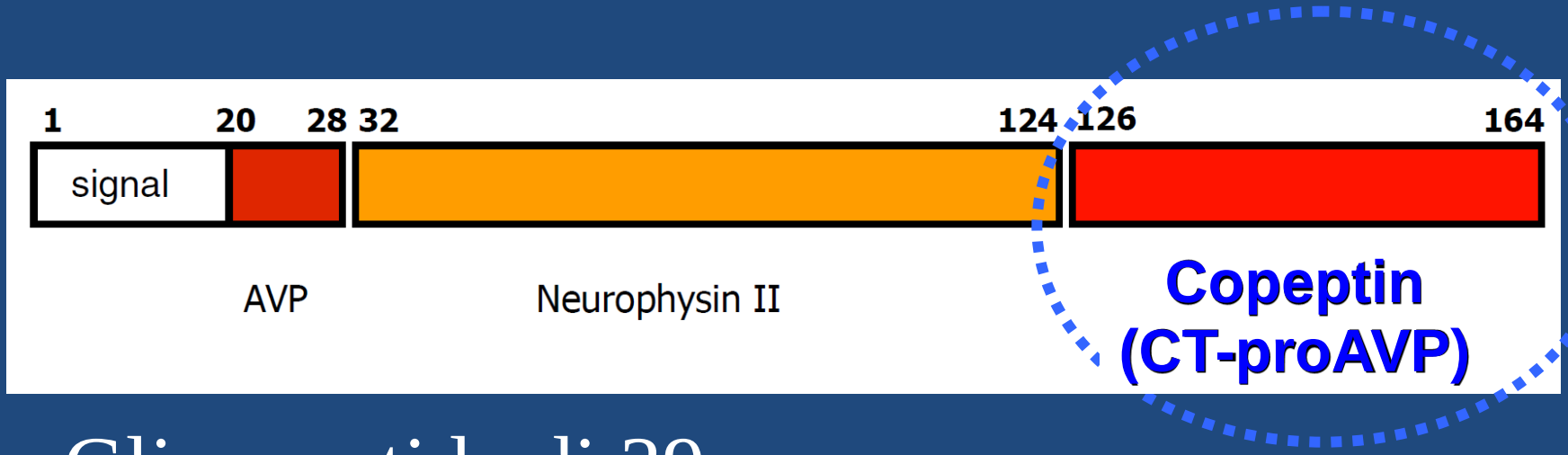
La Copeptina nella gestione del paziente con dolore toracico, il problema del rule out dell'infarto e dell'overcrowding in PS

Dott.ssa Cristina Runzo

Ospedale Mauriziano - Torino



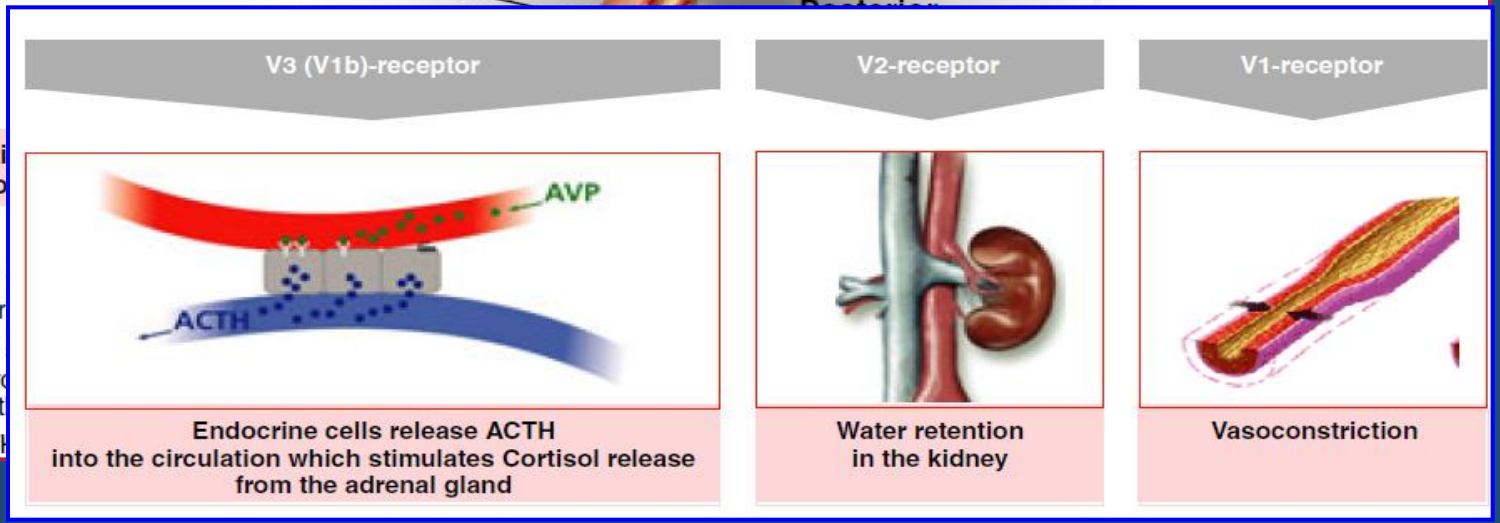
- Glicopeptide di 39 aa
- Parte C terminale del precursore dell'AVP (Arginina Vasopressina)
- Marker surrogato stabile e sensibile dell'AVP
- Secreto in modo equimolare con AVP

Synthesis of pro-AVP, the precursor hormone of AVP and Copeptin, in the neurons of the para-ventricular and the supraoptic nucleus

Hypothalamus

Synthesis of pro-AVP in parvocellular neurons

AVP svolge un ruolo importante nella risposta emodinamica allo stress endogeno



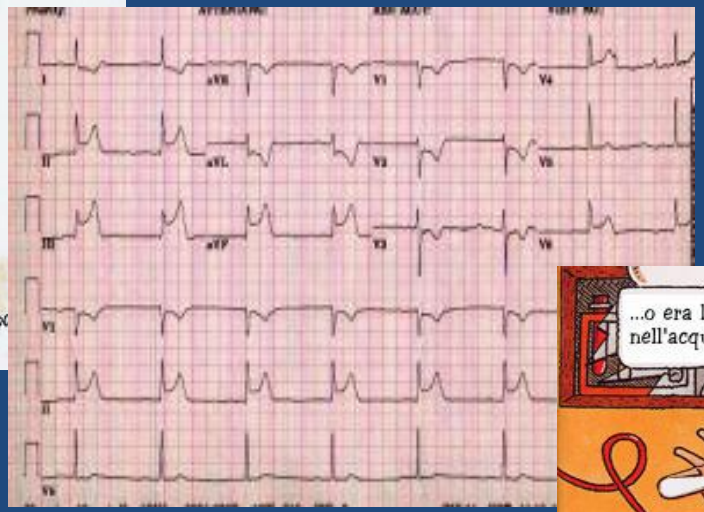
- Shock
- Sepsi
- Polmonite acquisita in comunità
- BPCO
- Stroke
- Scompenso cardiaco
- I

Infarto miocardico acuto

"…in **severe diseases** or **states**,
the nonosmotic release of AVP is depicted
by a **sharp increase in plasma copeptin**,
which has **diagnostic** and **prognostic** value"

Jochberger S, 2006; Katan M, 2010; Urwyler S, 2010


MI DICA... DOVE HA MALE?
HO MALE QUI...
E QUI... QUI... QUI... QUI...




...o era l'acido nell'acqua!?

Curva troponina

Un unico dosaggio della troponina di vecchia generazione può non rilevare dal 10 al 15% dei paz ad alto rischio cardiovascolare

Curva troponina: 0 – 6 – 12 ore (lunga permanenza paz in PS con consumo di risorse e carico di lavoro)

Hamm CW et all: **Cardiac biomarkers for rapid evaluation of chest pain.** Circulation 2001


STEFENA


23 3 2012

Incremental Value of Copeptin for Rapid Rule Out of Acute Myocardial Infarction

Tobias Reichlin, MD,* Willibald Hochholzer, MD,* Claudia Stelzig, MSc,* Kirsten Laule, MSc,* Heike Freidank, MD,† Nils G. Morgenthaler, MD,‡ Andreas Bergmann, PhD,‡ Mihael Potocki, MD,* Markus Noveanu, MD,* Tobias Breidthardt, MD,* Andreas Christ, MD,* Tujana Boldanova, MD,* Ramona Merki, MD,* Nora Schaub, MD,* Roland Bingisser, MD,* Michael Christ, MD,* Christian Mueller, MD*

Basel, Switzerland; and Henningsdorf, Germany

J Am Coll Cardiol 2009;54:60-8

- **Obiettivo del lavoro**: valutazione efficacia nell'esclusione di SCA del dosaggio della copeptina insieme alla troponina

- 487 paz consecutivi non selezionati con rischio cardiovascolare moderato/alto con dolore toracico suggestivo per SCA all'arrivo in DEA

Incremental Value of Copeptin for Rapid Rule Out of Acute Myocardial Infarction

J Am Coll Cardiol 2009;54:60-8

Livelli di copeptina all'arrivo in PS

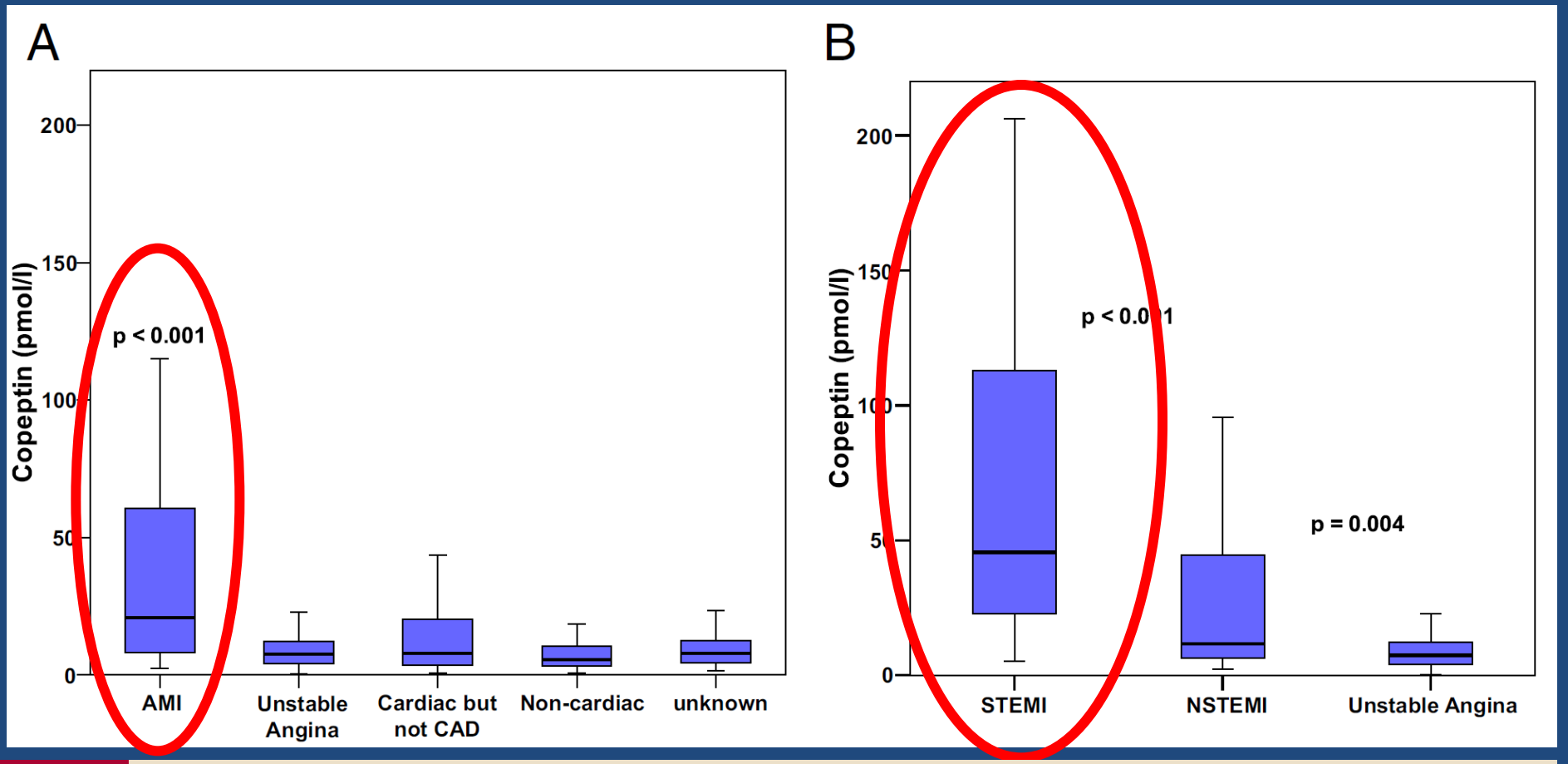


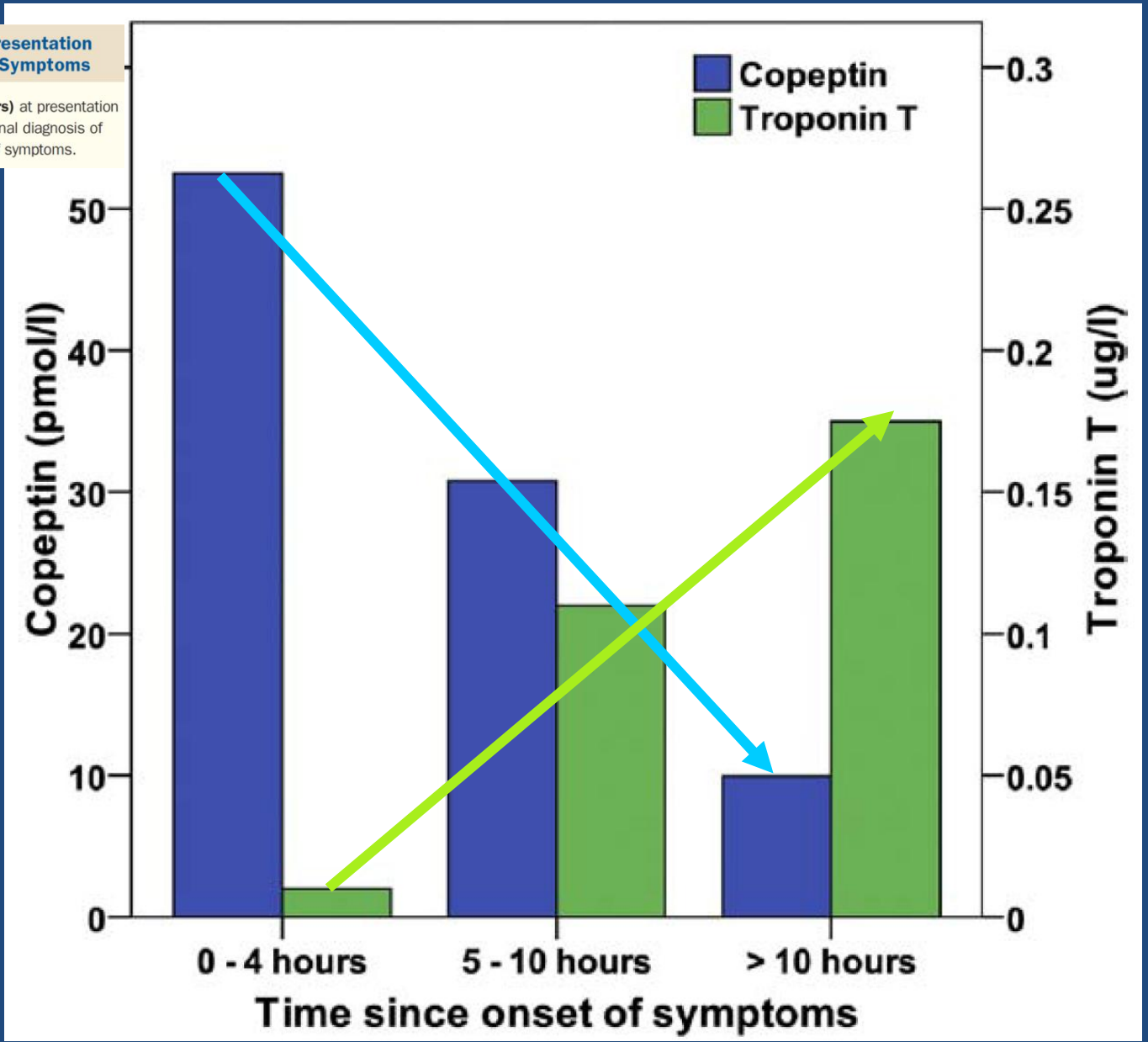
Figure 1 Copeptin Levels at Presentation

Copeptin levels at presentation to the emergency department **(A)** in all patients according to adjudicated final diagnosis and **(B)** in patients with acute coronary syndrome only. **Boxes** represent interquartile ranges and **whiskers** display ranges (without outliers further than 1.5 interquartile ranges from the end of the box). AMI = acute myocardial infarction; CAD = coronary artery disease; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

Valori di copeptina e troponina all'arrivo in PS in relazione all'esordio dei sintomi

Figure 2 **Copeptin and Troponin T Levels at Presentation in Relation to Time Since Onset of Symptoms**

Median levels of copeptin **(blue bars)** and troponin T **(green bars)** at presentation to the emergency department in patients with the adjudicated final diagnosis of acute myocardial infarction according to the time since onset of symptoms.



J Am Coll Cardiol 2009;54:60-8

Incremental Value of Copeptin for Rapid Rule Out of Acute Myocardial Infarction

J Am Coll Cardiol 2009;54:60-8

…la copeptina sembra essere il partner ideale della troponina per la **rapida esclusione di SCA**…

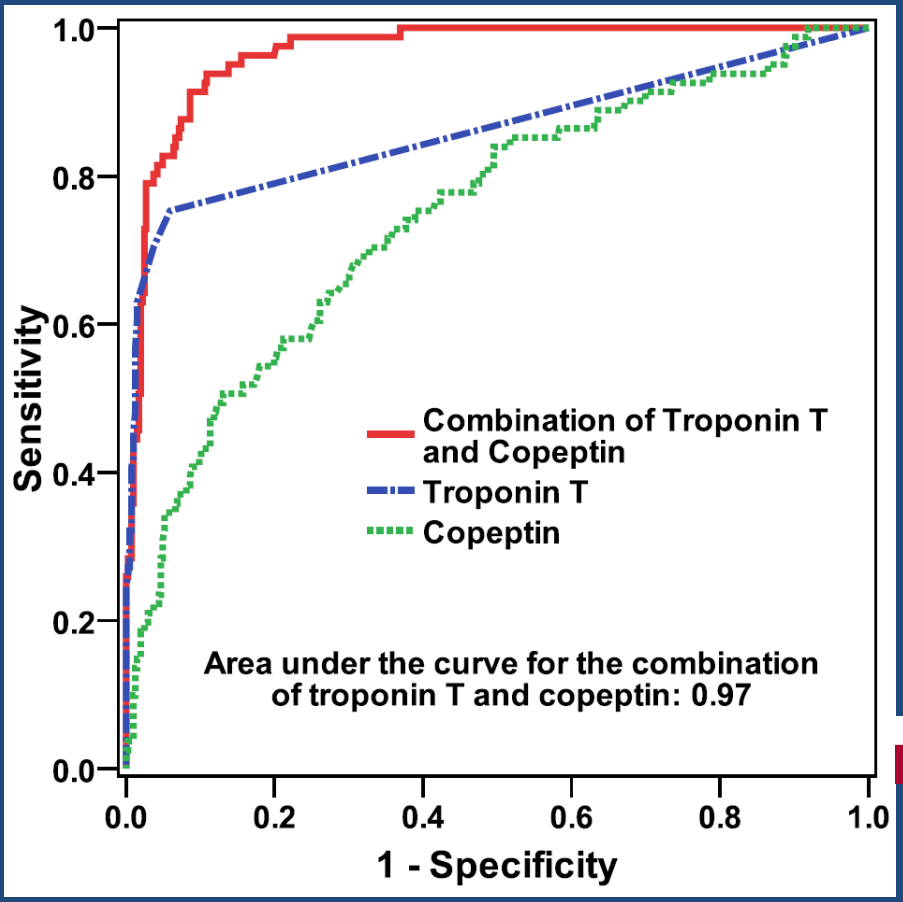


Figure 4 ROC Curves at Presentation for the Diagnosis of AMI

Table 3 Copeptin Value Used With Troponin T ≤0.01 μg/l at Presentation to Rule Out Acute Myocardial Infarction

Copeptin Cutoff Level (pmol/l)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
9	100	62.8	34.9	100
14	98.8	77.1	46.2	99.7
20	96.3	83.5	53.8	99.1
24	95.1	86.2	57.9	98.9

Copeptin Improves Early Diagnosis of Acute Myocardial Infarction

J Am Coll Cardiol 2010;55:2096-106

Till Keller, MD,* Stergios Tzikas, MD,* Tanja Zeller, PHD,* Ewa Czyz, MD,* Lars Lillpopp,* Francisco M. Ojeda, PHD,* Alexander Roth, PHD,* Christoph Bickel, MD,‡ Stephan Baldus, MD,§ Christoph R. Sinning, MD,* Philipp S. Wild, MD,* Edith Lubos, MD,*‖ Dirk Peetz, MD,† Jan Kunde, PHD,¶ Oliver Hartmann, MSC,¶ Andreas Bergmann, PHD,¶ Felix Post, MD,* Karl J. Lackner, MD,† Sabine Genth-Zotz, MD,* Viviane Nicaud, MA,# Laurence Tiret, PHD,# Thomas F. Münzel, MD,* Stefan Blankenberg, MD*

Mainz, Koblenz, Hamburg, and Henningsdorf, Germany; Boston, Massachusetts; and Paris, France

1386 pazienti con alto rischio cardiovascolare – studio multicentrico

Conclusions

In triage of chest pain patients, determination of copeptin in addition to troponin improves diagnostic performance, especially early after CPO. **Combined determination of troponin and copeptin provides a remarkable negative predictive value** virtually independent of CPO time and therefore aids in early and safe rule-out of myocardial infarction

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Biomarkers

Copeptin Helps in the Early Detection of Patients With Acute Myocardial Infarction

Primary Results of the CHOPIN Trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction)

Alan Maisel, MD,*† Christian Mueller, MD,‡ Sean-Xavier Neath, MD, PHD,† Robert H. Christenson, PHD,§ Nils G. Morgenthaler, MD, PHD,‖ James McCord, MD,¶ Richard M. Nowak, MD,¶ Gary Vilke, MD,† Lori B. Daniels, MD, MAS,† Judd E. Hollander, MD,# Fred S. Apple, PHD,** Chad Cannon, MD,†† John T. Nagurney, MD,‡‡ Donald Schreiber, MD,§§ Christopher deFilippi, MD,§ Christopher Hogan, MD,‖‖ Deborah B. Diercks, MD,¶¶ John C. Stein, MD, MAS,## Gary Headden, MD,*** Alexander T. Limkakeng, JR, MD, MHSC,††† Inder Anand, MD, DPHIL (OXON),‡‡‡ Alan H. B. Wu, PHD,## Jana Papassotiriou, PHD,§§§ Oliver Hartmann, MS,§§§ Stefan Ebmeyer, MD,§§§ Paul Clopton, MS,* Allan S. Jaffe, MD,‖‖‖ W. Frank Peacock, MD¶¶¶

- Studio multicentrico condotto su 1967 pazienti afferenti in PS entro 6 ore da insorgenza dolore toracico tipico
- Primary outcome: diagnosi di SCA
- Follow up fino a 180 gg

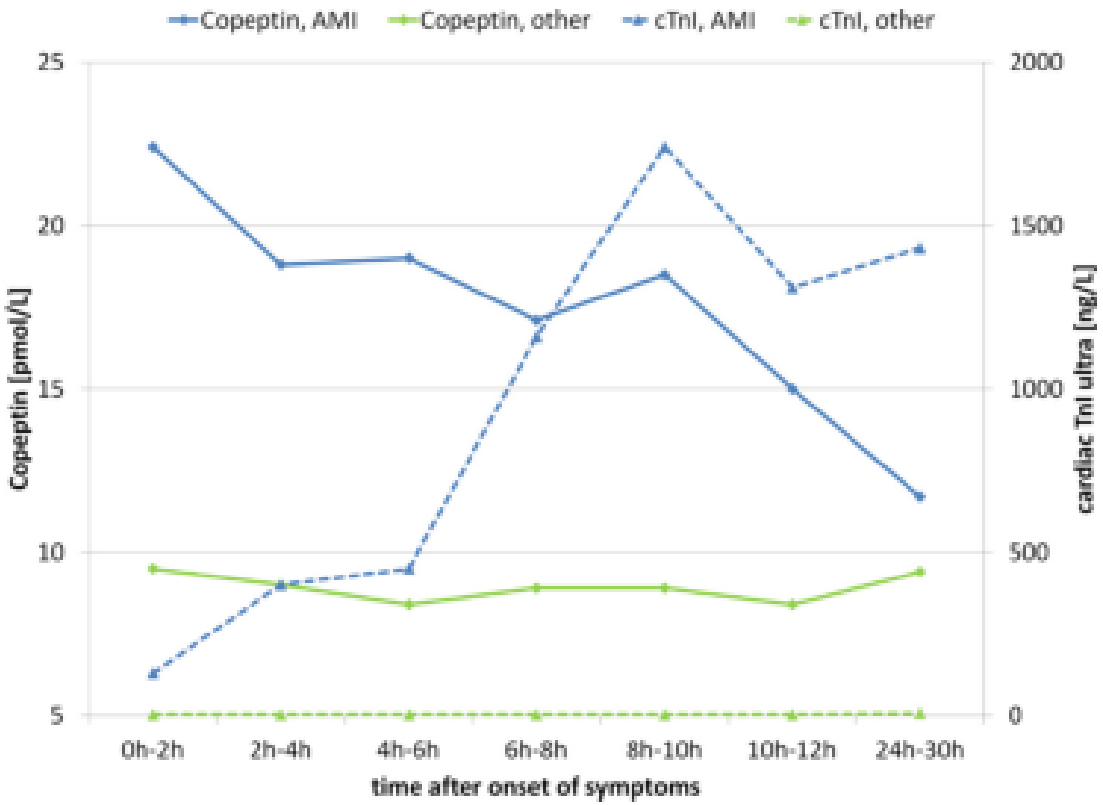

Figure 2 **Biomarker Kinetics by AMI Diagnosis**

Median copeptin **(solid lines)** and cTnI **(dashed lines)** concentrations by time since symptom onset and GSD (acute myocardial infarction [AMI] in **blue**, patients diagnosed with other disease in **green**). Analysis based on data from blood draws at 0, 2, 6, and 24 h. Other abbreviation as in Figure 1.

Copeptin Helps in the Early Detection of Patients With Acute Myocardial Infarction

Primary Results of the CHOPIN Trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction)

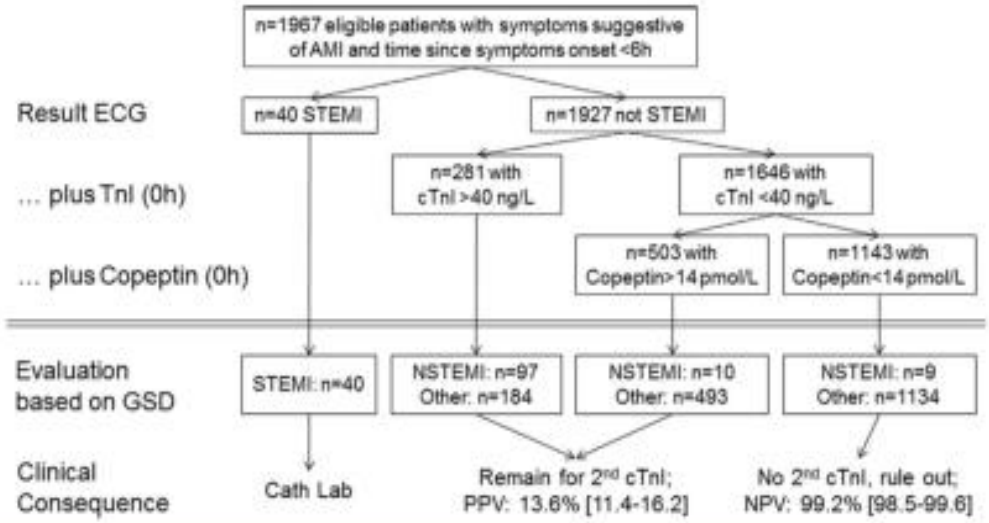

Figure 3 Primary Endpoint

Patient distribution according to initial electrocardiogram (ECG), cTnI (cutoff 99th percentile; 40 ng/L), and copeptin (cutoff 14 pmol/L) status at presentation (0 h). Assuming that STEMI patients will be identified by using ECG, sensitivity was 92.2% (95% confidence interval [CI]: 85.9 to 95.9) and specificity was 62.6% (95% CI: 60.4 to 64.8) to identify NSTEMI patients. Therefore, negative predictive value (NPV) for copeptin levels <14 pmol/L and cTnI levels <40 ng/L is 99.2% (95% CI: 98.5 to 99.6). The positive predictive value (PPV) for patients with a positive cTnI or positive copeptin for NSTEMI is 13.6% (95% CI: 11.4 to 16.2). In absolute numbers, 10 (53%) of 19 NSTEMI patients with a negative cTnI value have an elevated copeptin value. For a final diagnosis of AMI, patients either cTnI or copeptin positive are assumed to undergo a second cTnI measurement. Conversely, patients negative for both copeptin and cTnI are assumed to be ruled out of having an AMI. Other abbreviations as in Figures 1 and 2.

Copeptin Helps in the Early Detection of Patients With Acute Myocardial Infarction

Primary Results of the CHOPIN Trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction)

Conclusions

This large multicenter trial suggests that the combination of copeptin and troponin at the time of presentation provides an NPV strong enough to avoid serial testing past 3 h and hence improves medical decision making in patients with chest pain presenting to the ED. Future research should investigate the cost savings to EDs through use of such a strategy.

European Heart Journal Advance Access published April 30, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu178

CLINICAL RESEARCH
Acute coronary syndromes

Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study

902 pazienti assegnati al "gruppo standard" o al "gruppo copeptina"

Pazienti con valori di troponina e copeptina negativi all'ingresso erano dimissibili dopo valutazione medica

Primary end-point: sviluppo di MACE (major adverse cardiac events) a 30 gg

European Heart Journal Advance Access published April 30, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu178

CLINICAL RESEARCH
Acute coronary syndromes

Pazienti con rischio cardiovascolare intermedio-basso e con dolore toracico suggestivo per SCA

Lo studio è stato condotto dai medici del PS e con i protocolli vigenti per il paziente con sospetta SCA

European Heart Journal Advance Access published April 30, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu178

CLINICAL RESEARCH

Acute coronary syndromes

Table 2 **Primary endpoint analyses**

	Standard group (n = 451)	Copeptin group (n = 451)	Absolute difference in MACE proportion (97.5% one-sided CI)
MACE at 30 days			
Yes	23	23	–
No	422	422	–
Unknown	6	8	–
MACE % (95% CI): (absolute numbers)			
Intention to treat analysis	5.17 (3.30–7.65) (23/445)	5.19 (3.32–7.69) (23/443)	−0.02 (−2.94)
Per protocol analysis	5.34 (3.38–7.97) (22/412)	3.01 (1.51–5.33) (11/365)	2.33 (−0.46)

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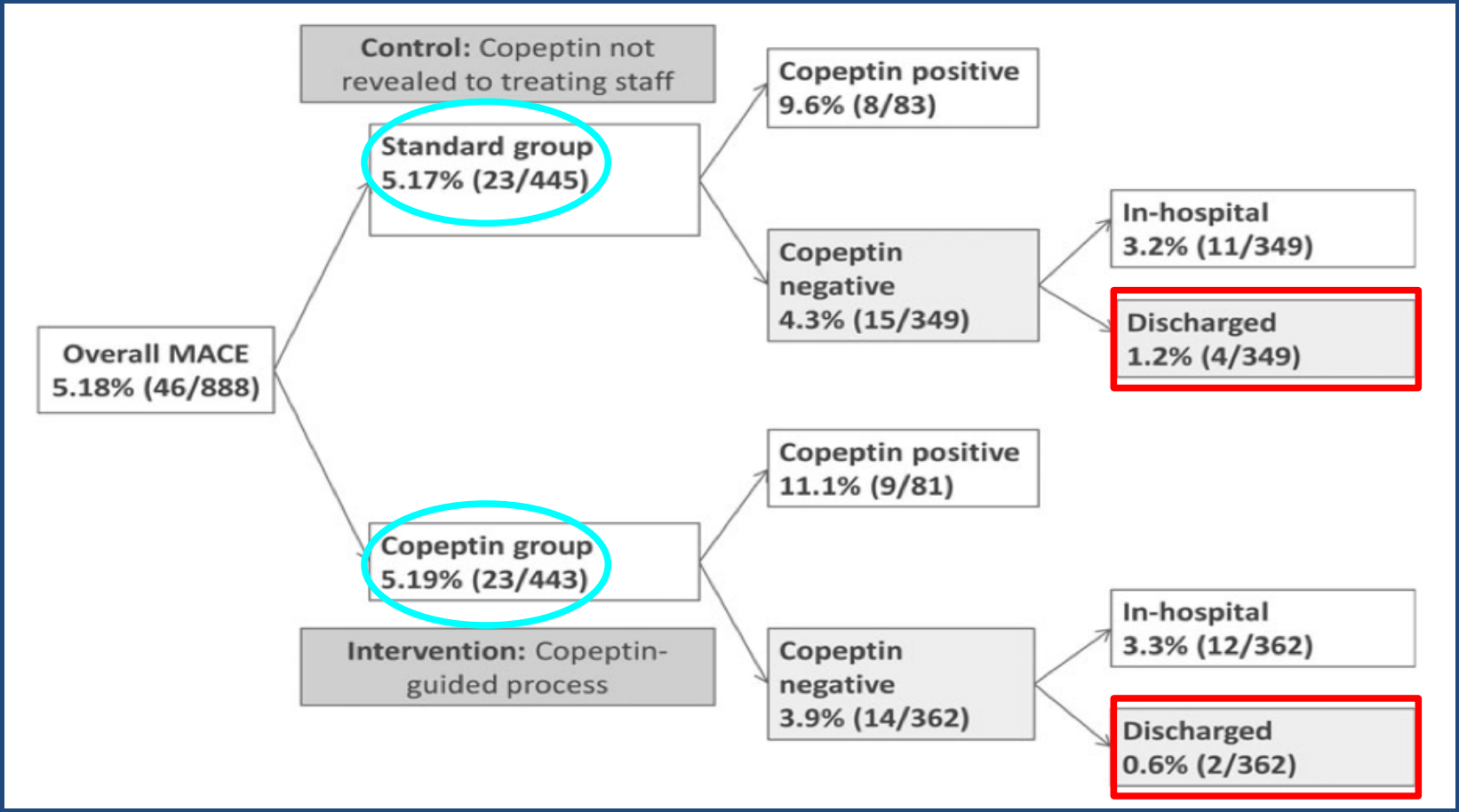
CLINICAL RESEARCH
Acute coronary syndromes

Sicurezza



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CLINICAL RESEARCH
Acute coronary syndromes

Table 3 **Secondary endpoints**

	All patients *n* = (902)	Standard group (*n* = 451)	Copeptin group (*n* = 451)	*P*-value
In-hospital course				
Discharge from ED	39.8 (359)	12.0 (54)	67.6 (305)	<0.001
LOS in hours (median/IQR)				
LOS for all patients	6 (4–11)	7 (5–13)	4 (3–8)	<0.001
LOS in 0–1-day group[a]	5 (4–8)	7 (4–9)	4 (2–6)	<0.001

Rule out e ricoveri “inutili”

European Heart Journal Advance Access published April 30, 2014

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European Heart Journal
doi:10.1093/eurheartj/ehu178

CLINICAL RESEARCH
Acute coronary syndromes

Conclusioni

"It needs to be emphasized that any biomarker strategy must be embedded in a process of thorough physician work-up and clinical judgement."

After clinical work-up and single combined testing of troponin and copeptin to rule-out AMI, early discharge of low- to intermediate risk patients with suspected ACS seems to be safe and has the potential to shorten length of stay in the ED. However, our results need to be confirmed in larger clinical trials or registries, before a clinical directive can be propagated.

A. O. Ordine Mauriziano di Torino

Acute coronary syndrome Rapid Rule Out With Copeptin: THE ARROW-C PILOT STUDY

B·R·A·H·M·S
Part of Thermo Fisher Scientific

Analisi costo-beneficio di copeptina combinata con troponina per rapida esclusione dell'infarto miocardico acuto
Ligand Assay 18(1) 2013; 68-72

Obiettivo del lavoro

Definire l'efficacia del dosaggio combinato di copeptina e hs-TnI nell'escludere precocemente una SCA in una popolazione con dolore toracico tipico

Materiali e metodi

01/02/2011 – 30/04/2011

235 paz consecutivi
con sospetta SCA

- ✓ Anamnesi
- ✓ Esame obiettivo
- ✓ ECG a12 determinazioni
- ✓ Routine ematica con troponina
- ✓ Valutazione fattori di rischio cardiovascolare

- **Troponina I** (Tosoh ST AIA-PACK TnI 3rd gen.)

effettuato dosaggio all'arrivo in PS, dopo 3 e dopo 6 ore

- **Copeptina** (BRAHMS LUMItest CT-proAVP)

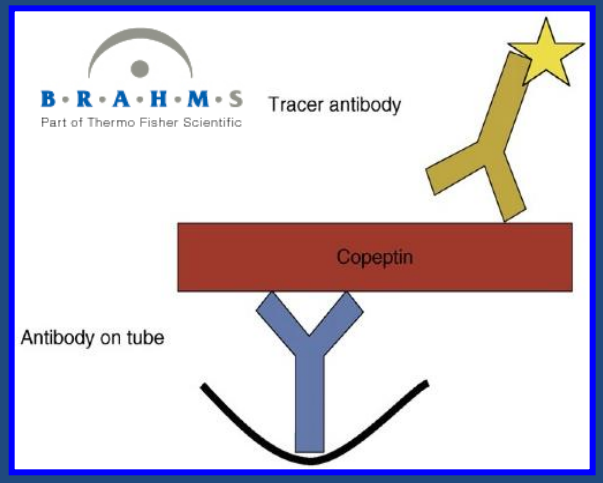
effettuato dosaggio all'arrivo in PS

Caratteristiche laboratoristiche

- ✔Volume campione: 50 µl
- ✔Tipo di campione: siero, plasma
- ✔Disponibilità dei risultati: circa 30 minuti
- ✔Dosaggio automatizzato in immunofluorescenza

Valore cut off di copeptina

14 pmol/L



Caratteristiche della popolazione in presenza o meno di SCA

	NSTEMI	UA	STEMI	NO SCA
N°	32	2	25	176
Età media (anni)	70.5	61.5	66.7	63.1
Sesso maschile (%)	21 (65.6)	2 (100)	16 (64)	109 (61.9)
Diabete (%)	6 (18.7)	1 (50)	5 (20)	30 (17)
Ipertensione (%)	24 (75)	2 (100)	15 (60)	98 (55.7)
Dislipidemia (%)	14 (43.7)	2 (100)	5 (20)	46 (26.1)
Storia di CAD (%)	17 (53)	1 (50)	5 (20)	43 (24.4)
Valore medio copeptina (pmol/L)	83.68	6.59	266.6	33.29

235 paz totali

- ✓ STEMI (n=25)
- ✓ Angina instabile (n=2)
- ✓ hs -TnI > 0,06 ng/ml all'arrivo (n=43)

165 pazienti con hs-TnI < 0,06 all'arrivo in PS

hs -TnI > 0,06 dopo l'arrivo in PS...

	NSTEMI +	NSTEMI-	Totale
Copeptina pos	5	48	53
Copetina neg	0	112	112
Totale	5	160	165

Sensibilità 100%	VPP 9.43%
Specificità 70%	VPN 100%

….risvolti pratici...

165 pazienti iniziali
[con hs-T<0.06 ng/mlall'arrivo]

112 pazienti con copetina neg (no SCA)

15 pazienti ricoverati non per SCA

97 pazienti [**58.8%**] si sarebbero potuti dimettere dopo il primo controllo senza ulteriori accertamenti (curva hs-Tn I)

Tempo risparmiato per paziente

5 ore 41 minuti

NHS
National Institute for
Health and Clinical Excellence

BRAHMS copeptin assay to rule out myocardial infarction in patients with acute chest pain

Issued: June 2011

NICE medical technology guidance 4
guidance.nice.org.uk/mtg4

6 Conclusions

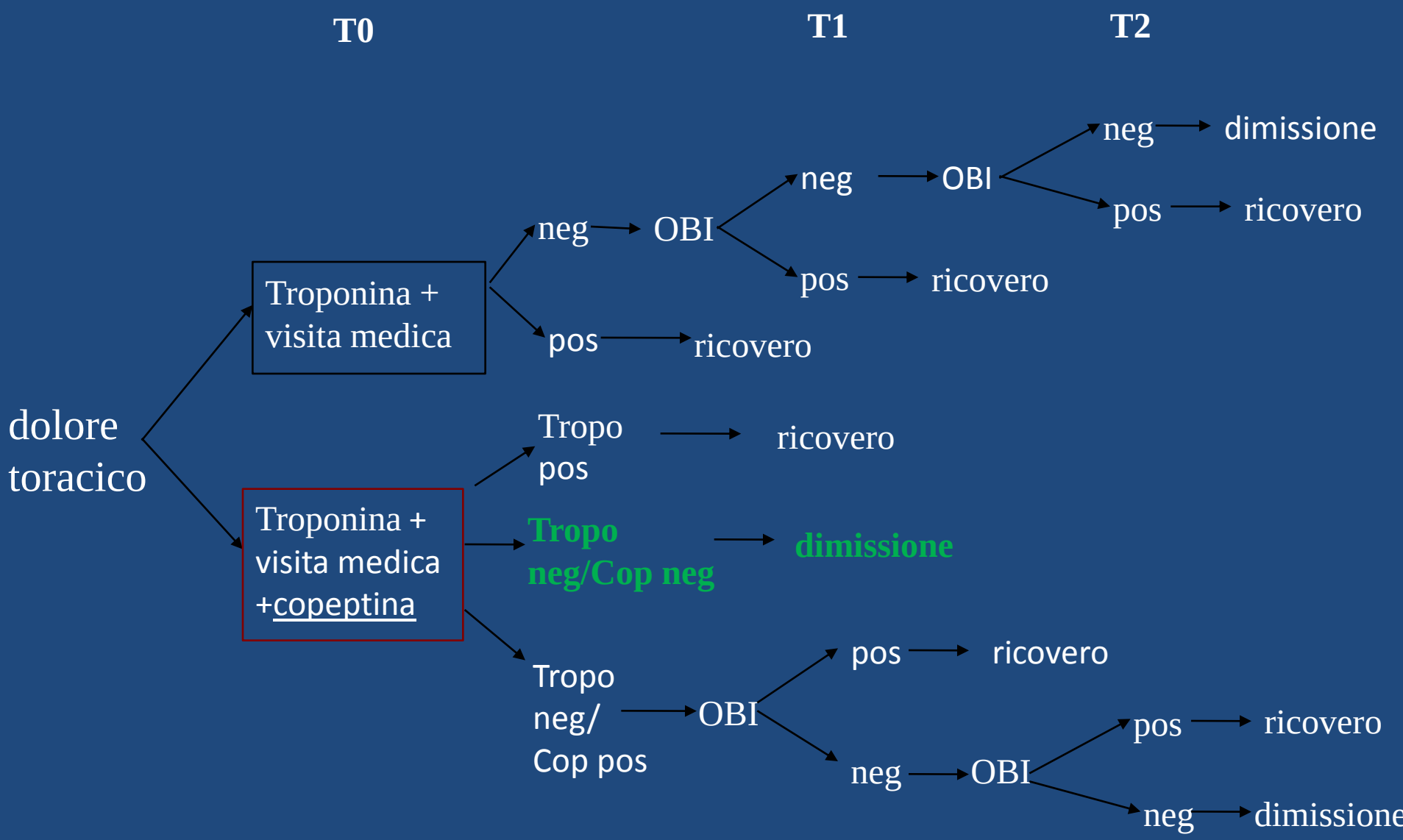
6.1 The Committee considered that the BRAHMS copeptin assay is a promising new development for the early ruling out of myocardial infarction in patients presenting with chest pain. However, there was uncertainty about the proportion of patients presenting with chest pain who would benefit from its use, and about the amount of time and resources that would be saved in practice.

6.2 The Committee concluded that good quality clinical studies are needed to support the potential of the BRAHMS copeptin assay to offer advantages to patients and the NHS. The Committee wished to give strong encouragement to further research, with relevant outcome measures, on the use of the BRAHMS copeptin assay for the early ruling out of myocardial infarction.

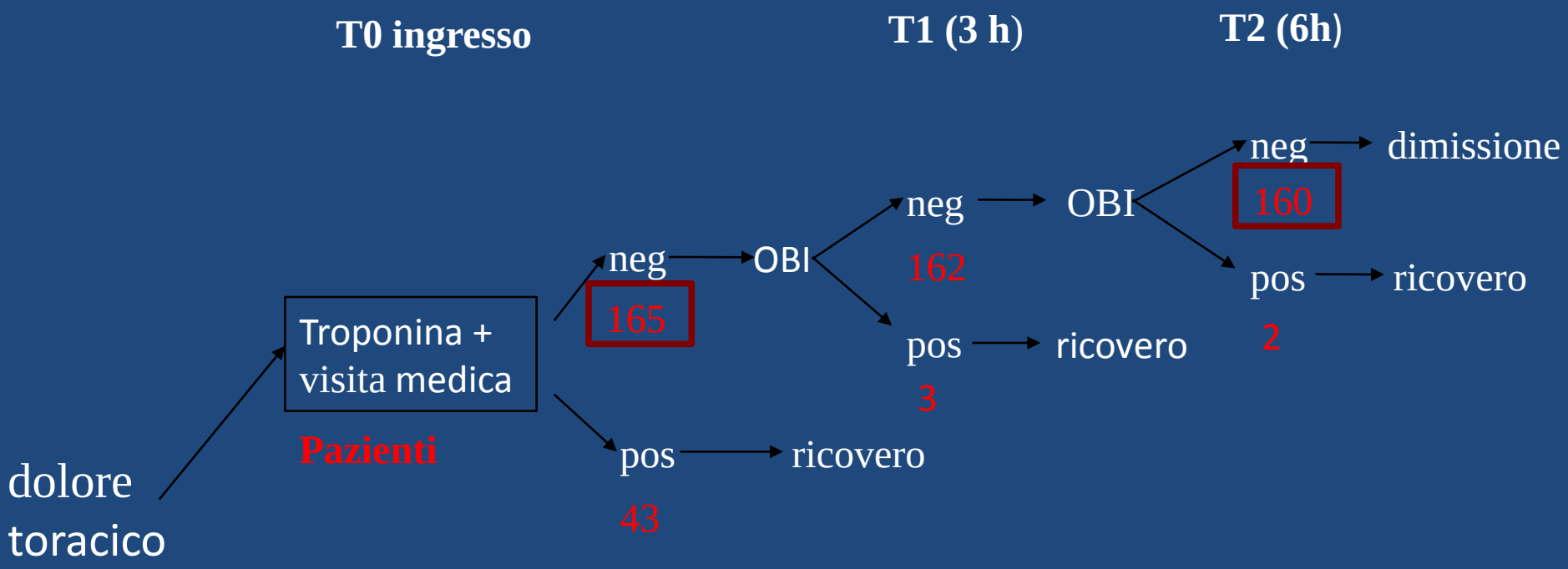
NHS
National Institute for
Health and Clinical Excellence

Considerazioni economiche

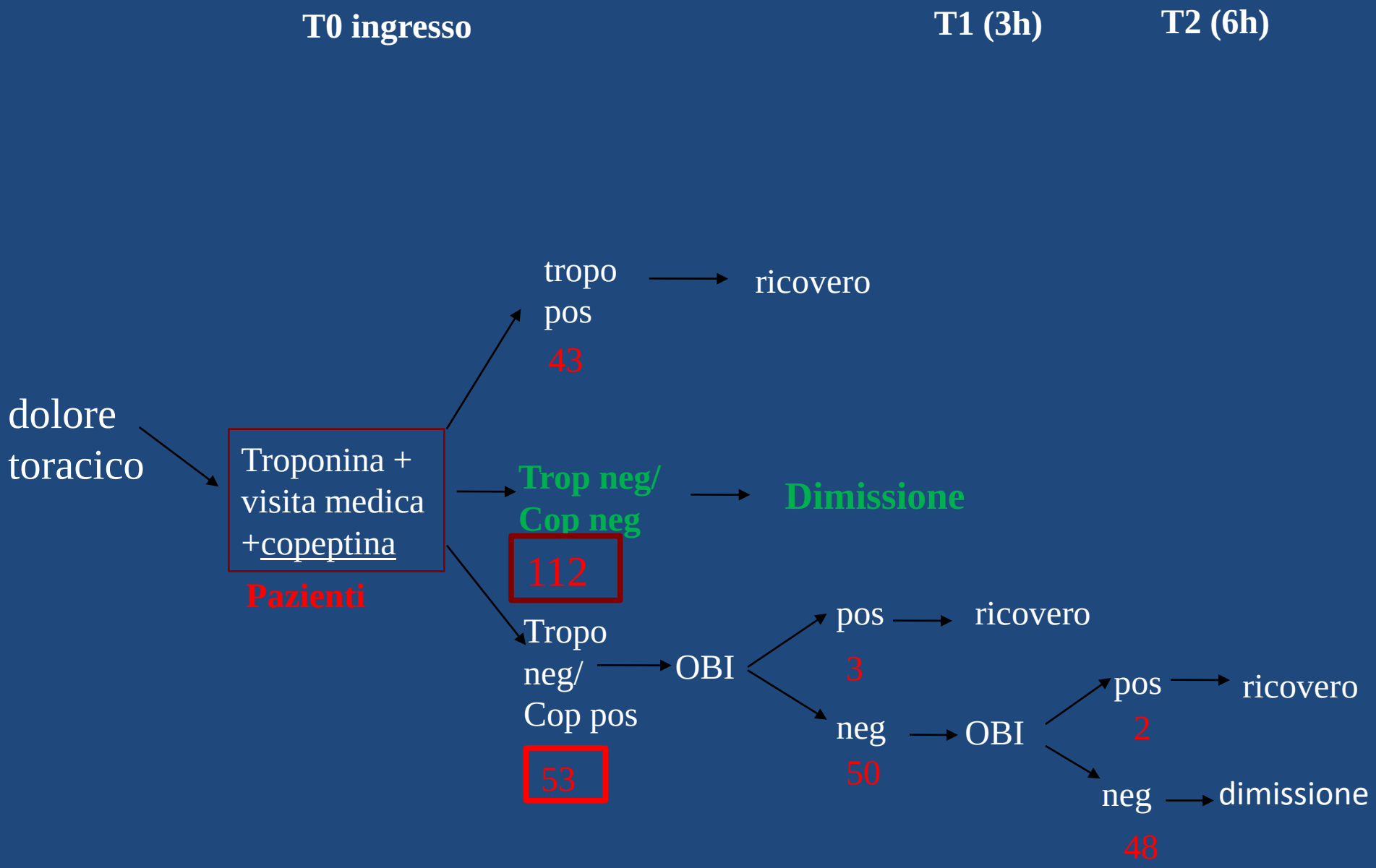
- Il risparmio economico utilizzando una “dual marker strategy” (troponina + copeptina) è stato di **£58.24 per paziente**
- Il principale risparmio è stato determinato dalla riduzione di permanenza del paziente in PS
- L’analisi di sensibilità ha dimostrato che il parametro che più influenza il risparmio economico è la **riduzione della degenza del paz in PS** (inferiore a due ore!!)



Struttura del modello



Valorizzazione



Valorizzazione

Costi

- TROPONINA (per dosaggio): 5 €
- COPEPTINA (per dosaggio): 16 €
- COSTO OSSERVAZIONE/PAZ/DIE: 1200 €
- COSTO OSSERVAZIONE/PZ/H: **50** €
- TARIFFA OSS/PAZ/H: **31** €
- TARIFFA OSS/PAZ/6H: **187** €

Beneficio/costo per osservazione

Costo di 1 pz. in oss **solo** con Troponina: € 260

Costo di 1 pz in oss con troponina + copeptina: € 135

Risparmio per pz: € 125

Rapporto beneficio/costo: 7,13

Tariffa/costo

Tariffa osservazione/pz: € 187

Costo di 1 pz in oss **solo** con troponina: € 260

Deficit netto per pz: € 73

Tariffa/costo

Tariffa osservazione/pz: € 187

Costo di 1 pz in oss con troponina + copeptina: € 135

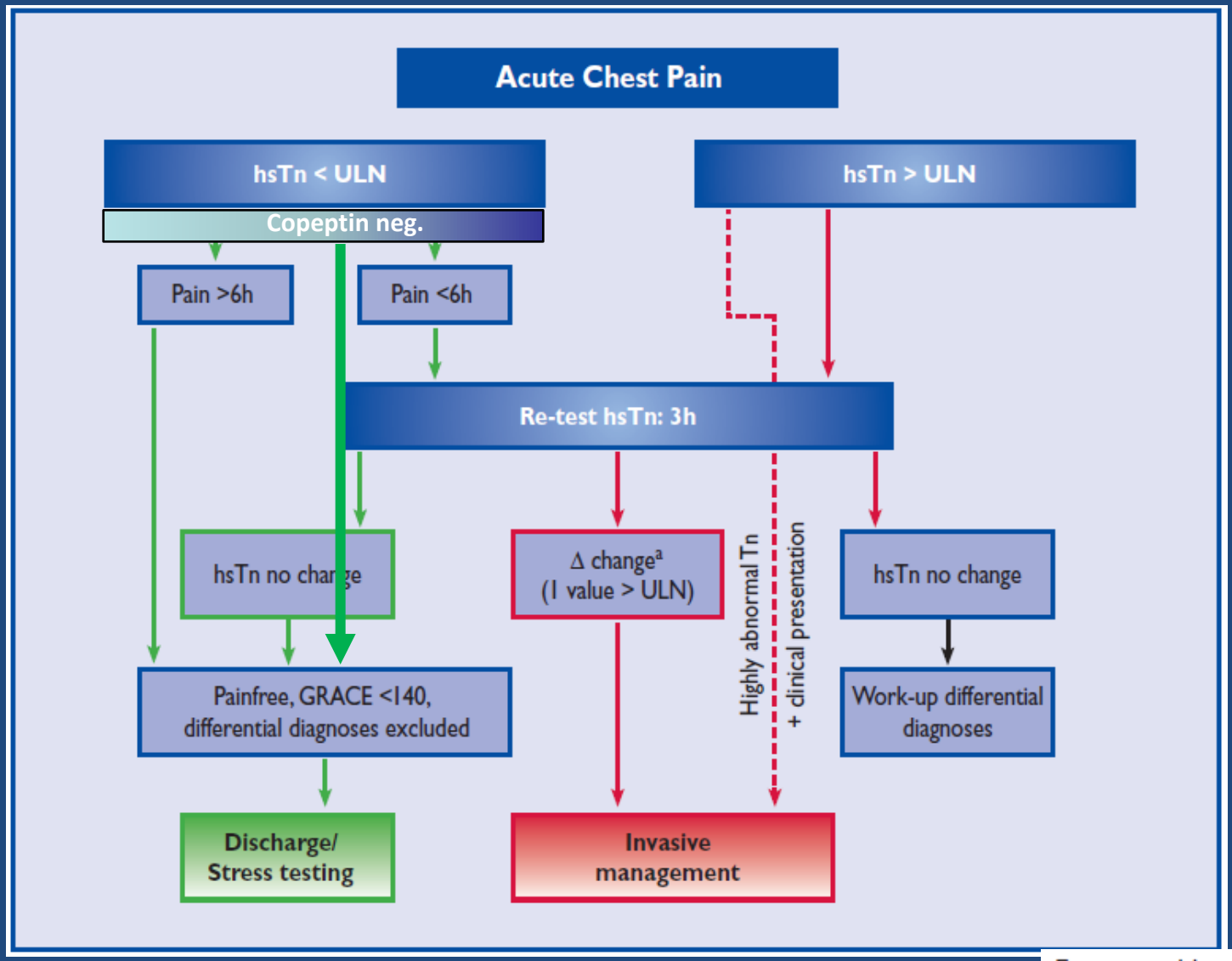
Beneficio netto per pz: € 52

Rapporto beneficio/costo: 4,25

Conclusioni

- Il dosaggio combinato di troponina e copeptina pare essere utile nel “mondo reale”:
- per ridurre la permanenza in DEA di una quota significativa di pazienti che non hanno una SCA
- per ridurre la spesa per i pazienti con dolore toracico
- per evitare di dimettere pazienti con SCA

New proposed guideline for the management of patients with suspected ACS



M Mockel, EHJ (2014)

European Heart Journal
doi:10.1093/eurheartj/ehr236

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