Akut dispne ve biyomarkerlar

Doç. Dr. Meltem AKKAŞ

Hacetttepe Üniversitesi Acil Tıp Anabilim Dalı

Biyomarker

Normal biyolojik süreçlerin, patolojik süreçlerin veya terapötik işleme verilen farmakolojik cevabın göstergesi olarak, objektif olarak ölçülebilen ve değerlendirilebilen özellliktir

Dispne tanı, prognoz ve/veya tedavisinde kullanılan

Klavuzlara girmiş

Kardiyo-pulmoner biyomarkerlar

Natriüretik Peptidler

- prepro-BNP (132 aa) _ proBNP (108 aa) _ BNP (32 aa)

  NT-proBNP (76 aa)
- BNP ve NT-proBNP ventriküllerin gerilimi sonucu
- Miyositlerden ve muhtemelen bir miktar da perimiyokardiyal fibroblastlardan salgılanır
- BNP yarı ömrü yaklaşık 20 dk
- NT-proBNP yarı ömrü yaklaşık 90-120 dk
- BNP; natriürezi uyarır, GFR arttırır ve periferik arter dilatasyonuna yol açarak kardiyak dolum basınçlarını azaltır.
- BNP; AII, aldosteron, arginin-vazopresin etkilerini antagonize eder

TABLE 2 Selected Potential Causes of Elevated Natriuretic Peptide Levels (38–41)

Cardiac
HF, including RV syndromes
Acute coronary syndromes
Heart muscle disease, including LVH
Valvular heart disease
Pericardial disease
Atrial fibrillation
Myocarditis
Cardiac surgery
Cardioversion
Toxic-metabolic myocardial insults, including cancer chemotherapy
Noncardiac
Advancing age
Anemia
Renal failure
Pulmonary: obstructive sleep apnea, severe pneumonia
Pulmonary hypertension
Critical illness
Bacterial sepsis
Severe burns

Modified from Table 8 of the 2013 HF guideline (9).

HF, indicates heart failure; LVH, left ventricular hypertrophy; and RV, right ventricular.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION,
THE AMERICAN HEART ASSOCIATION, INC., AND THE HEART FAILURE SOCIETY OF AMERICA
PUBLISHED BY ELSEVIER

VOL. 70, NO. 6, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.04.025

CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

Biomarkers: Recommendation for Prevention of HF

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
IIa	B-R	For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF (85,86).	NEW: New data suggest that natriuretic peptide biomarker screening and early intervention may prevent HF.
See Online Data Supplements A and B.			

Biomarkers: Recommendation for Diagnosis

COR	LOE	RECOMMENDATION	COMMENT/RATIONALE
I	A	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF (15–24,28–30).	MODIFIED: 2013 acute and chronic recommendations have been combined into a diagnosis section.
See Online Data Supplements A and B.			

Biomarkers: Recommendations for Prognosis

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
I	A	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (16,87–92).	2013 recommendation remains current.
I	A See Online Data Supplements A and B.	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF (27,93–100).	MODIFIED: Current recommendation emphasizes that it is admission levels of natriuretic peptide biomarkers that are useful.
IIb	B-NR See Online Data Supplements A and B.	In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification (27,95,98,99,103,114–119).	MODIFIED: 2013 recommendations have been combined into prognosis section, resulting in LOE change from A to B-NR.

Biomarkers of myocardial fibrosis (e.g., soluble ST2 receptor, galectin-3, high-sensitivity cardiac troponin, and others) are predictive of hospitalization and death in patients with HF and also are additive to natriuretic peptide biomarker levels in their prognostic value (117,119–126). A combination of biomarkers may ultimately prove to be more informative than single biomarkers (127).

European Journal of Heart Failure (2016) 18, 891–975
doi:10.1002/ejhf.592

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendations regarding applied diagnostic measurements

Recommendations	Class [a]	Level [b]	Ref [c]
Upon presentation a measurement of plasma natriuretic peptide level (BNP, NT-proBNP or MR-proANP) is recommended in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea.	I	A	531–534
At admission in all patients presenting with suspected AHF, the following diagnostic tests are recommended:			
a. 12-lead ECG;	I	C	
b. chest X-ray to assess signs of pulmonary congestion and detect other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms;	I	C	
c. the following laboratory assessments in the blood: cardiac troponins, BUN (or urea), creatinine, electrolytes (sodium, potassium), glucose, complete blood count, liver function tests and TSH.	I	C	
Echocardiography is recommended immediately in haemodynamically unstable AHF patients and within 48 hours when cardiac structure and function are either not known or may have changed since previous studies.	I	C	

AHF = acute heart failure; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; ECG = electrocardiogram; MR-proANP = mid-regional pro A-type natriuretic peptide; NT-proBNP = N-terminal pro-B type natriuretic peptide; TSH = thyroid-stimulating hormone

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

thebmj

BMJ 2015;350:h910 doi: 10.1136/bmj.h910 (Published 4 March 2015)

RESEARCH

The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting

Emmert Roberts *academic clinical fellow in psychiatry*[1], Andrew J Ludman *consultant cardiologist*[2], Katharina Dworzynski *senior research fellow*[3], Abdallah Al-Mohammad *consultant cardiologist*[4], Martin R Cowie *professor of cardiology*[5], John J V McMurray *professor of cardiology*[6], Jonathan Mant *professor of primary care research*[7], on behalf of the NICE Guideline Development Group for Acute Heart Failure

[1]Maudsley Hospital, South London and the Maudsley Mental Health Trust, London, UK; [2]Royal Devon & Exeter NHS Foundation Trust, Wonford, Exeter EX2 5DW, UK; [3]National Clinical Guideline Centre, Royal College of Physicians, London, UK; [4]South Yorkshire Cardiothoracic Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [5]National Heart and Lung Institute, Imperial College London (Royal Brompton Hospital), London, UK; [6]British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [7]Primary Care Unit, Department of Public Health & Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK

Abstract

Objectives To determine and compare the diagnostic accuracy of serum natriuretic peptide levels (B type natriuretic peptide, N terminal probrain natriuretic peptide (NTproBNP), and mid-regional proatrial natriuretic peptide (MRproANP)) in people presenting with acute heart failure to acute care settings using thresholds recommended in the 2012 European Society of Cardiology guidelines for heart failure.

Design Systematic review and diagnostic meta-analysis.

Data sources Medline, Embase, Cochrane central register of controlled trials, Cochrane database of systematic reviews, database of abstracts of reviews of effects, NHS economic evaluation database, and Health Technology Assessment up to 28 January 2014, using combinations of subject headings and terms relating to heart failure and natriuretic peptides.

Eligibility criteria for selecting studies Eligible studies evaluated one or more natriuretic peptides (B type natriuretic peptide, NTproBNP, or MRproANP) in the diagnosis of acute heart failure against an acceptable reference standard in consecutive or randomly selected adults in an acute care setting. Studies were excluded if they did not present sufficient data to extract or calculate true positives, false positives, false negatives, and true negatives, or report age independent natriuretic peptide thresholds. Studies not available in English were also excluded.

Results 37 unique study cohorts described in 42 study reports were included, with a total of 48 test evaluations reporting 15 263 test results. At the lower recommended thresholds of 100 ng/L for B type natriuretic peptide and 300 ng/L for NTproBNP, the natriuretic peptides have sensitivities of 0.95 (95% confidence interval 0.93 to 0.96) and 0.99 (0.97 to 1.00) and negative predictive values of 0.94 (0.90 to 0.96) and 0.98 (0.89 to 1.0), respectively, for a diagnosis of acute heart failure. At the lower recommended threshold of 120 pmol/L, MRproANP has a sensitivity ranging from 0.95 (range 0.90-0.98) to 0.97 (0.95-0.98) and a negative predictive value ranging from 0.90 (0.80-0.96) to 0.97 (0.96-0.98). At higher thresholds the sensitivity declined progressively and specificity remained variable across the range of values. There was no statistically significant difference in diagnostic accuracy between plasma B type natriuretic peptide and NTproBNP.

Conclusions At the rule-out thresholds recommended in the 2012 European Society of Cardiology guidelines for heart failure, plasma B type natriuretic peptide, NTproBNP, and MRproANP have excellent ability to exclude acute heart failure. Specificity is variable, and so imaging to confirm a diagnosis of heart failure is required. There is no statistical difference between the diagnostic accuracy of plasma B type natriuretic peptide and NTproBNP. Introduction of natriuretic peptide measurement in the investigation of patients with suspected acute heart failure has the potential to allow rapid and accurate exclusion of the diagnosis.

Kalp Yetmezliği Tanısı

Akut olmayan durumlarda KY dışlama[1]

BNP < 35 pg / mL

NT-pro-BNP < 125 pg / mL

Akut durumlarda KY dışlama[1]

BNP < 100 pg / mL

NT-proBNP < 300 pg /mL

MR-proANP < 120 pg/ mL

Ponikowski P, Voors AA, Anker SD et.al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975.

Table 1 Suggested natriuretic peptide cutoff values for acute decompensated heart failure

		ACEP recommendation	CKD	BMI >35kg/m²
Exclude				
	BNP	<100	<200[5]	54
	NTproBNP	<300	<300[21]	NA
Identify				
	BNP	>500		NA
	NTproBNP			
	<50 years	>450	>1,200[6]	NA
	50–75 years	>900	>4,502[6]	NA
	>75 years	>1,800		NA

Note: ACEP recommendations.[1,9]

Abbreviations: ACEP, American College of Emergency Physicians; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NA, not applicable; BNP, brain natriuretic peptide; CKD, chronic kidney disease; BMI, body mass index.

- Bununla birlikte, yüksek NP seviyeleri, çok çeşitli kardiyak ve kardiyak olmayan nedenlerle de ilişkili olabileceği için AKY tanısını otomatik olarak doğrulamaz
- Dekompanse son dönem KY, flaş akciğer ödemi ve ya sağ KY olan bazı hastalarda beklenmedik şekilde düşük NP seviyeleri tespit edilebilir

Ponikowski P, Voors AA, Anker SD et.al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975.

D-dimer

- D-dimer, fibrin yıkım ürünü
- Negatif prediktif değeri yüksek, pozitif prediktif değeri düşük
- Klinik olasılık skorları ile beraber D-dimer ölçümü, PTE şüphesi ile acile başvuran hastaların %30'unda ileri tetkik yapmadan PTE dışlanmasına neden olur
- ELISA yöntemi ile D-dimer ölçümünde tanısal sensitivite %95.
- Yaşla beraber D-dimer spesifitesi azalır (>80 yaşta %10)
- Yaşa bağlı cut-off değeri kullanımı önerilmektedir.

❖ *50 yaşa kadar cut-off değeri 500 microgram/L*

❖ *>50 yaş hastalarda cut-off değeri için yaşx10 microgram/L formülü*

Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033-69.

Thromb Haemost. 2009 May;101(5):886-92.

VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies.

Carrier M[1], Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, Rodger M, Wuillemin WA, Le Gal G.

Abstract

Clinical outcome studies have shown that it is safe to withhold anticoagulant therapy in patients with suspected pulmonary embolism (PE) who have a negative D-dimer result and a low pretest probability (PTP) either using a PTP model or clinical gestalt. It was the objective of the present study to assess the safety of the combination of a negative VIDAS D-dimer result in combination with a non-high PTP using the Wells or Geneva models to exclude PE. A systematic literature search strategy was conducted using MEDLINE, EMBASE, the Cochrane Register of Controlled Trials and all EBM Reviews. Seven studies (6 prospective management studies and 1 randomised controlled trial) reporting failure rates at three months were included in the analysis. Non-high PTP was defined as "unlikely" using the Wells' model, or "low/intermediate" PTP using either the Geneva score, the Revised Geneva Score, or clinical gestalt. Two reviewers independently extracted data onto standardised forms. A total of 5,622 patients with low/intermediate or unlikely PTP were assessed using the VIDAS D-dimer. PE was ruled out by a negative D-dimer test in 2,248 (40%, 95% confidence intervals [CI] 38.7 to 41.3%) of them. The three-month thromboembolic risk in patients left untreated on the basis of a low/intermediate or unlikely PTP and a negative D-dimer test was 3/2,166 (0.14%, 95% CI 0.05 to 0.41%). In conclusion, the combination of a negative VIDAS D-dimer result and a non-high PTP effectively and safely excludes PE in an important proportion of outpatients with suspected PE.

Published in final edited form as:
J Thromb Haemost. 2012 April ; 10(4): 572–581. doi:10.1111/j.1538-7836.2012.04647.x.

D-dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography

Background—Increasing the threshold to define a positive D-dimer could reduce unnecessary computed tomographic pulmonary angiography (CTPA) for suspected PE but might increase rates of missed PE and missed pneumonia, the most common nonthromboembolic diagnosis seen on CTPA.

Objective—Measure the effect of doubling the standard D-dimer threshold for "PE unlikely" Revised Geneva (RGS) or Wells' scores on the exclusion rate, frequency and size of missed PE and missed pneumonia.

Methods—Patients evaluated for suspected PE with 64-channel CTPA were prospectively enrolled from EDs and inpatient units of four hospitals. Pretest probability data were collected in real time and the D-dimer was measured in a central laboratory. Criterion standard was CPTA interpretation by two independent radiologists combined with clinical outcome at 30 days.

Results—Of 678 patients enrolled, 126 (19%) were PE+ and 93 (14%) had pneumonia. Use of either Wells≤4 or RGS≤6 produced similar results. For example, with RGS≤6 and standard threshold (<500 ng/mL), D-dimer was negative in 110/678 (16%), and 4/110 were PE+ (posterior probability 3.8%), and 9/110 (8.2%) had pneumonia. With RGS≤6 and a threshold <1000 ng/mL, D-dimer was negative in 208/678 (31%) and 11/208 (5.3%) were PE+, but 10/11 missed PEs were subsegmental, and none had concomitant DVT. Pneumonia was found in 12/208 (5.4%) with RGS≤6 and D-dimer<1000 ng/mL.

Conclusions—Doubling the threshold for a positive D-dimer with a PE unlikely pretest probability could reduce CTPA scanning with a slightly increased risk of missed isolated subsegmental PE, and no increase in rate of missed pneumonia.

Clin Chem. 2005 May;51(5):825-9. Epub 2005 Mar 11.

D-dimer concentrations in normal pregnancy: new diagnostic thresholds are needed.

Kline JA, Williams GW, Hernandez-Nino J.

Abstract

BACKGROUND:

Pregnancy is known to increase the D-dimer concentration above the conventional normal threshold of 0.50 mg/L, leading to an increased false-positive D-dimer test when venous thromboembolism (VTE) is clinically suspected in a pregnant patient. Our aim was to determine the effect of normal pregnancy on the D-dimer concentration.

METHODS:

Healthy women who were seeking to become pregnant and had no preexisting condition known to increase the D-dimerconcentration were identified. Quantitative D-dimer measurements (MDA turbidimetric assay) and fibrinogen assays were performed before conception, at each trimester, and at 4 weeks postpartum. Patients were excluded for fetal loss or preeclampsia.

RESULTS:

A total of 50 women were enrolled in the study, and blood samples were obtained at preconception and all trimesters from 23 women. The mean (SD) preconception D-dimer concentration was 0.43 (0.49) mg/L, and 79% of women had a D-dimer concentration <0.50 mg/L. D-Dimer increased with each trimester such that only 22% of women in the second trimester and none (of 23) in the third trimester (95% confidence interval, 0-14%) had a D-dimer concentration <0.50 mg/L. We found no correlation between either the D-dimer and fibrinogen concentrations or between the increases in D-dimer and fibrinogen with pregnancy.

CONCLUSIONS:

Normal pregnancy causes a progressive increase in circulating D-dimer. **The D-dimer test has no use in ruling out VTE in the third trimester if a cutoff of 0.50 mg/L is used.** A large management study is needed to establish new thresholds for the D-dimer to rule out VTE in each trimester.

European Heart Journal (2014) 35, 3033–3080
doi:10.1093/eurheartj/ehu283

ESC GUIDELINES

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

- D-dimer ölçümünün hamilelikteki faydası tartışmalı
- Gebelik boyunca fizyolojik olarak artar
- Normal D-dimer cut-off değeri kullanılmalı
- D-dimer yüksek ise, alt ekstremite Doppler US
- DVT (+) ise, tedavi

- Normal D-dimer düzeyi, kronik PE’yi dışlamaz
- Küçük segmental PE de sensitivite düşüktür
- Akut hastalık, AMI, Aort diseksiyonu, malignensi, travma, cerrahi sonrası, sepsis, DIC, kronik böbrek hastalığı, ileri yaş, romatoid faktör, d-dimer düzeyini yükseltir
- Bu hastalarda d-dimer değerlendirmesi konusunda fikir birliği yok
- Tedavi izleminde kullanımı araştırılıyor

Stokes NR, Dietz BW, Liang JJ. Cardiopulmonary laboratory biomarkers in the evaluation of acute dyspnea. Open Access Emerg Med.2016 May 17;8:35-45

MR-proANP ve MR-proADM

ANP

Atriyal gerilime bağlı atriyumdan salınır

Natriüretik, vazodilatör

Adrenomedullin (ADM)

Çok sayıda dokudan salınır

Güçlü vazodilatör, hipotansif, natriüretik

MR-proANP ve MR-proADM, stabil, ölçümü mümkün

Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 19, 2010
ISSN 0735–1097/$36.00
doi:10.1016/j.jacc.2010.02.025

FOCUS ISSUE: BIOMARKERS IN CARDIOVASCULAR DISEASE

Clinical Research

Biomarkers and Acute Dyspnea

Mid-Region Pro-Hormone Markers for Diagnosis and Prognosis in Acute Dyspnea

Results From the BACH (Biomarkers in Acute Heart Failure) Trial

Alan Maisel, MD,*** Christian Mueller, MD,† Richard Nowak, MD,‡ W. Frank Peacock, MD,§ Judd W. Landsberg, MD,‖ Piotr Ponikowski, MD, PHD,¶ Martin Mockel, MD,# Christopher Hogan, MD,** Alan H. B. Wu, PHD,†† Mark Richards, MD, PHD,‡‡ Paul Clopton, MS,* Gerasimos S. Filippatos, MD,§§ Salvatore Di Somma, MD,‖‖ Inder Anand, MD, DPHIL (OXON),¶¶ Leong Ng, MD,## Lori B. Daniels, MD, MAS,*** Sean-Xavier Neath, MD, PHD,*** Robert Christenson, PHD,††† Mihael Potocki, MD,† James McCord, MD,‡ Garret Terracciano, BS,‡‡‡ Dimitrios Kremastinos, MD,§§ Oliver Hartmann, MSC,§§§ Stephan von Haehling, MD,†† Andreas Bergmann, PHD,§§§ Nils G. Morgenthaler, MD, PHD,§§§ Stefan D. Anker, MD, PHD#‖‖

San Diego, La Jolla, and San Francisco, California; Basel, Switzerland; Detroit, Michigan; Cleveland, Ohio; Wroclaw, Poland; Berlin, Germany; Richmond, Virginia; Christchurch, New Zealand; Athens, Greece; Rome, Italy; Minneapolis, Minnesota; Leicester, United Kingdom; and Baltimore, Maryland

Objectives Our purpose was to assess the diagnostic utility of mid-regional pro–atrial natriuretic peptide (MR-proANP) for the diagnosis of acute heart failure (AHF) and the prognostic value of mid-regional pro-adrenomedullin (MR-proADM) in patients with AHF.

Background There are some caveats and limitations to natriuretic peptide testing in the acute dyspneic patient.

Methods The BACH (Biomarkers in Acute Heart Failure) trial was a prospective, 15-center, international study of 1,641 patients presenting to the emergency department with dyspnea. A noninferiority test of MR-proANP versus B-type natriuretic peptide (BNP) for diagnosis of AHF and a superiority test of MR-proADM versus BNP for 90-day survival were conducted. Other end points were exploratory.

Results MR-proANP (≥120 pmol/l) proved noninferior to BNP (≥100 pg/ml) for the diagnosis of AHF (accuracy difference 0.9%). In tests of secondary diagnostic objectives, MR-proANP levels added to the utility of BNP levels in patients with intermediate BNP values and with obesity but not in renal insufficiency, the elderly, or patients with edema. Using cut-off values from receiver-operating characteristic analysis, the accuracy to predict 90-day survival of heart failure patients was 73% (95% confidence interval: 70% to 77%) for MR-proADM and 62% (95% confidence interval: 58% to 66%) for BNP (difference $p < 0.001$). In adjusted multivariable Cox regression, MR-proADM, but not BNP, carried independent prognostic value ($p < 0.001$). Results were consistent using NT-proBNP instead of BNP ($p < 0.001$). None of the biomarkers was able to predict rehospitalization or visits to the emergency department with clinical relevance.

Conclusions MR-proANP is as useful as BNP for AHF diagnosis in dyspneic patients and may provide additional clinical utility when BNP is difficult to interpret. MR-proADM identifies patients with high 90-day mortality risk and adds prognostic value to BNP. (Biomarkers in Acute Heart Failure [BACH]; NCT00537628) (J Am Coll Cardiol 2010;55:2062–76) © 2010 by the American College of Cardiology Foundation

MR-proANP ve MR-proADM

- MR-proANP acil servise dispne ile başvuran hastalarda, AKY tanı ve dışlama değeri BNP den düşük değil.

MR-proANP : cutoff point $120 pmol/L, sensitivity 97%, specificity 59.9%, accuracy 73.6%

BNP: cutoff point $100 pg/mL, sensitivity 95.6%, specificity 61.9%, accuracy 72.7%

- MR-proADM, akut dekompanze KY olan dispneik hastalarda, 90 günlük mortalite riskini belirlemede, BNP ve NT-proBNP'den daha üstün[1]
- Yüksek MR-proANP ve MR-proADM düzeylerinde mortalite daha yüksek[1]

[1]Maisel A, Mueller C, Nowak R, et al. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol*. 2010;55(19):2062–2076.

MR-proANP ve MR-proADM

Tanı ve prognostik potansiyelleri umut verici ancak; ,

Şu anda klinik faydaları belirsiz,

Rutin kullanım için ileri çalışmalar gerekli

Galectin 3

- β-galaktozid bağlayıcı proteinler ailesinin bir üyesi
- Kalp, böbrek, kan damarları, makrofajlarda
- Kardiyak fibroblast proliferasyonuna ve kollajen birikintisine neden olur
- İmmunite ve inflamatuvar cevapta rol oynar

ACC.15
TCT@ACC-IS | Innovation in Intervention

A773
JACC March 17, 2015
Volume 65, Issue 10S

Heart Failure and Cardiomyopathies

GALECTIN-3 FOR HEART FAILURE RISK STRATIFICATION IN PATIENTS AFTER ACUTE CORONARY SYNDROMES (ACS): INSIGHTS FROM THE SOLID-TIMI 52 TRIAL

Moderated Poster Contributions
Heart Failure and Cardiomyopathies Moderated Poster Theater, Poster Hall B1
Saturday, March 14, 2015, 10:45 a.m.-10:55 a.m.

AKS sonrası, Gal-3'teki yükselme, KY ve ve kardiyovasküler ölüm ile ilişkili bulundu

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION,
THE AMERICAN HEART ASSOCIATION, INC., AND THE HEART FAILURE SOCIETY OF AMERICA
PUBLISHED BY ELSEVIER

VOL. 70, NO. 6, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.04.025

CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association
Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

IIb	B-NR

See Online Data Supplements A and B.

In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification (27,95,98,99,103,114-119).

MODIFIED: 2013 recommendations have been combined into prognosis section, resulting in LOE change from A to B-NR.

Biomarkers of myocardial fibrosis (e.g., soluble ST2 receptor, galectin-3, high-sensitivity cardiac troponin, and others) are predictive of hospitalization and death in patients with HF and also are additive to natriuretic peptide biomarker levels in their prognostic value (117,119-126). A combination of biomarkers may ultimately prove to be more informative than single biomarkers (127).

Soluble ST2

- ST2 = Tümörijenite 2'nin Supresyonu
- İnterlökin I reseptör ailesinden, İnterlökin 1 reseptör like I olarak da biliniyor
- İnterlökin 33 reseptörü
- Deneysel modellerde kardiyoprotektif olduğu, myokard fibrozisini, kardiyomiyosit hipertrofisini, apoptozisi azalttığı ve miyokard fonksiyonunu iyileştirdiği kanıtlanmış
- Kardiyomiyositler ve pulmoner endotelyal hücrelerden salgılanır

- sST2, AKY de anlamlı miktarda yüksek olmakla beraber, NT-proBNP, KY tanısında daha üstün[1]
- Yüksek sST2 düzeyleri, akut dekompanze KY ve AKS hastalarında, hastalık şiddeti ve artmış morbidite ile ilişkilidir[2]
- KOAH, pulmoner hipertansiyon, astım ve pnömoni de dahil olmak üzere patolojik akciğer hastalığında sST2 artar [3,4,5]

[1]Januzzi JL Jr, Peacock WF, Maisel AS, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. *J Am Coll Cardiol*. 2007;50(7):607–613.

[2]Dieplinger B, Egger M, Haltmayer M, et al. Increased soluble ST2 predicts long-term mortality in patients with stable coronary artery disease: results from the Ludwigshafen risk and cardiovascular health study. *Clin Chem*. 2014;60(3):530–540.

[3]Brown AM, Wu AH, Clopton P et.al. ST2 in emergency department chest pain patients with potential acute coronary syndromes. *Ann Emerg Med*. 2007;50(2):153–158.

[4]Martinez-Rumayor A, Camargo CA, Green SM et al.. Soluble ST2 plasma concentrations predict 1-year mortality in acutely dyspneic emergency department patients with pulmonary disease. *Am J Clin Pathol*. 2008;130(4):578–584.

[5]Oshikawa K, Kuroiwa K, Tago K, et al. Elevated soluble ST2 protein levels in sera of patients with asthma with an acute exacerbation. *Am J Respir Crit Care Med*. 2001;164(2):277–281.

sST2

- Spesifikliği zayıf olup, dispne etiyolojisini belirlemede yararı sınırlı
- AKS, KY ve diğer kardiyopulmoner hastalar için prognostik değer sağlar.
- Klinik pratikte ST2 kullanımı için, daha fazla araştırmaya ihtiyaç vardır.

Review Article

Soluble ST2: A Biomarker to Monitor Heart Failure Progression and Treatment

Marin Nishimura[1], MD; Justin Sharim[2], MD; Yu Horiuchi[3], MD; Olga Barnett[4], MD; Nicholas Wettersten[1], MD; Alan S Maisel[1], MD

[1]Division of Cardiovascular Medicine, University of California San Diego, [2]Department of Medicine, University of California, [3]Division of Cardiovascular

ABSTRACT

Measurement of cardiac biomarkers has become routine for the care of patients with heart failure (HF). While troponin and natriuretic peptides are well-entrenched in the guidelines, soluble ST2 (sST2) is a novel biomarker that has shown consistent performance and is ready for clinical use. Multiple studies support the use of sST2 in both acute and chronic HF for prognostication. We suggest a novel scheme to guide HF management based on ambulatory sST2 levels.

Journal of
Clinical Medicine

MDPI

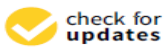
Review

Cardiac Biomarkers in the Emergency Department: The Role of Soluble ST2 (sST2) in Acute Heart Failure and Acute Coronary Syndrome—There is Meat on the Bone

Aneta Aleksova [1,*], Alessia Paldino [1], Antonio Paolo Beltrami [2], Laura Padoan [3], Massimo Iacoviello [4], Gianfranco Sinagra [1], Michele Emdin [5,6] and Alan S. Maisel [7]

1 Cardiovascular Department, Azienda Sanitaria Universitaria di Trieste and Department of Medical Surgical and Health Sciences, University of Trieste, 34100 Trieste, Italy; alessiapaldino@gmail.com (A.P.); gianfranco.sinagra@asuits.sanita.fvg.it (G.S.)
2 Department of Medicine, University of Udine, 33100 Udine, Italy; antonio.beltrami@uniud.it
3 Sport and Exercise Medicine Division, Department of Medicine, University of Padova, 35122 Padova, Italy; argonauta92@hotmail.it
4 University Cardiology Unit, Cardiothoracic Department, University Policlinic Hospital of Bari, 70124 Bari, Italy; massimo.iacoviello@gmail.com
5 Department of Life science, Scuola Superiore Sant'Anna, 56127 Pisa, Italy; emdin@ftgm.it
6 Fondazione Toscana Gabriele Monasterio, National Research Council, 56124 Pisa, Italy
7 Division of Cardiology, University of California San Diego, San Diego, CA 92093, USA; asmaisel@gmail.com
* Correspondence: aaleksova@units.it; Tel.: +39-3405507762

Received: 30 January 2019; Accepted: 19 February 2019; Published: 22 February 2019



Abstract: Soluble ST2 (sST2) has recently emerged as a promising biomarker in the field of acute cardiovascular diseases. Several clinical studies have demonstrated a significant link between sST2 values and patients' outcome. Further, it has been found that higher levels of sST2 are associated with an increased risk of adverse left ventricular remodeling. Therefore, sST2 could represent a useful tool that could help the risk stratification and diagnostic and therapeutic work-up of patients admitted to an emergency department. With this review, based on recent literature, we have built sST2-assisted flowcharts applicable to three very common clinical scenarios of the emergency department: Acute heart failure, type 1, and type 2 acute myocardial infarction. In particular, we combined sST2 levels together with clinical and instrumental evaluation in order to offer a practical tool for emergency medicine physicians.

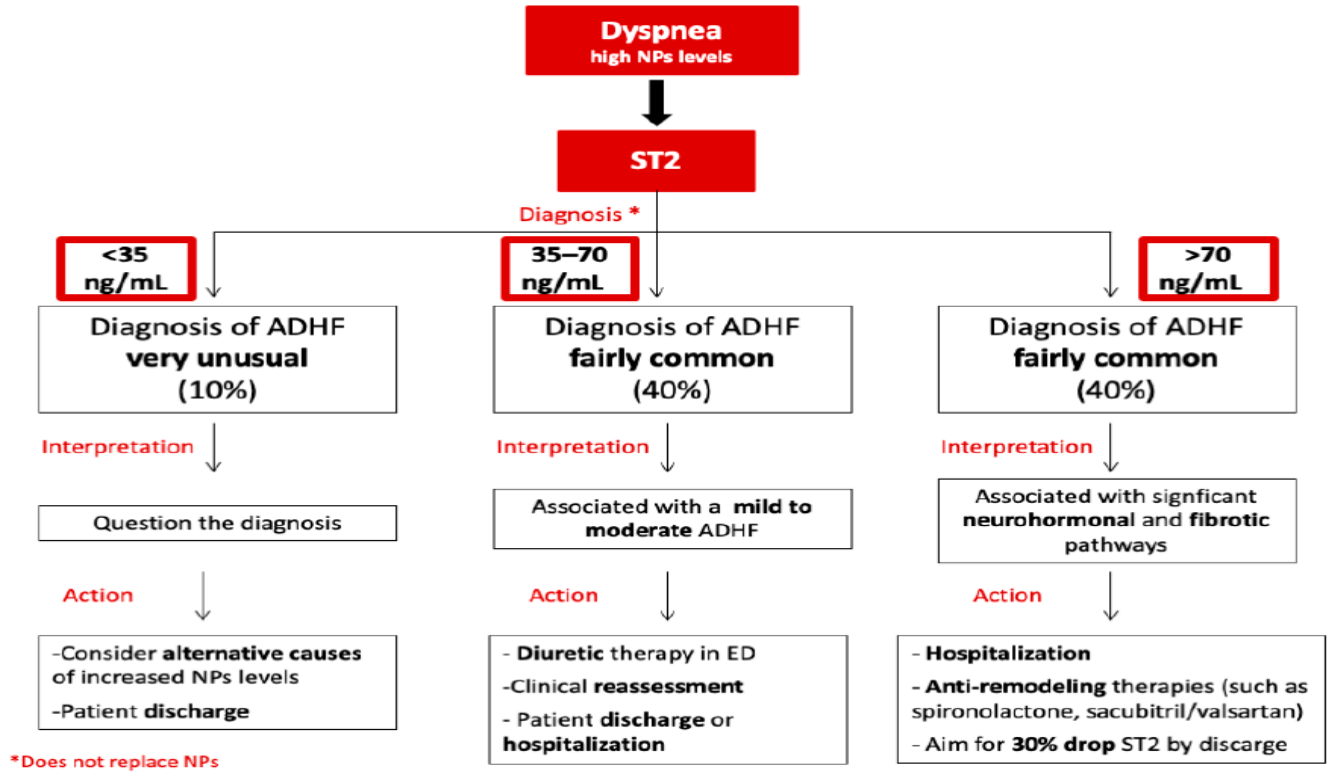
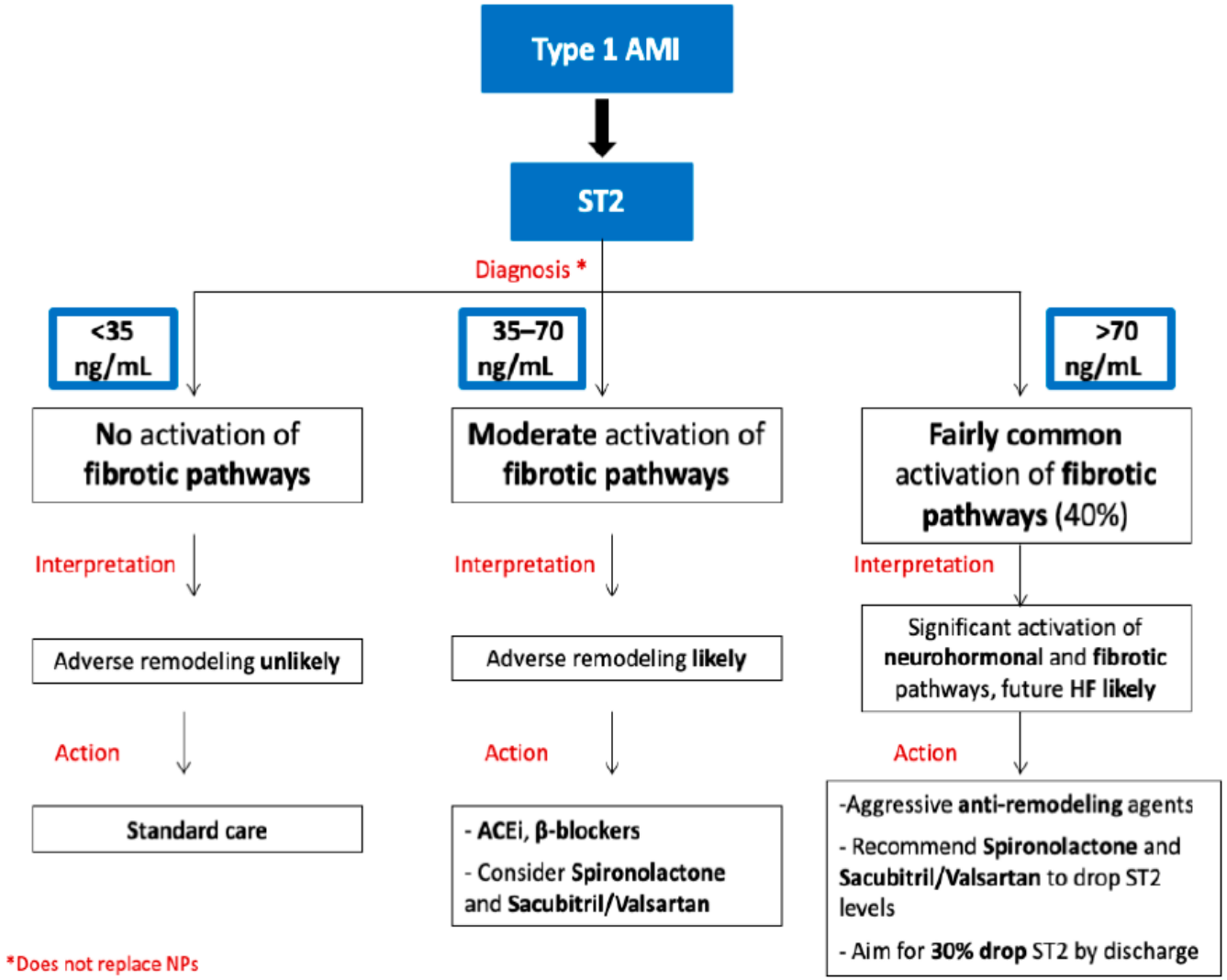
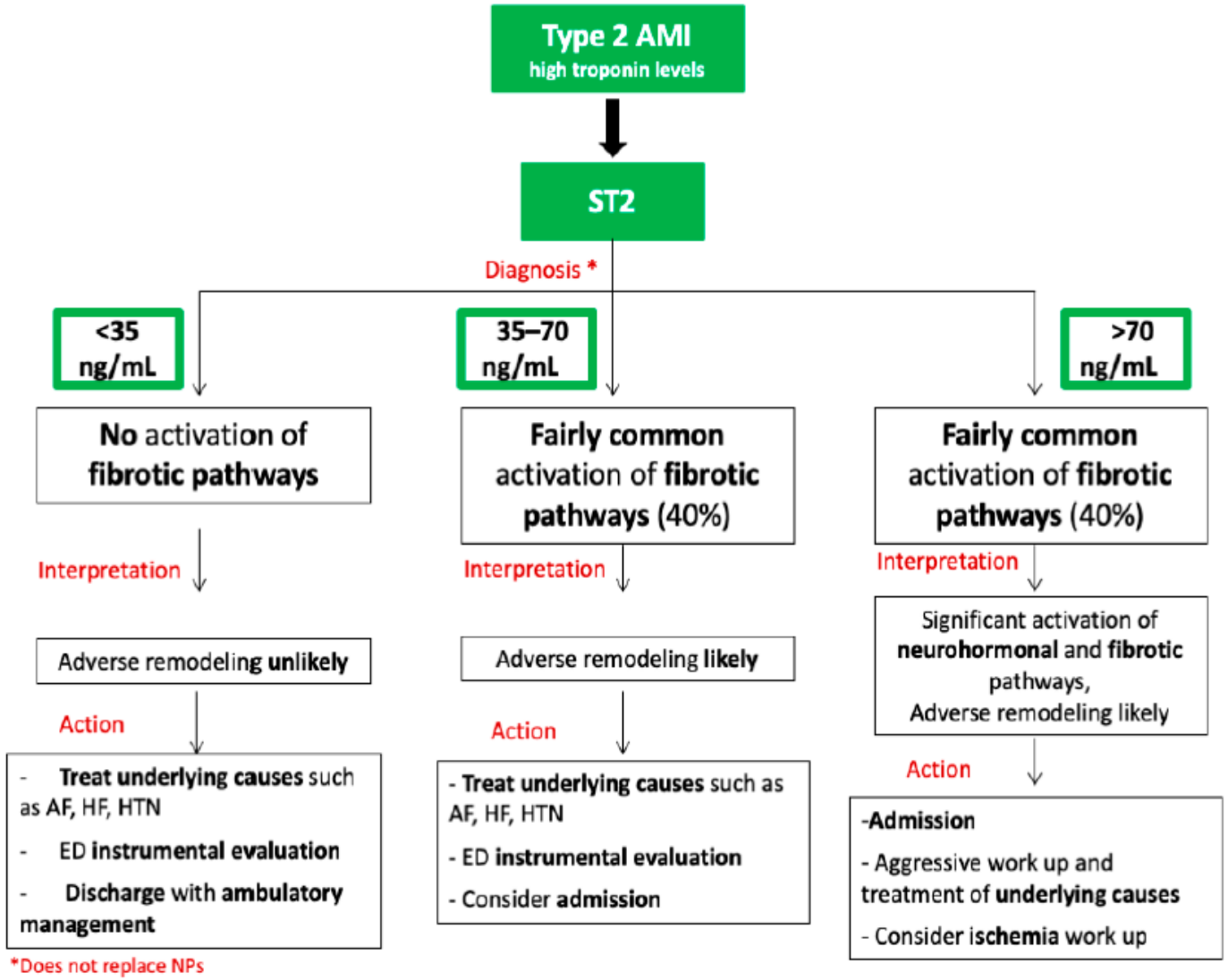


Figure 1. Flowchart showing the proposed soluble ST2 (sST2) aided management of patients with dyspnea and elevated natriuretic peptides (NPs). In patients with dyspnea and elevated NPs, sST2 levels can help to identify 3 classes of patients. If sST2 < 35 ng/mL, the diagnosis of acute decompensated heart failure (ADHF) is unusual. In patients with 35 ≤ sST2 ≤ 70 ng/mL, ADHF is more common but mild to moderate. If sST2 > 70 ng/mL, ADHF is fairly common, requiring hospitalization and anti-remodeling therapies. Suggested actions for each class of patients are shown in the panels below.


Type 1 AMI
ST2
Diagnosis *
<35 ng/mL
35–70 ng/mL
>70 ng/mL
No activation of fibrotic pathways
Moderate activation of fibrotic pathways
Fairly common activation of fibrotic pathways (40%)
Interpretation
Interpretation
Interpretation
Adverse remodeling unlikely
Adverse remodeling likely
Significant activation of neurohormonal and fibrotic pathways, future HF likely
Action
Action
Action
Standard care
- ACEi, β-blockers
- Consider Spironolactone and Sacubitril/Valsartan
-Aggressive anti-remodeling agents
- Recommend Spironolactone and Sacubitril/Valsartan to drop ST2 levels
- Aim for 30% drop ST2 by discharge
*Does not replace NPs


Type 2 AMI
high troponin levels
ST2
Diagnosis *
<35 ng/mL
35–70 ng/mL
>70 ng/mL
No activation of fibrotic pathways
Fairly common activation of fibrotic pathways (40%)
Fairly common activation of fibrotic pathways (40%)
Interpretation
Interpretation
Interpretation
Adverse remodeling unlikely
Adverse remodeling likely
Significant activation of neurohormonal and fibrotic pathways, Adverse remodeling likely
Action
Action
Action
- Treat underlying causes such as AF, HF, HTN
- ED instrumental evaluation
- Discharge with ambulatory management
- Treat underlying causes such as AF, HF, HTN
- ED instrumental evaluation
- Consider admission
-Admission
- Aggressive work up and treatment of underlying causes
- Consider ischemia work up
*Does not replace NPs

Troponin

AMI teşhisi için kullanılması önerilen tek biyobelirteç, yüksek sensivitesi ve spesifitesi nedeniyle kardiyak troponinlerdir [1,2,3,4]

[1] Amsterdam EA, Wenger NK, Brindis RG, et al, for the ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 23. 130(25):e344-426.

[2]O'Gara PT, Kushner FG, Ascheim DD, et al, for the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Jan 29. 127(4):e362-425.

[3]Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14. 37(3):267-315.

[4]American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Jan 29. 61(4):e78-140:78-140. [Medline].

Table 5. Summary of Recommendations for Cardiac Biomarkers and the Universal Definition of MI

Recommendations	COR	LOE	References
Diagnosis			
Measure cardiac-specific troponin (troponin I or T) at presentation and 3–6 h after symptom onset in all patients with suspected ACS to identify pattern of values	I	A	21, 64, 67–71, 152–156
Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features	I	A	21, 72–74, 157
Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values	I	A	67, 68, 72
With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS	III: No Benefit	A	158–164
Prognosis			
Troponin elevations are useful for short- and long-term prognosis	I	B	71, 73, 165, 166
Remeasurement of troponin value once on d 3 or 4 in patients with MI may be reasonable as an index of infarct size and dynamics of necrosis	IIb	B	164, 165
BNP may be reasonable for additional prognostic information	IIb	B	87, 88, 167–171

ACS indicates acute coronary syndromes; BNP, B-type natriuretic peptide; CK-MB, creatine kinase myocardial isoenzyme; COR, Class of Recommendation; LOE, Level of Evidence; and MI, myocardial infarction.

Blood has to be drawn promptly for troponin (cardiac troponin T or I) measurement. The result should be available within 60 min. The test should be repeated 6–9 h after initial assessment if the first measurement is not conclusive. Repeat testing after 12–24 h is advised if the clinical condition is still suggestive of ACS.	I	A
A rapid rule-out protocol (0 and 3 h) is recommended when highly sensitive troponin tests are available (see *Figure 5*).	I	B

Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14. 37(3):267-315.

Table 2 Causes of elevated troponin

Myocardial infarction
Heart failure
End-stage renal disease
Pulmonary embolism
COPD
Sepsis and other critical illness
Acute cerebrovascular event
Intense exercise
Cardiac contusion
Acute pericarditis and myocarditis
Tachyarrythmias
Cardioversion
Cardiopulmonary resuscitation
Coronary vasospasm
Cardiac surgery, percutaneous coronary intervention
False-positive test

Note: Information from Inbar R, Shoenfeld Y.[76]
Abbreviation: COPD, chronic obstructive pulmonary disease.

- Akut Pulmoner Emboli vakalarının 1/3'ünden fazlasında, muhtemelen sağ ventriküler gerilmesine bağlı troponin yükselir[1]
- Troponin, PE tanısında duyarlı ve spesifik olmasa da kısa dönem mortalite riski ile ilişkilendirilmiştir[2,3]

[1]Meyer T, Binder L, Hruska N et.al. Cardiac troponin I elevation in acute pulmonary embolism is associated with right ventricular dysfunction. *J Am Coll Cardiol*. 2000;36(5):1632–1636.

[2]Hakemi EU, Alyousef T, Dang G et.al. The prognostic value of undetectable highly sensitive cardiac troponin I in patients with acute pulmonary embolism. *Chest*. 2015;147(3):685–694.

[3]Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation*. 2007;116(4):427–433.

- KOAH akut alevlenmelerinde troponin T de dört kat artış [1]
- KOAH alevlenmeleri, ARDS ve kronik pulmoner hipertansiyonu olan hastalarda, kardiyak troponinde yükselme, tüm nedenlere bağlı ölüm oranları ile ilişkili [2,3,4]
- Akut KY de troponin düzeyleri yüksek ise, AMI yokluğunda dahi, mortalite riski artar

[1]Soyseth V, Bhatnagar R, Holmedahl NH, et al. Acute exacerbation of COPD is associated with fourfold elevation of cardiac troponin T. *Heart*. 2013;99(2):122–126.

[2]Pavasini R, d'Ascenzo F, Campo G, et al. Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: systematic review and meta-analysis. *Int J Cardiol*. 2015;191:187–193.

[3]Kelley WE, Januzzi JL, Christenson RH. Increases of cardiac troponin in conditions other than acute coronary syndrome and heart failure. *Clin Chem*. 2009;55(12):2098–2112.

[4]Torbicki A, Kurzyna M, Kuca P, et al. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. *Circulation*. 2003;108(7):844–848

Diğer biyomarkerlar

Myeloperoxidase, Growth differentiation factor 15, Lipoprotein associated, Phospholipase A2, Fatty acid-binding protein, İschaemia-modified-albumin, Copeptin, Chromogranin A, Urocortin, Apelin, Secretory sphingomyelinase, Cardiotrophin-1, Cystatin C, İnterleukin-6, Procalcitonin, Qsox, İnterleukin 8, C-terminal pro-endothelin-1, Neutrophil gelatinase associated lipocalin, miR423-5p, miR320a , miR22, proguanylin, Tumor necrosis factor receptor superfamily member 6 (FAS), C-C motif chemokine 3……

LİSTE ÇOK KALABALIK

Dispnede kardiyo-pulmoner biyomarkerlar
ÖZET

- Biyomarkerlar, hikaye ve fizik muayene sonuçlarına göre oluşan klinik şüphe bazında istenmeli ve kullanılmalı
- Akut dispnenin nedeni olarak Akut dekompanze KY tanısında hem BNP hem de NT-proBNP faydalı biyobelirteçlerdir
- D-dimer, düşük klinik riskli hastalarda PE'yi ekarte etmek için kullanılmalıdır
- Galektin 3'ün diagnostik faydası ise sınırlıdır
- sST2 ve Galectin 3, akut başlangıçlı dispne ile başvuran hastalarda prognostik marker

“It’s tough to make predictions, especially about the future.

The future ain’t what it used to be.”

Yogi Berra