

Il pro-BNP: vezzo, danno, utilità?

Cristiano Perani
ASST Spedali Civili di Brescia



Editorial

The Heart as an Endocrine Organ

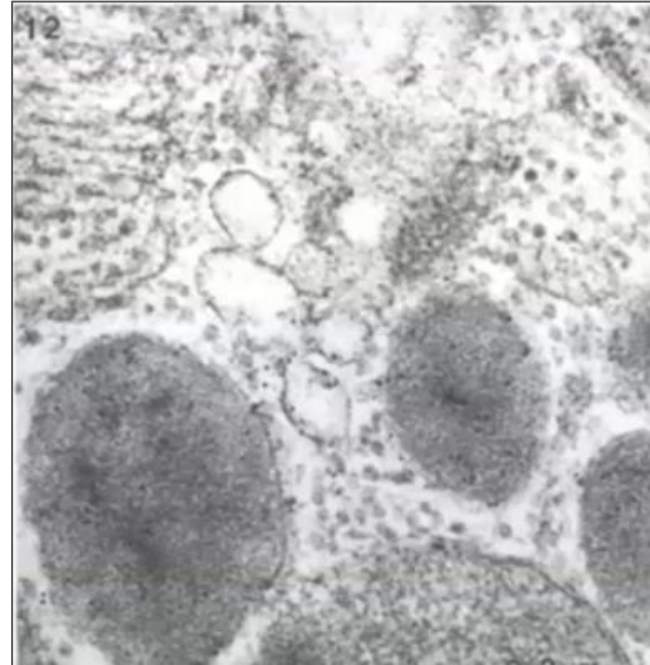
This work of William Harvey in the seventeenth century established the prime function of the heart as a pump, but a number of experiments carried out during this century can be interpreted to show that, under certain circumstances, the heart may also subserve an endocrine function. In 1921 Otto Loewi stimulated the cardiac sympathetic nerves of the isolated perfused turtle heart and noted that the rate and force of contraction of the heart were augmented. In addition, nerve stimulation also resulted in the release of a sympathomimetic substance into the perfusion fluid. Thus, Loewi observed that the fluid perfusing a turtle heart that had undergone sympathetic stimulation was capable of enhancing the contraction of another isolated turtle heart [1]. These experiments not only served as the basis for modern concepts of the mechanism of adrenergic neurotransmission, but they also demonstrated that the quantity of active adrenergic neurotransmitter substance released by an organ after sympathetic nerve stimulation could be sufficient to have a perceptible effect on the function of a tissue which is not stimulated directly.

Twelve years later Cannon and Rowesbotham extended Loewi's observation by showing that in the rat, which had been sensitized to the action of nerve stimulation by cocaine, stimulation of the cardioaccelerator nerve resulted in contraction of the desensitized nictitating membrane [2]. It was deduced that a chemical substance was released within the heart and was carried by the blood to the sensitized nictitating membrane. Additional support for this concept was provided by Sinschke and

Sarnoff who found that the contraction of the nictitating membrane following cardioaccelerator nerve stimulation could be prevented by treatment with the adrenergic blocking drug, dibenamine [3]. Hoffmann and collaborators demonstrated that the administration of acetylcholine to an isolated mammalian heart resulted in the liberation of an epinephrine-like substance capable of stimulating the contraction of a hypodynamic frog heart [4].

Cannon also showed that extracts of the heart have many of the biological properties of adrenaline [5]. von Euler demonstrated that the sympathomimetic compound in cattle heart was in fact norepinephrine [6]; Goodall measured its excretion [7], and Raab and Gilge showed that norepinephrine is also present in the human heart [8]. The close relationship between the sympathetic nerves and the norepinephrine content of the heart was suggested by the depletion of myocardial norepinephrine stores following postganglionic sympathectomy and degeneration of the sympathetic nerves to the heart [9,10]. It now appears likely that the norepinephrine stores of the mammalian heart are contained in the sympathetic nerves, particularly in the nerve endings, rather than in the muscle cells. Large quantities of epinephrine and norepinephrine are present in the adrenal chromaffin cells which line the cavity of the hearts of some primitive vertebrate forms [11,12]. This finding provides strong morphologic evidence that the heart contains cells capable of secreting catecholamines in organisms which are at a relatively low level on the phylogenetic scale.

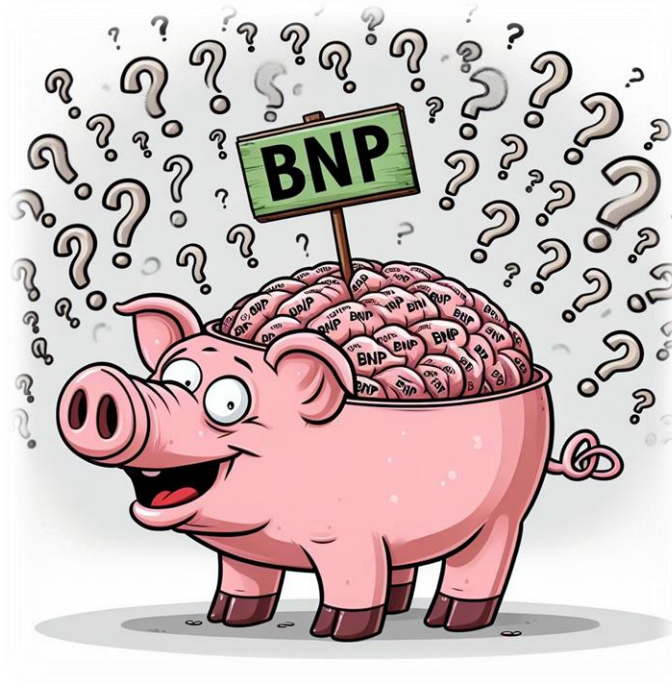
A Rapid and Potent Natriuretic Response to Intravenous Injection of Atrial Myocardial Extract in Rats



Braunwald Am J Med. 1964

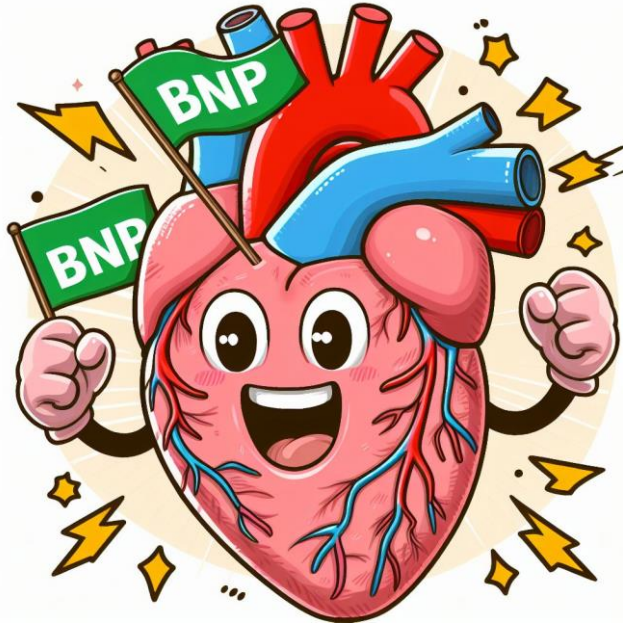
Bold and Zeidel, Life Sci. 1981

Peptidi natriuretici ... quella 'B' ?



Sudoh, T et al, A new natriuretic peptide in porcine brain. *Nature* **1988**

Peptidi natriuretici ... quella 'B' ?



Tateyama, Het al, Characterization of immunoreactive brain natriuretic peptide in human cardiac atrium. *Biochem. Biophys. Res. Commun.* **1990**



Sudoh, T et al, A new natriuretic peptide in porcine brain. *Nature* **1988**

Marcato allungamento
dei miociti



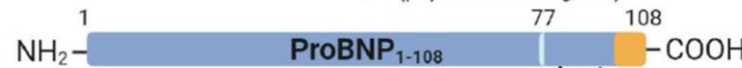
Trascrizione



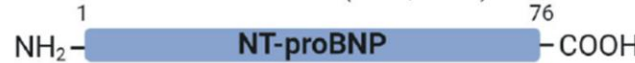
Traduzione



Processamento enzimatico
(peptidasi del segnale)



Processamento enzimatico
(furina, corina)



+



BNP

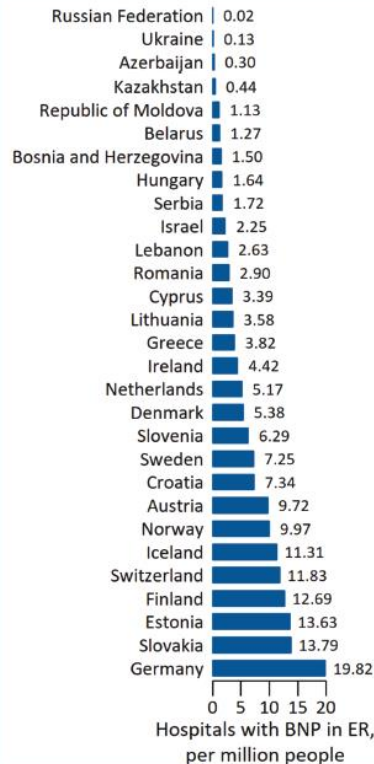
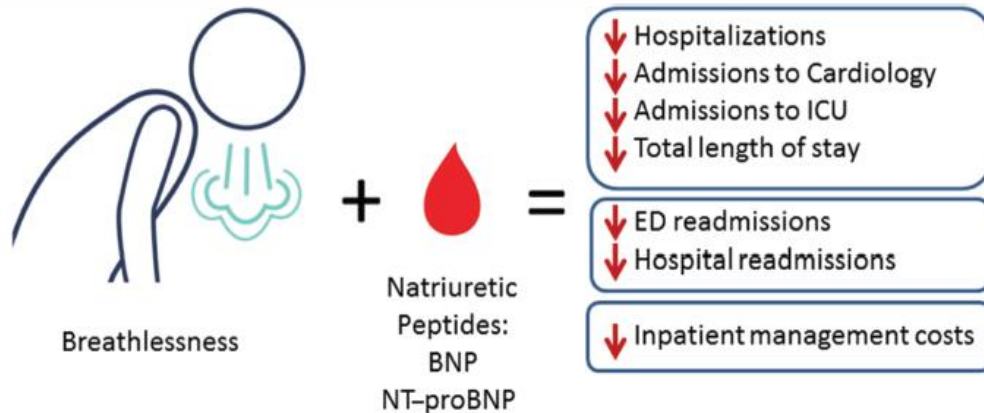
perptide 32 amminoacidi

- + Natriuresi
- + Diuresi
- + Vasodilatazione
- Sistema RAA

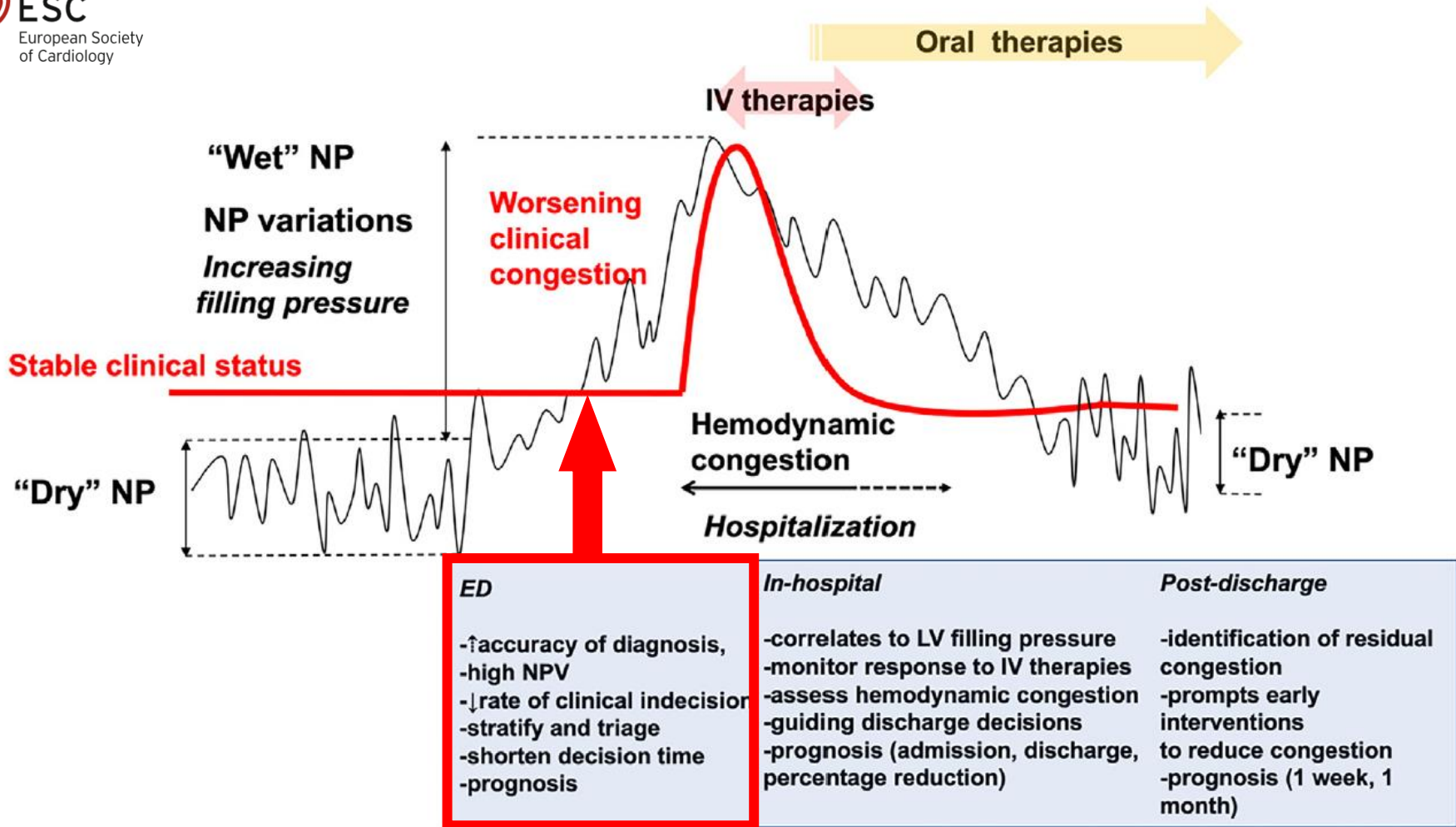
NT-ProBNP

Precursore inattivo
prodotto in misura
equimolare

The ‘Peptide for Life’ Initiative: a call for action to provide equal access to the use of natriuretic peptides in the diagnosis of acute heart failure across Europe



... ci credono moltissimo



**Natriuretic Peptides: Role in the Diagnosis and Management
of Heart Failure: A Scientific Statement From the Heart
Failure Association of the European Society of Cardiology,
Heart Failure Society of America and Japanese Heart Failure
Society**



«Natriuretic peptides **should be measured in all patients presenting with symptoms** suggestive of new onset or worsening HF, such as dyspnoea and/or fatigue, because **their use facilitates both early diagnosis or the early exclusion** of HF. Use of these biomarkers has the highest class of recommendation to support exclusion of HF due to their **very high negative predictive value (94-97%)**»

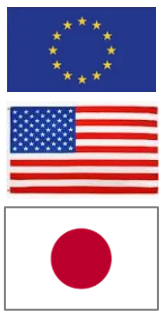


Natriuretic Peptides: Role in the Diagnosis and Management of Heart Failure: A Scientific Statement From the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society

Table 1. Recommendations for measurement of BNP or NT-proBNP in heart failure guidelines

	Recommendations	Class	Evidence
2022 AHA/ACC/HFSA	In patients presenting with dyspnea, measurement of BNP or NT-proBNP is useful to support a diagnosis or exclusion of HF.	I	A
	In patients with chronic HF, measurements of BNP or NT-proBNP levels are recommended for risk stratification.	I	A
	In patients hospitalized for HF, measurement of BNP or NT-proBNP levels at admission is recommended to establish prognosis.	I	A
	In patients at risk of developing HF, BNP or NT-proBNP-based screening followed by team-based care, including a cardiovascular specialist, can be useful to prevent the development of LV dysfunction or new-onset HF.	IIa	B-R
	In patients hospitalized for HF, a predischarge BNP or NT-proBNP level can be useful to inform the trajectory of the patient and establish a postdischarge prognosis.	IIa	B-NR
2021 ESC	Plasma concentrations of natriuretic peptides are recommended as initial diagnostic tests in patients with symptoms suggestive of HF to rule out the diagnosis. Elevated concentrations support a diagnosis of HF, are useful for prognostication, and may guide further cardiac investigation.	I	B
2017 JCS/JHFS	Confirm the diagnosis of HF.	I	A
	Assess the severity of HF.	I	A
	Assess the prognosis of HF.	I	A
	Monitor the efficacy of HF treatment.	IIa	B
	Screen patients susceptible to HF.	IIa	C

BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.



History
Signs/symptoms reflecting
congestion/hypoperfusion

NP's testing

Cut-off



RULE OUT

RULE IN

Exclude AHF
(NPV 94-98%)

Continue
AHF workup

NP grey zone

Exclude AHF

Ancillary testing
Chest-X ray, Lung
ultrasound, Echo

Confirm AHF diagnosis

Clinical profiles:
ADHF, Acute pulmonary edema,
Right-sided HF, Cardiogenic shock

Problemi analitici

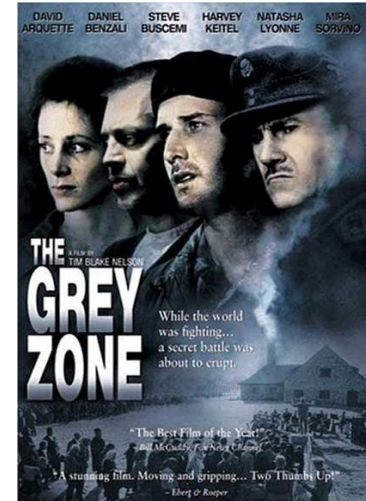
i peptidi natriuretici hanno un'intrinseca variabilità biologica (dry state)

25-30% per NT-pro-BNP

40% per BNP

La zona grigia:

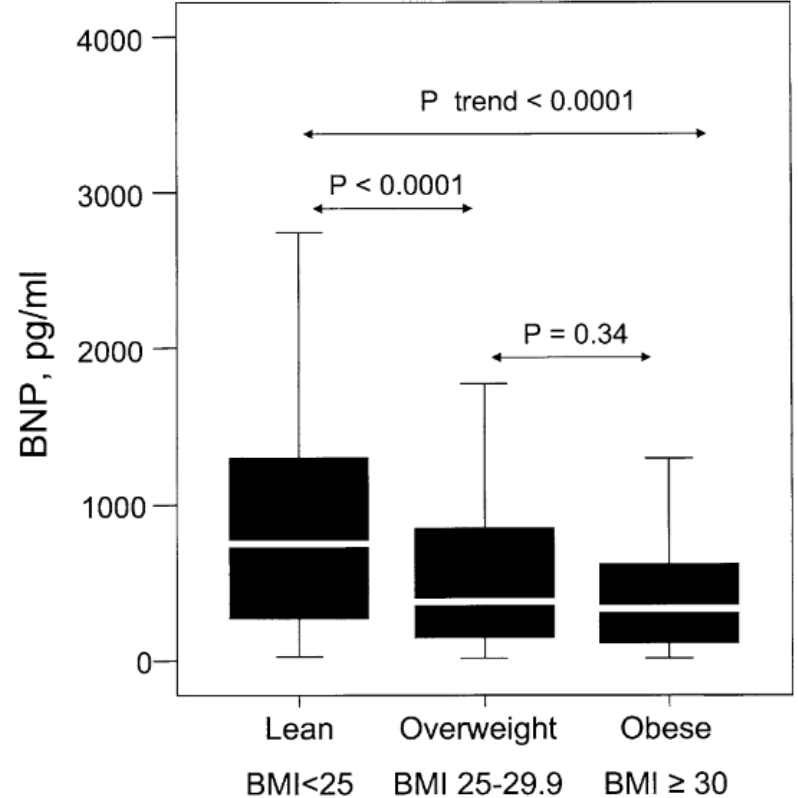
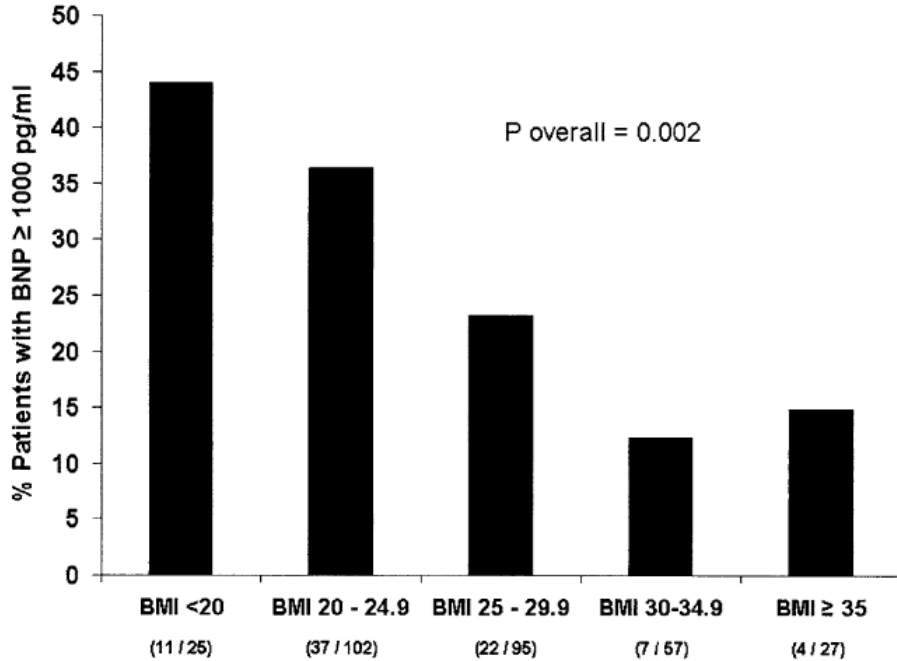
il 20% dei pazienti con dispnea acuta.
Nel 50% dei casi avranno diagnosi finale di scompenso cardiaco.





B-Type Natriuretic Peptide Levels in Obese Patients With Advanced Heart Failure

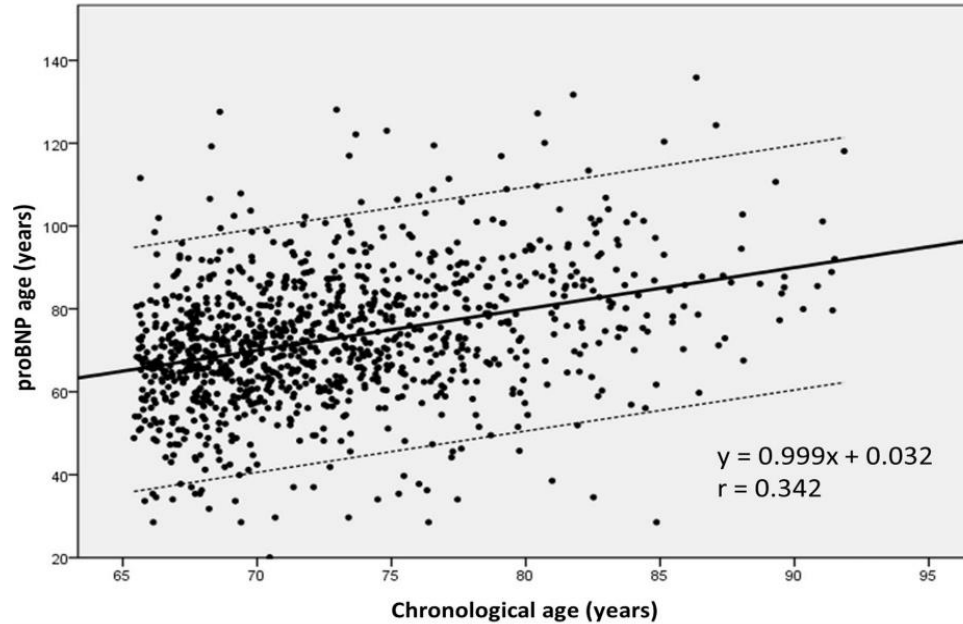
Tamara B. Horwich, MD, Michele A. Hamilton, MD, FACC, Gregg C. Fonarow, MD, FACC



The Use of Brain Natriuretic Peptide in the Evaluation of Heart Failure in Geriatric Patients

Mihai Marinescu ^{1,2,*}, Violeta Diana Oprea ^{1,2,†}, Aurel Nechita ^{1,3,†}, Dana Tutunaru ^{1,2},

Diagnostics 2023



Per il differente metabolismo del BNP rispetto al NT-proBNP quest'ultimo è strettamente influenzato con età, riducendo la sua specificità

METABOLISMO

BNP

Emivita 20'

Proteasi
plasmatiche

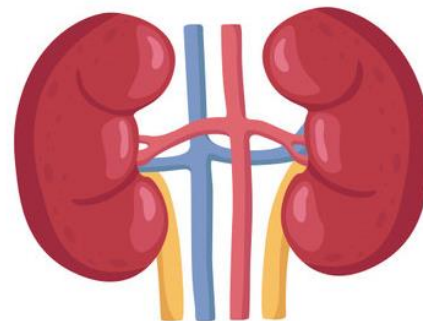
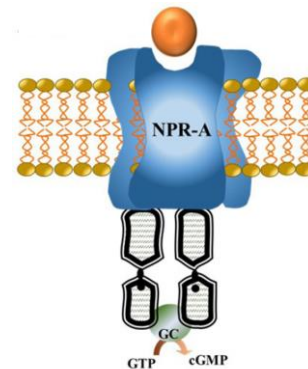
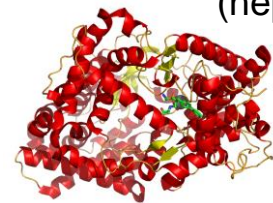
Internalizzazione cellulare
recettore-mediata

Escrezione urinaria

NT-proBNP

Emivita 60-120'

Escrezione urinaria



Review

B-Type Natriuretic Peptide (BNP) Revisited—Is BNP Still a Biomarker for Heart Failure in the Angiotensin Receptor/Neprilysin Inhibitor Era?

Lo studio PARADIGM-HF ha mostrato **un aumento iniziale dei livelli di BNP nei primi mesi di trattamento, seguito da una diminuzione nel tempo.**

While BNP is a neprilysin substrate, NT-proBNP is not. Due to the action of sacubitril, use of ENTRESTO would be expected to raise BNP levels, without having a direct effect on NT-proBNP. Therefore, only NT-proBNP, and not BNP, may be a suitable biomarker for the monitoring of heart failure patients treated with ENTRESTO.

**Fattori
confondenti** per
interpretazione
dei valori
di peptidi
natriuretici

**Fattori che aumentano
le concentrazioni di peptidi
natriuretici**

- Età avanzata
- Terapia con inibitori della neprilisina*
- Insufficienza renale
- Farmaci cardi tossici
- Sindrome coronarica acuta
- Disfunzione ventricolare destra
- Iperensione polmonare
- Embolia polmonare
- Aritmie (fibrillazione atriale)
- Anemia/condizioni di circolo iperdinamico (sepsi, ipertiroidismo)

**Fattori che diminuiscono
le concentrazioni di peptidi
natriuretici**

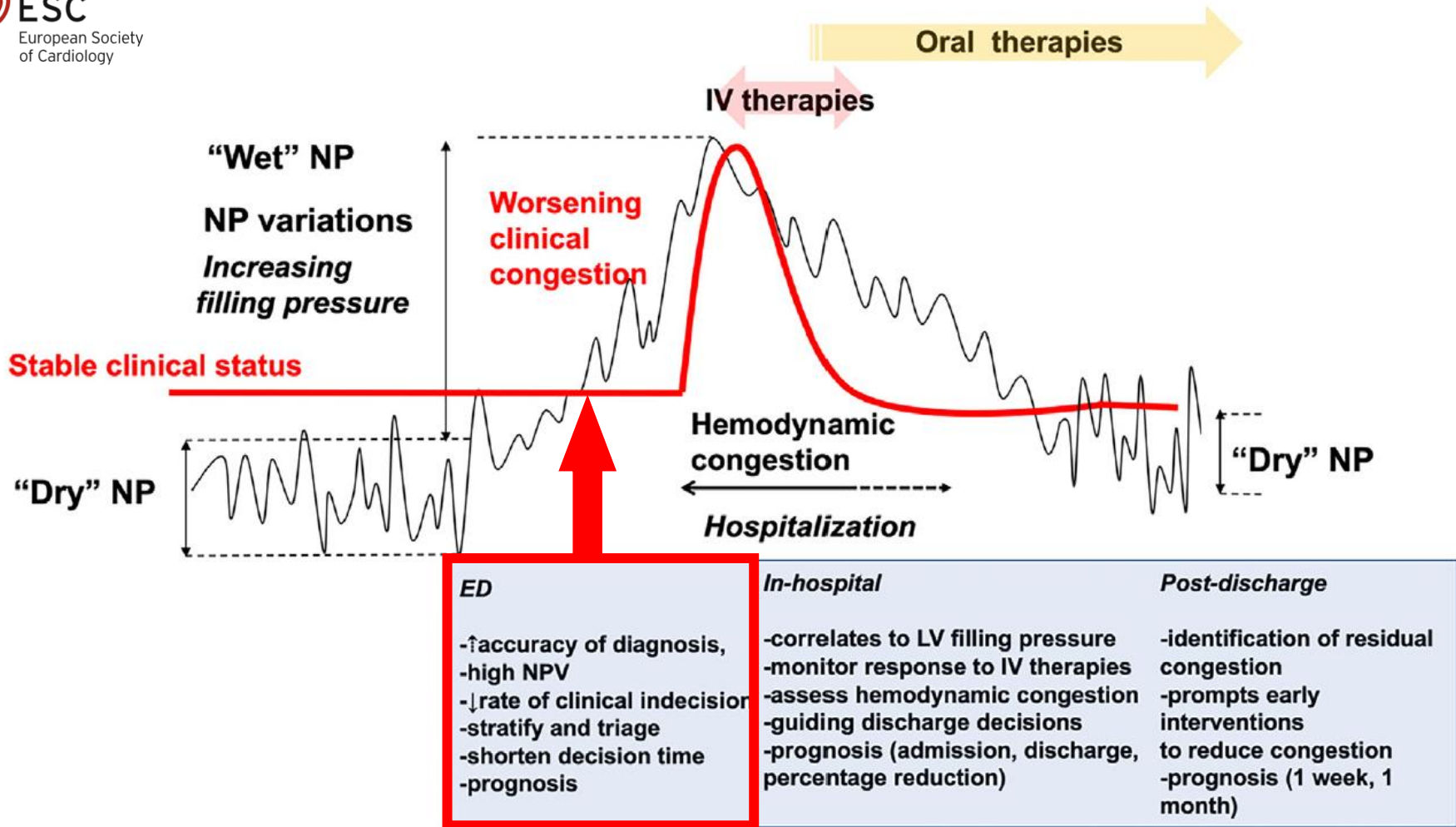
- Obesità
- Edema polmonare acuto (*flash*)
- Pericardite costrittiva
- Tamponamento cardiaco

*Solo per il peptide natriuretico di tipo B.



**pronto
soccorso**







**Bedside
evaluation**



Lung ultrasound-implemented diagnosis of acute decompensated heart failure in the Emergency Department - A SIMEU multicenter study

2015

Pivetta E, Goffi A, Lupia E, Tizzani M, Porrino G, Ferreri E, Volpicelli G, Balzaretto P, Banderali A, Iacobucci A, Locatelli S, Casoli G, Stone MB, Maule MM, Baldi I, Merletti F, Cibinel G; *for the SIMEU Group for Lung Ultrasound in the Emergency Department in Piedmont.*

multicenter, prospective cohort study
1005 patients presenting with acute dyspnea in seven Italian Eds

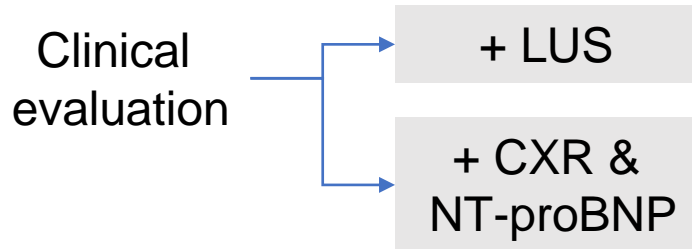


	Sens	Spec	LR+	LR-
Clinical work-up	85.3%	90%	8,6	0,02
LUS implemented	97%	97.4%	37,5	0,03
X-Ray	69.5%	82.1%	3,9	0,4
BNP/NT-proBNP	85%	61.7%	2,2	0,2

Lung ultrasound integrated with clinical assessment for the diagnosis of acute decompensated heart failure in the emergency department: a randomized controlled trial

Emanuele Pivetta^{1,2*}, Alberto Goffi^{3,4,5}, Peiman Nazerian⁶, Davide Castagno⁷, Camilla Tozzetti⁸, Pietro Tizzani^{2,9}, Maria Tizzani², Giulio Porrino², Enrico Ferreri², Valeria Busso², Fulvio Morello², Cristina Paglieri², Monica Masoero¹⁰, Elisa Cassine¹¹, Federica Bovo¹⁰, Stefano Grifoni⁶, Milena M. Maule¹, and Enrico Lupia^{2,12}, on behalf of the Study Group on Lung Ultrasound from the Molinette and Careggi Hospitals[†]

randomized trial conducted in
two emergency departments
N 518





Ann Emerg Med. 2022

Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Heart Failure Syndromes

Approved by ACEP Board of Directors, June 23, 2022




- 1. In adult patients presenting to the emergency department with suspected acute heart failure syndrome, is the diagnostic accuracy of point-of-care lung ultrasound sufficient to direct clinical management?**

Patient Management Recommendations

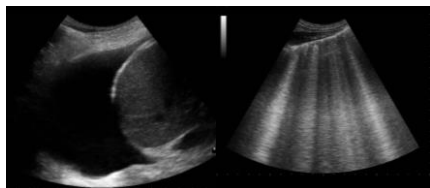
Level A recommendations. None specified.

Level B recommendations. Use point-of-care lung ultrasound as an imaging modality in conjunction with medical history and physical examination to diagnose acute heart failure syndrome when diagnostic uncertainty exists as the accuracy of this diagnostic test is sufficient to direct clinical management.*

Lung ultrasound in acute and chronic heart failure: a clinical consensus statement of the European Association of Cardiovascular Imaging (EACVI)

Luna Gargani ^{1*}, Nicolas Girerd ², Elke Platz ³, Pierpaolo Pellicori ⁴,
Ivan Stankovic ⁵, Alberto Palazzuoli⁶, Emanuele Pivetta ^{7,8},
Marcelo Haertel Miglioranza ^{9,10}, Hatem Soliman-Aboumarie ^{11,12},
Eustachio Agricola ¹³, Giovanni Volpicelli ¹⁴, Susanna Price ¹⁵,
Erwan Donal ¹⁶, Bernard Cosyns ¹⁷, and Aleksandar N. Neskovic ⁵

ACUTE HEART FAILURE



Aim

Advantages

DIAGNOSIS

Rule in and rule out acute left-sided HF in patients with dyspnoea.

Multiple, diffuse, bilateral B-lines rule in AHF.

Absence of multiple, diffuse, bilateral B-lines rules out AHF.

LUS improves diagnostic accuracy compared with standard strategy (chest X-ray + NT-proBNP).

LUS reduces time to correct diagnosis.

LUS detects subclinical pulmonary congestion in patients with HF who have mild or absent signs and symptoms.

MONITORING

Monitor decongestion during AHF hospitalization.

Reduction of the number of B-lines.

Reduction of the size of pleural effusion, if any.

Bedside monitoring to support decision-making in diuretic therapy and fluid management.

A significant reduction of B-lines during hospitalization is associated with a lower risk of rehospitalization for AHF and death at 6 months.

PROGNOSIS

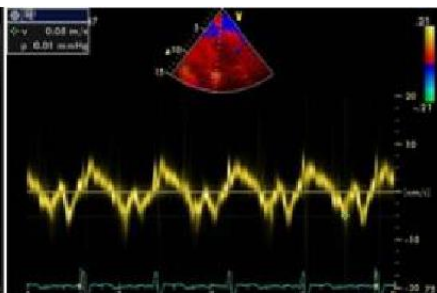
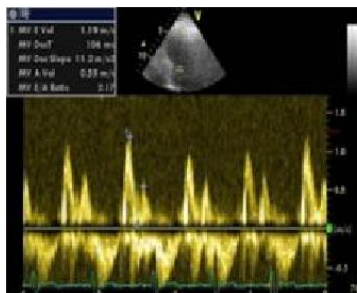
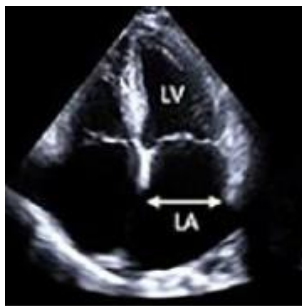
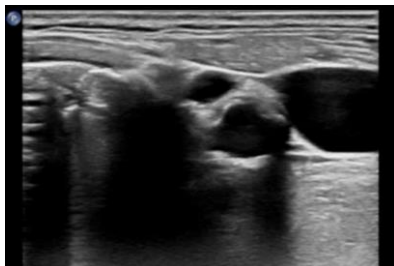
Determine the timing of discharge.

Detect persistent subclinical congestion at discharge to identify patients at higher risk of rehospitalization for AHF or death.

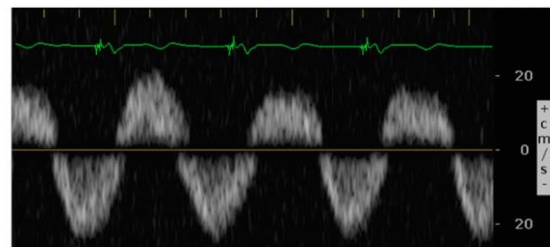
Persistent B-lines at discharge, even with resolved signs and symptoms of HF.

A high number of B-lines at discharge predict rehospitalization for AHF and death at 3 months.

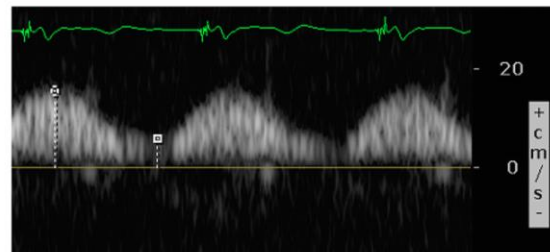
ACUTE HEART FAILURE



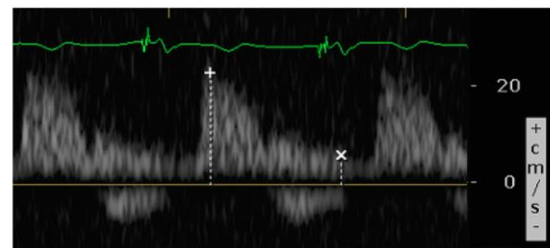
Hepatic vein Doppler



Portal vein Doppler

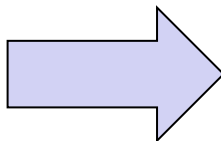


Intra-renal Doppler



Pre-discharge and early post-discharge management of patients hospitalized for acute heart failure: A scientific statement by the Heart Failure Association of the ESC

**Guideline-directed
medical therapy**



Pre-discharge

Multi-modality
assessment of
decongestion*

Post-discharge visits

Monitoring

- Congestion
- SBP and HR
- NPs
- S-Creatinine
- S-Potassium

Relationship of atrial fibrillation and N terminal pro brain natriuretic peptide in heart failure patients

Entezar Nasab Mehrabi^{1,2}, Vahid Toupchi-Khosroshahi^{2,3} and Seyyed Shamsadin Athari^{4*}






➔ the presence of AF, the diagnosis of acute HF with BNP and NT-proBNP is not reliable

➔ **Thigh relationship between AF and high levels of BNP and NT-proBNP.** The mean level of NT-proBNP in AF was between 800 and 1100 pg/mL and is related with the **duration of AF and size of left atrium**

➔ NT-proBNP levels can be a reliable measure to **estimate the probability of AF recurrence** in conditions after heart surgery or in patients with mild heart failure

Review

B-Type Natriuretic Peptide as a Significant Brain Biomarker for Stroke Triage Using a Bedside Point-of-Care Monitoring Biosensor

Dorin Harpaz ^{1,2,*}, Raymond C. S. Seet ³, Robert S. Marks ² and Alfred I. Y. Tok ¹

BNP and NT-proBNP for stroke triaging:

- **Increased mortality**
- **Cardioembolic Etiology**
- **Stroke Recurrence**

after ischaemic stroke, if the patient has elevated NT-proBNP in the absence of HF, long-term rhythm monitoring should be performed for unrecognized AF.



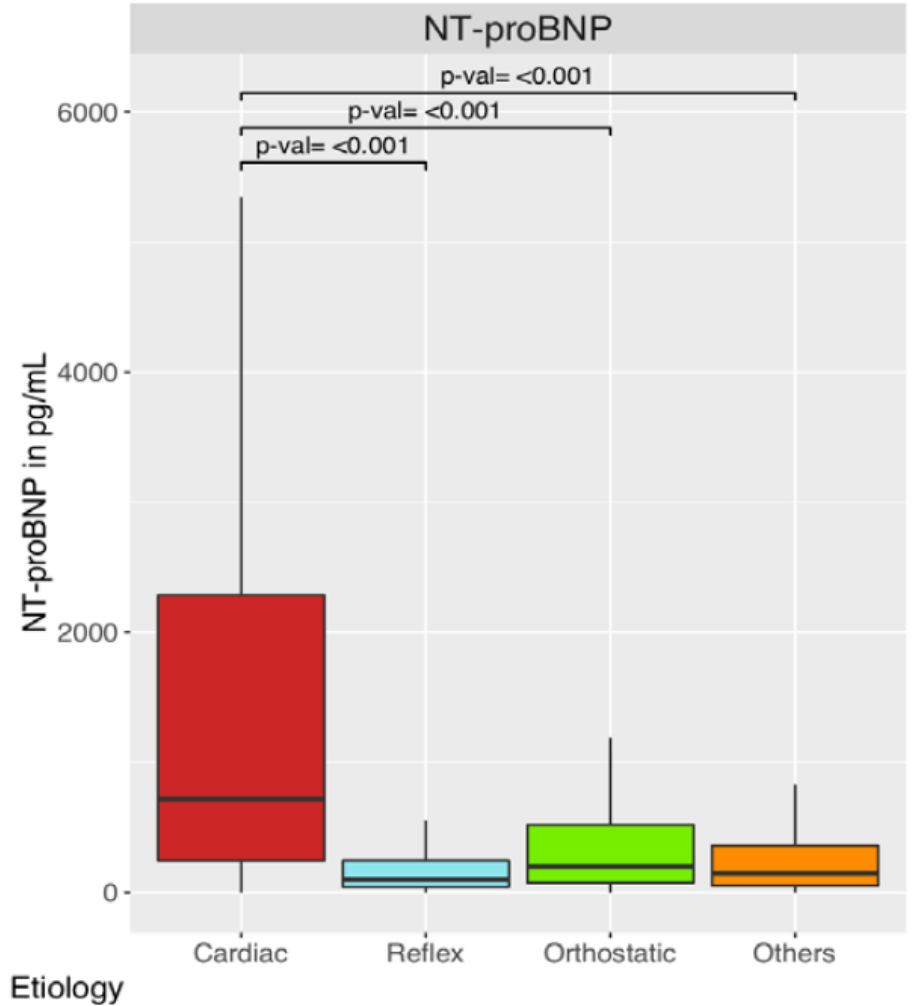
Nt-proBNP e sincope?



B-Type Natriuretic Peptides and Cardiac Troponins for Diagnosis and Risk-Stratification of Syncope

du Fay de Lavallaz et al, *Circulation* 2019

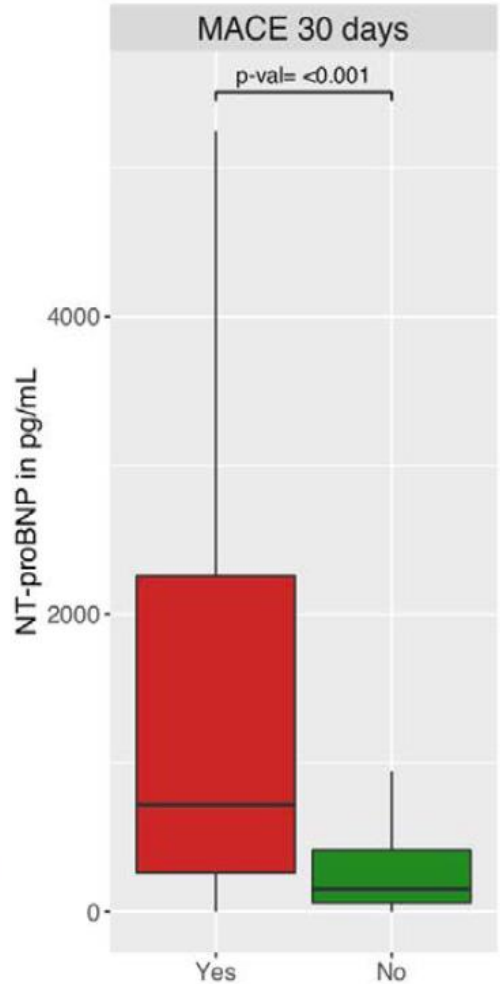
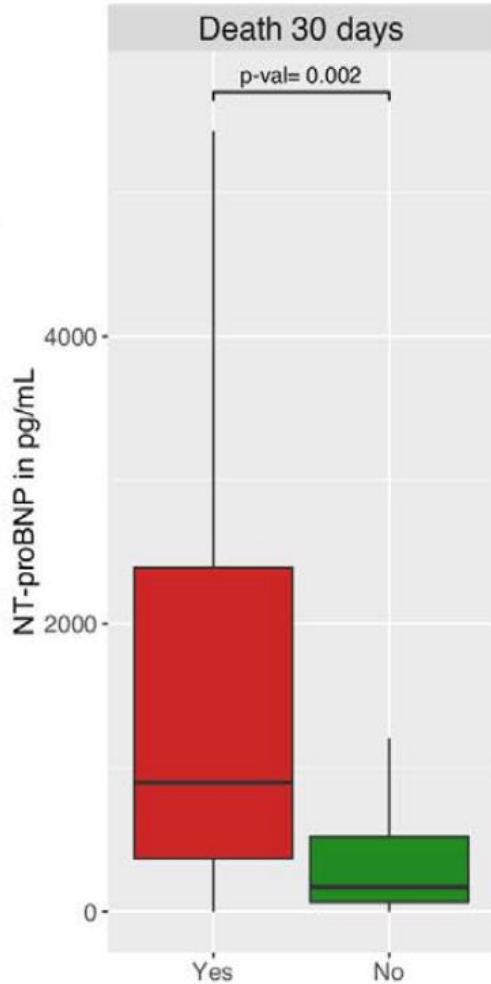
prospective diagnostic
multicenter study
1538 patients



B-Type Natriuretic Peptides and Cardiac Troponins for Diagnosis and Risk-Stratification of Syncope

du Fay de Lavallaz et al, *Circulation* 2019

prospective diagnostic
multicenter study
1538 patients



SCORE DI STRATIFICAZIONE PROGNOSTICA SINCOPE

Canadian Syncope Risk Score

- Predisposition to vasovagal sympt.
- **Heart disease history**
- sBP <90 or >180 mmHg
- Elevated troponin
- Abnormal QRS axis
- QRS duration >130 ms
- Corrected QT interval >480 ms
- ED diagnosis

EGSYS (Evaluation of Guidelines in SYNcope Study) Score for Syncope

- Abnormal EKG and/or **heart disease**
- Palpitations before syncope
- Syncope during effort
- Syncope in supine position
- Autonomic prodromes (Nausea/vomiting)
- Predisposing and/or precipitating factors

ROSE (Risk Stratification of Syncope in the Emergency Department) Rule

- **BNP Level ≥ 300 pg/ml**
- Bradycardia ≤ 50 bpm
- Rectal examination +
- Anemia (Hb ≤ 9 g/dl)
- Chest pain Associated with syncope
- ECG showing Q wave (Not in lead III)
- Saturation $\leq 94\%$ on room air

Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis

Stefano Barco^{1*}, Seyed Hamidreza Mahmoudpour^{1,2}, Benjamin Planquette^{3,4}, Olivier Sanchez^{3,4}, Stavros V. Konstantinides^{1,5}, and Guy Meyer^{3,4}

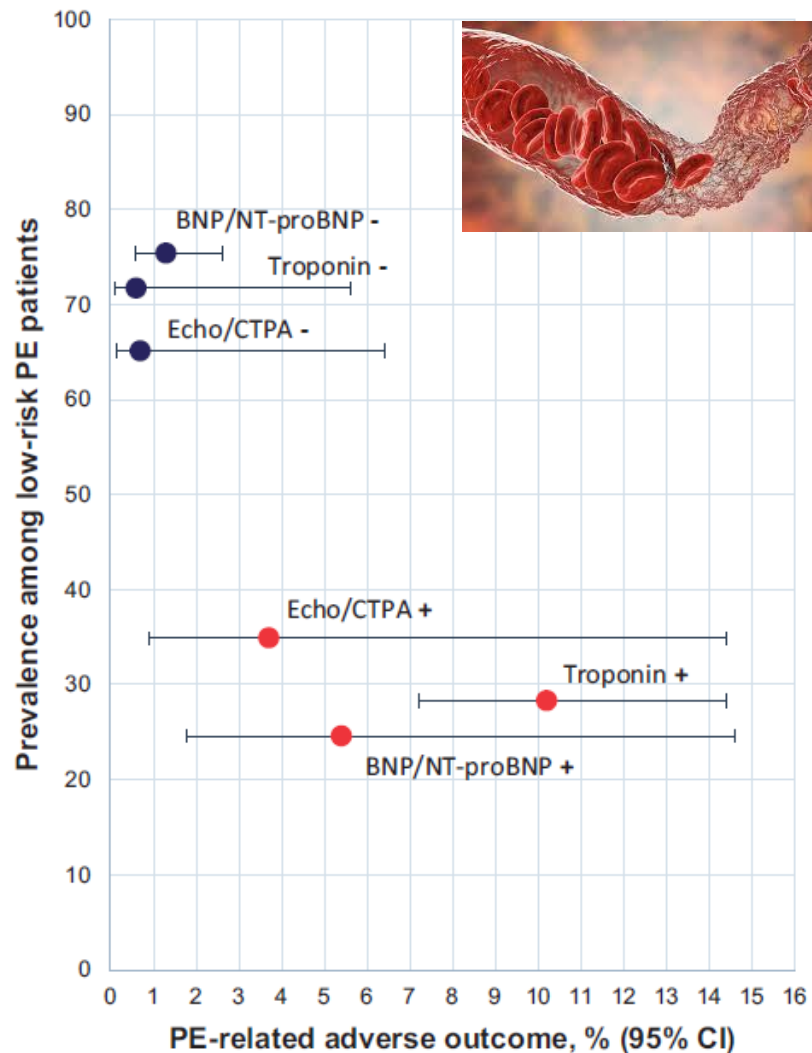
ADVERSE OUTCOME

Early death, haemodynamic collapse, and/or recurrent venous thromboembolism.

**NATRIURETIC PEPTIDES
EARLY MORTALITY**

OR 3.71

95% CI 0.81–17.02



Risk Stratification in Patients with Acute Pulmonary Embolism: Current Evidence and Perspectives

Antonio Leidi ^{1,†}, Stijn Bex ^{1,†}, Marc Righini ², Amandine Berner ¹, Olivier Groscurin ¹
and Christophe Marti ^{1,*}

Table 3. Prognostic value of markers of right ventricular dysfunction for short-term mortality.

Marker	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)
Troponin [34]	0.66 (0.61 to 0.70)	0.66 (0.65 to 0.67)	2.13 (1.84 to 2.47)	0.51 (0.40 to 0.60)
BNP [35]	0.88 (0.65 to 0.96)	0.70 (0.64 to 0.75)	2.13 (1.84 to 2.47)	0.51 (0.40 to 0.60)
NT-proBNP [35]	0.93 (0.14 to 1.00)	0.58 (0.14 to 0.92)	2.93 (2.28 to 3.77)	0.17 (0.05 to 0.58)
RVD US [35]	0.70 (0.46 to 0.86)	0.57 (0.47 to 0.66)	1.48 (1.05 to 2.08)	0.82 (0.65 to 1.03)
RVD CT [35]	0.65 (0.35 to 0.85)	0.56 (0.39 to 0.71)	1.63 (1.27 to 2.08)	0.53 (0.31 to 0.89)

CI: confidence interval; PLR: positive likelihood ratio; NLR: negative likelihood ratio; BNP: brain natriuretic peptide; NT-proBNP: N-terminal brain natriuretic peptide; RVD: right ventricular dysfunction; US: ultrasonography; CT: computer tomography.

Early mortality risk		Indicators of risk			
		Haemodynamic instability ^a	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1	RV dysfunction on TTE or CTPA ^b	Elevated cardiac troponin levels ^c
High		+	(+) ^d	+	(+)
Intermediate	Intermediate–high	-	+ ^e	+	+
	Intermediate–low	-	+ ^e	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

“Elevation of further laboratory biomarkers, such as NT-proBNP >600 ng/L... may provide additional prognostic information ...”

Natriuretic Peptides to Predict Short-Term Mortality in Patients With Sepsis: A Systematic Review and Meta-analysis

- B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) levels are often elevated in patients with sepsis.
- The optimal cutoffs for mortality prediction remain incompletely understood.
- BNP and NT-proBNP levels of 622 pg/mL and 4000 pg/mL **predicted short-term mortality.**



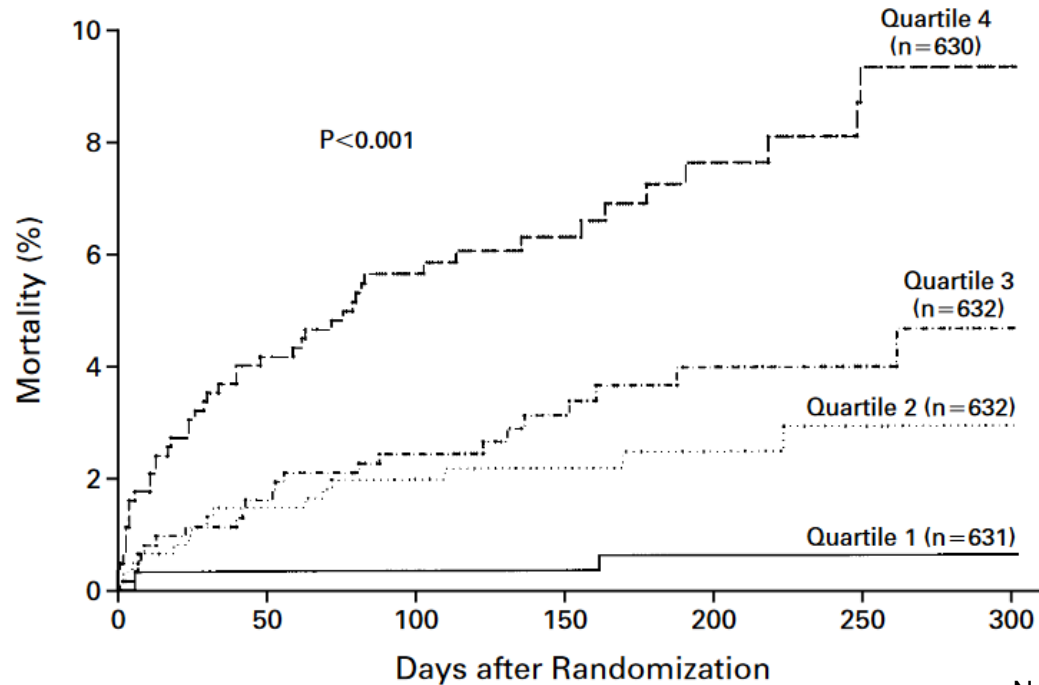
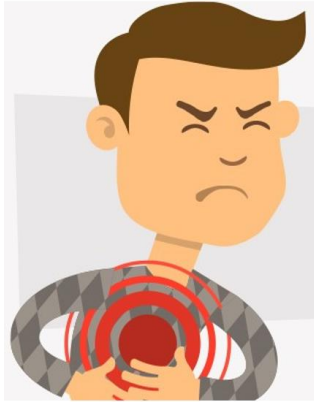
Determinants:

- myocytic stretch in **ventricular dysfunction**
- **proinflammatory molecules**
(lipopolysaccharide, interleukin 1, C-reactive protein, and cardiotrophin 1)
- **concomitant renal failure**
- **catecholamine infusions**
- **volume resuscitation**



THE PROGNOSTIC VALUE OF B-TYPE NATRIURETIC PEPTIDE IN PATIENTS WITH ACUTE CORONARY SYNDROMES

JAMES A. DE LEMOS, M.D., DAVID A. MORROW, M.D., M.P.H., JANE H. BENTLEY, B.Sc.,
TORBJØRN OMLAND, M.D., PH.D., M.P.H., MARC S. SABATINE, M.D., CAROLYN H. McCABE, B.S.,
CHRISTIAN HALL, M.D., PH.D., CHRISTOPHER P. CANNON, M.D., AND EUGENE BRAUNWALD, M.D.



... E altri ancora

Ma ci interessa?

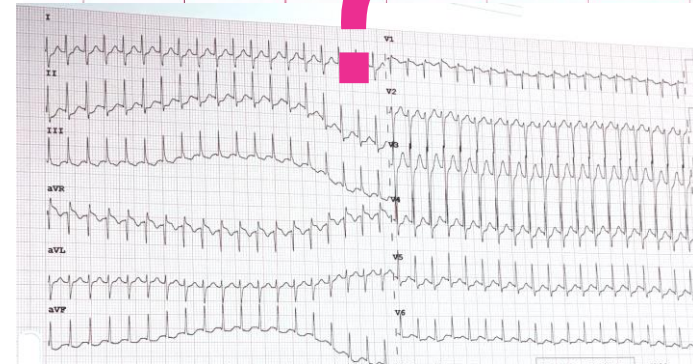
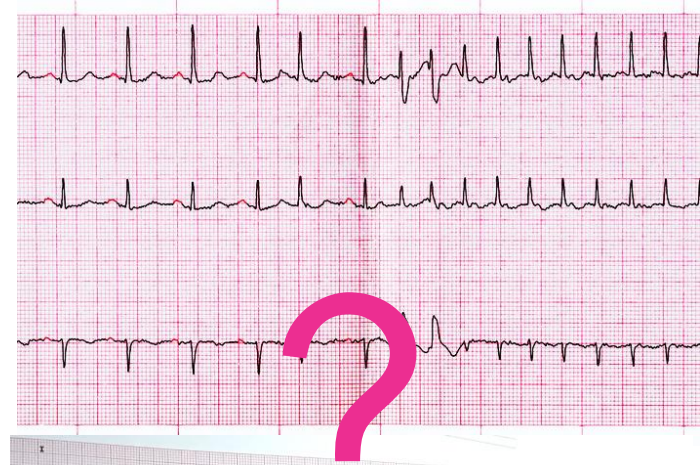
Diagnostic challenges in supraventricular tachycardia: anticipating value of natriuretic peptides

Ertan Yetkin

TPSV sostenute determinano un maggior rilascio dei peptide natriuretici: ANP, BNP, e CNP.

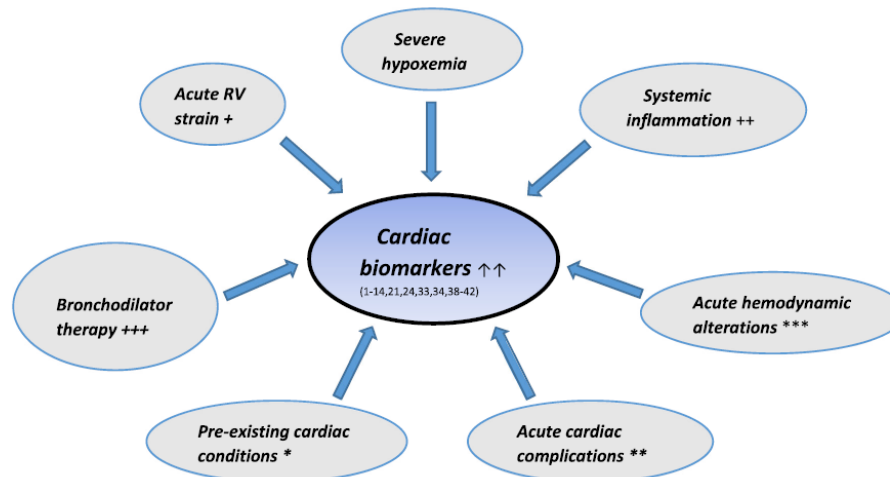
In particolare di ANP ma ha un'emivita molto breve, al confronto del BNP (e NT-proBNP)

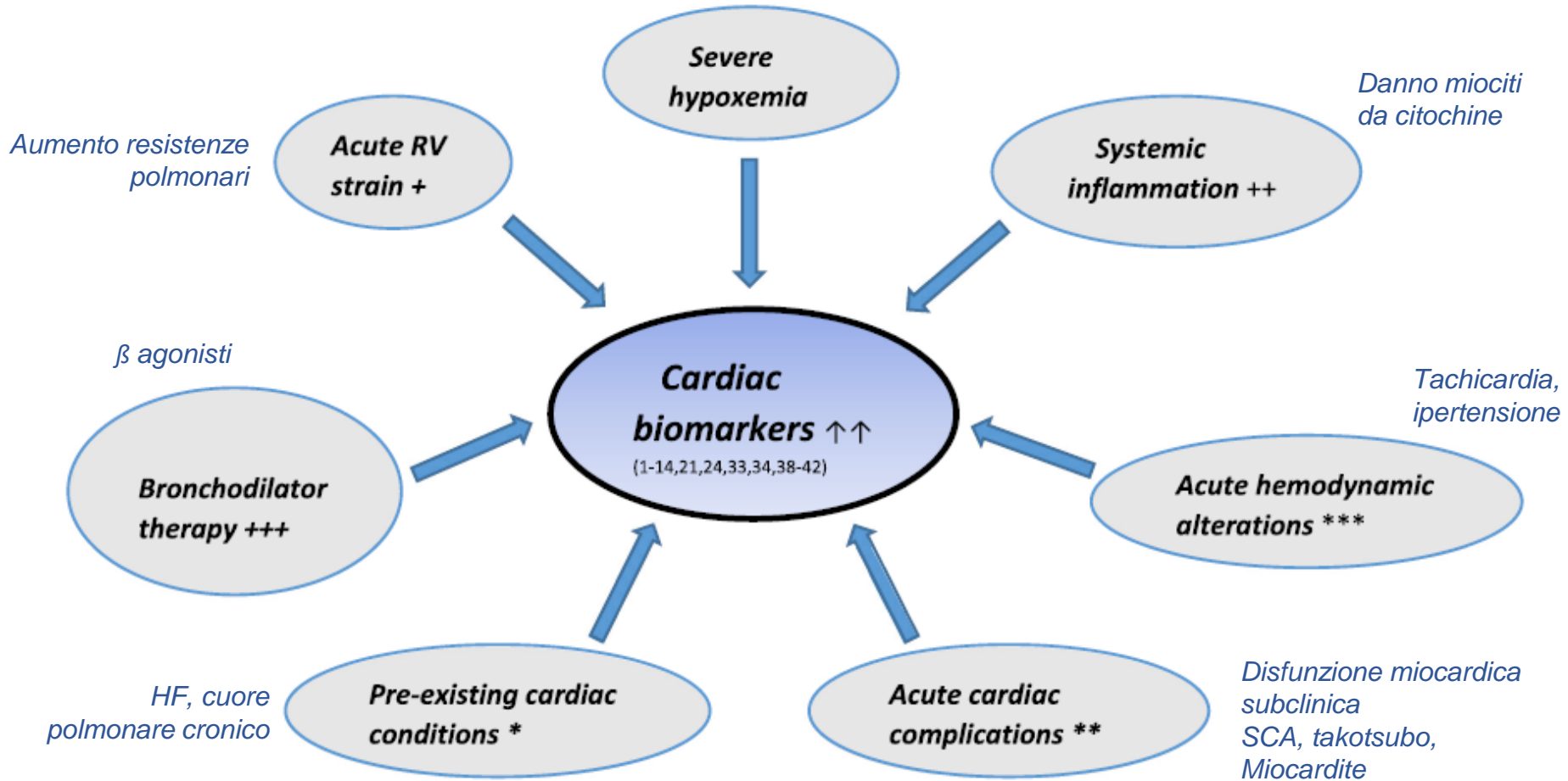
“High levels of natriuretic peptides within 30 min of postattack period would certainly increase the likelihood of SVT. Measurement of natriuretic peptides as early as possible at emergency department in those patients might be of clinical relevance».



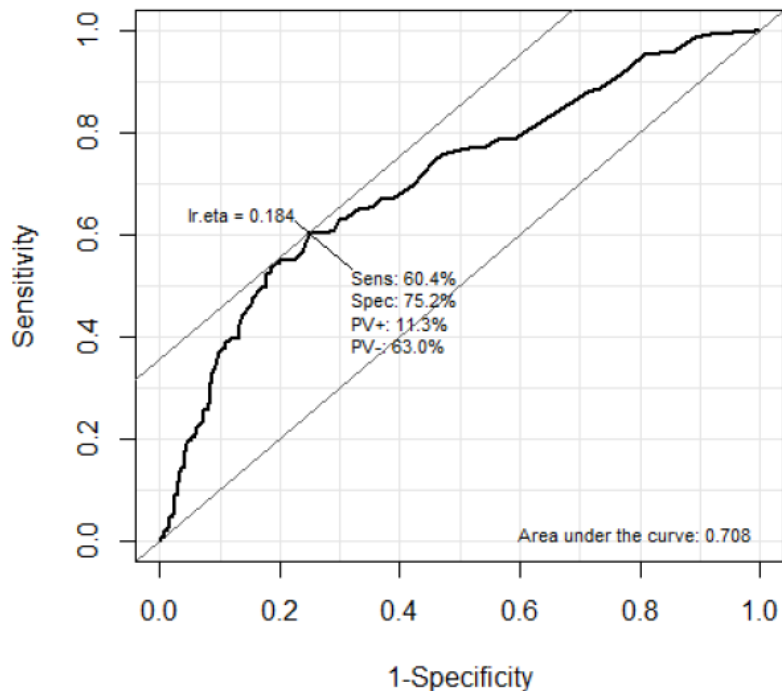
Cardiac Biomarkers in the Setting of Asthma Exacerbations: a Review of Clinical Implications and Practical Considerations

Kenan Yalta¹ · Tulin Yalta² · Muhammet Gurdogan¹ · Orkide Palabiyik³ · Ertan Yetkin⁴





Effectiveness of Initial Troponin I and Brain Natriuretic Peptide Levels as Biomarkers for Predicting Delayed Neuropsychiatric Sequelae in Patients with CO Poisoning: A Retrospective Multicenter Observational Study



DANGER
CARBON
MONOXIDE

BNP – DNS

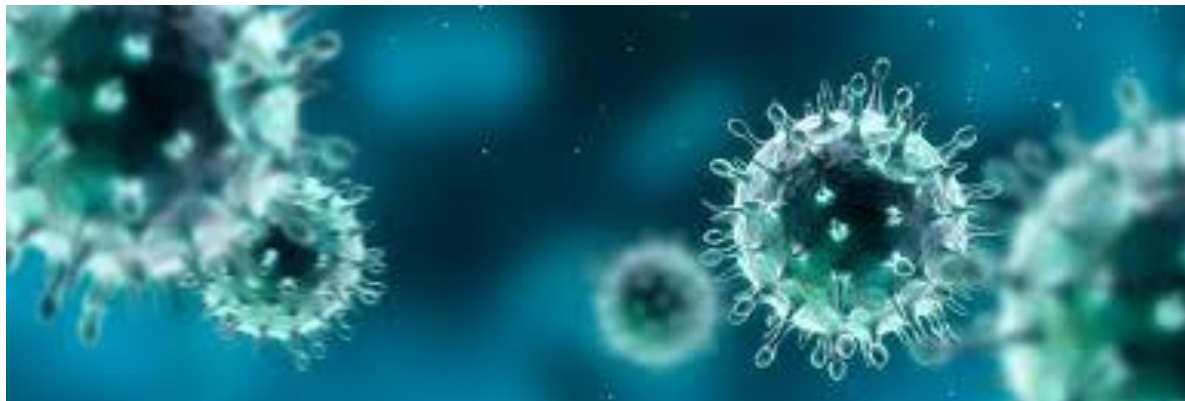
OR 2,80

95% CI 1,81-3,47

Incremento precoce (1h)

Prognostic value of pro-adrenomedullin and NT-proBNP in patients referred from the emergency department with influenza syndrome

Salvador Valero Cifuentes ¹, Eva García Villalba ¹, Antonia Alcaraz García ¹,
María José Alcaraz García ¹, Ángeles Muñoz Pérez ¹, Pascual Piñera Salmerón ¹,
Enrique Bernal Morell ¹





ELSEVIER

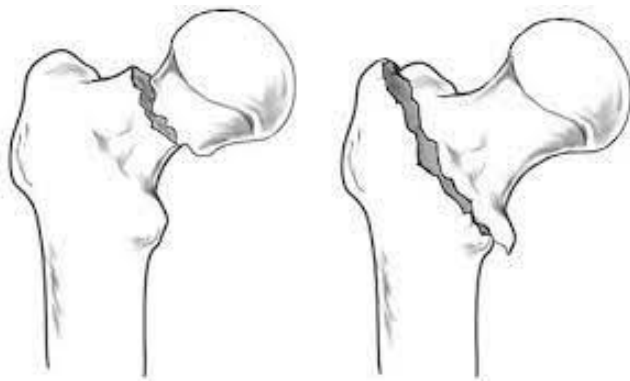
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Journal of Orthopaedics

journal homepage: www.elsevier.com/locate/jor

Brain Natriuretic Peptide levels on hospital admission are a useful predictor of cardiac complications and mortality in geriatric patients with proximal femur fractures

Helena Franco^{a,b,*}, Chris Wainwright^c, Jonathan Chernilo^{d,e}, Ezekiel S.L. Tan^d, William O'Callaghan^{a,d,f}



«... manda gli esami, aspettiamo il BNP...»



**I biomarker sono di supporto al
giudizio clinico**

**I biomarkers NON sostituiscono il
giudizio clinico**

Specialmente alcuni ...



Ospedale Niguarda

Sistema Socio Sanitario



Regione Lombardia



VII EDIZIONE

RITORNO al FUTURO della **MEDICINA d'URGENZA**

curiosità, critica e **innovazione**



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2024

