Universitair Medisch Centrum
Utrecht

A new test to diagnose cardiovascular disease.
Should I use it in my practice?

Arno W Hoes, MD, PhD

Julius Center for Health Sciences & Primary Care

University Medical Center Utrecht

First patient next Monday?

Your *real* patient nr 1 next Monday

56 year old man

- 8.00 a.m.
- since 4 a.m. : "chest discomfort"
- transpiring (as always)
- hypertension for 15 years
- atypical angina
- physical examination
    - 150/90 mm Hg
    - heart rate 100
- nitrates: no relief

Novel sales representatives

Nice novel point-of-care test for MI?

Aus einer Hand:

Die aufeinander abgestimmten Formate zur Bestimmung von Troponin T

■ **TROPT® sensitive**
Qualitativer immunologischer Schnelltest aus Vollblut. Als bedside-Test auf der Station und in der Arztpraxis.

■ **CARCIAC T (CARDIAC *reader*)**
Quantitative Bestimmung aus Vollblut für den Einsatz als bedside-Test auf der Station, in der Notaufnahme und in der Arztpraxis.

■ **Elecsys® Troponin T**
Quantitative Bestimmung aus Serum oder Plasma für den Einsatz im Labor an Elecsys® Analysegeräten.
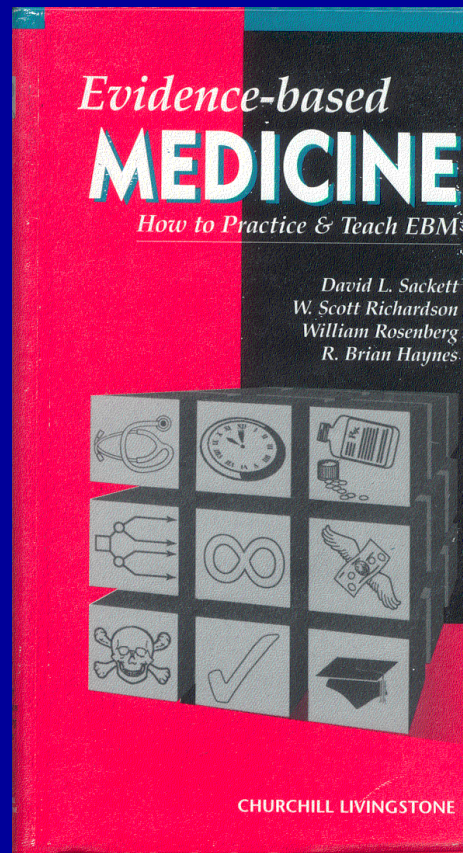
You are in doubt: MI ?

What will you do?

1. the new POC troponin T test
2. ECG in your practice
3. ambulance!
4. watchful waiting

EBM-era:
on the search for clinically relevant evidence

Evidence-based
MEDICINE
How to Practice & Teach EBM

David L. Sackett
W. Scott Richardson
William Rosenberg
R. Brian Haynes

CHURCHILL LIVINGSTONE

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"Study in emergency department Budapest"

- 500 consecutive ER patients; 25 had MI

	MI yes	MI no	
Tn T pos	22	30	52
Tn T neg	3	445	448
	25	475	500

Which diagnostic parameter most relevant ?

1. sensitivity (87%)

2. specificity (94%)

3. positive predictive value (42%)

4. negative predictive value (99%)

5. none: useless table

Sensitivity and specificity ?

"Doctor, I have a heart attack and I would like to know whether the troponin test is indeed positive"

or

"Doctor, I do not have a heart attack but I am still curious whether the troponin test is negative"

Natural interest in predictive values !

- probability disease given positive test

- probability non-disease given negative result

Note:

Probability disease = f (test result**S**)

No diagnosis is set by just one test in daily clinical practice !

- natural hierarchy

- new test: interest in *added* value
  i.e. *in addition to* tests available anyway:
  typically overt patient characteristics, signs & symptoms

- new test: sometimes interest in *alternative* value
  i.e. as alternative to other added test

Natural hierarchy in diagnostic tests !

determined by accessibility, patient burden, costs

- overt patient characteristics
  e.g. age, sex, medical history
- additional patient characteristics
  e.g. detailed (family) history
- symptoms and signs
- simple additional tests (POC tests, ECG etc)
- more complicated, patient-burdening tests
 (imaging, biopsies, etc)

Clinically relevant diagnostic research

1. Relevant domain: *real* patients

   - typically patients suspected of the disease in relevant setting

2. Multiple tests

   - no diagnosis is set by means of just one test

3. Hierarchy: *added* diagnostic value

   - i.e. in addition to what is routinely available anyway

4. Results easily applicable in daily practice

   - eg algorithm, diagnostic score

# 1. Relevant domain: real patients

- patient *suspected* of the disease in daily practice

- patients in whom a diagnostic problem exists

- i.e. patients in whom test may be used

- comparison (severely) diseased with healthy controls? nonsense!!!

2. Multiple tests
3. Natural hierarchy: *added* value

- diagnosing is multivariable and hierarchic process

- value new test *in addition to* what is typically known

UMC

CRP in suspected pneumonia

Hopstaken et al. Br J Gen Pract 2003;53:358-
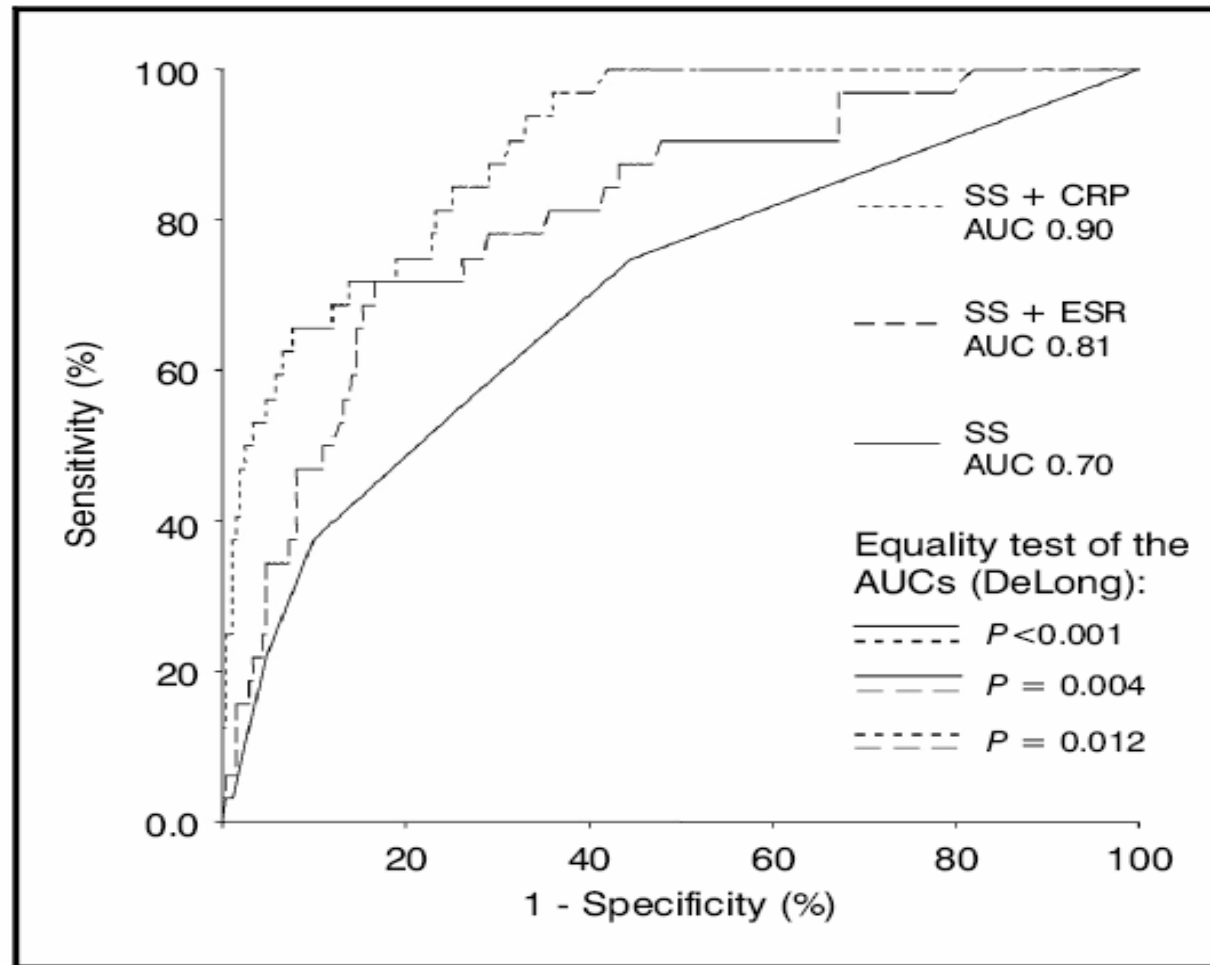
4. Results easily applicable in clinical practice

- diagnostic algorithm / rule

- diagnostic score with associated probabilities

UMC

An easily applicable diagnostic score?

Diagnostic variables	Score
Male gender	1
Oral contraceptive use	1
Presence of malignancy	1
Recent surgery	1
Absence of trauma	1
Vein distension	1
Calf difference ≥3cm	2
Abnormal D-dimer test	6

Risk category	Score	Prevalence DVT (%)
Very low risk	≤ 3	0.7
Low risk	4 - 6	4.5
Moderate risk	7 - 9	21.7
High risk	≥ 10	51.3

Oudega et al. Thromb Haemost 2005; 94: 200-5

Clinically relevant diagnostic research

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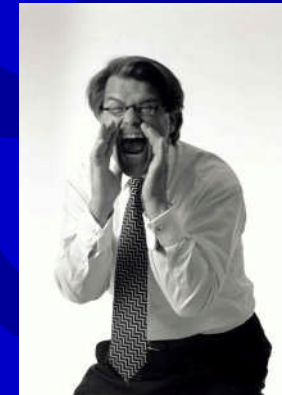
Novel cardiac biomarkers?
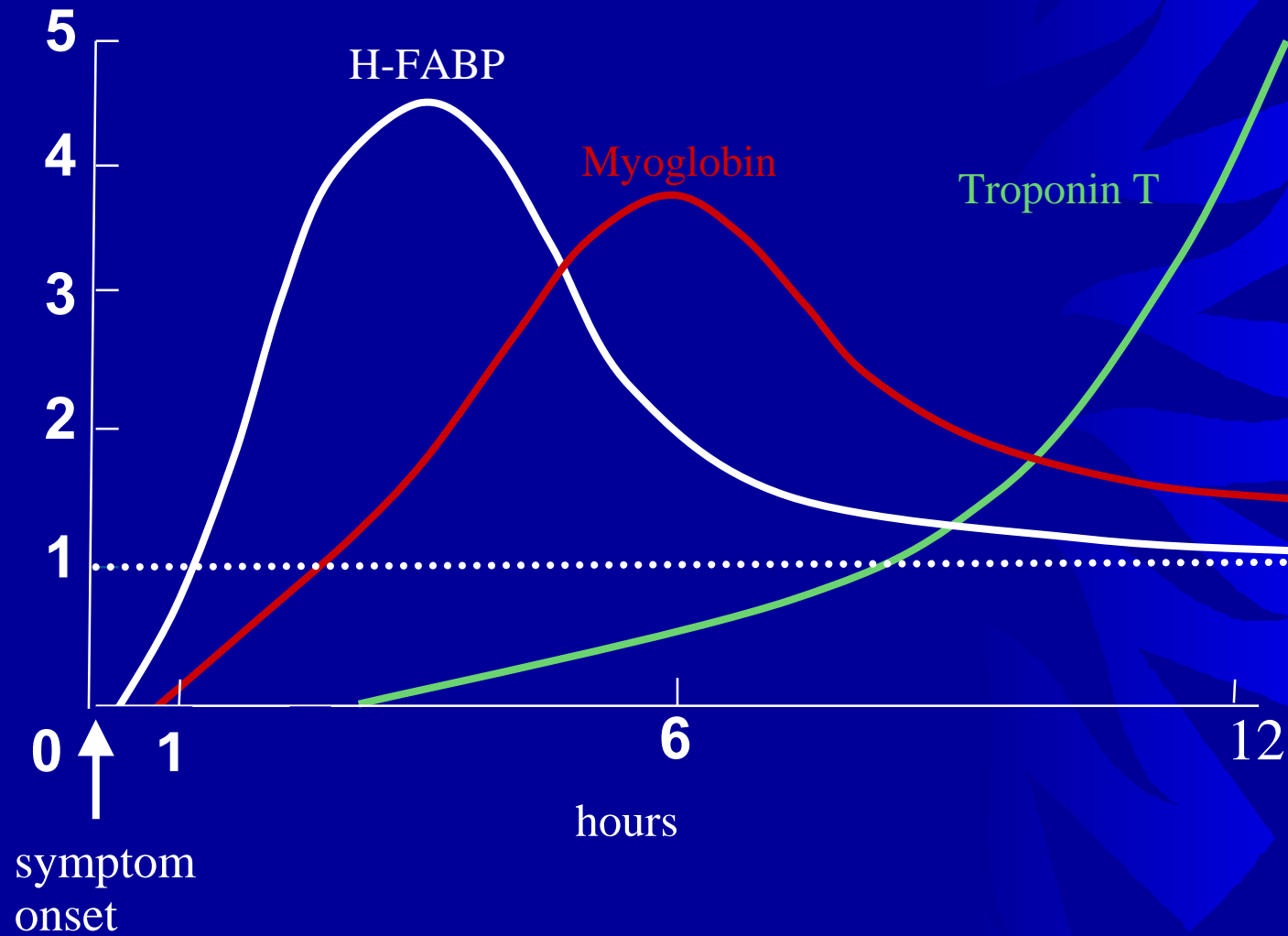
FAME study

- Fatty acid binding protein for Acute Myocardial infarction Evaluation

- 300 suspected patients in primary care

- *added value* point-of-care H-FABP test

- recruitment just finished
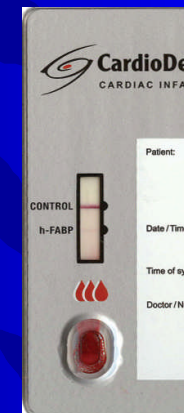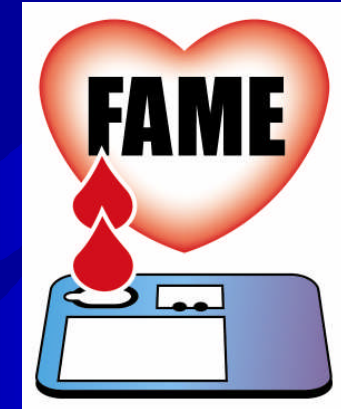
Your *real* patient nr 2 next Monday

Male, 81 years of age

- increasingly dyspnoeic
- MI 1987
- ex- and current smoker
- yearly "bronchitis"
- Rx: aspirin, metoprolol
- physical examination:
    - "some"crepitations
    - "some" edema
    - third heart sound?
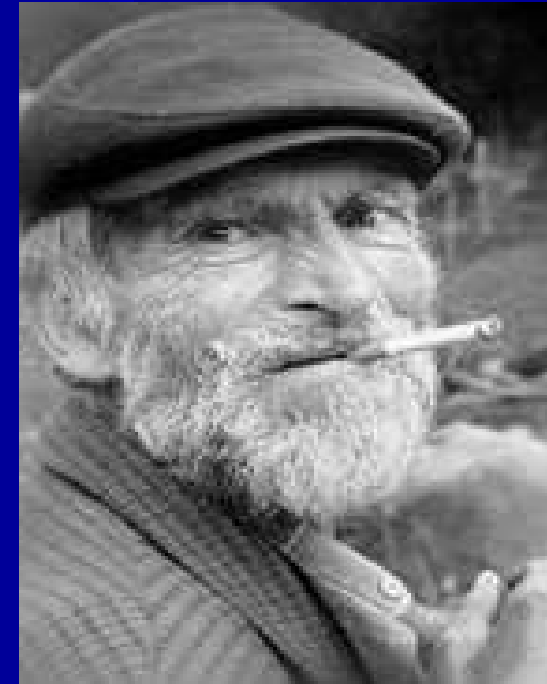
A novel point-of-care BNP test?

BNP: A RELIABLE MARKER FOR HEART FAILURE

- 98% diagnostic accuracy versus other clinical findings in patients with or without disease history (9).

- Corrected 96% of misdiagnoses of patients with suspected CHF (9), without the use of other invasive or expensive diagnostic tests (10).

- ≥ 98% Negative Predictive Value and 95.6% specificity utilizing 100 pg/ml cutoff (10).
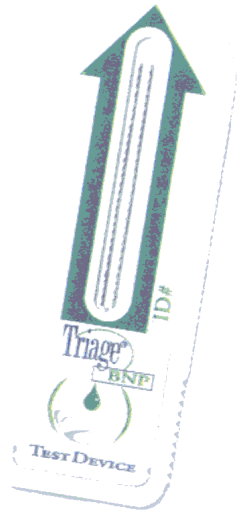
The Triage® BNP Test provides meaningful diagnostic information not available from other clinical assessments.

Triage®
BNP
TEST

You are in doubt: heart failure?

What will you do?

1. POC BNP test
2. ECG
3. spirometry
4. referral (cardiologist; echo)
5. test treatment (frusemide)?
6. watchful waiting

Patients suspected of heart failure ("best guess")

- **true positive** (cyan)
- **true negative** (green)
- **false positive** (orange)
- **false negative** (red)

12%   18%

12%

58%

UMC
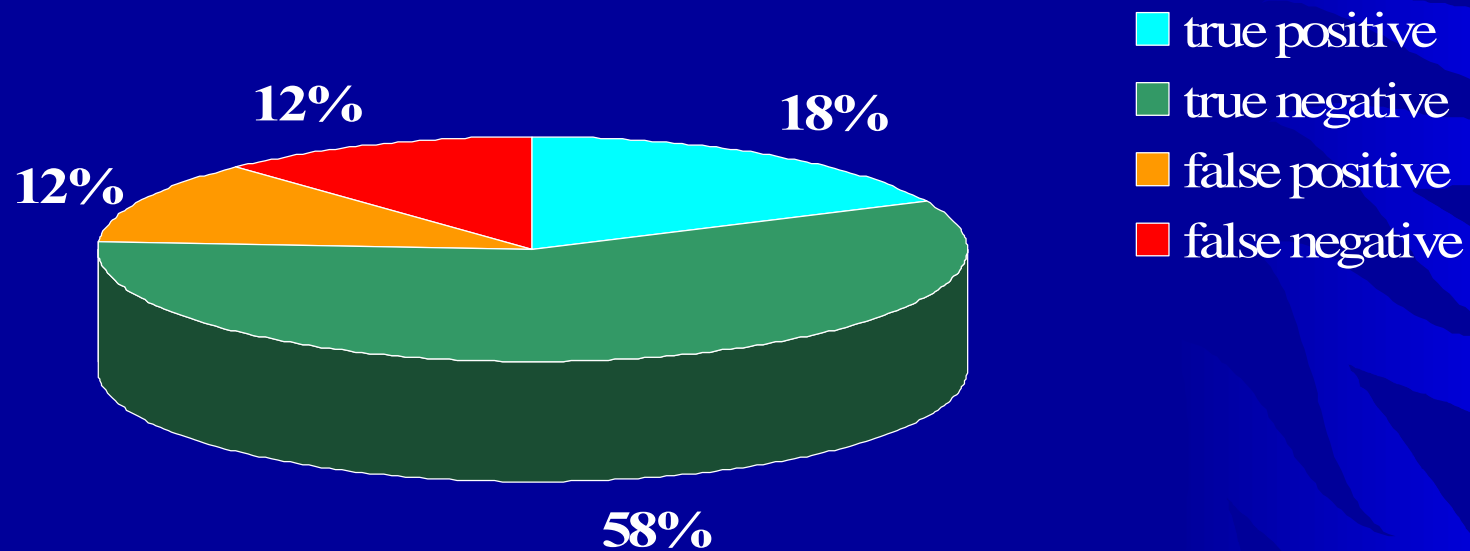
Clinically relevant evidence?

comparison of BNP in those with heart failure compared to healthy controls
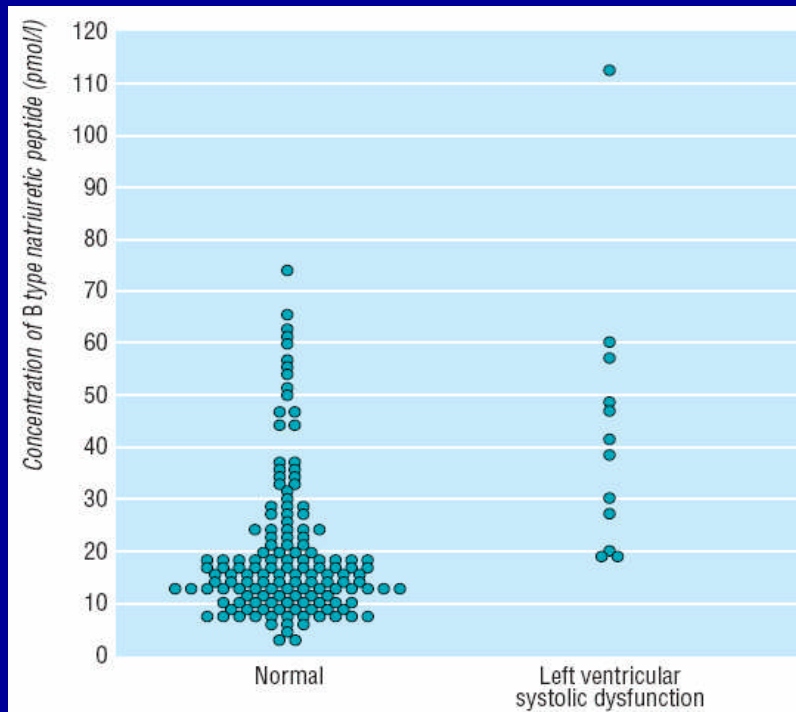
Fig 1 Distribution of plasma concentrations of B type natriuretic peptide in normal elderly people and in those with left ventricular systolic dysfunction confirmed by echocardiography

Smith et al. BMJ 2000;320:906-8

Clinically relevant evidence?

diagnostic value of BNP among patients
suspected of heart failure

Cowie et al, Lancet 1997; 350: 1349-

Receiver-operating-characteristic curves for natriuretic peptides and cardiothoracic ratio (CTR) on posteroanterior chest radiography

AUC

BNP 0.75

Cowie et al, Lancet 1997; 350: 1349-

<u>Very</u> recent evidence

UHFO-DD:

Optimal diagnostic strategy in primary care?

- 728 suspected patients in primary care

- diagnostic out-patient clinics in 8 hospitals
- diagnostic cocktail plus 6 months follow-up

- reference standard expert panel: 28% heart failure

Clinical model (AUC 0.82!!!)

age

MI, CABG, PTCA

diuretic, ACE-inhibitor

displaced apex beat

pulmonary crackles

heart murmur

elevated jugular pressure

Added value additional tests

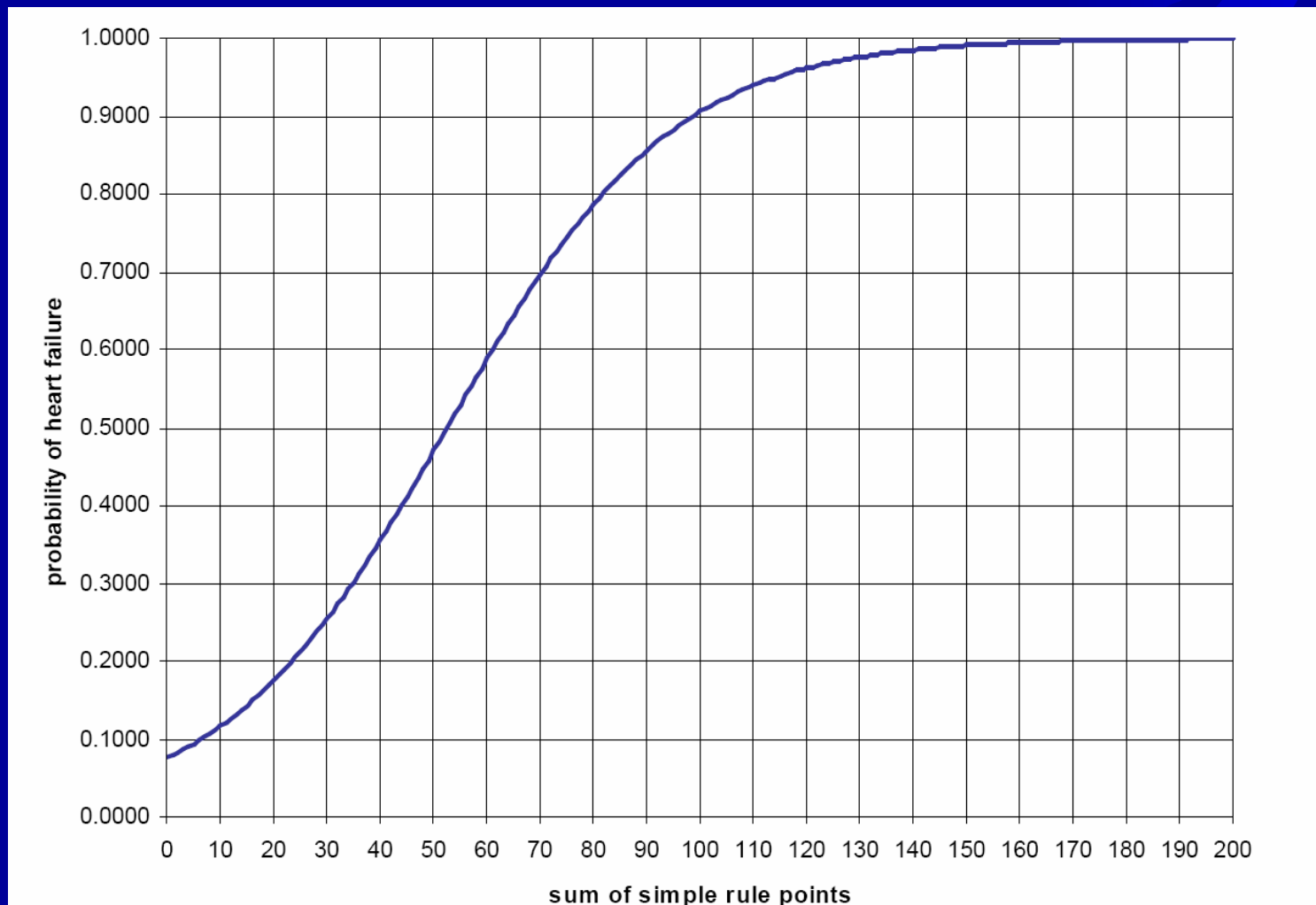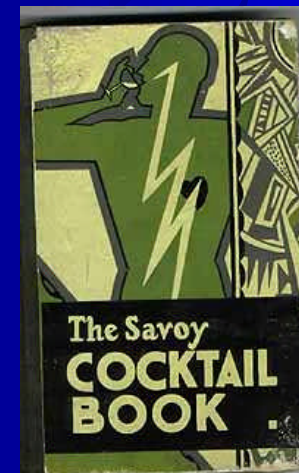|	c-statistic (AUC)
Clinical + lung function	0.82
Clinical + ECG	0.83
Clinical + Chest X-ray	0.85
Clinical + NT-proBNP	0.86

Score and probability heart failure

Managing heart failure is complicated

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008

Authors/Task Force Members: Kenneth Dickstein (Chairperson) (Norway)*, Alain Cohen-Solal (France), Gerasimos Filippatos (Greece), John J.V. McMurray (UK), Piotr Ponikowski (Poland), Philip Alexander Poole-Wilson (UK), Anna Strömberg (Sweden), Dirk J. van Veldhuisen (The Netherlands), Dan Atar (Norway)
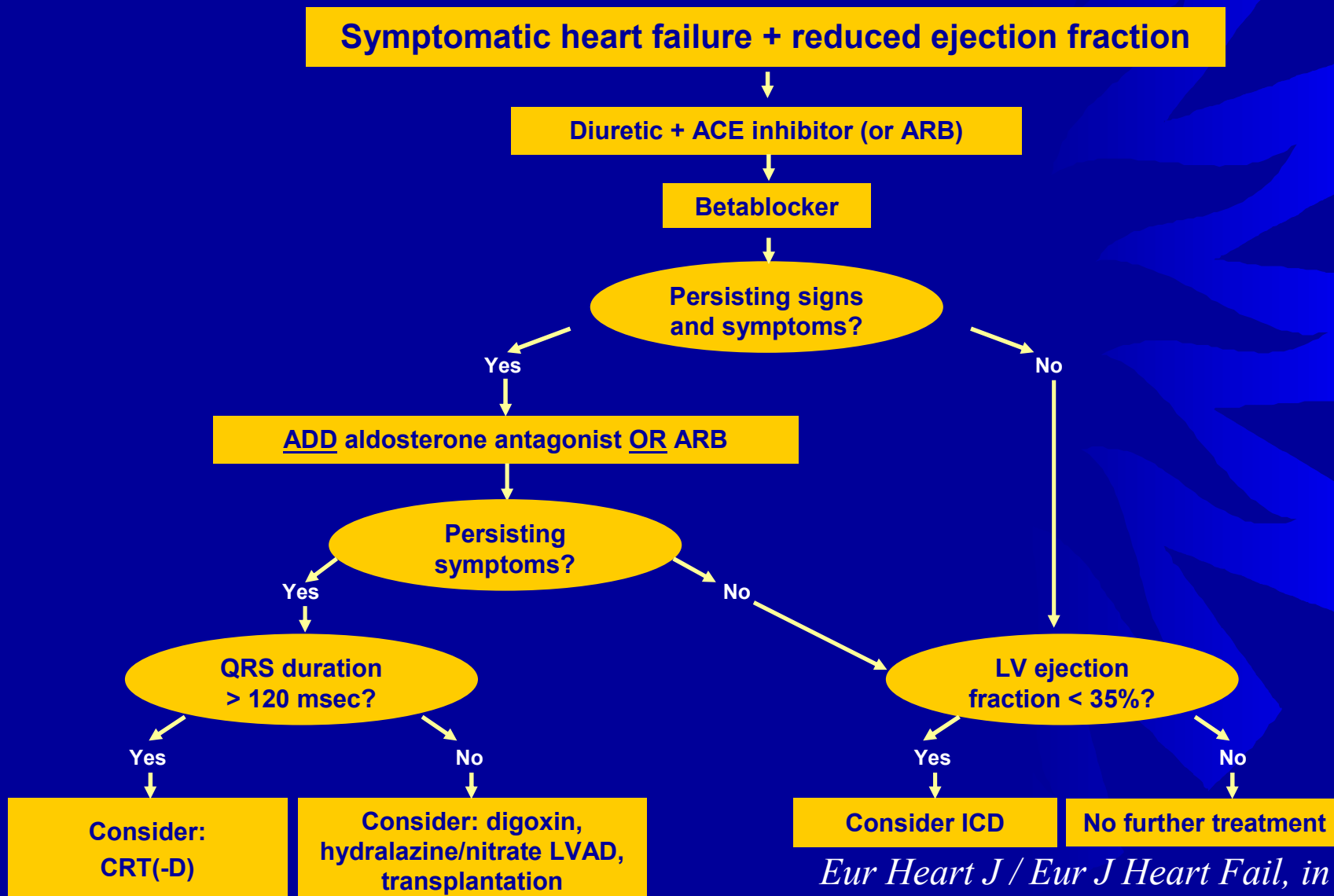Alexandr   Giuliana Priori
(Italy), K

ESC Commi   nn Camm (UK),
Raffaele De   mos Filippatos
(Greece), Cl   Dalby Kristensen
(Denmark),   y).
Michal Tend

Document R   hio (Switzerland),
Jeroen Bax (ella (Italy),
Perry M. Elli   Hasin (Israel),
Anders Hernborg (Sweden), Tiny Jaarsma (The Netherlands), Michel Komajda (France), Ran Kornowski (Israel), Massimo Piepoli (Italy), Bernard Prendergast (UK), Luigi Tavazzi (Italy), Jean-Luc Vachiery (Belgium), Freek W. A. Verheugt (The Netherlands), Jose Luis Zamorano (Spain), Faiez Zannad (France)

- involvement of primary care
- a single document
- nationel adaptations / translations
- gaps in the evidence

Treatment algorithm in systolic HF

Symptomatic heart failure + reduced ejection fraction

↓

Diuretic + ACE inhibitor (or ARB)

↓

Betablocker

↓

Persisting signs and symptoms?

Yes ↙   ↘ No

ADD aldosterone antagonist OR ARB

↓

Persisting symptoms?

Yes ↙   ↘ No

QRS duration > 120 msec?

Yes ↓   ↓ No

Consider: CRT(-D)

Consider: digoxin, hydralazine/nitrate LVAD, transplantation

LV ejection fraction < 35%?

Yes ↓   ↓ No

Consider ICD

No further treatment

Eur Heart J / Eur J Heart Fail, in press

Treatment in diastolic HF (HFPEF)

- diuretics guided by symptomatology

- blood pressure and rhythm control

- ACE-inhibitors / ARBs (?)

- betablockers (?)

Implementation still far from optimal

		ACE	BB
Rutten 2003	🇳🇱	46%	9%
Cleland 2002	🇪🇺	60%	34%
Otero 2007	🇪🇸	77%	27%
Scherer 2007	🇩🇪	58%	58%

"fear of side effects of ACE-inhibition…"

"fear of side effects and deterioration following BB, notably in patients with comorbidity"

Heart failure management programs work

Table 2 — Effect of a nurse-and-physician-directed heart failure clinic on hospitalisation, death and days in hospital

Variable	Intervention group (incidence rate) n = 118	Usual care group n = 122	Rate ratio (95% CI)	RD (95% CI; NNT)
Hospitalisation for CHF and/or death	23 (20.7 per 100 patient years)	47 (42.2 per 100 patient years)	0.49 (0.30 to 0.81)	0.215 (0.07 to 0.36; 5)
Death (all-cause)	12 (10.8 per 100 patient years)	23 (20.6 per 100 patient years)	0.52 (0.26 to 1.05)	0.098 (10)
Days in hospital	359 (324 per 100 patient years)	644 (578 per 100 patient years)	0.56 (0.49 to 0.64)	2.54 (0.4)

CHF, congestive heart failure; NNT, numbers needed to treat; RD, rate difference.

DEAL study: (ex)GP and nurse led out-patient clinic

Bruggink-André de la Porte, et al. Heart 2007;93:819-25

Recent developments:
an excellent *patient* and *carer* website

- English
- German

near future

- Spanish
- Dutch

www.heartfailurematters.org

Recent developments: STATINS ?

Table 2. Prespecified Composite Cardiovascular Outcomes and Fatal and Nonfatal Events.*					
Variable	**Placebo (N = 2497)**		**Rosuvastatin (N = 2514)**		**Hazard Ratio (95% CI)**
	No. of Patients	Event Rate	No. of Patients	Event Rate	
Outcome					
Primary outcome	732	12.3	692	11.4	0.92 (0.83–1.02)
Death from cardiovascular causes	487		488		
Nonfatal myocardial infarction	141		115		
Nonfatal stroke	104		89		
Secondary outcome					
Death from any cause†	759	12.2	728	11.6	0.95 (0.86–1.05)
Any coronary event‡	588	10.0	554	9.3	0.92 (0.82–1.04)
Fatal event					
Death from cardiovascular causes§	593	9.6	581	9.3	0.97 (0.87–1.09)
Sudden death	327	5.3	316	5.0	0.96 (0.82–1.12)
In primary outcome	284		284		
In coronary events	283		272		
Worsening heart failure	191	3.1	193	3.1	1.00 (0.82–1.22)

The long-awaited CORONA trial

Kjekshus et al. N Engl J Med 2007;357:2248-

Recent developments: BNP-guided therapy?

Plasma Brain Natriuretic Peptide-Guided Therapy to Improve Outcome in Heart Failure
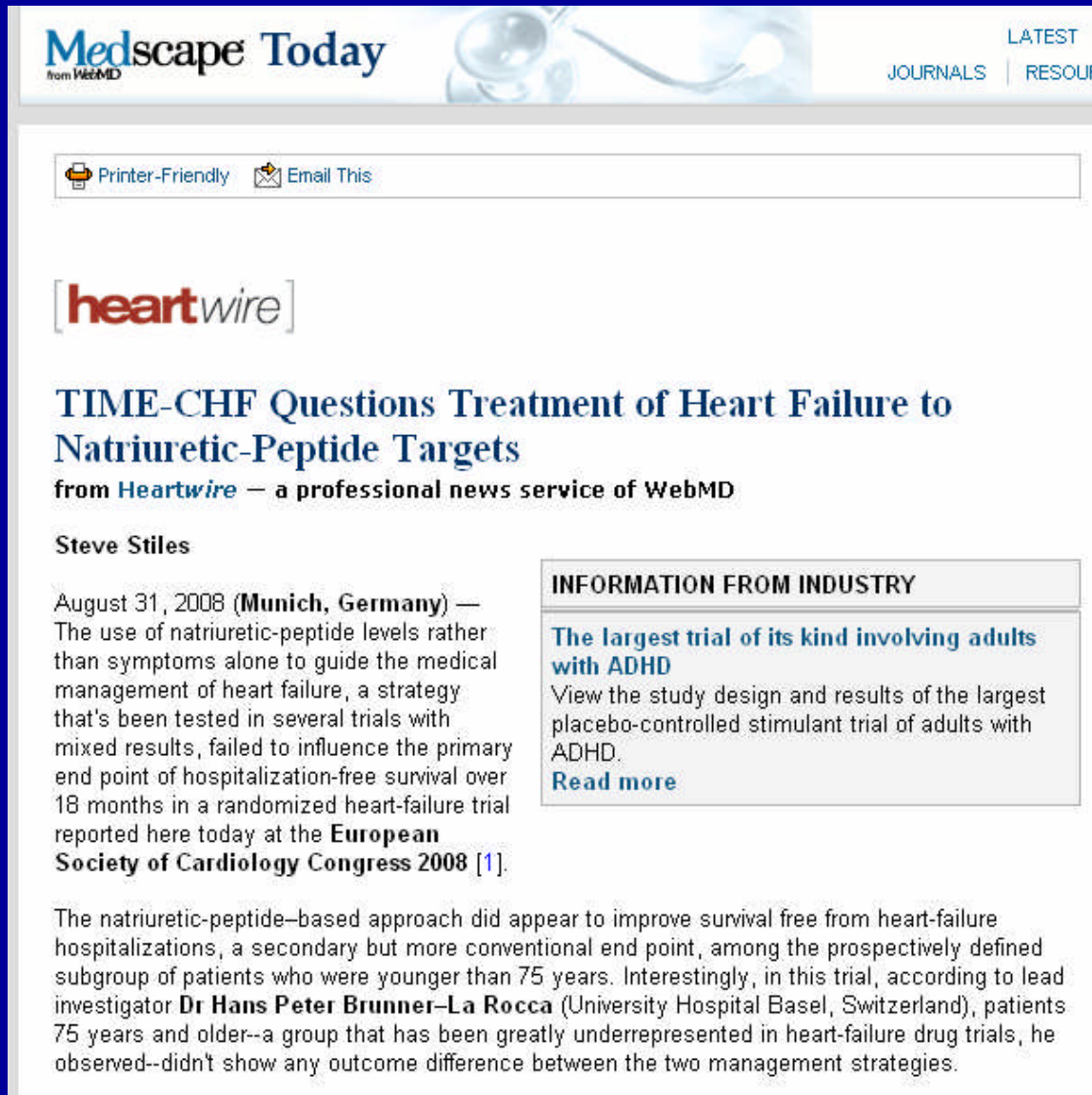
The STARS-BNP Multicenter Study

Patrick Jourdain, MD,*†‡ Guillaume Jondeau, MD, PHD,§ François Funck, MD,‡ Pascal Gueffet, MD,‖
Alain Le Helloco, MD,¶ Erwan Donal, MD,¶ Jean F. Aupetit, MD,# Marie C. Aumont, MD,§
Michel Galinier, MD, PHD,** Jean C. Eicher, MD,†† Alain Cohen-Solal, MD, PHD,‡‡
Yves Juillière, MD, PHD§§

Paris, Pontoise, Nantes, Rennes, Lyon, Toulouse, Dijon, and Vandoeuvre Les Nancy, France

Objectives   The aim of this multicenter study was to evaluate the prognostic impact of a therapeutic strategy using plasma brain natriuretic peptide (BNP) levels.

Background   The prognosis of chronic heart failure (CHF) remains poor, even among patients treated in specialized departments.

Methods   A total of 220 New York Heart Association functional class II to III patients considered optimally treated with angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and diuretics by CHF specialists were randomized to medical treatment according to either current guidelines (clinical group) or a goal of decreasing BNP plasma levels <100 pg/ml (BNP group). Outpatient visits were scheduled every month for 3 months, then every 3 months. The primary combined end point was CHF-related death or hospital stay for CHF.

Results   Both groups were similar for baseline clinical and biological characteristics. Left ventricular ejection fraction was slightly lower in the BNP group than in the clinical group (29.9 ± 7.7% vs. 31.8 ± 8.4%, p = 0.05). At the end of the first 3 months, all types of drugs were changed more frequently in the BNP group. Mean dosages of ACEIs and beta-blockers were significantly higher in the BNP group (p < 0.05), whereas the mean increase in furosemide dosage was similar in both groups. During follow-up (median 15 months), significantly fewer patients reached the combined end point in the BNP group (24% vs. 52%, p < 0.001).

Conclusions   In optimally treated CHF patients, a BNP-guided strategy reduced the risk of CHF-related death or hospital stay for CHF. The result was mainly obtained through an increase in ACEI and beta-blocker dosages.   (J Am Coll Cardiol 2007;49:1733–9) © 2007 by the American College of Cardiology Foundation

Jourdain et al. JACC 2007;49:1733-

VERY recent development: not in 75 plus?

Medscape Today

LATEST | JOURNALS | RESOUR

Printer-Friendly   Email This

[heartwire]

TIME-CHF Questions Treatment of Heart Failure to Natriuretic-Peptide Targets

from Heartwire — a professional news service of WebMD

Steve Stiles

August 31, 2008 (Munich, Germany) — The use of natriuretic-peptide levels rather than symptoms alone to guide the medical management of heart failure, a strategy that's been tested in several trials with mixed results, failed to influence the primary end point of hospitalization-free survival over 18 months in a randomized heart-failure trial reported here today at the European Society of Cardiology Congress 2008 [1].

INFORMATION FROM INDUSTRY

The largest trial of its kind involving adults with ADHD
View the study design and results of the largest placebo-controlled stimulant trial of adults with ADHD.
Read more

The natriuretic-peptide–based approach did appear to improve survival free from heart-failure hospitalizations, a secondary but more conventional end point, among the prospectively defined subgroup of patients who were younger than 75 years. Interestingly, in this trial, according to lead investigator Dr Hans Peter Brunner–La Rocca (University Hospital Basel, Switzerland), patients 75 years and older--a group that has been greatly underrepresented in heart-failure drug trials, he observed--didn't show any outcome difference between the two management strategies.

Conclusions: heart failure

- there's a new guideline: adapt/translate it!

- diuretics, ACE-I and betablockers in "all"

- statins: not yet in all
- BNP-guided therapy: not yet in primary care

- patient education crucial: management programmes

- website for patients/carers

UMC

Conclusions: a new test to detect CVD?

- clinically relevant diagnostic research is crucial
- much available diagnostic research is flawed

- 4 prerequisites: (1) relevant patient domain
  (2) multiple tests (3) hierarchy (i.e. *added* value test)
  and (4) applicability: rule/score

- suspected MI: value of new point-of-care tests?
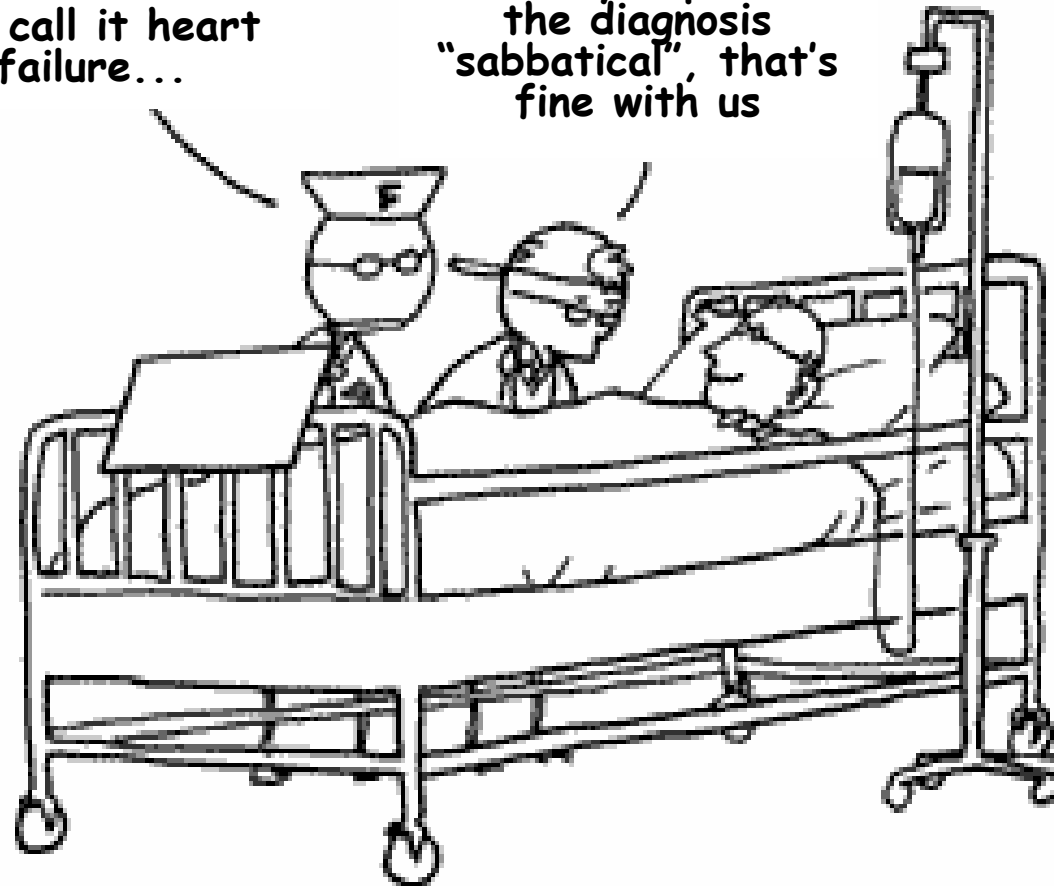- suspected heart faliure: (NTpro) BNP has added value!