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Accurate and Rapid Diagnosis of Myocardial Infarction Using a High-Sensitivity Troponin I 1-Hour Algorithm

Johannes Tobias Neumann[1], Nils Arne Sörensen[1], Tjark Schwemer[1], Francisco Ojeda[1], Rafael Bourry[1], Vanessa Sciacca[1], Sarina Schäfer[1,2], Christoph Waldeyer[1], Christoph Sinning[1], Thomas Renné[3], Martin Than[5], Will Parsonage[4], Karin Wildi[6], Nataliya Makarova[1,2], Renate B. Schnabel[1,2], Ulf Landmesser[7], Christian Mueller[6], Louise Cullen[4], Jaimi Greenslade[4], Tanja Zeller[1,2], Stefan Blankenberg[1,2], Mahir Karakas[1,2], **Dirk Westermann[1,2]**

[1] **Department of General and Interventional Cardiology, University Heart Center Hamburg Eppendorf, Hamburg, Germany**
[2] German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany
[3] Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[4] Royal Brisbane and Women's Hospital, Department of Emergency Medicine, Brisbane 4006, Australia
[5] Christchurch Hospital, Christchurch, New Zealand
[6] Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, Switzerland
[7] Department of Cardiology, Charite Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany

Conflicts of interest

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Dirk Westermann:

To this presentation: none

In general:

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Background

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- There is clinical need to rapidly and safely **rule-in** or **rule-out acute myocardial infarction (AMI)** in patients with acute chest pain in order to

  1. initiate fast evidence based treatment for patients with AMI

  2. limit overuse of scarce medical resources in the emergency room (ER) discharging patients without acute cardiac conditions.

- Guidelines recommend[1,2] measuring high sensitivity assayed troponins directly **after admission and after 3 hours** detecting elevated levels based on the **99th percentile** of the specific assays together with an increase/decrease.

- Recent studies (ADAPT (2-hour)[3] and APACE (1- hour)[4] cohort) challenge current guidelines with intervals shorter than 3 hours.

1 Hamm et al. EHJ 2011 and 2 Thygesen et al. EHJ 2012; 3 Than et al. JACC 2012; 4 Reichlin et al. CMAJ 2015

Aim of the study

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To investigate the application of
high sensitivity assayed troponin I (TnI) for

a) a rapid 1-hour rule-out and rule-in compared to a 3-hours approach

b) a lower and more sensitive cut-off value compared to the 99th percentile

in the Biomarkers in Acute Cardiovascular Care (BACC) cohort
investigating 1,045 patients with acute chest pain.

Study design

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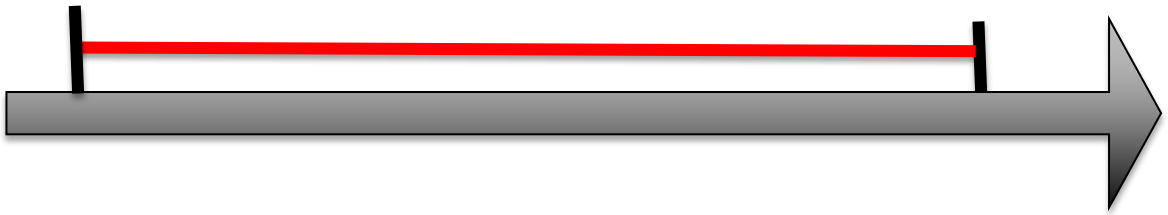
BACC (n = 1,045) patients with acute chest pain suggestive of AMI:

Clinical routine troponin assay and clinical treatment based on ESC guidelines[1]:



+ clinical judgement, imaging and ECG to establish final diagnosis during the complete hospital stay

(NSTEMI vs. no AMI)

(as recommended by ESC guidelines[1])

hsTnT: troponin T assay **(**Elecsys® troponin T high sensitive, Roche Diagnostics)

1 Hamm et al. EHJ 2011

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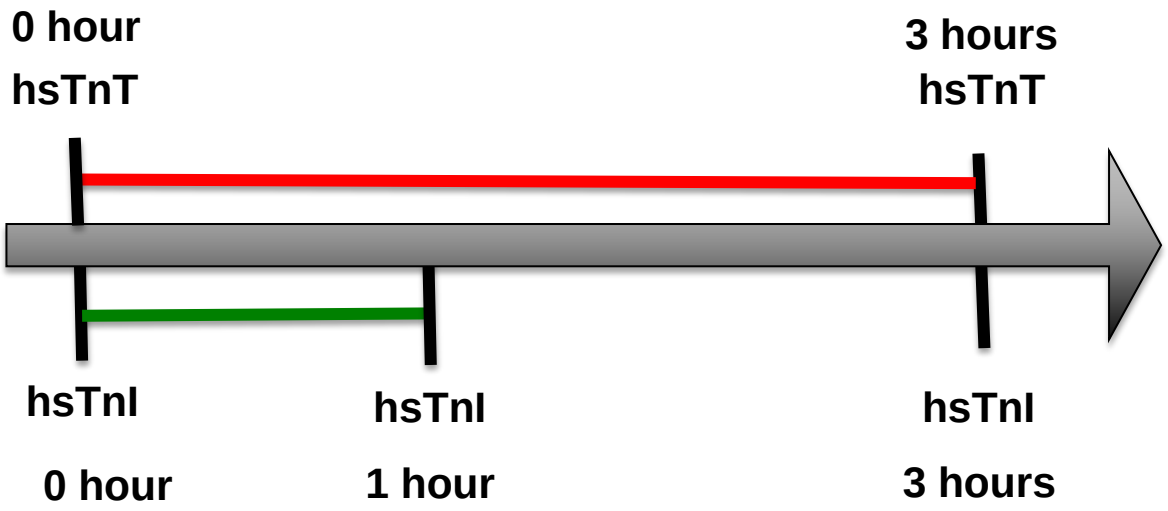

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+ without adding additional information

hsTnT: troponin T assay **(**Elecsys® troponin T high sensitive, Roche Diagnostics)

hsTnI: troponin I assay (STAT high sensitive Troponin I, ARCHITECT i2000SR, Abbott Diagnostics, USA)

1 Hamm et al. EHJ 2011

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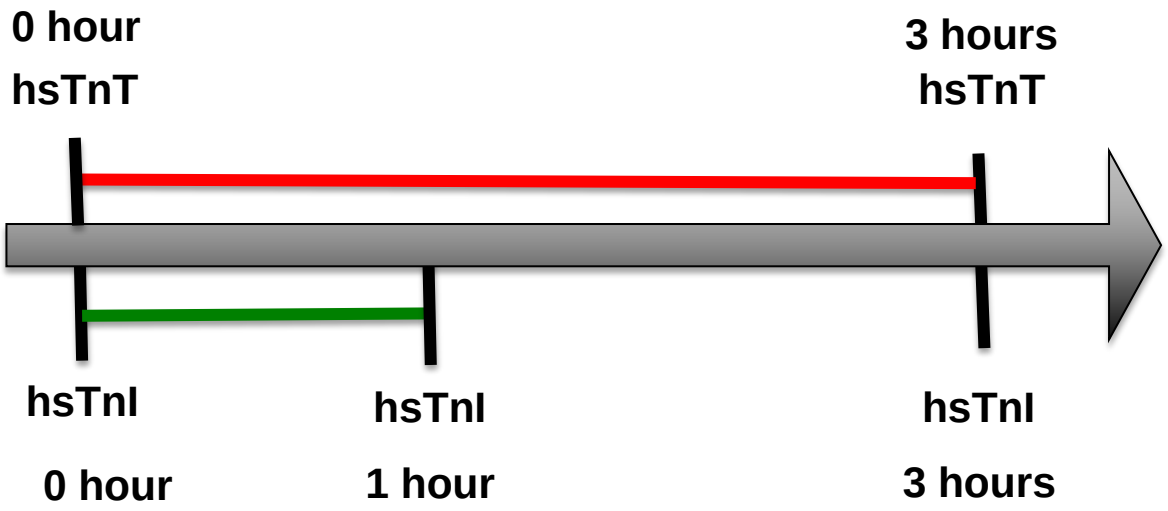

+ clinical judgement, imaging and ECG to establish final diagnosis during the complete hospital stay

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+ without adding additional information

Calculate best performing cut-off and apply it → Validate results in other cohorts → Applicate cut-off in general population

1 Hamm et al. EHJ 2011

Statistical methods

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- Baseline characteristics are described by quartiles for continuous variables and by absolute and relative frequencies for categorical variables.
- For the diagnostic algorithms considered negative and positive predictive values were computed (together with 95% confidence intervals).
- Equality of predictive values was tested[1].

1 Kosinski et al. Stat Med 2013

Baseline data

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	All (N=1,045)	NSTEMI (N=184)	Non-AMI (N=793)	p-value
Demographics				
Age (years)	65.0 (52.0, 75.0)	70.0 (60.4, 77.0)	64.0 (50.7, 74.0)	< 0.001
Male (%)	678 (64.9)	124 (67.4)	505 (63.7)	n.s.
BMI (kg/m²)	26.0 (23.5, 29.4)	26.2 (23.7, 29.7)	26.0 (23.5, 29.4)	n.s.
Risk Factors				
Hypertension (%)	731 (70.0)	147 (79.9)	541 (68.2)	0.0017
Hyperlipoproteinemia (%)	459 (43.9)	103 (56.0)	327 (41.2)	< 0.001
Diabetes (%)	150 (14.5)	39 (21.3)	102 (12.9)	0.0051
Former smoker (%)	334 (32.0)	59 (32.1)	259 (32.7)	n.s.
Current smoker (%)	241 (23.1)	41 (22.3)	169 (21.3)	n.s.
History of CAD/Bypass/PCI (%)	353 (33.8)	80 (43.5)	255 (32.2)	0.0044
History of AMI (%)	165 (15.8)	41 (22.4)	114 (14.4)	0.0097

STEMI (57) and SAP (11) patients were excluded from the non-AMI group

Best performing cut-off

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	NSTEMI 1	
Cut-off (ng/L)	NPV (95% CI)	False Negative
3	100.0 (97.1-100.0)	0
4	99.6 (98.0-100.0)	1
5	99.7 (98.3-100.0)	1
5,2 (10% coefficient of variation)	99.7 (98.4-100.0)	1
6	99.7 (98.6-100.0)	1
7	99.6 (98.4-99.9)	2
8	99.4 (98.3-99.9)	3
9	99.4 (98.4-99.9)	3
10	99.3 (98.2-99.8)	4
15	98.9 (97.8-99.6)	7
20	98.8 (97.7-99.5)	8
27 (99th percentile)	98.4 (97.2-99.2)	11

Rule-out AMI 1h vs. 3h

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Suggested 1-hour algorithm
NSTEMI rule-out:
hsTnI ≤ **6 ng/L** at 0h and 1h

resulted in 402 out of 1,045 patients being discharged

Cut-off	Time after admission	NPV NSTEMI 1 (95% CI)	Sensitivity NSTEMI 1 (95% CI)	NPV NSTEMI (95% CI)	Sensitivity NSTEMI (95% CI)
6ng/L	1-hour	99.7 (98.6-100.0)	99.1 (94.9-100.0)	99.0 (97.5-99.7)	97.6 (94.1-99.4)
	3-hour	100.0 (98.5-100.0)	100.0 (94.9-100.0)	99.5 (98.1-99.9)	98.8 (95.8-99.9)
		p = n.s. vs. 1h		**p = n.s. vs. 1h**	

NPV: negative predictive value; NSTEMI 1: non STEMI type 1 in view of Thygesen K et al. EHJ 2012

Higher performance of 6 ng/L vs. 27 ng/L

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Cut-off	Time after admission	NPV NSTEMI 1 (95% CI)	Sensitivity NSTEMI 1 (95% CI)	NPV NSTEMI (95% CI)	Sensitivity NSTEMI (95% CI)
6 ng/L	1-hour	99.7 (98.6-100.0)	99.1 (94.9-100.0)	99.0 (97.5-99.7)	97.6 (94.1-99.4)
	3-hour	100.0 (98.5-100.0)	100.0 (94.9-100.0)	99.5 (98.1-99.9)	98.8 (95.8-99.9)
27 ng/L (99th percentile)	1-hour	98.4* (97.2-99.2)	89.6 (82.2-94.7)	94.8* (92.9-96.3)	77.5 (70.5-83.6)
	3-hour	99.1# (98.1-99.7)	94.3 (88.1-97.9)	96.8# (95.3-98.0)	87.1 (81.2-91.8)

$p < 0.05$ for 6 ng/L at * 1h or # 3h

NPV: negative predictive value; NSTEMI 1: non STEMI type 1 in view of Thygesen K et al. EHJ 2012

Best performing Rule-In Algorithm

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Suggested 1-hour algorithm
NSTEMI rule-in:

hsTnI after 1h > **6 ng/L** together with a delta of **12 ng/L** to 0h

Criteria to diagnose patients as NSTEMI	PPV NSTEMI 1 (95% CI)	Specificity NSTEMI 1 (95% CI)	PPV NSTEMI (95% CI)	Specificity NSTEMI (95% CI)
1-hour rule-in	82.8 (73.2-90.0)	98.0 (96.7-98.9)	87.1 (79.6-92.6)	98.0 (96.7-98.9)
3-hour rule-in	78.6 (69.8-85.8)	96.8 (95.2-97.9)	84.6 (78.0-89.9)	96.8 (95.2-97.9)
	p = n.s. vs. 1h		**p = n.s. vs. 1h**	

PPV: positive predictive value; NSTEMI 1: non STEMI type 1 in view of Thygesen K et al. EHJ 2012

Validation in 2 independent cohorts

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	ADAPT (2-hour)		APACE (1-hour)	
	Non-AMI	NSTEMI	Non-AMI	NSTEMI
Number of patients	1,499	249	1,832	429
Age, years, Median	59 (49-70)	71 (60-79)	59 (47-73)	72 (59-80)
Male gender (%)	868 (57.9)	163 (65.5)	1,226 (66.9)	316 (73.7)

Rule used to diagnose *all* NSTEMI	NPV for rule-out (95% CI)	PPV for rule-in (95% CI)
Troponin I	**APACE[1]**	
Rule-out algorithm (≤ 6 ng/L and after 1h ≤ 6 ng/L)	99.2 (98.4-99.6)	
Rule-in algorithm (1h > 6 ng/L and e 12 ng/L)		80.4 (75.1-84.9)
Troponin I	**ADAPT[2]**	
Rule-out algorithm (≤ 6 ng/L and after 2h ≤ 6 ng/L)	99.7 (99.2-99.9)	
Rule-in algorithm (1h > 6 ng/L and e 12 ng/L)		81.5 (75.8-86.3)

1 Reichlin et al. CMAJ 2015, 2 Than et al. JACC 2012

Follow-up mortality

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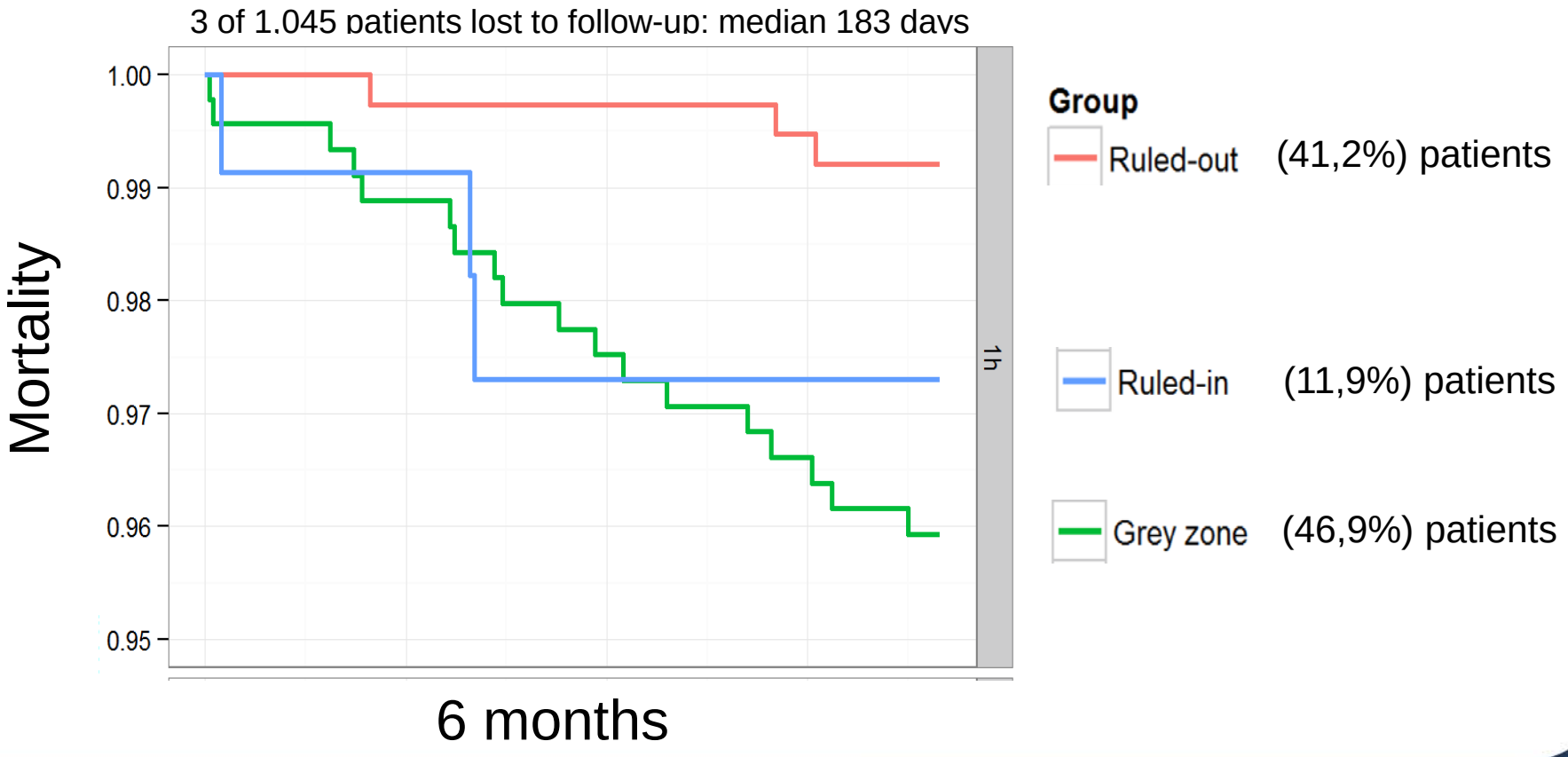
Suggested 1-hour algorithm

NSTEMI rule-out: hsTnI ≤ **6 ng/L** at 0h and 1h

NSTEMI rule-in: hsTnI after 1h > **6 ng/L** and a delta of **12 ng/L** to 0h

Greyzone: Patients not identified by both algorithms (elevated but stable TnI values)



Follow-up mortality

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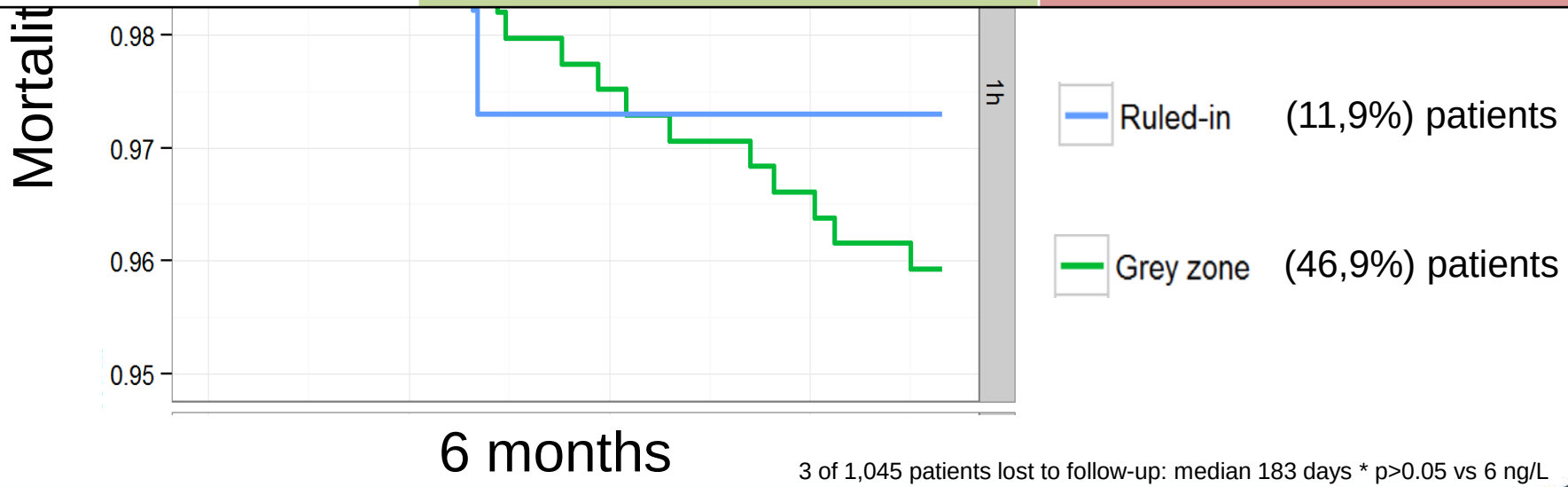
Rule-out	6 ng/L	27 ng/L (99th percentile)
6 months mortality	3 deaths (0.79%)	12 deaths (1.73%) *



3 of 1,045 patients lost to follow-up: median 183 days * p>0.05 vs 6 ng/L

Follow-up mortality in BiomarCaRE

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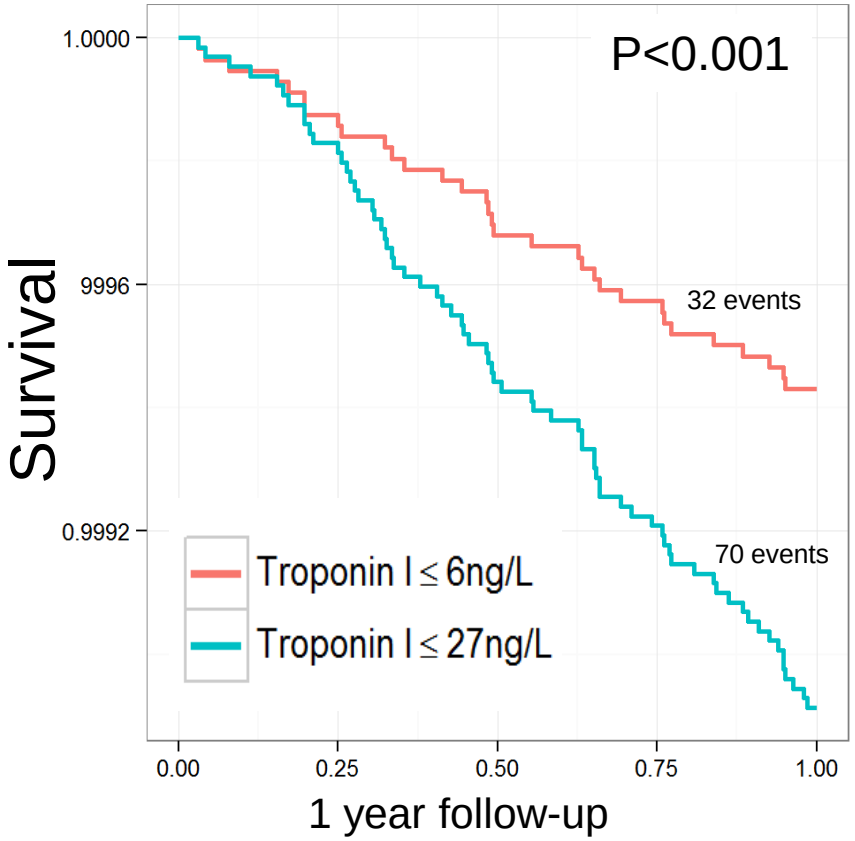
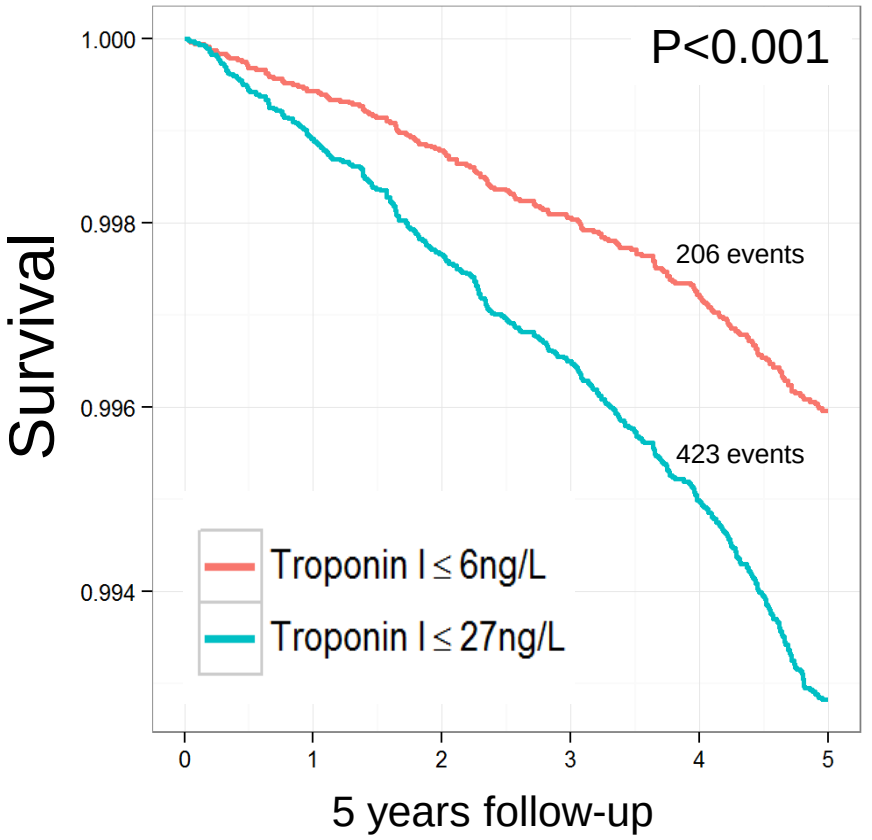
74,738 individuals (aged 51.0 years (42-60)) of the general population without prevalent CVD with follow up for cardiovascular mortality.





Conclusion

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- A 1-hour algorithm is safe to rule-out AMI.
- A sensitive troponin I cut-off (6 ng/L) performed better compared to the 99th percentile (27 ng/L) in view of lower follow-up mortality.
- Low troponin I values predict mortality in the general population.
- Further studies are needed to test the best cut-off for each troponin assay and to validate a 1-hour algorithm prospectively.

Acknowledgement

- To the patients included in the BACC, ADAPT and APACE cohorts.

- To the individuals of the BiomarCaRE cohort.

- To the study teams involved in all cohorts and trials