High-sensitivity Troponin T : Evidence and 2015 ESC Guideline

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Temporal Patterns Following AMI

Cardiac marker kinetics

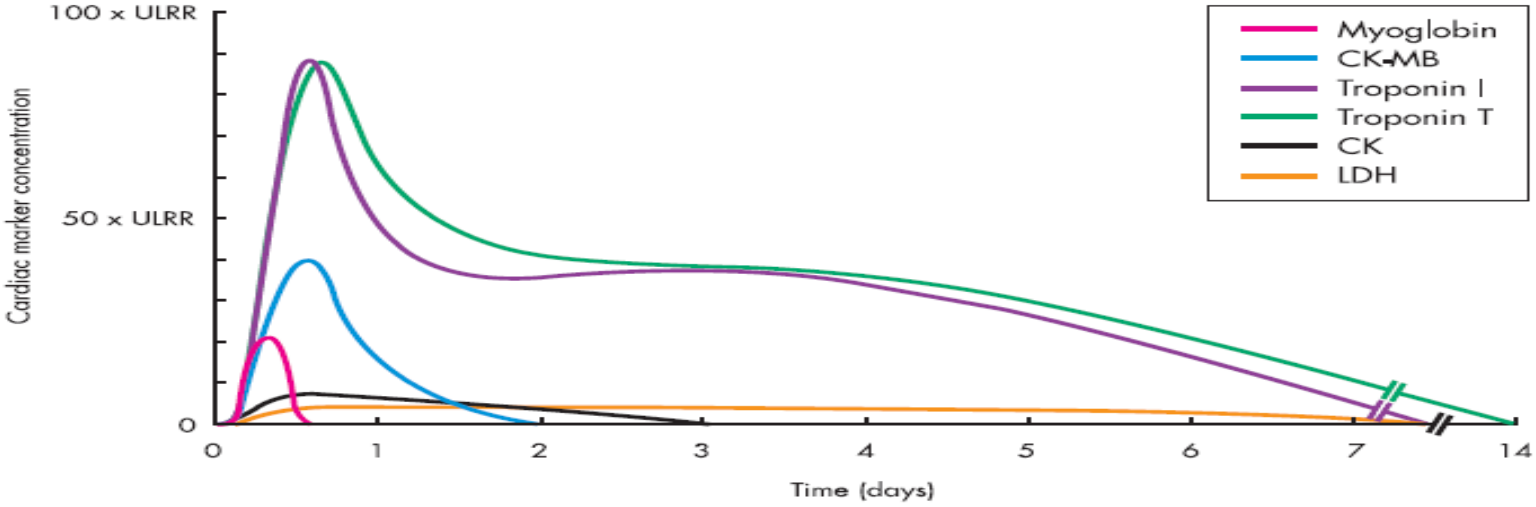

Table 2 Properties of cardiac marker proteins

Protein	Molecular mass (kD)	First detection*	Duration of detection	Sensitivity	Specificity
Fatty acid binding protein	12	1.5–2 hours	8–12 hours	+++	++
Myoglobin	16	1.5–2 hours	8–12 hours	+++	+
CK-MB	83	2–3 hours	1–2 days	+++	+++
Troponin I	33	3–4 hours	7–10 days	++++	++++
Troponin T	38	3–4 hours	7–14 days	++++	++++
CK	96	4–6 hours	2–3 days	++	++
Aspartate transaminase	~103	6–10 hours	3–5 days	++	+
LDH	135	6–10 hours	5–7 days	++	+

*Hours after symptom onset. CK, creatine kinase; LDH, lactate dehydrogenase.

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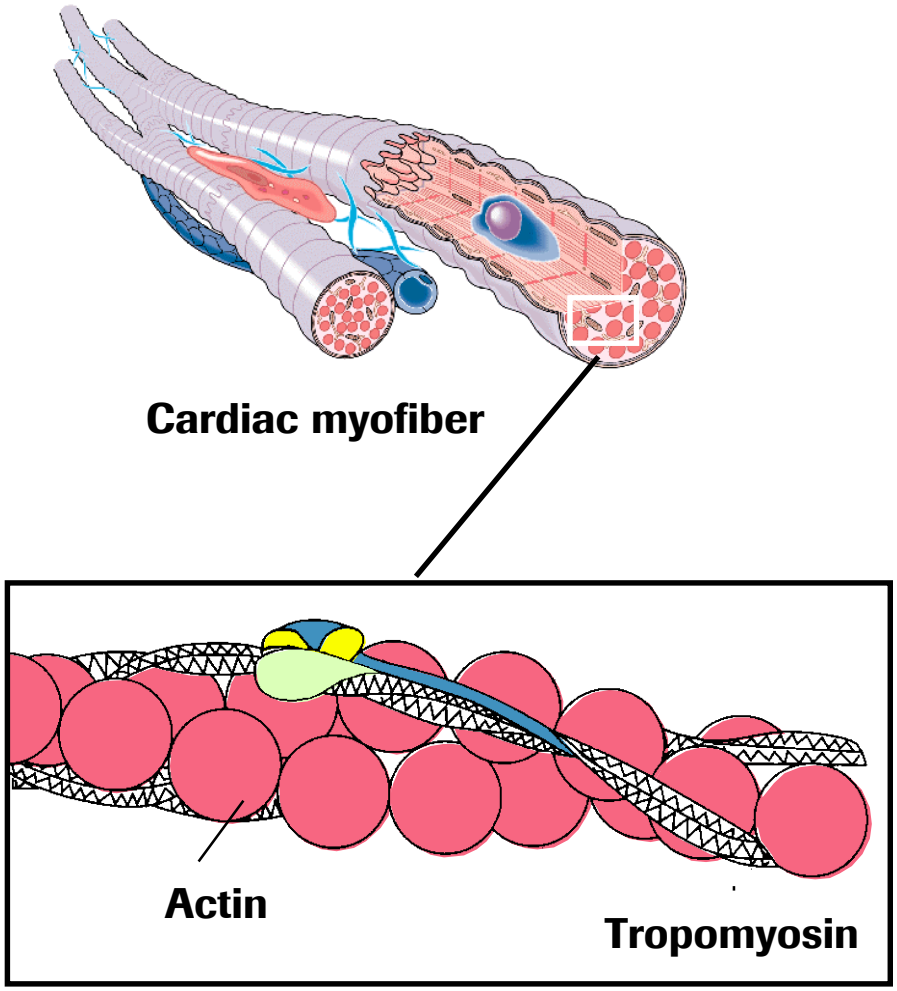
Biomarkers in Acute Coronary Syndrome

Troponin overview



Troponin is a globular protein complex part of the actin filament of striated muscle, distributed at regular interval along the tropomyosin filament

Regulates the contraction

Composed by 3 subunits

- **Troponin T:** attaches the Tn complex to tropomyosin
- **Troponin I:** inhibits actin-myosin interaction in absence of Ca^{++}
- **Troponin C:** Ca^{++} binding subunit

TnT and TnI have **cardiac specific** isoforms, cTnT and cTnI, that can be differentiated from those in skeletal muscle[1]

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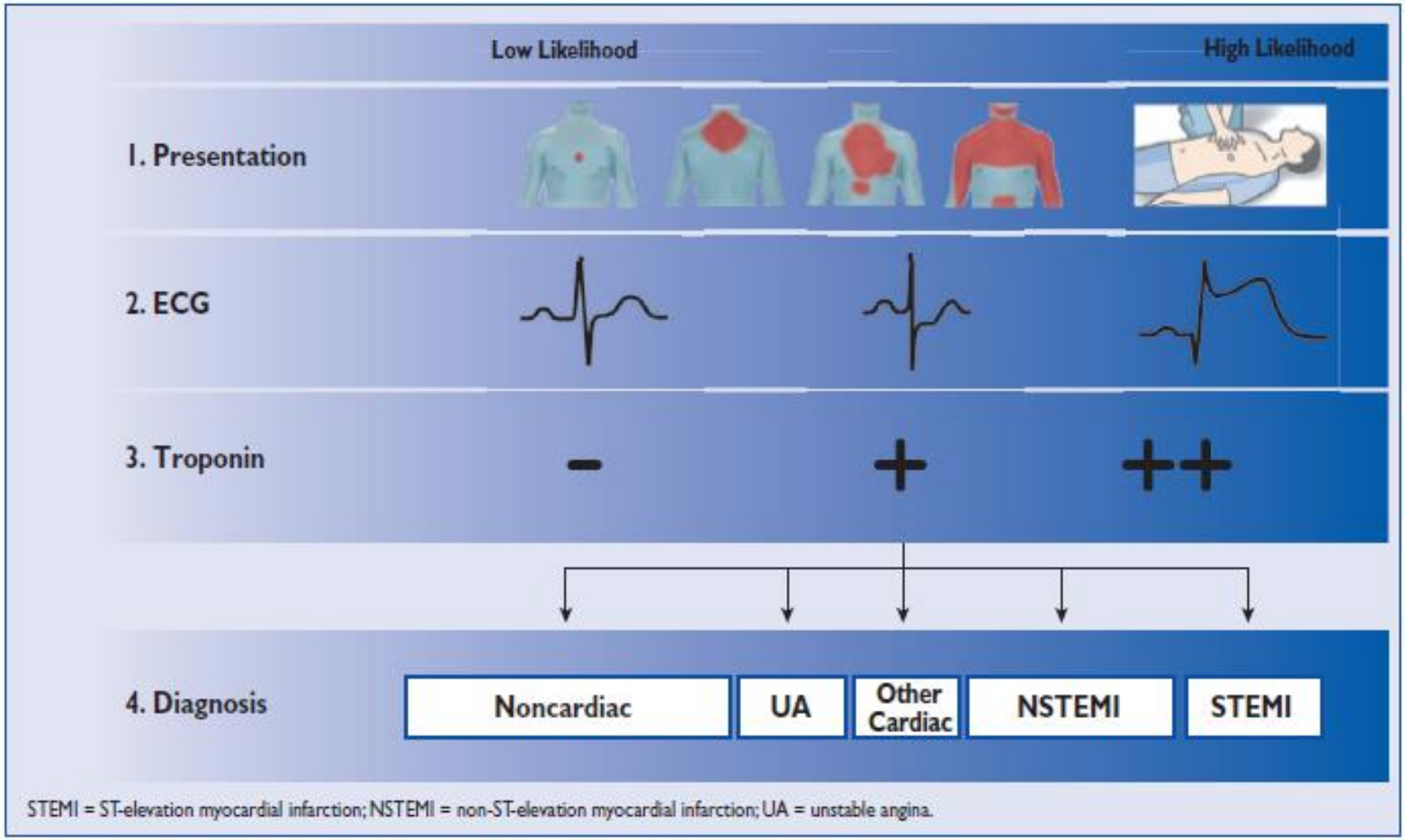
Initial Assessment of Patients with Suspected Acute Coronary Syndromes



STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina.

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How MI Is Diagnosed?

In the past, MI was diagnosed according to WHO criteria:

MI is diagnosed if 2 out the 3 of the following criteria are met:.

Clinical history

Findings on the ECG

Elevated enzyme

Troponin test emerged and replaced cardiac enzyme CKMB.

The MI cut-off of conventional troponin test was established using WHO definition, therefore, such cut-off value is at very high concentration. For example, the Gen 4 cTnT cut-off for MI is 100 ng/L (0.1 ng/mL)

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The New Universal Definition of MI

Today, MI is diagnosed by the new definition proposed by a global task force firstly in 2007

The Universal definition in 2007:
joint ESC / ACCF / AHA / WHF task force

Detection of **rise and/or fall** of cardiac biomarkers (preferably **troponin**) with at least one value **above the 99th percentile** in combination with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative for ischemia: ST-T changes or new LBBB or new Q-waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

The fundamental change from WHO definition

Biomarkers play more important role in MI diagnosis

Biomarker kinetic change (serial testing) is part of diagnostic criteria

Cut-off value is much lower at 99th percentile limit

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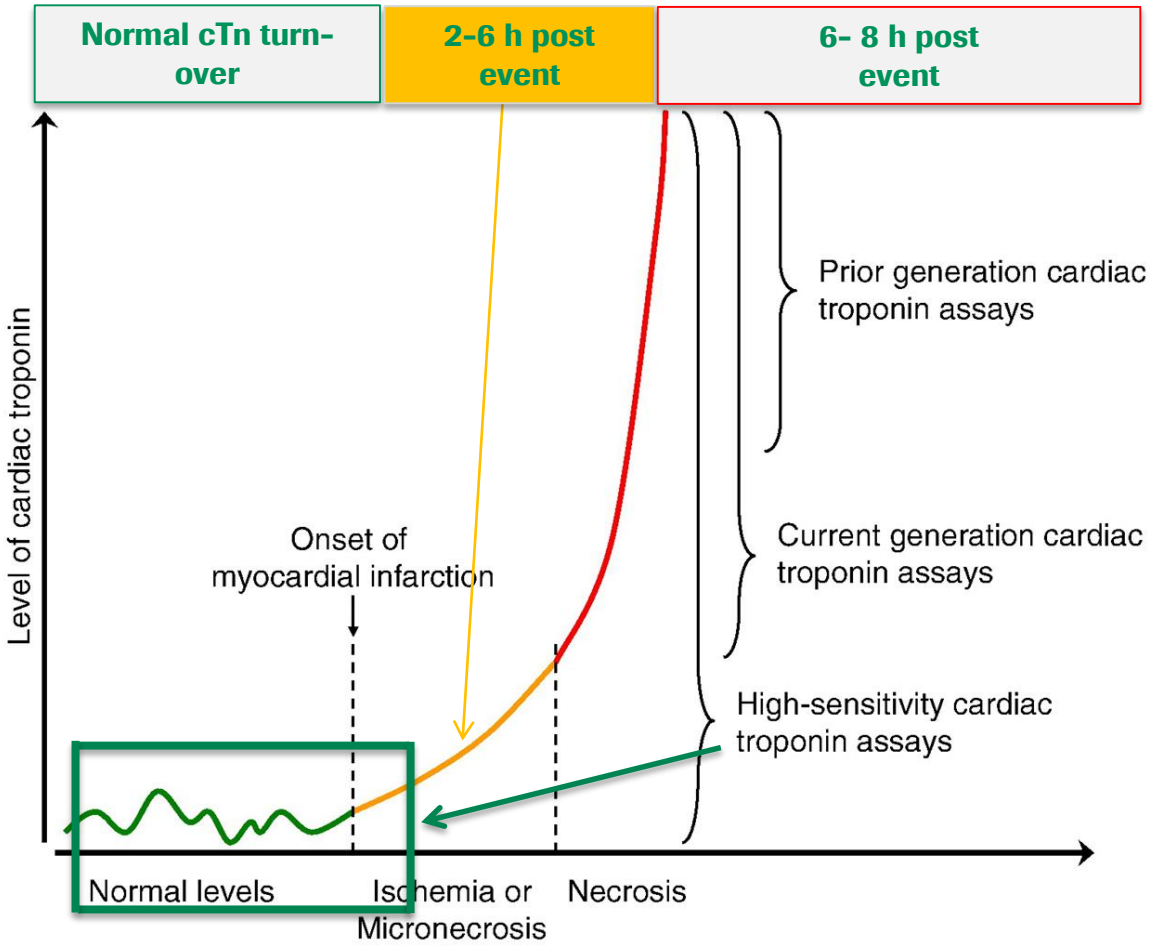
Progress in Cardiology

Influence of sensitivity and precision on early detection range of Tn rise



Adapted from: Hochholzer W et al. *Am Heart J* 2010; 160(4): 583-94.

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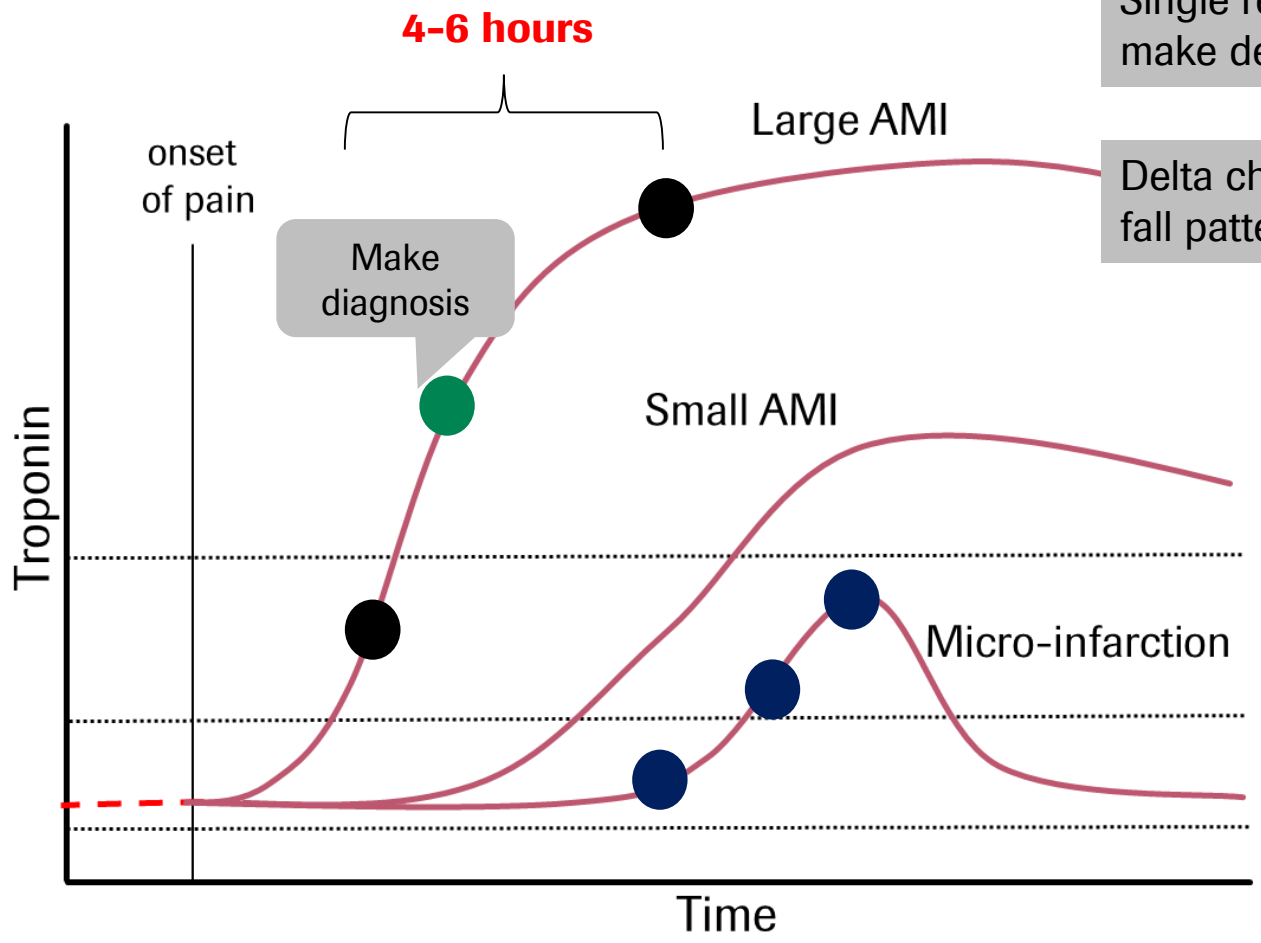
High sensitivity troponin changes the clinical paradigm



Single result above cutoff can't make decision

Delta change to see rise and fall pattern

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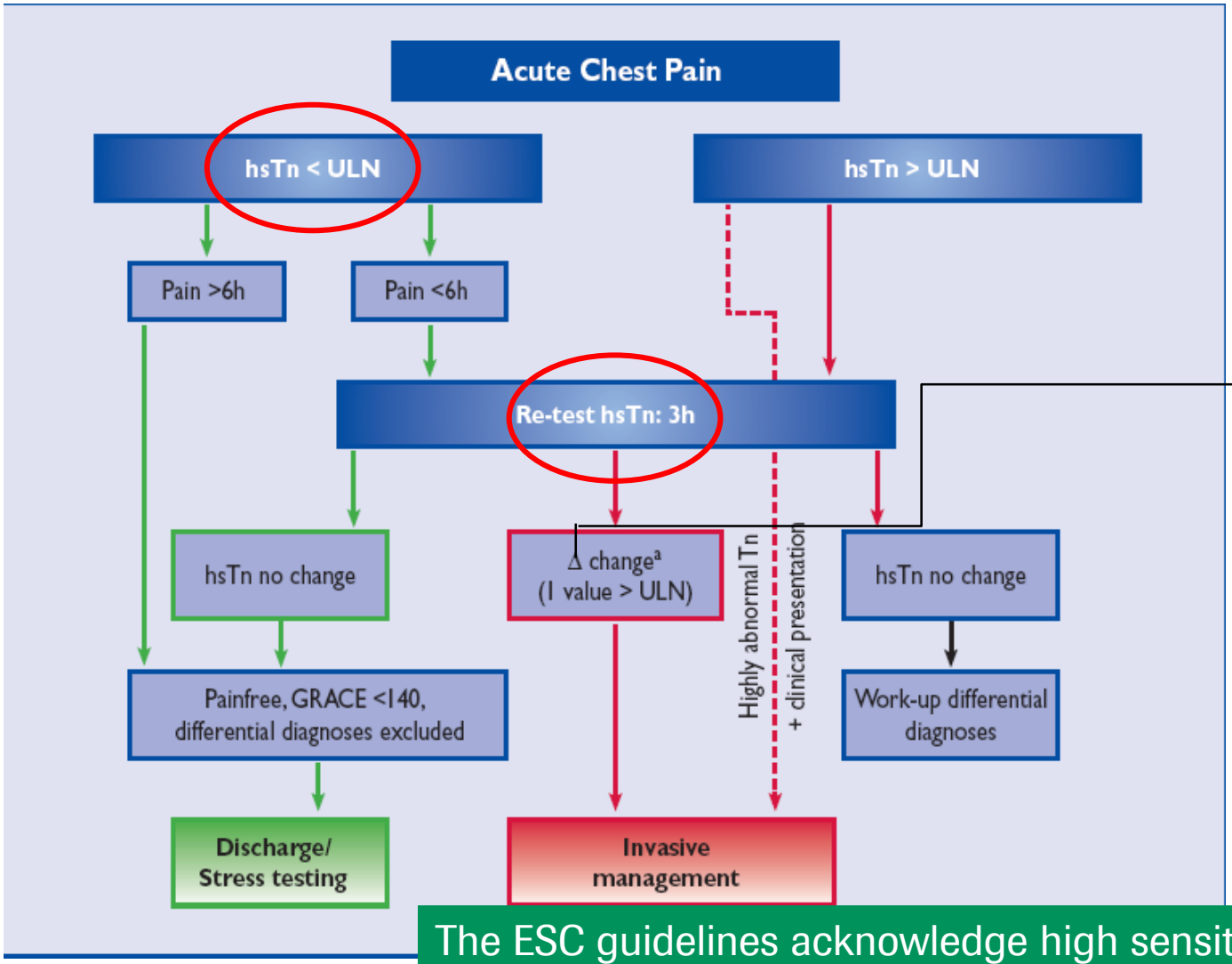
Rapid rule-out of ACS with high sensitivity troponin

ULN= upper limit of normal, 99th percentile of healthy controls.

GRACE = Global Registry of Acute Coronary Events



Δ change, dependent on assay

At the end of this step, th should g

The ESC guidelines acknowledge high sensitivity Tn clinical benefits to **rule-in** and **rule-out** ACS in patients presenting without persistent ST-segment elevation

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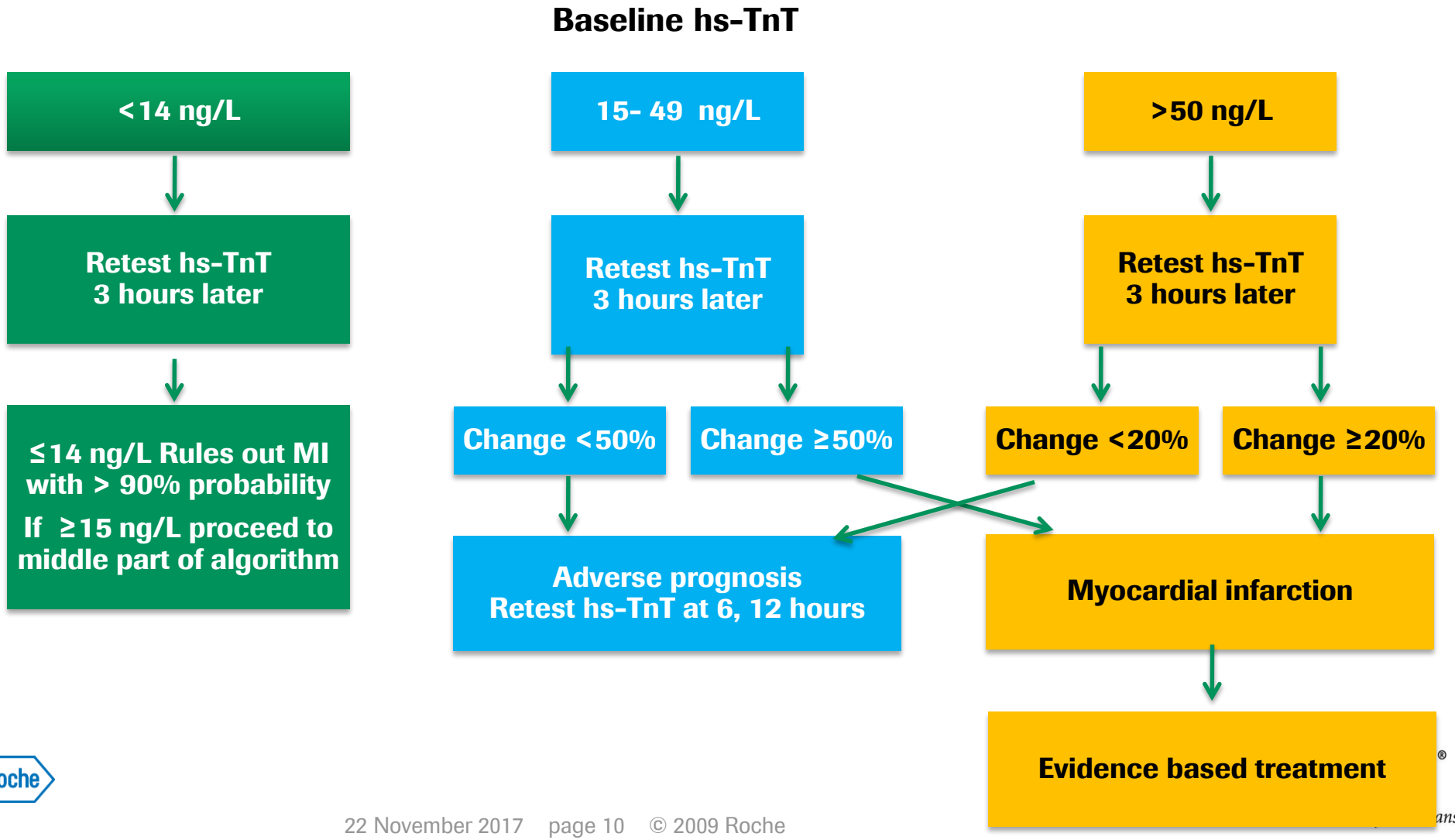
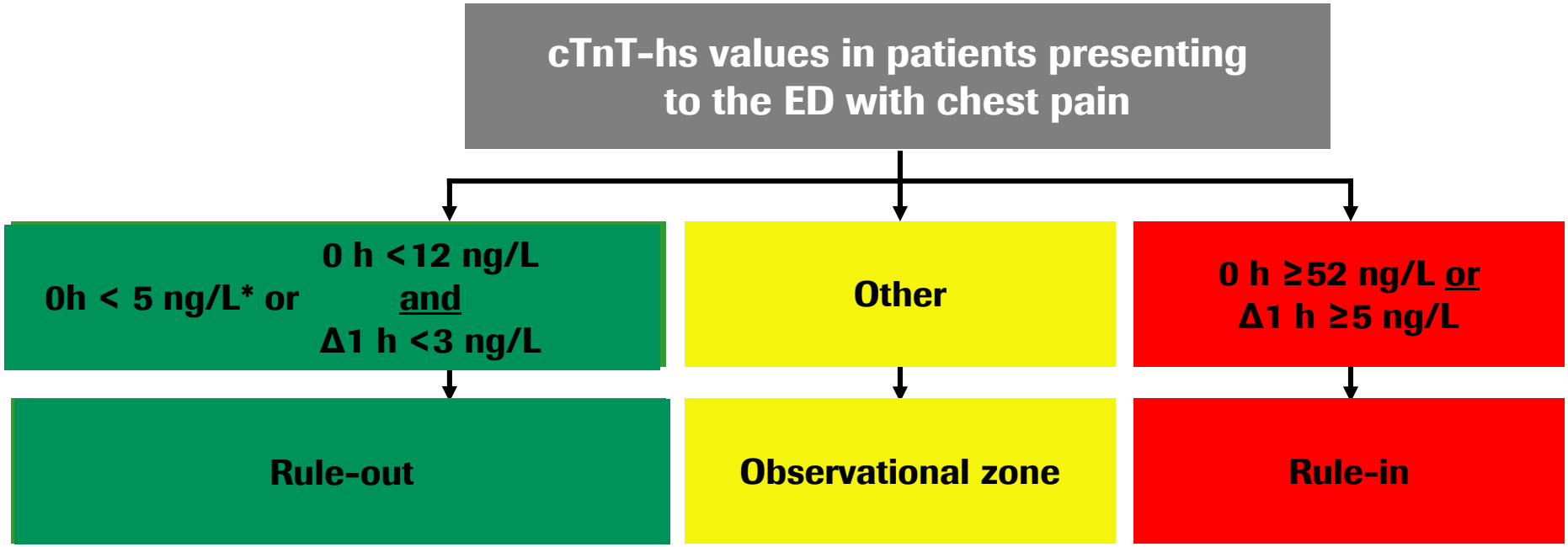
Implement 3-hour Algorithm in Clinical Routine



2015 ESC Guidelines

Recommended T0/1-h algorithm adapted for cTnT-hs



* Only applicable if chest pain onset > 3h

Source: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2015; Epub ahead of print (doi:10.1093/eurheartj/ehv320)

What are APACE and TRAPID-AMI study?

Multi-center clinical trials using cTnT-hs for a 1-hour AMI diagnosis

APACE

Advantageous Predictors of Acute Coronary Syndrome Evaluation

External study (2006-2013)

2,192 patients

6 centres in **3** countries
(CH, Italy, Spain)

TRAPID-AMI

High sensitivity cardiac Troponin T assay for RAPID rule-out of Acute Myocardial Infarction

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1,282 patients

12 sites in **9** countries on **3** continents
(US, Europe, Pacific)

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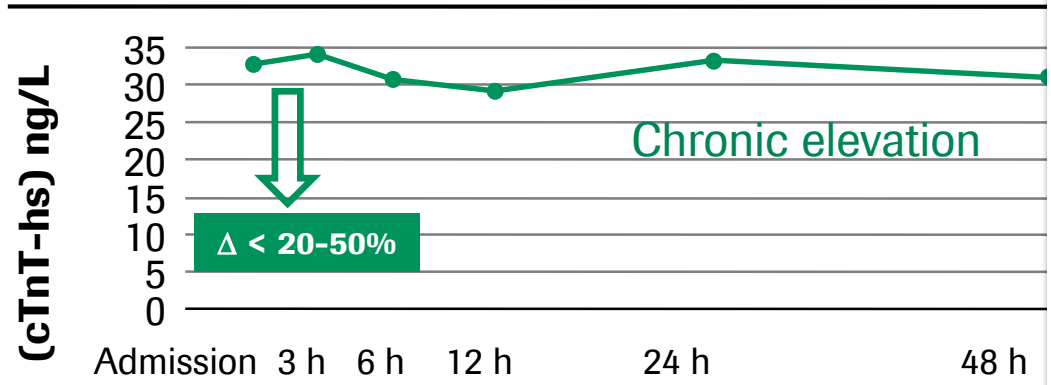
TnT-hs interpretation in patient on dialysis & chest pain

Different Troponin kinetic profile

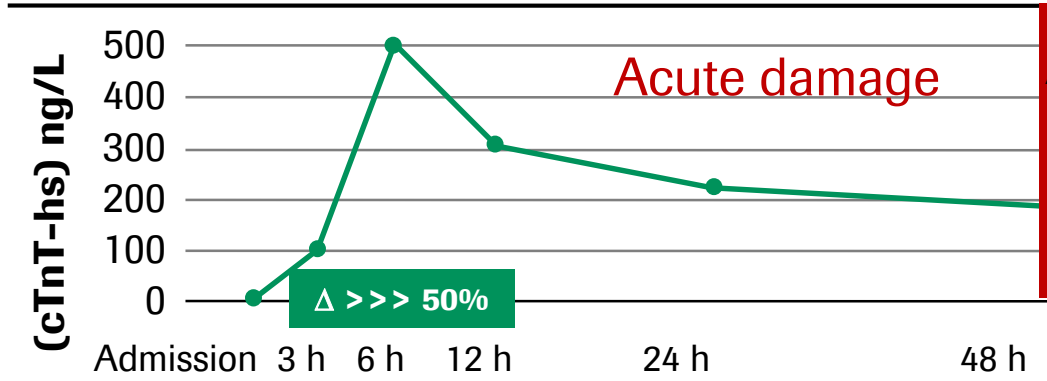
Patient case with end stage renal failure

Chronic elevations are important for CV risk stratification



- In the early 1990s, the role of cTn in end-stage renal disease (ESRD) was unclear and matter of debate. Through many expert studies, it had been shown that elevated cTnT results in ESRD are not false-positive, but reflect poor myocardial prognosis through potential **subclinical myocardial lesions** ("cardio-renal syndrome")[1]

Other patient case with AMI



As requested by the guidelines, serial sampling of cTn serves as to differentiate diagnosis of AMI from chronically elevated cTn levels (such as ESRD)

Source: Clinical case studies and result interpretation - *Elecsys® cardiac Troponin T-high sensitive test*
E. Giannitsis &. H. Katus

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Take Home Message

Elevated cTn ≠ MI
Kinetic rise/fall change of cTn can differentiate MI from other diseases

With the Universal definition of MI, troponin should has optimal precision for confident use of the 99th percentile cut off present rise and/or fall kinetic pattern (to rule out non-MI)

cTnT-hs complies with the optimal precision recommendation by the Universal Definition of MI: CV<10% at 99th percentile of 14 ng/L

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Take Home Message

Troponin is useful in NSTEMI detection, high sensitive troponin can detect more NSTEMI patients than conventional troponin

cTnT-hs is a high sensitivity assay. This is proven by the ESC guideline recommendation of 3-hour/1-hour algorithm using high sensitive troponin assay.

Using cTnT-hs, the positive result is true positive. Non-ACS patients may have elevated cTnT-hs. Regardless of the cause, elevations of hs-cTn values are associated with an adverse clinical outcome in most clinical conditions.

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Clinical Benefits of NT-proBNP

Diagnostic performance in cardiovascular disease

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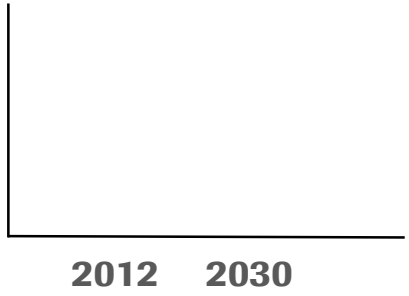
An introduction to the burden of HF

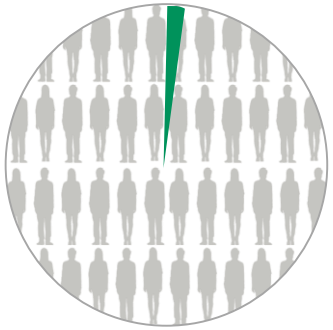
A common, costly, and often deadly disorder

Forecast



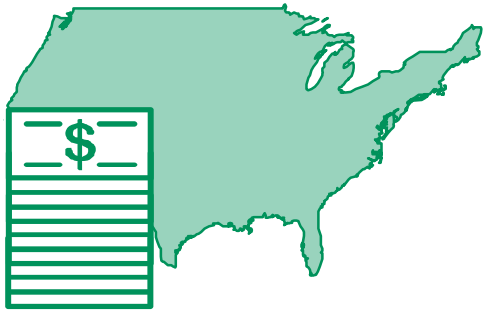
46% increase in HF is expected from 2012 to 2030[1]

Prevalence



- 1–2 % of adults in developed countries have HF[2]
- Rising to ≥10% among persons ≥ 70 years old[2]

Cost



863 billion USD[3] spent on worldwide HF care in 2010

HF, heart failure

1. Heidenreich, PA., et al. (2013). *Circ Heart Fail*, 6: 606–619. 2. McMurray, JJ., et al. (2012). *Eur Heart* J, 33:1787–1847. 3. Bloom, DE., et al. (2011). http://www3.weforum.org/docs/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf

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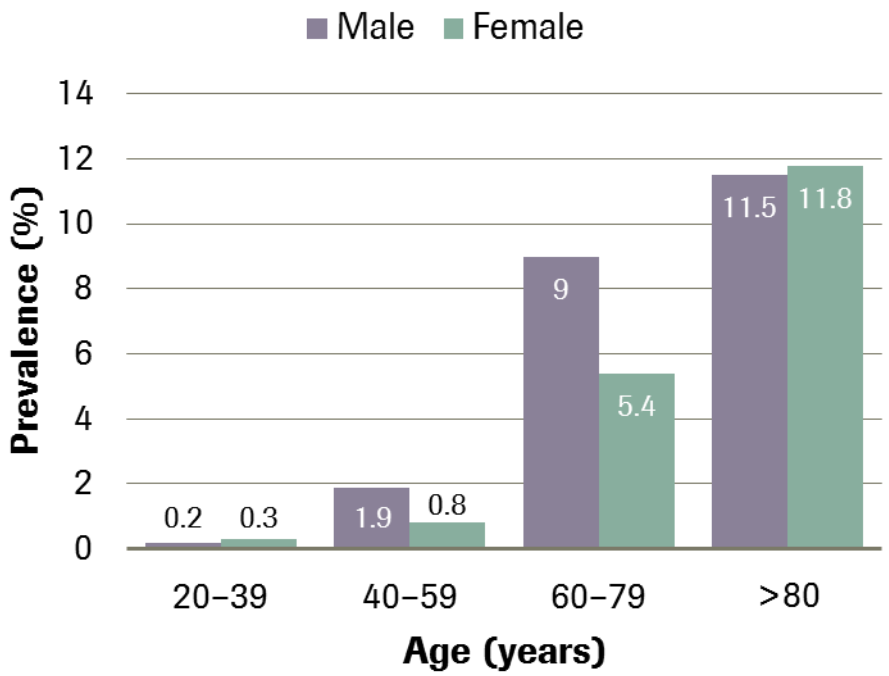
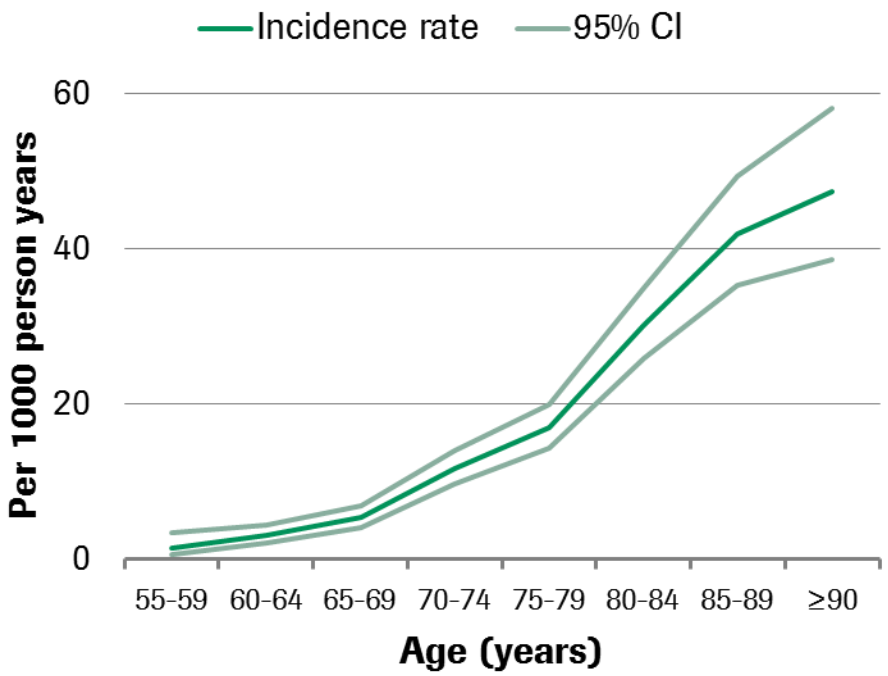
Prevalence and incidence rates of HF

Incidence rises with age

Prevalence of HF by age and sex (US data)[1]



Incidence of HF by age (EU data)[2]



1. Roger, V. L., et al. (2012). *Circulation, 125*(1), e2-e220; 2. Bleumink, G. S., et al. (2004). *Eur Heart J, 25*(18), 1614-1619.

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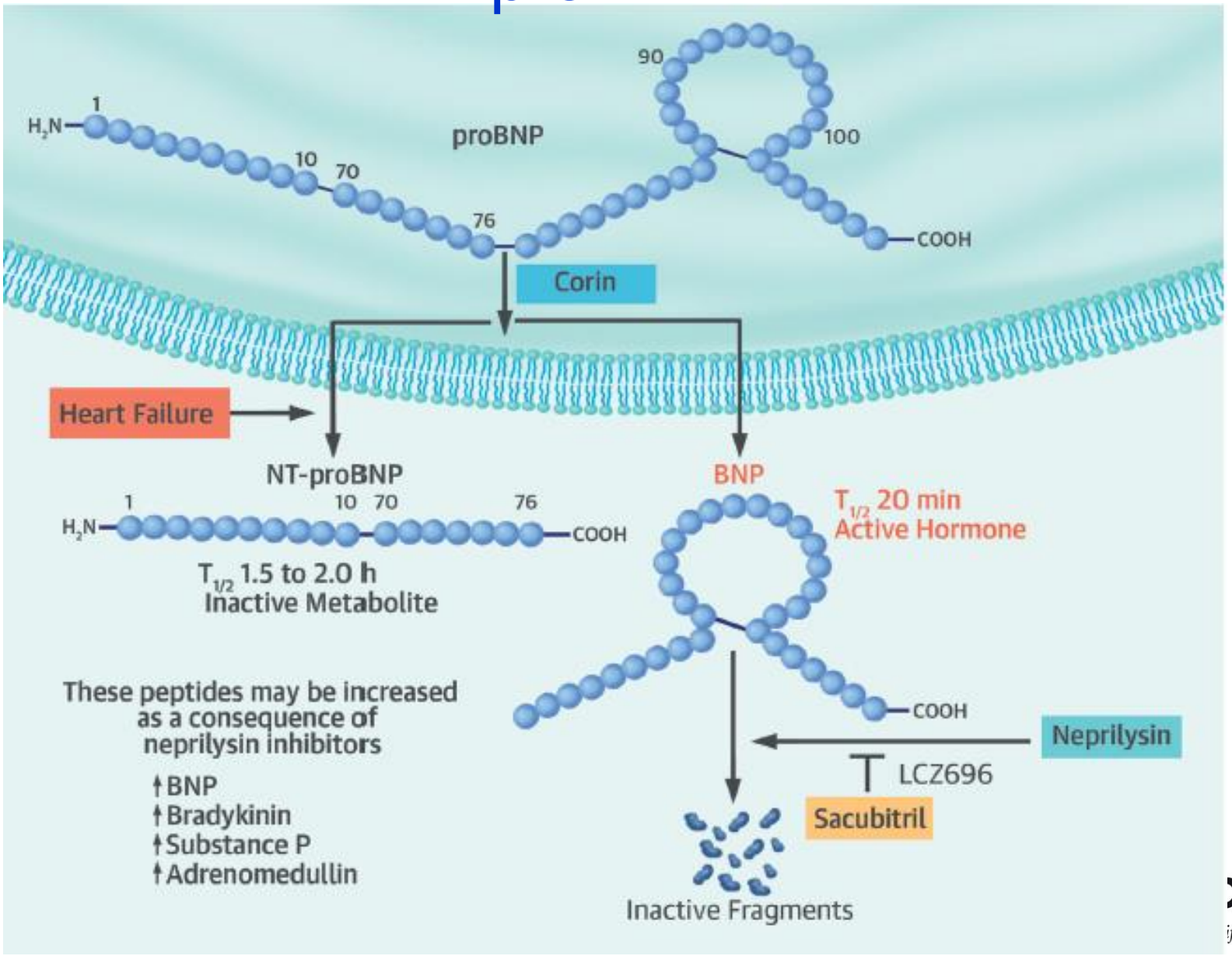
NT-proBNP in HF



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NT-proBNP and BNP
Major differences

	NT-proBNP*	BNP
Molecular mass	8.5 kDa	3.5 kDa
Half-life	90-120 minutes	20 minutes
Test tube*	EDTA, serum, heparinized	EDTA
Sample stability	72 hours	varies (4-20 hours)
Relative change value	Less than BNP (BV and CV)	More than NT-proBNP
Hormone	Inactive	Active
Standardized	Yes	No

*NT-proBNP on the point of care device requires whole blood and heparinized tube
BV, biologocal variation; CV coefficient variation; RCV, relative change value

Bayes-Genis & Januzzi. (2008). *NT-proBNP as a biomarker in CVD.*
Barcelona: Thomas Reuters

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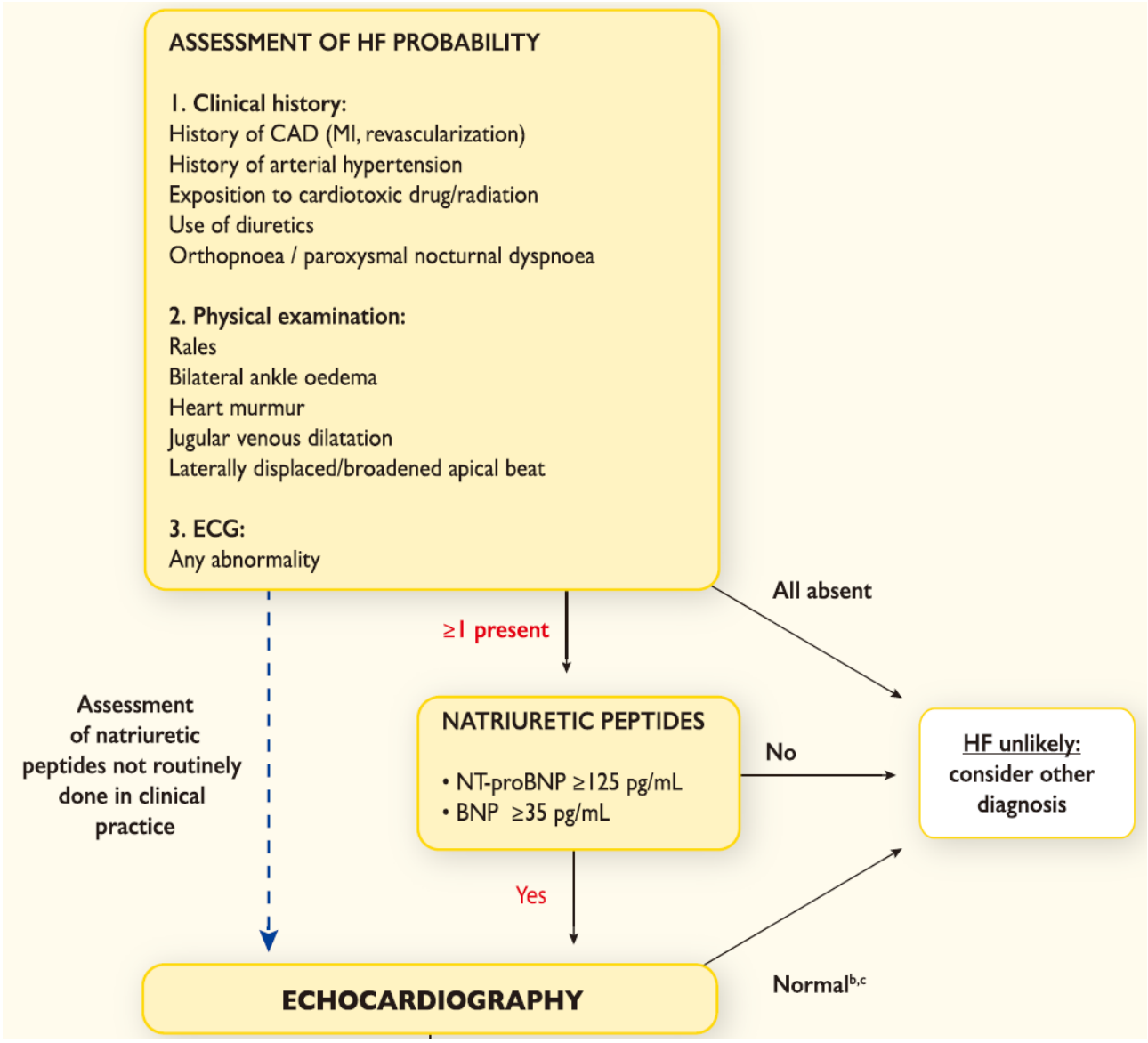
2016 ESC HF Guideline: Diagnosis



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2017 ACC/AHA HF Guideline

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	**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.
See Online Data Supplements A and B.			
IIa	B-NR	**During a HF hospitalization, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis (93, 96, 104-113).**	**NEW**: Current recommendation reflects new observational studies.
See Online Data Supplements A and B.			

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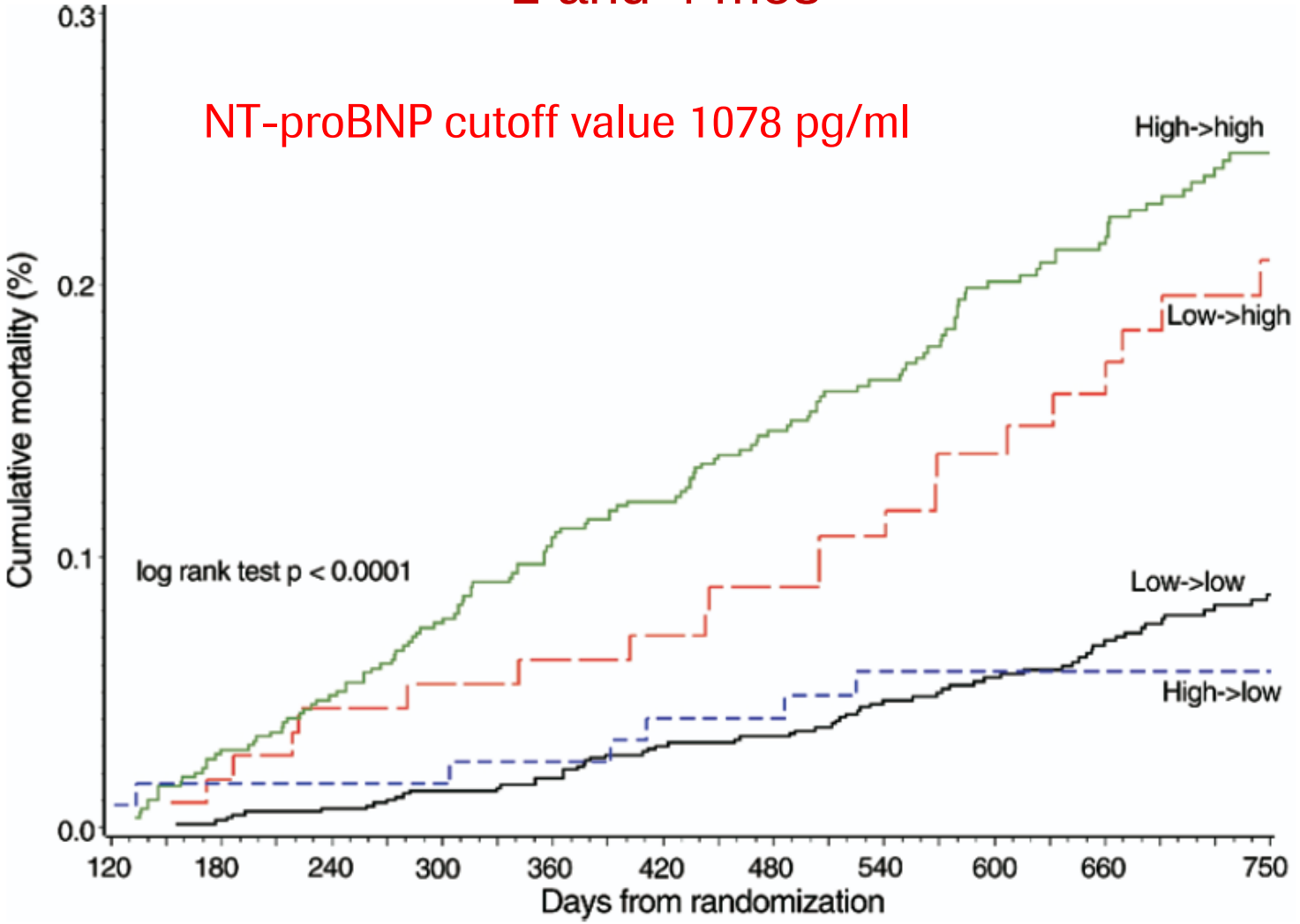
Natriuretic Peptide in HF:

Val-HeFT (Valsartan Heart Failure Trial)

1 and 4 mos



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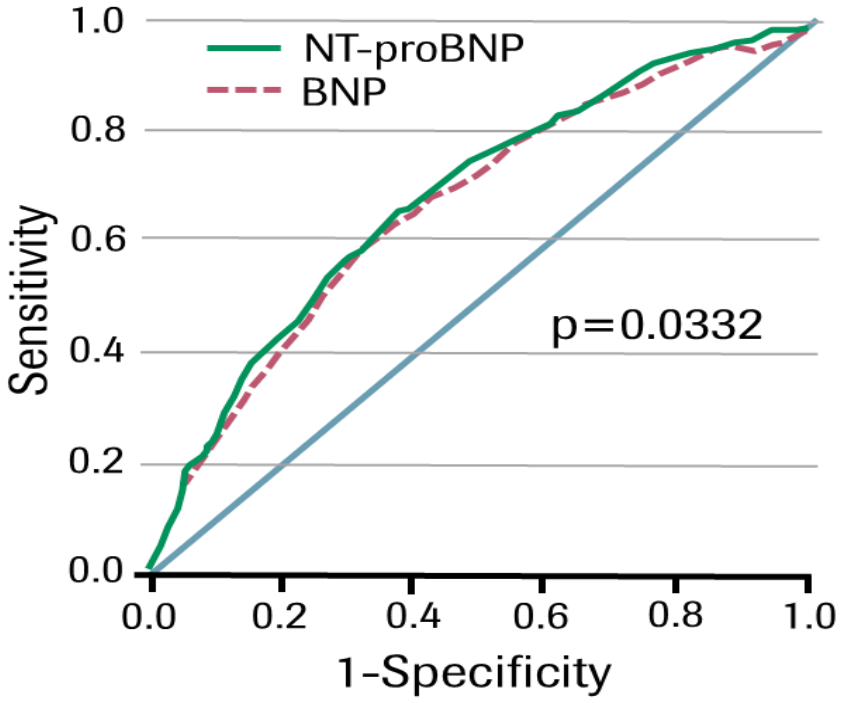
J Am Coll Cardiol 2008;52:997–1003

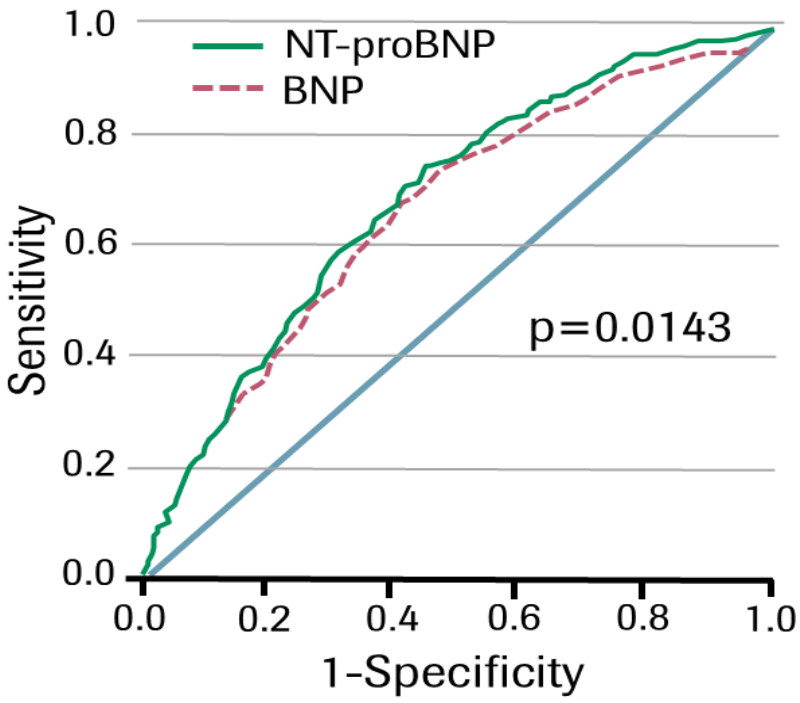
NT-proBNP has a significantly higher predictive value

3,916 patients with chronic and stable HF: ValHeFT trial

Mortality and morbidity



Hospitalization for HF



AUC, area under curve; HF, heart failure; Val-HeFT, valsartan heart failure trial

Masson, S. et al. (2006). *Clin Chem 52*, 1528–1538.

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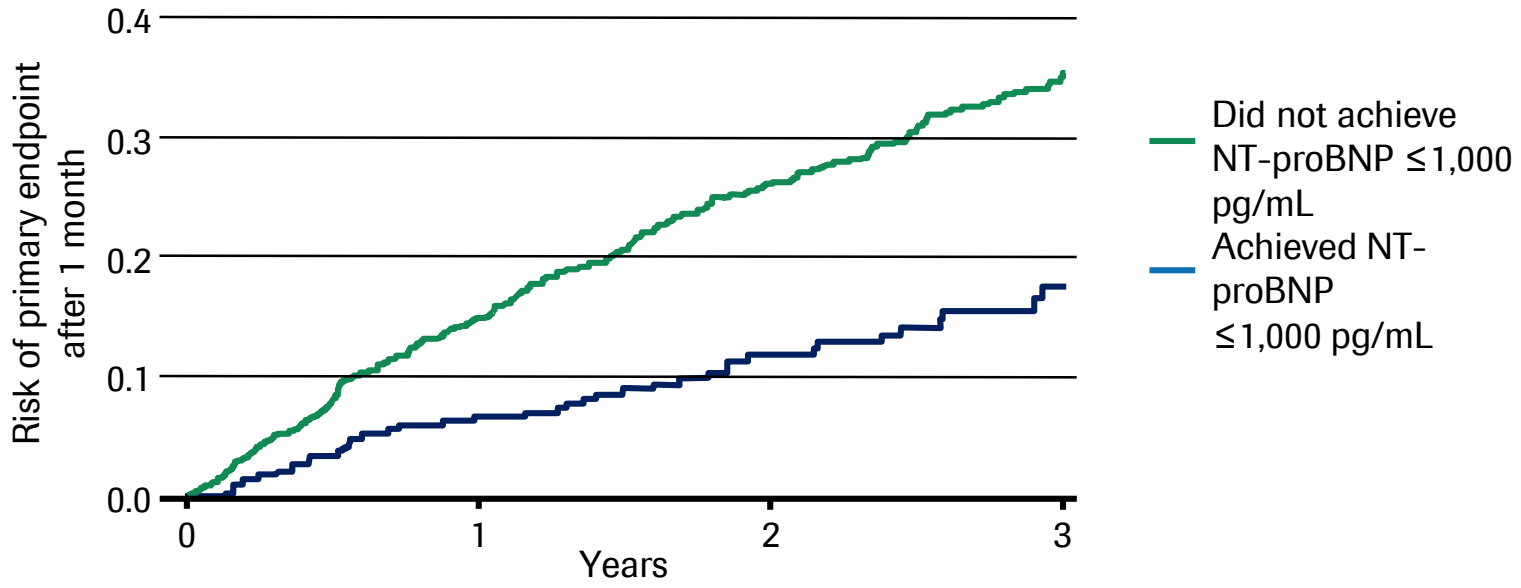
Recommendation

- A single value of NT-proBNP greater than 5000 pg/mL in HF patients predicts a greater risk of mortality and poor outcomes.
- The higher the NP concentration, the poorer the prognosis.

Lower NT-proBNP is associated with better outcomes

At 3 years of follow-up, the risk was ~50% less in patients who achieved NT-proBNP ≤1,000 pg/mL

Risk of primary endpoint if NT-proBNP value of 1,000 pg/mL achieved or not achieved 1 month after randomization



Primary endpoint: the first occurrence of CV death or HF hospitalization
CV, cardiovascular; HF, heart failure

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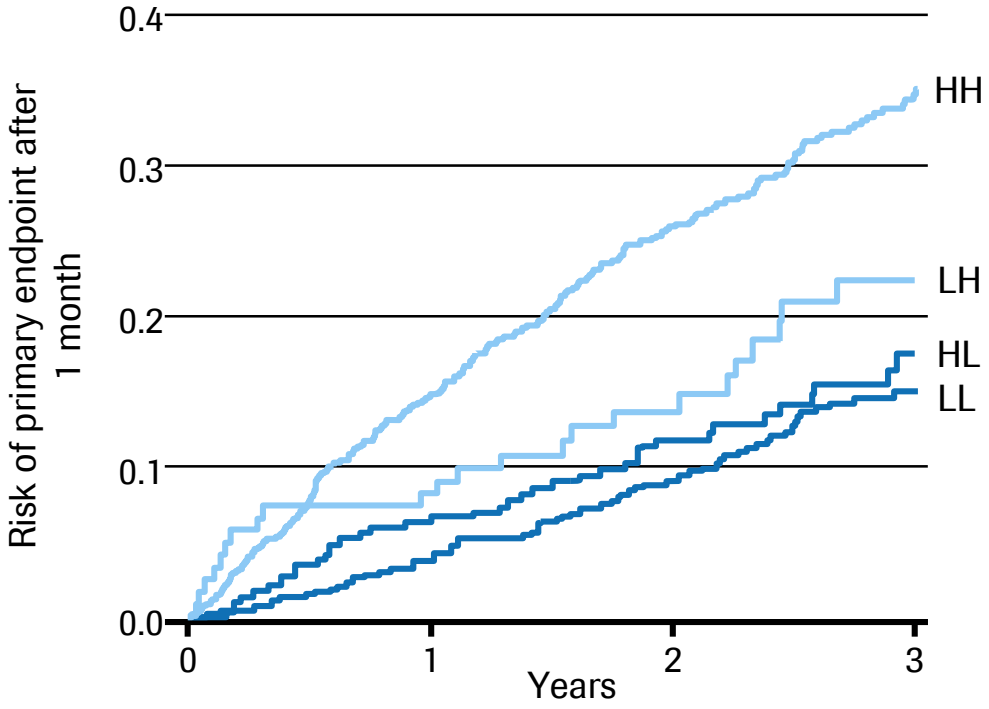
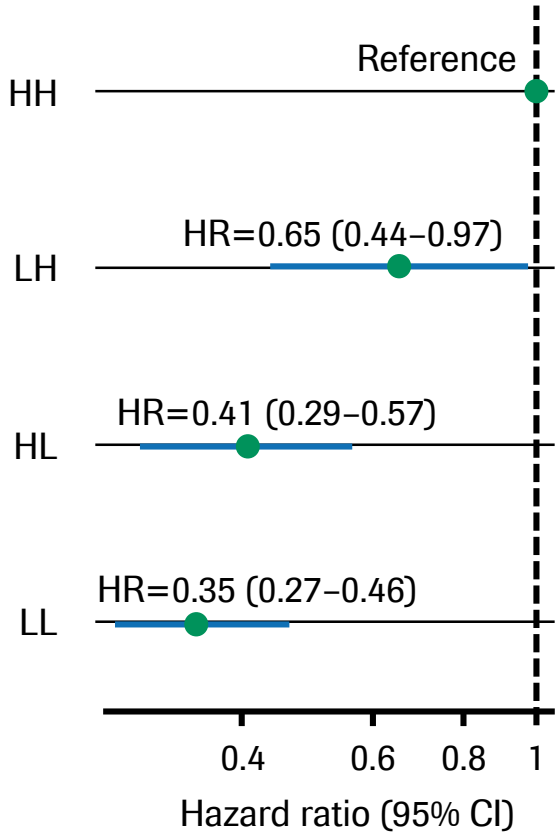
J Am Coll Cardiol 2016; 68:2425-36

NT-proBNP change is a significant predictor of subsequent events





High threshold >1,000 pg/mL
Low threshold ≤1,000 pg/mL

CI, confidence interval; HH, high-high; HL, high-low; HR, hazard ratio; LH, low-high; LL, low-low

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J Am Coll Cardiol 2016; 68:2425-36

Recommendation

- A baseline value of NT-proBNP is needed for a new HF patient in clinic
- NT-proBNP values > 1000 pg/mL indicate an increased risk of death or hospitalization

2017 ACC/AHA HF Guideline

Biomarkers: Recommendations for Prognosis			
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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.
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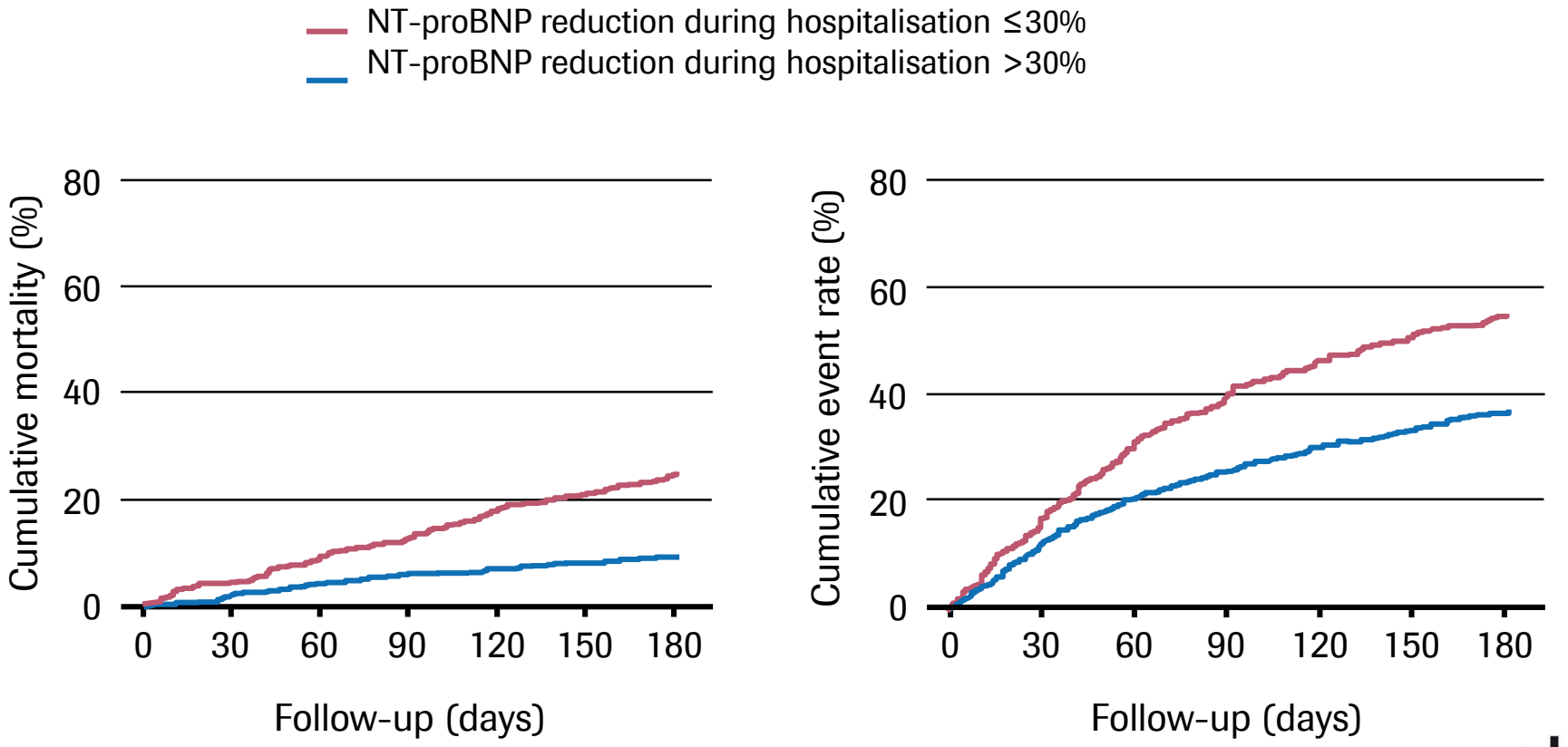
NT-proBNP delta correlates with death and CV events

Mortality twice as high in patients with reduction ≤30% vs. 30%



Heart 2014;100:115-125

CV, cardiovascular

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Recommendation

- A baseline value of NTproBNP is needed during the first 24 h of HF hospitalization.
- The reduction in NTproBNP levels > 30% between admission and discharge is helpful to predict better clinical outcome.
- The determination of discharge should not depend on NP levels.

NT-proBNP also provide prognostic significance in outpatient HF patients

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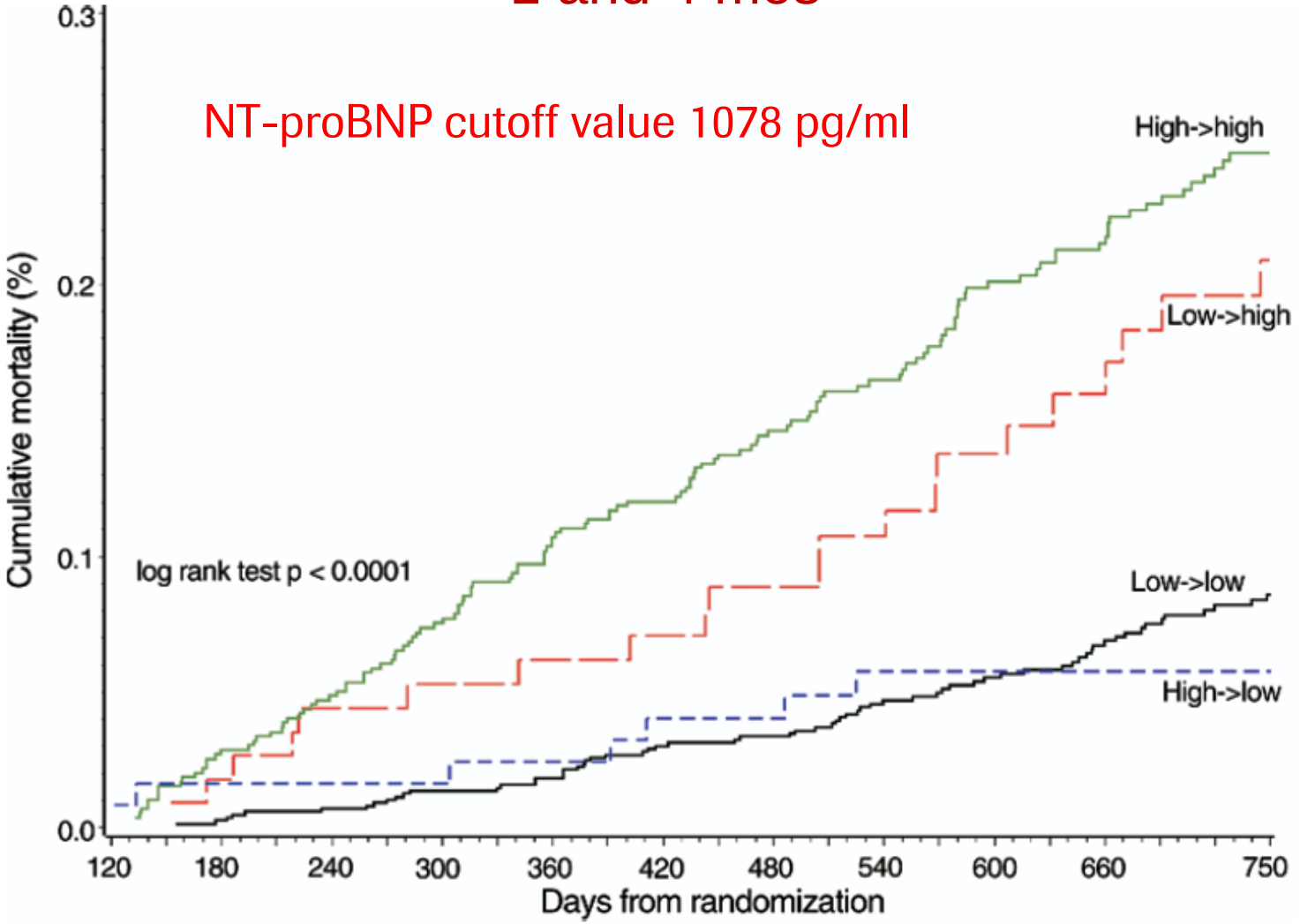
Natriuretic Peptide in HF:

Val-HeFT (Valsartan Heart Failure Trial)

1 and 4 mos



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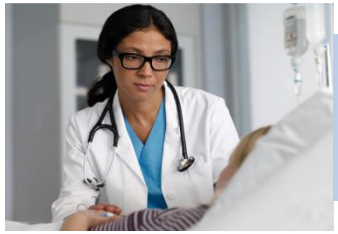
J Am Coll Cardiol 2008;52:997–1003

Test early. Treat right. Save lives.

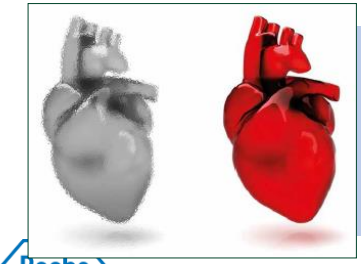
NT-proBNP the biomarker of choice in HF management

Adopting NT-proBNP to support your clinical-decision making management in HF

- **Rule-out: exclude diagnosis and identify patients whom need Echo to confirm the diagnosis in both acute and non-acute seeting**
- **Rule-in : age-adjusted cut-offs available for better diagnostic accuracy**



- **Improve patient care from diagnosis, prognosis to monitoring**



- **Support therapy change decision to add MRA and/or to replace ACEIs by sacubitril-valsartan**
- **Unlike BNP, NT-proBNP is a suitable biomarker for HF patients treated with sacubitril-valsartan**

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Doing now what patients need next

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