 82.3% and a negative predictive value (for ruling out AMI) of 94.7%. The use of cTnI (with the diagnostic cutoff value at the 99th percentile of 32 pg/mL) at admission had a sensitivity of 79.4% and a negative predictive value of 94.0%. Using levels obtained at 3 hours after admission, the sensitivity was 98.2% and the negative predictive value was 99.4% for both hsTnI and

Table 4. Diagnostic Performance for Identification of Acute Myocardial Infarction by Use of Serial cTnI and hsTnI Determination

	cTnI, % (95% CI)				hsTnI, % (95% CI)			
	On Admission		At 3 Hours		On Admission		At 3 Hours	
	>LoD	>99th Percentile	>LoD	>99th Percentile	>LoD	>99th Percentile	>LoD	>99th Percentile
Sensitivity	87.4 (83.3-90.8)	79.4 (74.6-83.7)	98.8 (96.9-99.7)	98.2 (96.0-99.3)	100.0 (98.0-100.0)	82.3 (77.3-86.5)	100.0 (98.0-100.0)	98.2 (95.9-99.4)
Specificity	88.6 (86.6-90.4)	94.5 (93.0-95.7)	78.9 (76.4-81.3)	89.8 (87.8-91.5)	35.3 (32.3-38.4)	92.1 (90.3-93.7)	1.9 (1.2-3.0)	90.4 (88.4-92.2)
Positive predictive value	69.3 (64.6-73.8)	80.9 (76.2-85.1)	58.0 (53.8-62.2)	73.9 (69.5-78.0)	30.8 (27.8-33.9)	75.1 (69.9-79.8)	22.7 (20.4-25.2)	74.7 (69.9-79.0)
Negative predictive value	96.0 (94.6-97.1)	94.0 (92.4-95.3)	99.5 (98.8-99.9)	99.4 (98.7-99.8)	100.0 (98.4-100.0)	94.7 (93.1-96.1)	100.0 (75.1-100.0)	99.4 (98.7-99.8)
No. positive/total[a]	411/1430	320/1430	555/1430	433/1430	915/1260	309/1260	1241/1260	371/1260

Abbreviations: cTnI, contemporary sensitive troponin I; hsTnI, highly sensitive troponin I; LoD, level of detection.

[a]Number of patients with positive test criteria/number of patients with available data on criteria.

Table 5. Diagnostic Performance for Identification of Acute Myocardial Infarction by Use of hsTnI Determination and Its Relative Change in Troponin Concentration[a]

	Change 0 to 3 Hours After Admission, % (95% CI)							
	≥20	≥30	≥50	≥75	≥100	≥150	≥200	≥250
hsTnI Change 0 to 3 Hours								
Sensitivity	77.3 (72.0-82.1)	72.7 (67.1-77.8)	67.0 (61.2-72.5)	61.0 (55.0-66.7)	57.4 (51.4-63.3)	52.8 (46.8-58.8)	50.4 (44.4-56.3)	48.2 (42.3-54.2)
Specificity	26.1 (23.3-28.9)	33.6 (30.7-36.7)	46.8 (43.7-50.0)	55.5 (52.3-58.7)	59.7 (56.6-62.8)	69.3 (66.3-72.2)	83.9 (81.5-86.2)	92.5 (90.7-94.1)
PPV	23.2 (20.5-26.0)	24.0 (21.2-27.0)	26.7 (23.4-30.1)	28.3 (24.8-32.1)	29.1 (25.4-33.1)	33.2 (28.8-37.8)	47.5 (41.7-53.3)	65.1 (58.2-71.5)
NPV	79.9 (75.1-84.2)	81.0 (76.9-84.7)	83.1 (79.7-86.2)	83.2 (80.1-85.9)	83.0 (80.0-85.7)	83.6 (80.9-86.1)	85.4 (83.0-87.6)	86.1 (83.9-88.1)
No. positive/total[b]	941/1260	854/1260	709/1260	607/1260	556/1260	449/1260	299/1260	209/1260
hsTnI >LoD on Admission and hsTnI Change 0 to 3 Hours								
Sensitivity	77.3 (72.0-82.1)	72.7 (67.1-77.8)	67.0 (61.2-72.5)	61.0 (55.0-66.7)	57.4 (51.4-63.3)	52.8 (46.8-58.8)	50.4 (44.4-56.3)	48.2 (42.3-54.2)
Specificity	60.2 (57.1-63.3)	67.8 (64.8-70.7)	80.9 (78.3-83.3)	89.6 (87.5-91.4)	93.4 (91.6-94.8)	96.8 (95.5-97.8)	98.1 (97.0-98.8)	98.6 (97.6-99.2)
PPV	35.9 (32.1-39.9)	39.4 (35.2-43.8)	50.3 (45.1-55.4)	62.8 (56.8-68.5)	71.4 (65.0-77.2)	82.8 (76.5-88.0)	88.2 (82.2-92.7)	90.7 (84.8-94.8)
NPV	90.2 (87.7-92.4)	89.6 (87.2-91.7)	89.5 (87.3-91.4)	88.8 (86.7-90.7)	88.4 (86.3-90.3)	87.7 (85.6-89.6)	87.3 (85.1-89.2)	86.8 (84.7-88.8)
No. positive/total[b]	708/1260	606/1260	434/1260	310/1260	254/1260	197/1260	171/1260	157/1260
hsTnI >99th Percentile on Admission and hsTnI Change 0 to 3 Hours								
Sensitivity	60.3 (54.3-66.0)	55.7 (49.7-61.6)	50.0 (44.0-56.0)	44.3 (38.4-50.3)	41.5 (35.7-47.5)	36.9 (31.2-42.8)	34.4 (28.9-40.3)	32.6 (27.2-38.4)
Specificity	96.8 (95.5-97.8)	98.0 (96.9-98.7)	99.1 (98.3-99.6)	99.2 (98.4-99.6)	99.4 (98.7-99.8)	99.4 (98.7-99.8)	99.5 (98.8-99.8)	99.6 (99.0-99.9)
PPV	84.6 (78.8-89.3)	88.7 (83.1-93.0)	94.0 (88.9-97.2)	94.0 (88.5-97.4)	95.1 (89.7-98.2)	94.5 (88.5-98.0)	95.1 (88.9-98.4)	95.8 (89.7-98.9)
NPV	89.4 (87.4-91.2)	88.5 (86.4-90.3)	87.3 (85.2-89.2)	86.1 (83.9-88.0)	85.5 (83.3-87.5)	84.5 (82.3-86.6)	84.0 (81.8-86.1)	83.7 (81.4-85.8)
No. positive/total[b]	221/1260	193/1260	161/1260	141/1260	131/1260	116/1260	107/1260	101/1260
hsTnI Change 0 to 3 Hours and hsTnI >99th Percentile After 3 Hours in Patients With hsTnI <99th Percentile on Admission								
Sensitivity	92.0 (80.8-97.8)	92.0 (80.8-97.8)	92.0 (80.8-97.8)	92.0 (80.8-97.8)	90.0 (78.2-96.7)	90.0 (78.2-96.7)	90.0 (78.2-96.7)	88.0 (75.7-95.5)
Specificity	97.4 (96.2-98.4)	97.6 (96.3-98.5)	97.9 (96.7-98.7)	97.9 (96.7-98.7)	98.1 (97.0-98.9)	98.1 (97.0-98.9)	98.7 (97.7-99.3)	99.0 (98.1-99.5)
PPV	66.7 (54.3-77.6)	67.6 (55.2-78.5)	70.8 (58.2-81.4)	70.8 (58.2-81.4)	72.6 (59.8-83.1)	72.6 (59.8-83.1)	78.9 (66.1-88.6)	83.0 (70.2-91.9)
NPV	99.5 (98.8-99.9)	99.5 (98.8-99.9)	99.5 (98.8-99.9)	99.5 (98.8-99.9)	99.4 (98.7-99.8)	99.4 (98.7-99.8)	99.4 (98.7-99.8)	99.3 (98.6-99.8)
No. positive/total[b]	78/951	76/951	72/951	71/951	68/951	67/951	59/951	54/951

Abbreviations: hsTnI, highly sensitive troponin I; LoD, level of detection; NPV, negative predictive value; PPV, positive predictive value.
[a] Cutoff of 32 pg/mL for the cTnI and 30 pg/mL for hTnI assays and LoD of 10 pg/mL for cTnI and 3.4 pg/mL for hTnI. Various relative troponin changes between admission and 3 hours and their combination with cTnI and hsTnI are presented. For each assay, analyses were performed on patients with their corresponding troponin I values below the upper range of the used assay on admission and 3 hours after admission.
[b] Number of patients with positive test criteria/number of patients with available data on criteria.

Table 6. Diagnostic Performance for Identification of Acute Myocardial Infarction by Use of cTnI Determination and Its Relative Change in Troponin Concentration[a]

	Change 0 to 3 Hours After Admission, % (95% CI)							
	≥20	≥30	≥50	≥75	≥100	≥150	≥200	≥250
cTnI Change 0 to 3 Hours								
Sensitivity	81.9 (77.3-85.9)	77.3 (72.4-81.7)	69.0 (63.7-74.0)	63.5 (58.0-68.7)	60.7 (55.2-66.1)	55.8 (50.3-61.3)	51.5 (46.0-57.1)	49.7 (44.1-55.3)
Specificity	79.7 (77.2-82.0)	81.0 (78.5-83.3)	82.0 (79.6-84.2)	83.8 (81.5-85.9)	84.9 (82.6-86.9)	89.0 (87.0-90.8)	90.7 (88.8-92.3)	92.0 (90.3-93.6)
PPV	54.4 (49.9-58.8)	54.5 (49.9-59.2)	53.1 (48.2-57.9)	53.6 (48.5-58.7)	54.2 (49.0-59.4)	60.1 (54.3-65.6)	62.0 (55.9-67.8)	64.8 (58.5-70.7)
NPV	93.7 (92.0-95.2)	92.4 (90.5-93.9)	90.0 (87.9-91.7)	88.6 (86.5-90.5)	88.0 (85.9-89.9)	87.2 (85.1-89.1)	86.4 (84.3-88.3)	86.1 (84.0-88.0)
No. positive/total[b]	491/1430	462/1430	424/1430	386/1430	365/1430	303/1430	271/1430	250/1430
cTnI >LoD on Admission and cTnI Change 0 to 3 Hours								
Sensitivity	70.2 (65.0-75.2)	65.6 (60.2-70.8)	57.4 (51.8-62.8)	51.8 (46.3-57.4)	49.1 (43.5-54.6)	44.2 (38.7-49.7)	39.9 (34.5-45.4)	38.0 (32.7-43.5)
Specificity	92.5 (90.8-94.0)	93.8 (92.2-95.1)	94.7 (93.3-96.0)	96.6 (95.3-97.6)	97.6 (96.6-98.5)	98.6 (97.8-99.2)	98.7 (97.9-99.3)	98.9 (98.1-99.4)
PPV	73.4 (68.1-78.2)	75.6 (70.2-80.5)	76.3 (70.5-81.5)	81.6 (75.7-86.7)	86.0 (80.2-90.7)	90.6 (84.9-94.6)	90.3 (84.2-94.6)	91.2 (85.1-95.4)
NPV	91.3 (89.5-92.9)	90.2 (88.4-91.9)	88.3 (86.3-90.0)	87.2 (85.2-89.0)	86.7 (84.6-88.5)	85.7 (83.6-87.6)	84.8 (82.7-86.7)	84.4 (82.3-86.3)
No. positive/total[a]	349/1430	317/1430	270/1430	226/1430	202/1430	171/1430	153/1430	144/1430
cTnI >99th Percentile on Admission and cTnI Change 0 to 3 Hours								
Sensitivity	62.3 (56.8-67.6)	58.0 (52.4-63.4)	49.7 (44.1-55.3)	44.2 (38.7-49.7)	41.4 (36.0-47.0)	36.5 (31.3-42.0)	32.2 (27.2-37.6)	30.4 (25.4-35.7)
Specificity	97.5 (96.4-98.3)	98.4 (97.4-99.0)	98.6 (97.8-99.2)	98.8 (98.0-99.4)	99.3 (98.6-99.7)	99.5 (98.9-99.9)	99.5 (98.9-99.9)	99.6 (99.1-99.9)
PPV	87.9 (83.0-91.8)	91.3 (86.6-94.8)	91.5 (86.4-95.2)	91.7 (86.3-95.5)	94.4 (89.3-97.6)	96.0 (90.8-98.7)	95.5 (89.7-98.5)	96.1 (90.4-98.9)
NPV	89.7 (87.9-91.4)	88.8 (86.9-90.5)	86.9 (84.9-88.7)	85.7 (83.7-87.6)	85.2 (83.1-87.1)	84.2 (82.1-86.1)	83.3 (81.1-85.2)	82.9 (80.8-84.9)
No. positive/total[b]	252/1430	226/1430	188/1430	164/1430	149/1430	129/1430	113/1430	105/1430
cTnI Change 0 to 3 Hours and cTnI >99th Percentile After 3 Hours in Patients With cTnI <99th Percentile on Admission								
Sensitivity	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)	92.5 (83.4-97.5)
Specificity	94.5 (93.0-95.8)	94.5 (93.0-95.8)	94.6 (93.1-95.9)	94.9 (93.4-96.2)	95.2 (93.7-96.4)	95.5 (94.1-96.7)	95.5 (94.1-96.7)	95.6 (94.2-96.8)
PPV	52.1 (42.8-61.3)	52.1 (42.8-61.3)	52.5 (43.1-61.8)	53.9 (44.4-63.2)	55.4 (45.7-64.8)	56.9 (47.0-66.3)	56.9 (47.0-66.3)	57.4 (47.5-66.9)
NPV	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)	99.5 (98.8-99.8)
No. positive/total[b]	134/1110	134/1110	133/1110	130/1110	126/1110	122/1110	121/1110	120/1110

Abbreviations: cTnI, contemporary sensitive troponin I; LoD, level of detection; NPV, negative predictive value; PPV, positive predictive value.

[a] Cutoff of 32 pg/mL for the cTnI and 30 pg/mL for hTnI assays and LoD of 10 pg/mL for cTnI and 3.4 pg/mL for hTnI. Various relative troponin changes between admission and 3 hours and their combination with cTnI and hsTnI are presented. For each assay, analyses were performed on patients with their corresponding troponin I values below the upper range of the used assay on admission and 3 hours after admission.

[b] Number of patients with positive test criteria/number of patients with available data on criteria.

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ORIGINAL ARTICLE

Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays

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ABSTRACT

BACKGROUND

The rapid and reliable diagnosis of acute myocardial infarction is a major unmet clinical need.

Medi-
W.H.,
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Metod

- Göğüs ağrısı ve AKS düşündüren semptomlarla başvuran hastalar çalışmaya dahil edilmiş.
- Semptomlarının ilk 12 saatinde olanlar dahil edilmiş.
- AMI tanısı bağımsız iki kardiyolog tarafından EKG, enzim, EKO, efor testi ve anjiografi sonuçlarına göre koyulmuş.
- 1,2,3 ve 6. saatlerde kan örnekleri alınmış.

Table 1. Baseline Characteristics of the Patients.

Characteristic	All Patients (N=718)	Patients Who Had an Acute Myocardial Infarction (N=123)	Patients Who Did Not Have an Acute Myocardial Infarction (N=595)	P Value
Age — yr				<0.001
Median	64	72	62	
Interquartile range	51–75	59–80	49–74	
Male sex — no. (%)	471 (66)	88 (72)	383 (64)	0.13
Risk factors — no. (%)				

Table 2. Diagnostic Performance of Cardiac Troponin Assays at Presentation.

Troponin Assay	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
		percent (95% confidence interval)		
Sensitive troponin assays				
Abbott–Architect Troponin I				
Limit of detection, 0.010 μg/liter	94 (88–97)	87 (84–89)	98 (97–99)	59 (52–66)
99th percentile, 0.028 μg/liter	86 (79–92)	92 (90–94)	97 (95–98)	69 (61–76)
10% coefficient of variation, 0.032 μg/liter	85 (77–90)	93 (90–95)	97 (95–98)	70 (62–78)
Roche High-Sensitive Troponin T				
Limit of detection, 0.002 μg/liter	100 (97–100)	14 (12–18)	100 (96–100)	19 (16–23)
99th percentile, 0.014 μg/liter*	95 (90–98)	80 (77–83)	99 (97–100)	50 (43–56)
Roche Troponin I				
Limit of detection, 0.100 μg/liter	92 (86–96)	88 (86–91)	98 (97–99)	62 (55–69)
99th percentile, 0.160 μg/liter	84 (76–90)	94 (91–95)	97 (95–98)	73 (65–80)
10% coefficient of variation, 0.300 μg/liter	75 (66–82)	97 (95–98)	95 (93–97)	83 (75–89)
Siemens Troponin I Ultra				
Limit of detection, 0.006 μg/liter	97 (91–99)	68 (64–72)	99 (97–100)	38 (32–44)
99th percentile, 0.040 μg/liter*	89 (82–94)	92 (89–94)	98 (96–99)	68 (60–76)
Standard assay				
Roche Troponin T 4th Generation				
99th percentile, unknown				
Limit of detection, 0.010 μg/liter	83 (76–90)	93 (91–95)	97 (95–98)	72 (64–79)
10% coefficient of variation, 0.035 μg/liter	72 (64–80)	97 (96–98)	94 (92–96)	85 (76–91)

* The criterion of 10% coefficient of variation was fulfilled at the 99th percentile.

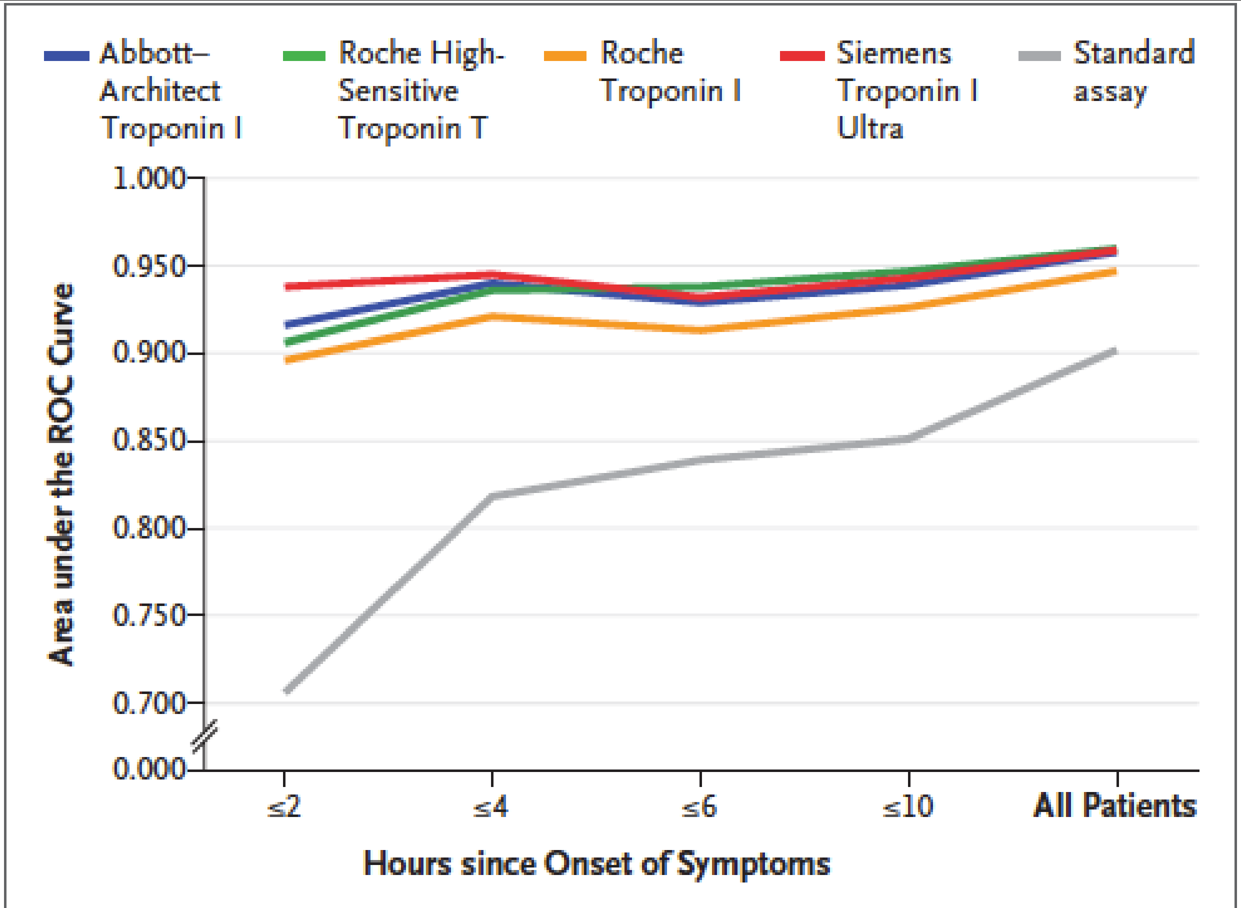

Figure 3. Diagnostic Accuracy of Cardiac Troponin Assays at Presentation According to Time since Onset of Chest Pain.

The area under the receiver-operating-characteristic curve (AUC) is shown, according to the time since the onset of chest pain, for the four sensitive cardiac troponin assays and the standard assay performed on blood samples obtained at presentation for the diagnosis of acute myocardial infarction.

Table 3 A	Diagnostic Performance of Cardiac Troponin at Presentation in Patients within 3 hours from Symptom Onset (n=222)				
		Sensitivity (95% CI)	Specificity (95% CI)	Negative Predictive Value (95% CI)	Positive Predictive Value (95% CI)
Sensitive Troponin Assays					
Abbott Troponin I					
Limit of Detection	(0.010 ug/l)	85 (66–96)	90 (85–94)	98 (94–99)	55 (39–70)
99th Percentile	(0.028 ug/l)	70 (50–86)	96 (92–98)	96 (92–98)	70 (50–86)
10% CV	(0.032 ug/l)	70 (50–86)	96 (93–99)	96 (92–98)	73 (52–88)
Roche High-Sensitive Troponin T					
Limit of Detection	(0.002 ug/l)	100 (87–100)	15 (11–21)	100 (88–100)	14 (10–20)
99th Percentile	(0.014 ug/l)*	85 (66–96)	84 (78–89)	98 (94–99)	42 (29–56)
Roche Troponin I					
Limit of Detection	(0.100 ug/l)	85 (66–96)	91 (86–95)	98 (95–99)	58 (41–73)
99th Percentile	(0.160 ug/l)	63 (42–81)	96 (93–99)	95 (91–98)	71 (49–87)
10% CV	(0.300 ug/l)	41 (22–61)	98 (95–99)	92 (88–96)	73 (45–92)
Siemens Troponin I Ultra					
Limit of Detection	(0.006 ug/l)	92 (75–99)	74 (67–80)	99 (95–100)	33 (22–45)
99th Percentile	(0.040 ug/l)*	77 (56–91)	95 (90–97)	97 (93–99)	67 (47–83)
Standard Troponin Assay					
Roche Troponin T 4th Generation					
99th Percentile	(unknown)				
Limit of Detection	(0.010 ug/l)	56 (35–75)	95 (91–98)	94 (90–97)	60 (39–79)
10% CV	(0.035 ug/l)	44 (26–65)	99 (96–100)	93 (88–96)	80 (52–95)

* Criterion of 10% CV fulfilled at 99th percentile

ORIGINAL ARTICLE

Normal presenting levels of high-sensitivity troponin and myocardial infarction

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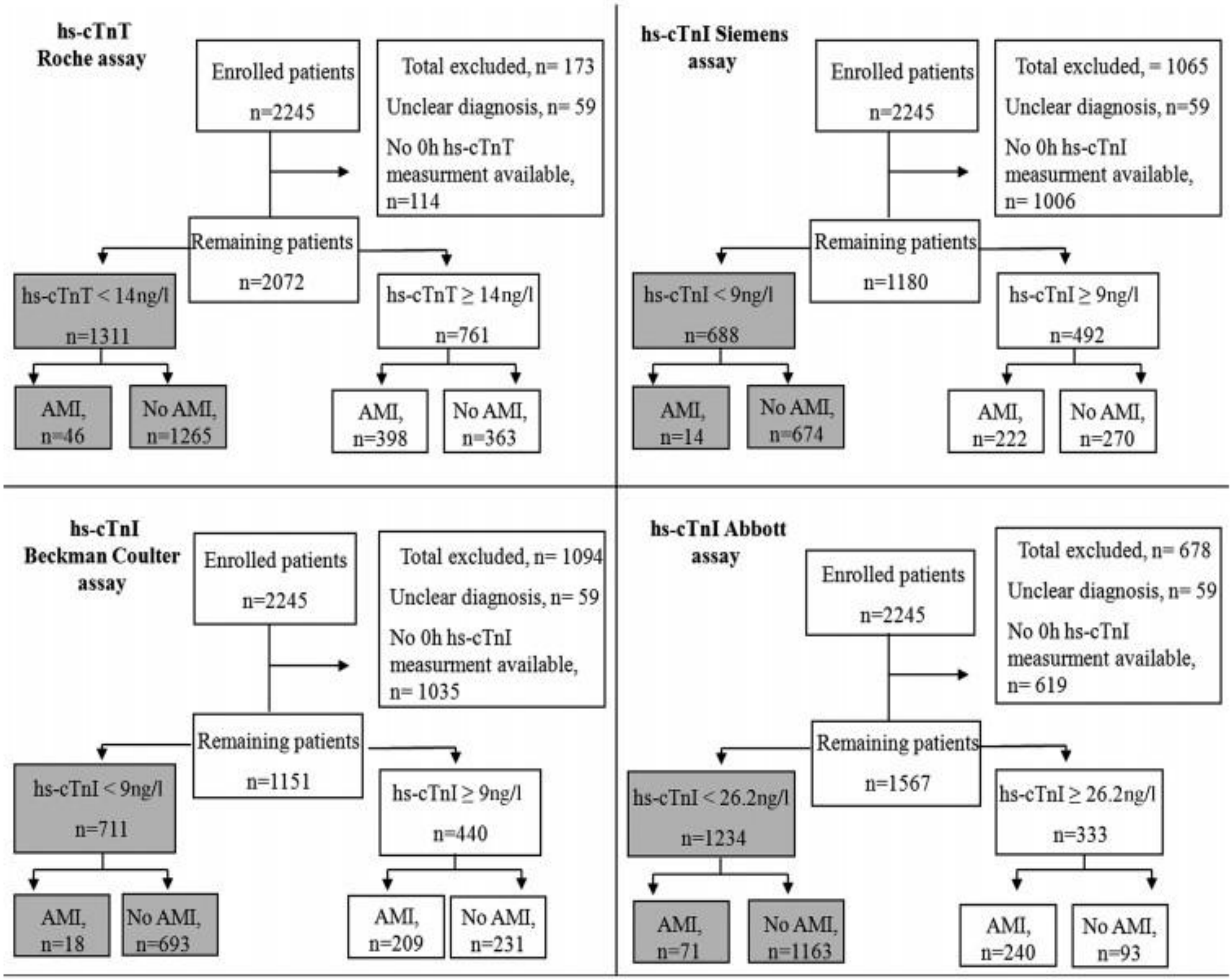
ABSTRACT

Objective To analyse whether levels of high-sensitivity cardiac troponin (hs-cTn) below their respective 99th percentile can be used as a single parameter to rule out acute myocardial infarction (AMI) at presentation.

Design Prospective, multicentre study.

Main outcome measures We measured hs-cTn using four different methods (hs-cTnT Roche, hs-cTnI Siemens,

In Europe and in the USA, almost 15 million patients per year present to the emergency department (ED) with chest pain or other symptoms suggestive of AMI.[2] As in most patients acute chest pain is caused by benign disorders and not by AMI, rapid rule out of AMI is fundamental.[3] Delayed rule out of AMI increases resource use and time spent in the ED, patient anxiety and the problem



hs-cTnT= high-sensitivity cardiac troponin T; hs-cTnI= high-sensitivity cardiac troponin I; AMI= acute myocardial infarction

Table 2 Sensitivity and specificity of different hs-cTn assays for AMI at respective upper limit stratified by time from symptom onset

Time from symptom onset (h)	Assay and cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All patients	hs-cTnT, 14 ng/l	89.6 (86.4 to 92.3)	77.7 (75.6 to 79.7)	52.3 (48.7 to 55.9)	96.5 (95.4 to 97.4)
	hs-cTnI, 9 ng/l (S)	94.1 (90.3 to 96.7)	71.4 (68.4 to 74.3)	45.1 (40.7 to 49.6)	98.0 (96.6 to 98.9)
	hs-cTnI, 9 ng/l (B)	92.1 (87.8 to 95.2)	75.0 (72.1 to 77.8)	47.5 (42.8 to 52.3)	97.5 (96.1 to 98.5)
	hs-cTnI, 26.2 ng/l (A)	77.2 (72.1 to 81.7)	92.6 (91.0 to 94.0)	72.1 (66.9 to 76.8)	94.3 (92.8 to 95.5)
<3	hs-cTnT, 14 ng/l	73.8 (64.5 to 81.9)	84.2 (80.2 to 87.6)	55.6 (47.1 to 64.0)	92.3 (89.0 to 94.8)
	hs-cTnI, 9 ng/l (S)	93.8 (82.8 to 98.7)	79.8 (74.1 to 84.8)	48.9 (38.3 to 59.6)	98.4 (95.4 to 99.7)
	hs-cTnI, 9 ng/l (B)	88.6 (75.4 to 96.2)	85.0 (79.6 to 89.4)	53.4 (41.4 to 65.2)	97.5 (94.2 to 99.2)
	hs-cTnI, 26.2 ng/l (A)	50.8 (38.2 to 63.2)	97.9 (95.6 to 99.2)	85.0 (70.2 to 94.3)	89.6 (85.7 to 92.7)
≥3	hs-cTnT, 14 ng/l	94.7 (91.7 to 96.8)	75.6 (73.1 to 78.0)	51.5(47.5 to 55.5)	98.1 (97.0 to 98.9)
	hs-cTnI, 9 ng/l (S)	94.2 (89.8 to 97.0)	68.6 (65.1 to 72.0)	44.3 (39.3 to 49.3)	98.0 (96.1 to 99.0)
	hs-cTnI, 9 ng/l (B)	92.9 (88.2 to 96.2)	71.8 (68.3 to 75.1)	46.3 (41.1 to 51.6)	97.5 (95.7 to 98.7)
	hs-cTnI, 26.2 ng/l (A)	84.4 (79.3 to 88.7)	91.0 (89.0 to 92.7)	70.3 (64.7 to 75.5)	95.9 (94.4 to 97.1)
<6	hs-cTnT, 14 ng/l	83.9 (78.5 to 88.5)	79.6 (76.8 to 82.3)	52.1 (46.8 to 57.3)	94.9 (93.1 to 96.4)
	hs-cTnI, 9 ng/l (S)	92.0 (85.3 to 96.3)	73.6 (69.5 to 77.4)	44.0 (37.6 to 50.6)	97.6 (95.5 to 98.9)
	hs-cTnI, 9 ng/l (B)	88.9 (81.4 to 94.1)	77.2 (73.2 to 80.9)	46.6 (39.6 to 53.7)	96.9 (94.6 to 98.4)
	hs-cTnI, 26.2 ng/l (A)	65.3 (56.9 to 73.0)	94.8 (92.7 to 96.3)	73.4 (64.9 to 80.9)	92.5 (90.2 to 94.4)
≥ 6	hs-cTnT, 14 ng/l	95.5 (91.8 to 97.8)	75.6 (72.4 to 78.6)	52.5 (47.5 to 57.5)	98.3 (97.0 to 99.2)
	hs-cTnI, 9 ng/l (S)	96.0 (90.8 to 98.7)	69.0 (64.5 to 73.2)	46.1 (39.9 to 52.4)	98.4 (96.3 to 99.5)
	hs-cTnI, 9 ng/l (B)	95.0 (89.4 to 98.1)	72.6 (68.2 to 76.7)	48.3 (41.7 to 54.9)	98.2 (96.1 to 99.3)
	hs-cTnI, 26.2 ng/l (A)	87.4 (81.4 to 92.0)	90.3 (87.7 to 92.5)	71.2 (64.5 to 77.3)	96.3 (94.4 to 97.7)

Cut-off set at the 99th percentile of a healthy reference population.
(A), Abbott; (B), Beckman Coulter; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; hs-cTnI, high-sensitivity cardiac troponin I; NPV, negative predictive value; PPV, positive predictive value; (S), Siemens.

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Original Contribution

Early rule out of acute myocardial infarction in ED patients: value of combined high-sensitivity cardiac troponin T and ultrasensitive copeptin assays at admission☆,☆☆

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A R T I C L E I N F O

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A B S T R A C T

Objective: We sought to evaluate the added value of ultrasensitive copeptin (us-copeptin) for early rule out of acute myocardial infarction in a prospective cohort of emergency department (ED) patients with acute chest pain.
Methods: This was a prospective study including consecutive patients with acute chest pain presenting to the ED within 12 hours of symptom onset. High-sensitivity cardiac troponin T (hs-cTnT, Roche Diagnostics, Meylan, France) and us-copeptin (ThermoFisher Scientific, Clichy, France) were blindly assayed from venous blood samples obtained at admission. Diagnosis was made by 2 ED physicians using all available data and serial cardiac troponin I as the biochemical standard. Diagnostic performances of us-copeptin combined with hs-cTnT were assessed using logistic regression. Analysis was conducted in all patients and in patients without ST-elevation

- İlk 12 saatte göğüs ağrısı nedeniyle acil servise başvuran hastalar çalışmaya alınmış.
- Girişte ve 6. saatte ve gerek duyulursa ilerleyen saattlerde enzim çalışılmış.
- İki bağımsız kardiyolog tüm sonuçları yorumlayarak nihai kararı vermişler.

Table 1
Baseline characteristics of the study population

Patients' characteristics	Variable
Age (y)	61.4 (47.7-75.1)
Sex, n (%)	
Female	71 (36.6%)
Male	123 (63.4%)
Diagnosis, n (%)	
STEMI	27 (13.9%)
NSTEMI	25 (12.9%)
UA	31 (16%)
AP	9 (4.6%)
NCAD	102 (52.6%)
Time since chest pain onset (h)	
STEMI	4.25 (2.19-6.82)
NSTEMI	3.65 (2.75-12)
UA	3.76 (2.32-6.50)
AP	2.82 (2.63-4.5)
NCAD	5.32 (3.05-9.68)

Table 2

Diagnostic performance of individual hs-cTnT and us-copeptin and their combination for diagnosis of AMI or NSTEMI

Diagnosis	Decision rule	Sensitivity	Specificity	PPV	NPV
AMI	Hs-cTnT > 14 ng/L	76.9% (63.2-87.5)	85.2% (78.3-90.6)	65.6% (52.3-77.3)	91% (84.8-95.3)
	Hs-cTnT > 18 ng/L	75% (61.1-86)	89.4% (83.2-94)	72.2% (58.4-83.5)	90.7% (84.6-95)
	Us-copeptin > 13.11 pmol/L	69.2% (54.9-81.3)	70.4% (62.2-77.8)	46.2% (34.8-57.8)	86.2% (78.6-91.9)
	Hs-cTnT > 14 ng/L or us-copeptin > 13.11 pmol/L	96.2% (86.8-99.5)	63.4% (54.9-71.3)	49% (39-59.1)	97.8% (92.4-99.7)
	Hs-cTnT > 18 ng/L or us-copeptin > 13.11 pmol/L	96.2% (86.8-99.5)	64.8% (56.3-72.6)	50% (39.8-60.2)	97.9% (92.5-99.7)
NSTEMI	Hs-cTnT > 14 ng/L	76% (54.9-90.6)	85.2% (78.3-90.6)	47.5% (31.5-63.9)	95.3% (90-98.2)
	Hs-cTnT > 18 ng/L	76% (54.9-90.6)	89.4% (83.2-94)	55.9% (37.9-72.8)	95.5% (90.4-98.3)
	Us-copeptin > 13.11 pmol/L	60% (38.7-78.9)	70.4% (62.2-77.8)	26.3% (15.5-39.7)	90.9% (83.9-95.6)
	Hs-cTnT > 14 ng/L or us-copeptin > 13.11 pmol/L	96% (79.6-99.9)	63.4% (54.9-71.3)	31.6% (21.4-43.3)	98.9% (94-100)
	Hs-cTnT > 18 ng/L or us-copeptin > 13.11 pmol/L	96% (79.6-99.9)	64.8% (56.3-72.6)	32.4% (22-44.3)	98.9% (94.2-100)

Diagnostic performance for diagnosis of AMI or NSTEMI was assessed in all study patients (N = 194, upper panel) or in patients with the exclusion of STEMI (n = 167, lower panel), respectively. Performance values are shown along with 95% CI. Decision thresholds were determined using the 99th percentile of a general population (Hs-cTnT > 14 ng/L) or max Youden index (2000 bootstraps) (Hs-cTnT > 18 ng/L, us-copeptin > 13.11 pmol/L).

Abbreviation: PPV, positive predictive value.

RESEARCH CMAJ

Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain

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Competing interests: Louise Cullen has received consultancy fees from Abbott Diagnostics, research grants from Abbott Diagnostics and Alere, speaker fees from Alere, Pfizer and Radiometer Pacific, and travel assistance from Boehringer Ingelheim. Richard Troughton has received speaker fees from St. Jude Medical Inc.

Abstract

Background: High-sensitivity troponin assays are now available for clinical use. We investigated whether early measurement with such an assay is superior to a conventional assay in the evaluation of acute coronary syndromes.

Methods: Patients presenting to an emergency department with chest pain who did not have ST-segment elevation were prospectively recruited from November 2007 to De-

dence interval [CI] 88.1%–95.0%) and a specificity of 79.7% (95% CI 78.6%–80.5%) for the diagnosis of non–ST-segment myocardial infarction. The sensitivity of the assay at presentation was 100% among patients who presented four to six hours after symptom onset. By one year, the high-sensitivity troponin T assay was found to be superior than the conventional assay in predicting death (hazard ratio [HR] 5.4, 95% CI 2.7–10.7) and heart failure (HR 27.8, 95% CI 6.6–

- Kardiyak iskemi düşündüren semptomlarla başvuran hastalar çalışmaya alınmış.

- EKG'de ST segment elevasyonu olan hastalar çalışmadan dışlanmış.
- HsTnT (0,2 saat) ve std TnI (0, 2 ve 6. saatte) ölçülmüşler.
- Tanı bağımsız bir gözlemci tarafından koyulmuş.
- Tanı std TnI'nın 30 ng/L'den daha fazla olması ve %20'lik ve bir artış ile EKG ve anjiografi sonuçlarına göre koyulmuş.

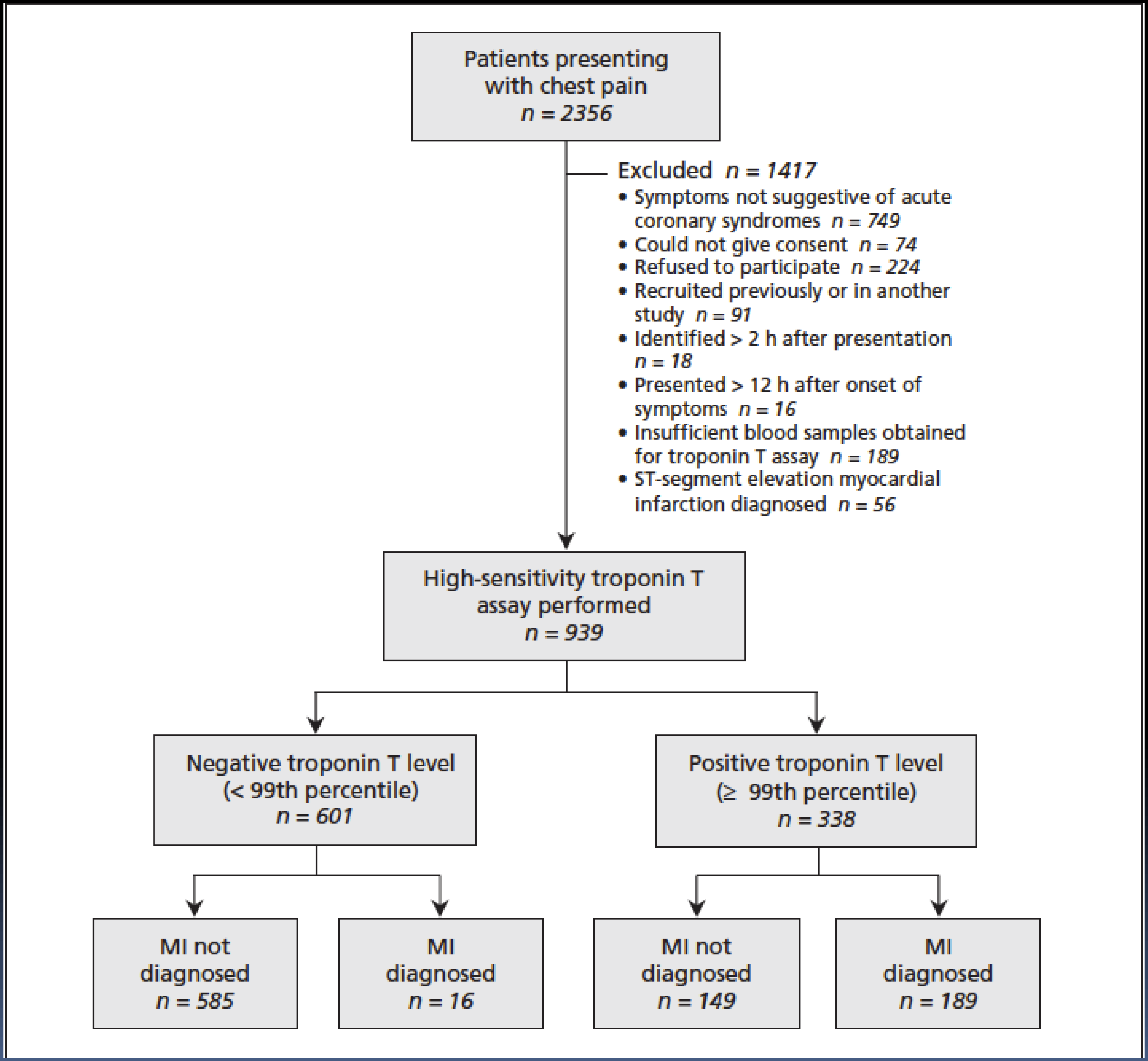
Patients presenting with chest pain n = 2356
Excluded n = 1417
• Symptoms not suggestive of acute coronary syndromes n = 749
• Could not give consent n = 74
• Refused to participate n = 224
• Recruited previously or in another study n = 91
• Identified > 2 h after presentation n = 18
• Presented > 12 h after onset of symptoms n = 16
• Insufficient blood samples obtained for troponin T assay n = 189
• ST-segment elevation myocardial infarction diagnosed n = 56
High-sensitivity troponin T assay performed n = 939
Negative troponin T level (< 99th percentile) n = 601
Positive troponin T level (≥ 99th percentile) n = 338
MI not diagnosed n = 585
MI diagnosed n = 16
MI not diagnosed n = 149
MI diagnosed n = 189

Table 2: Performance of high-sensitivity troponin T assay in diagnosing myocardial infarction at presentation and two hours later

Cut-off value of assay; performance measure	Time of assay; % (95% CI)	
	At presentation	2 h after presentation
≥ 14 ng/L (99th percentile)*		
Sensitivity	88.3 (83.3–91.8)	92.2 (88.1–85.0)
Specificity	81.7 (80.5–82.7)	79.7 (78.6–80.5)
Positive-predictive value	57.5 (54.5–59.7)	55.9 (53.4–57.6)
Negative-predictive value	96.2 (94.7–97.3)	97.3 (95.9–98.3)
Accuracy	83.2 (81.2–84.7)	82.4 (80.6–83.7)
≥ 5 ng/L (limit of detection†)		
Sensitivity	93.7 (89.4–96.4)	95.6 (91.7–97.8)
Specificity	58.4 (57.3–59.2)	53.7 (52.6–54.3)
Positive-predictive value	38.6 (36.9–39.8)	36.6 (35.1–37.4)
Negative-predictive value	97.1 (95.1–98.3)	97.8 (95.8–98.9)
Accuracy	66.1 (64.3–67.3)	62.8 (61.1–63.8)
≥ 3 ng/L (limit of blank‡)		
Sensitivity	95.6 (91.8–97.8)	98.1 (94.9–99.4)
Specificity	47.8 (46.7–48.4)	42.2 (41.3–42.6)
Positive-predictive value	33.9 (32.5–34.6)	32.3 (31.2–32.7)
Negative-predictive value	97.5 (95.3–98.8)	98.7 (96.6–99.6)
Accuracy	58.3 (56.6–97.8)	45.5 (45.0–46.9)

Note: CI = confidence interval.
*At or above the 99th percentile of the general population.
†Limit of detection = the lowest quantity or concentration of an analyte that can be reliably detected with a given analytical method.
‡Limit of blank = the highest apparent concentration of an analyte expected to be found in a sample containing no analyte.

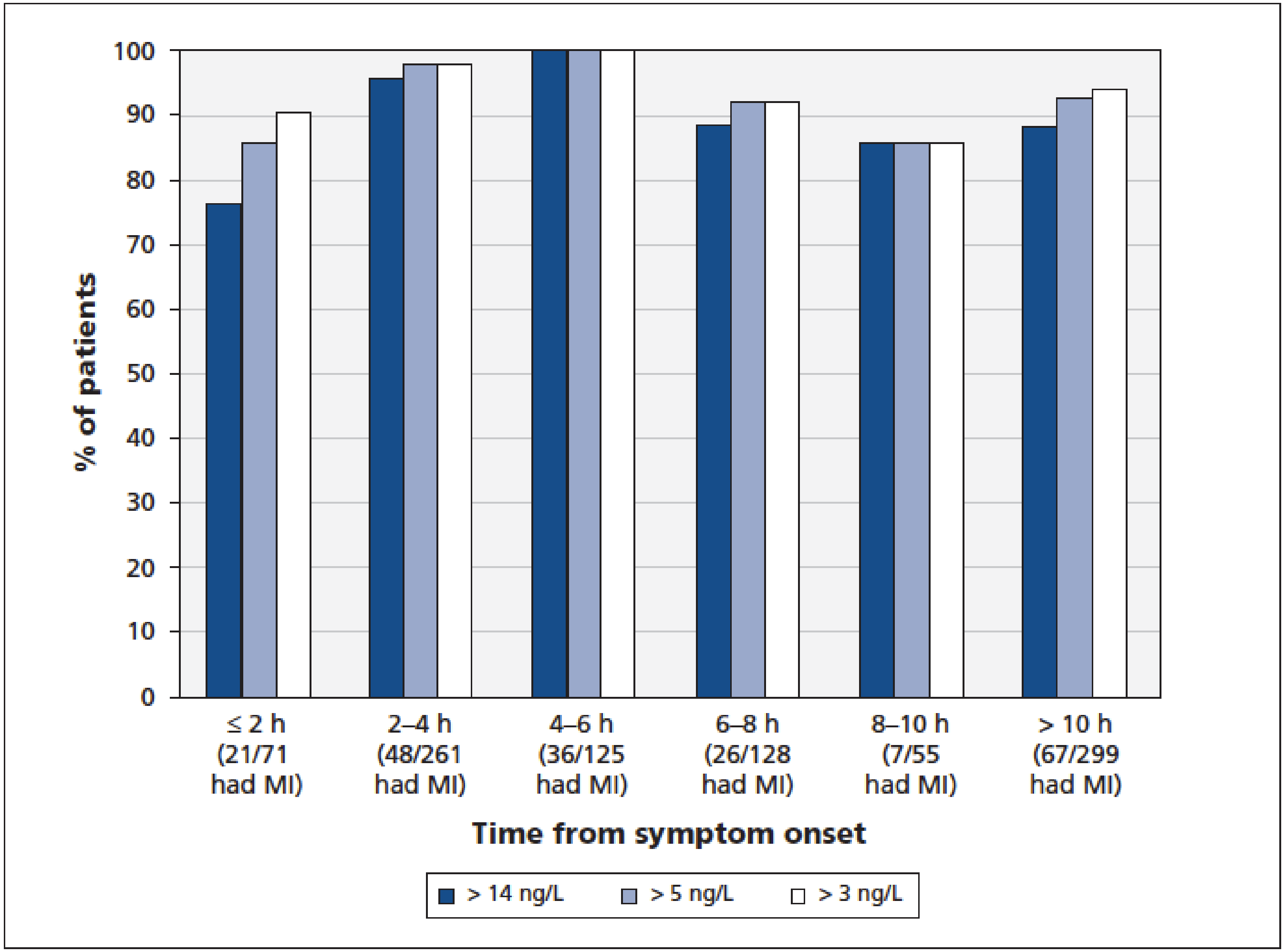

Figure 3: Sensitivity of the high-sensitivity troponin T assay at presentation at different cut-off points for the diagnosis of non–ST-segment elevation myocardial infarction (MI), by time from symptom onset. Cut-off points: 14 ng/L = 99th percentile of the general population; 5 ng/L = limit of detection (the lowest quantity or concentration of an analyte that can be reliably detected with a given analytical method); 3 ng/L = limit of blank (the highest apparent concentration of an analyte expected to be found in a sample containing no analyte).

High-sensitivity troponin T for early rule-out of myocardial infarction in recent onset chest pain

Sally Aldous,[1] Chris Pemberton,[2] A Mark Richards,[2,3] Richard Troughton,[1] Martin Than[4]

ABSTRACT

Objective To investigate whether a high-sensitivity troponin assay, shown to improve early detection of acute myocardial infarction (AMI), permits accelerated rule-in/rule-out of AMI.

Methods Patients who presented to the emergency department within 4 h of the onset of chest pain suggestive of acute coronary syndrome were prospectively recruited

The current definition of AMI requires a rise and/or fall in the cTn concentration,[1] which helps distinguish acute elevations from chronically raised levels in conditions such as cardiomyopathy, valvular disease and renal dysfunction.[5 9 13 15 16] Emphasis on the dynamic change in cTn concentrations from baseline to follow-up ('delta') has intensified as more patients with non-ischaemic

- İlk dört saat içinde iskemik tipte ağrı düşündüren semptomlarla başvuran hastalar çalışmaya alınmış.
- Tn'de ilk ölçüme göre %20'lik artış olması, ilki yüksek olan ancak ikincide %20'den fazla düşme olan hastalarda ise EKG, stress testi ve koroner anjiografi sonuçlarına göre MI tanısı koyulmuş.
- Nihai tanılar bağımsız bir kardiyolog tarafından konulmuş.

Table 1 Patient characteristics

Characteristic	All patients (n=385)	Patients with AMI (n=82)	Patients without AMI (n=303)	p Value
Age in years, median (IQR)	65 (56–76)	67 (59–78)	64 (55–75)	0.084
Male, n (%)	233 (60.5)	59 (72.0)	174 (57.4)	0.022
Ethnicity, n (%)				
NZ European	305 (79.2)	61 (74.4)	244 (80.5)	0.223
Other European	50 (13.0)	13 (15.9)	37 (12.2)	0.362
Maori/Pacific Islander	18 (4.7)	7 (8.5)	11 (3.6)	0.076
Other	12 (3.1)	1 (1.2)	11 (3.6)	N/A
Prior IHD, n (%)	201 (52.2)	36 (43.9)	165 (54.5)	0.105
Prior heart failure, n (%)	45 (11.7)	6 (7.3)	39 (12.9)	0.526
Prior revascularization, n (%)	126 (32.7)	20 (24.4)	106 (35.0)	0.088
Prior stroke, n (%)	6 (1.6)	0	6 (2.0)	0.192
Peripheral vascular disease, n (%)	16 (4.2)	3 (3.7)	13 (4.3)	0.808
Hypertension, n (%)	262 (68.1)	59 (72.0)	203 (67.0)	0.160
Dyslipidaemia, n (%)	239 (62.1)	48 (58.5)	191 (63.0)	0.799
Smoking, n (%)	239 (62.1)	52 (63.4)	187 (61.7)	0.538
Diabetes, n (%)	58 (15.1)	10 (12.2)	48 (15.8)	0.984
Family history of IHD, n (%)	254 (66.0)	57 (69.5)	197 (65.0)	0.112
Creatinine, μmol/l, median (IQR)	89 (78–103)	95 (84–117)	88 (77–100)	0.001
Time to presentation, h, median (IQR)	2.7 (2.0–3.3)	2.8 (2.1–3.3)	2.6 (2.0–3.3)	0.213

AMI, acute myocardial infarction; IHD, ischaemic heart disease; NZ, New Zealand.

Table 2 Diagnostic accuracy of high-sensitivity troponin T (hsTnT) values and different time points from presentation

n=385 (%)	Sensitivity	Specificity	PPV	NPV	Accuracy
0 h	90.7 (82.9–94.8)	82.2 (80.2–83.4)	57.6 (52.8–60.6)	97.0 (94.6–98.5)	83.9 (80.7–85.9)
	74.5 (67.7–79.0)	97.0 (95.2–98.3)	87.1 (79.3–92.5)	93.3 (91.6–94.5)	92.2 (89.4–94.2)
0–1 h	93.9 (87.2–97.3)	79.2 (77.4–80.1)	55.0 (51.1–57.0)	98.0 (95.7–99.1)	82.3 (79.5–83.8)
	82.9 (76.2–97.4)	96.0 (94.2–97.4)	85.0 (78.2–90.0)	95.4 (93.6–96.7)	93.2 (90.4–95.3)
0–2 h	95.1 (88.7–98.1)	77.9 (76.2–78.7)	53.8 (50.2–55.5)	98.3 (96.2–99.3)	81.6 (78.8–82.8)
	86.6 (79.9–91.4)	95.0 (93.2–96.3)	82.6 (76.2–87.1)	96.3 (94.5–97.6)	93.2 (90.4–95.3)
0–24 h	97.6 (92.0–99.3)	76.9 (75.4–77.4)	53.3 (50.3–54.3)	99.1 (97.2–99.8)	81.3 (78.9–82.0)
	100 (96.1–100)	94.7 (93.7–94.7)	83.7 (80.5–83.7)	100 (98.9–100)	95.8 (94.2–95.8)

PPV, Positive predictive value; NPV, Negative predictive value.

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CLINICAL RESEARCH
Coronary artery disease

Early diagnosis of acute myocardial infarction in patients with pre-existing coronary artery disease using more sensitive cardiac troponin assays

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See page 944 for the editorial comment on this article (doi:10.1093/eurheartj/ehs009)

- İlk 12 saatte başvuran ve AMI düşündüren göğüs ağrılı hastalar çalışmaya alınmış.
- Kardiyak enzimler 0,6 ve 9. saatlerde ölçülmüş.
- Nihai tanı iki bağımsız kardiyolog tarafından konulmuş.
- Kılavuzlara göre AMI tanısı konulmuş
  - Klinik bulgular, EKG, enzimde %30'luk artış.

Table 2 Final diagnoses of the patients

	All patients (n = 1098)	History of CAD[a] (n = 401)	No history of CAD (n = 697)	P-value*
Acute myocardial infarction	173 (16)	77 (19)	96 (14)	0.02
ST-segment elevation	41 (4)	15 (4)	26 (4)	0.99
Non-ST-segment elevation	132 (12)	62 (16)	70 (10)	0.01
UA	152 (14)	108 (27)	44 (6)	<0.001
Cardiac cause, but not CAD	147 (13)	39 (10)	108 (16)	0.01
Non-cardiac cause	528 (48)	136 (34)	392 (56)	<0.001
Unknown	98 (9)	41 (10)	57 (8)	0.25

[a]CAD, coronary artery disease.
*χ^2 test for comparison of proportions of patients with a history of coronary artery disease and patients without coronary artery disease.

Table 4 Diagnostic performance of sensitive troponin assays at the 99th percentile; at 10% coefficient of variation for the standard assay (95% CI)

		History of CAD	No history of CAD	P-value*
Sensitive troponin assays				
Roche high-sensitive troponin T 99th percentile [0.014 ng/mL (14 ng/L)]	Sensitivity	94 (85–98)	94 (87–98)	0.998
	Specificity	59 (54–65)	81 (78–84)	<0.001
	Negative predictive value	97 (94–99)	99 (97–100)	0.452
	Positive predictive value	35 (29–41)	45 (39–52)	0.137
Siemens troponin I ultra 99th percentile [0.040 ng/mL (40 ng/L)]	Sensitivity	91 (82–96)	89 (81–94)	0.880
	Specificity	85 (80–88)	91 (88–93)	0.007
	Negative predictive value	98 (95–99)	98 (97–99)	0.883
	Positive predictive value	58 (49–67)	62 (53–69)	0.832
Abbott-Architect troponin I 99th percentile [0.028 ng/mL (28 ng/L)]	Sensitivity	83 (73–91)	85 (77–92)	0.918
	Specificity	87 (83–91)	93 (91–95)	0.016
	Negative predictive value	96 (93–98)	98 (96–99)	0.292
	Positive predictive value	61 (51–70)	66 (57–74)	0.719
Standard troponin assay				
Roche troponin T 4th generation 99th percentile (unknown) 10% CV (0.035 ng/mL)	Sensitivity	69 (57–79)	83 (57–77)	0.988
	Specificity	97 (94–99)	95 (96–99)	0.788
	Negative predictive value	93 (90–95)	95 (93–96)	0.417
	Positive predictive value	84 (73–92)	83 (73–90)	0.958

CAD, coronary artery disease; CV, coefficient of variation.
*χ^2 test for comparison of proportions of patients with a history of coronary artery disease and patients without coronary artery disease.

Table 4A. Diagnostic Performance of Cardiac Troponin in Patients with History of Coronary Artery Disease, presenting within 3 Hours from Symptom Onset (n=167)

	Sensitivity (95%CI)	Specificity (95%CI)	Negative Predictive Value (95%CI)	Positive Predictive Value (95%CI)
Sensitive Troponin Assays				
Roche High-Sensitive Troponin T				
Limit of Detection (0.003 ng/ml [3 ng/L])	100 (87-100)	8 (4-14)	100 (71-100)	17 (11-23)
99thPercentile (0.014 ng/ml [14 ng/L])*	85 (65-96)	61 (52-69)	96 (89-99)	29 (19-40)
Siemens Troponin I Ultra				
Limit of Detection (0.006 ng/ml [6 ng/L])	100 (87-100)	34 (26-42)	100 (93-100)	22 (15-30)
99th Percentile (0.040 ng/ml [40 ng/L])*	88 (70-97)	88 (81-93)	98 (93-99)	58 (41-73)
Abbott-Architect Troponin I				
Limit of Detection(0.010 ng/ml [10 ng/L])	88 (70-97)	77 (70-84)	97 (92-99)	42 (29-56)
99th Percentile (0.028 ng/ml [28 ng/L])	77 (56-91)	91 (85-95)	96 (91-98)	61 (42-77)
10% CV (0.032 ng/ml [32 ng/L])	77 (56-91)	93 (87-97)	96 (91-98)	67 (47-83)
Standard Troponin Assay				
Roche Troponin T 4th Generation				
99th Percentile (unknown)				
Limit of Detection (0.010 ng/ml)	58 (37-77)	90 (84-94))	92 (86-96)	52 (33-71)
10% CV (0.035 ng/ml)	50 (30-70)	98 (94-100)	91 (65-95)	81 (54-96)

*criterion of 10% variation coefficient (10% CV) fulfilled at the 99th percentile

ORIGINAL ARTICLE

Diagnostic and prognostic impact of copeptin and high-sensitivity cardiac troponin T in patients with pre-existing coronary artery disease and suspected acute myocardial infarction

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ABSTRACT

Objective The early diagnosis of acute myocardial infarction (AMI) can be particularly challenging in patients with known coronary artery disease (CAD) due to pre-existing ECG changes and chronic increases in cardiac troponin (cTn) levels.

million have had an acute myocardial infarction (AMI).[1] The rapid and accurate diagnosis of AMI is critical for the initiation of effective evidence-based medical management and treatment,[2 3] but there is still an unmet clinical need. Delayed 'rule in' increases morbidity and mortality, particularly in

- İlk 12 saatte göğüs ağrısı ile acil servise başvuran tüm hastalar çalışmaya alınmış.
- 0,6 ve 9. saat enzim çalışılmış.
- İki bağımsız kardiyolog nihai tanıyı koymuş.
  - Hikaye, fizik muayene, enzim düzeyleri, EKG, EKO, efor testi, koroner anjiografi
- Normali üstüne çıkmak veya enzim düzeylerinde %30'luk artış yada azalma anlamlı kabul edilmiş.

Table 1 Baseline characteristics of patients

	All patients n=1170	CAD n=433 (37%)	No CAD n=737 (63%)	p Value
Age (years)				<0.001
Median	64	72	59	
IQR	51–76	59–79	49–72	
Male gender, n (%)	781 (67)	327 (76)	454 (62)	<0.001
Risk factors, n (%)				
Hypertension	744 (64)	360 (83)	384 (52)	<0.001
Hypercholesterolaemia	523 (45)	305 (70)	218 (30)	<0.001
Diabetes	225 (19)	130 (30)	95 (13)	<0.001
Current smoking	281 (24)	82 (19)	199 (27)	0.002
History of smoking	410 (35)	206 (48)	204 (28)	<0.001
History, n (%)				
Chronic obstructive pulmonary disease	121 (10)	71 (16)	50 (7)	<0.001
Renal insufficiency	123 (11)	92 (21)	31 (4)	<0.001
Peripheral artery disease	80 (7)	59 (14)	21 (3)	<0.001
Previous stroke	69 (6)	34 (8)	35 (5)	0.04

Table 3 Diagnostic performance of copeptin and different troponin assays and their combination at presentation in patients with and without pre-existing coronary artery disease (CAD)

	Sensitivity (95% CI)	Specificity (95% CI)	Negative predictive value (95% CI)	Positive predictive value (95% CI)
Patients with pre-existing CAD				
Copeptin 9 pmol/l (cut-off)	75.6 (64.6 to 84.7)	56.3 (51.0 to 61.6)	91.3 (86.8 to 94.7)	27.6 (21.7 to 34.1)
Roche troponin T fourth generation (cTnT)				
cTnT 0.01 μg/l (cut-off)	78.2 (67.4 to 86.8)	90.1 (86.6 to 93.0)	95.0 (92.1 to 97.0)	63.5 (53.1 to 73.1)
+ Copeptin 9 pmol/l (cut-off)	98.7 (93.0 to 99.8)	53.5 (48.2 to 58.8)	99.5 (97.1 to 99.9)	31.8 (26.0 to 38.1)
Roche high-sensitive troponin T (hs-cTnT)				
hs-cTnT 0.014 μg/l (cut-off)	93.6 (85.7 to 97.9)	60.2 (55.0 to 65.4)	97.7 (94.8 to 99.3)	34.1 (27.8 to 40.9)
+ Copeptin 9 pmol/l (cut-off)	98.7 (93.0 to 99.8)	41.4 (36.2 to 46.7)	99.3 (96.3 to 99.9)	27.0 (22.0 to 32.6)
Patients without pre-existing CAD				
Copeptin 9 pmol/l (cut-off)	67.9 (58.2 to 76.7)	69.4 (65.7 to 73.0)	92.8 (90.1 to 95.0)	27.2 (21.9 to 33.0)
Roche troponin T fourth generation (cTnT)				
cTnT 0.01 μg/l (cut-off)	83.0 (74.5 to 89.6)	94.6 (92.6 to 96.2)	97.1 (95.4 to 98.3)	72.1 (63.3 to 79.9)
+ Copeptin 9 pmol/l (cut-off)	98.1 (93.3 to 99.7)	66.9 (63.1 to 70.5)	99.5 (98.3 to 99.9)	33.2 (28.0 to 38.8)
Roche high-sensitive troponin T (hs-cTnT)				
hs-cTnT 0.014 μg/l (cut-off)	94.3 (88.1 to 97.9)	81.8 (78.5 to 84.7)	98.9 (97.5 to 99.6)	46.5 (39.7 to 52.4)
+ Copeptin 9 pmol/l (cut-off)	99.1 (94.8 to 99.8)	60.1 (56.1 to 63.9)	99.7 (98.5 to 100.0)	29.4 (24.7 to 34.4)