Randomized trial of high sensitivity Troponin T in the Emergency Department

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AMERICAN COLLEGE of CARDIOLOGY

RAPID-TnT: Randomized trial of high sensitivity Troponin T in the Emergency Department

Clinical outcomes over 12 months follow-up

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ACC.21

Disclosures

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  - Roche Diagnostics
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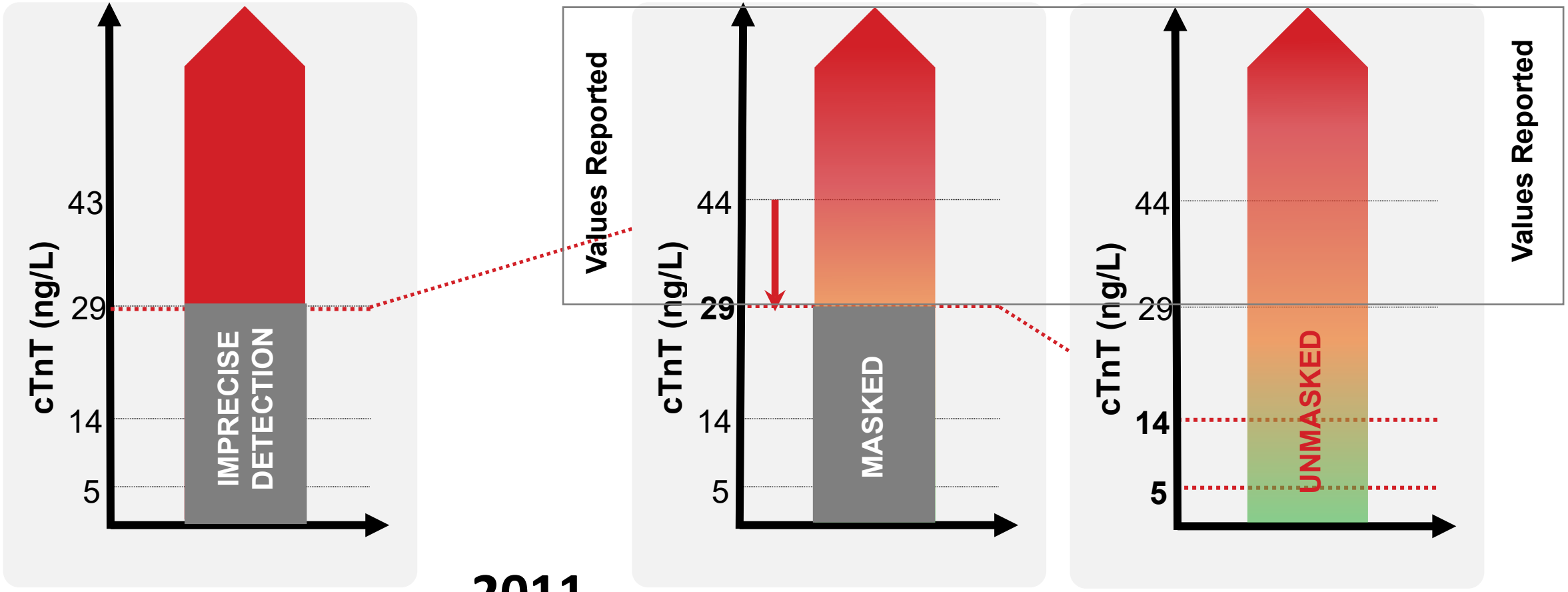
BACKGROUND

- Suspected ACS in the Emergency Department is one of the most common presentations to emergency services and is very resource intensive

- High-sensitivity troponins assays, when integrated into early ED workup, can rule-out ACS with robust diagnostic certainty.
  - Clinical benefits of subsequent changes in “down-stream testing” are not well defined

- The impact on late-outcomes, as a result of changes in acute care practices, has not been fully evaluated in patient-level randomized clinical trials

Staged Implementation of cTnT to hs-cTnT: Masking



cTnT
(ULN: <29ng/L on 4th Gen Assay = ~44ng/L on 5th Gen Assay)

2011

hs-cTnT
(ULN: <29ng/L, below 29ng/L masked)

hs-cTnT
(ULN: <14 ng/L, >4 ng/L reported)

Chew DP et al,. Randomized Comparison of High-Sensitivity Troponin Reporting in Undifferentiated Chest Pain Assessment. Circ Cardiovasc Qual Outcomes. 2016 Aug 9. pii: CIRCOUTCOMES.115.002488.

RAPID TnT

KEY STUDY QUESTION

- What is the impact of the superior reporting precision of hs-cTnT assays when incorporated into a rapid 0/1-hour protocol in terms of ***all-cause death or MI***?

  Two Planned Evaluations:

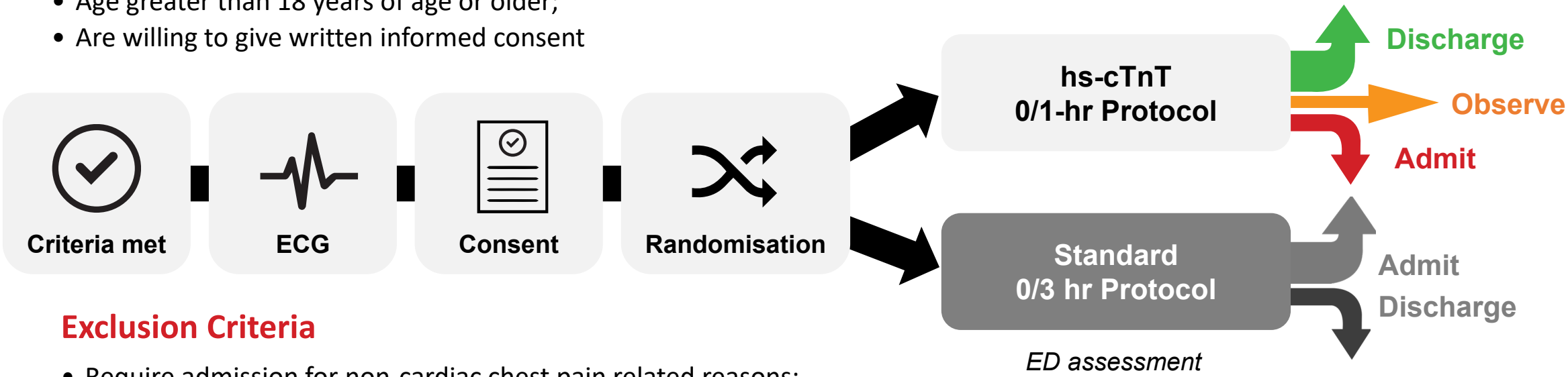
  - *Safety of early discharge* based on *0/1-hour hs-cTnT rule out* at 30-days: Non-inferiority (previously reported ESC 2019)
  - *Effectiveness of care* informed by *0/1-hour hs-cTnT unmasked reporting* within 12-months: Superiority comparison (current analysis)

- **Primary Hypothesis:** Clinical care based on a 0/1-hour unmasked hs-cTnT protocol will reduce 12-month death or MI
- **Key Secondary hypothesis:** Clinical care based on a 0/1-hour unmasked hs-cTnT protocol will reduce 12-month death or MI among patients with an initial troponin ≤29ng/L

RAPID TnT: STUDY SCHEMATIC

Inclusion Criteria

- Clinical features of chest pain or suspected ACS as the principal cause for investigation;
- Baseline electrocardiogram (ECG) interpreted as not definitive for coronary ischemia;
- Age greater than 18 years of age or older;
- Are willing to give written informed consent



Exclusion Criteria

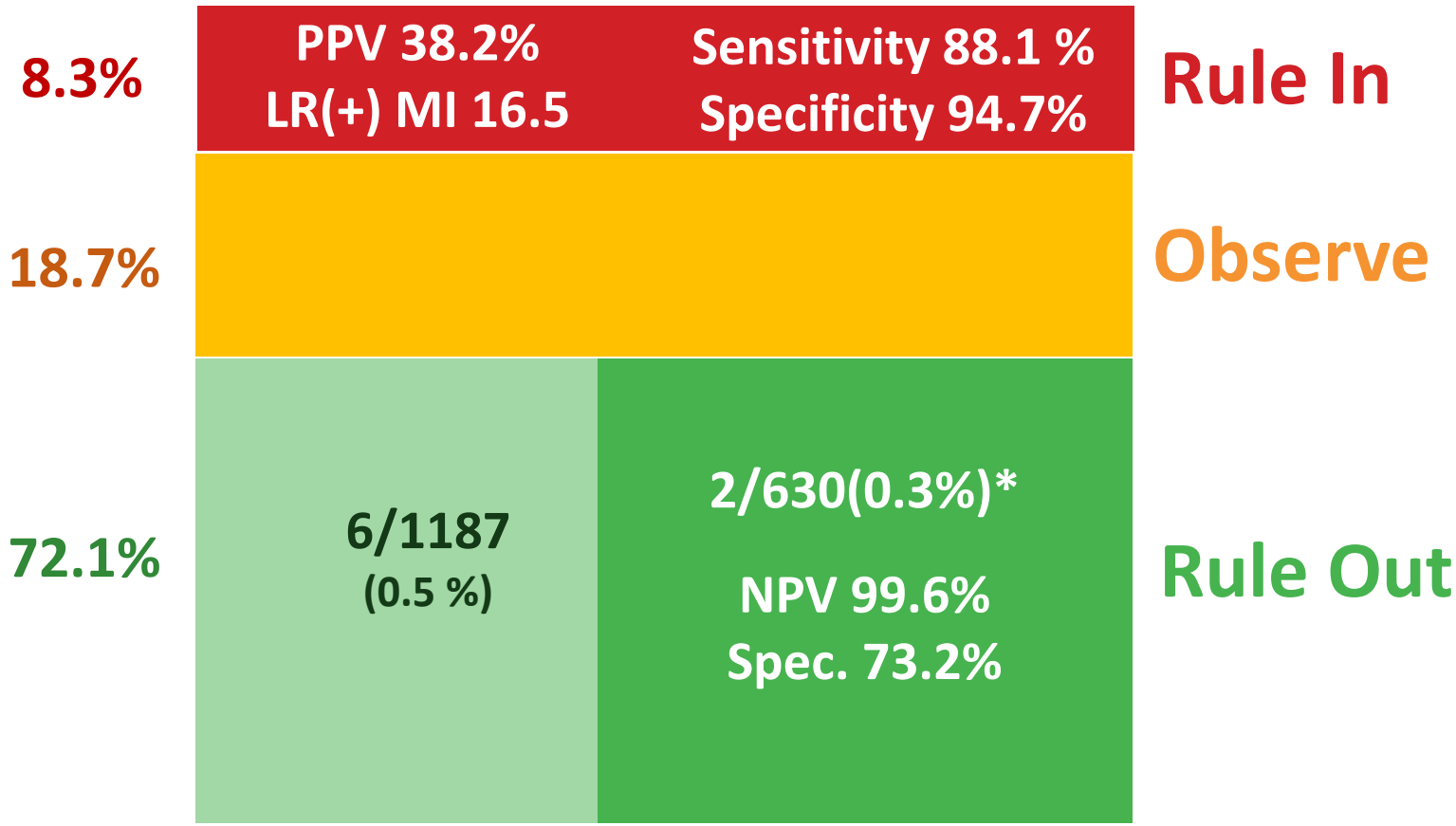
- Require admission for non-cardiac chest pain related reasons;
- Presented as a result of a transfer from another hospital;
- Are representing with chest pain within 30 days of last presentation;
- Require permanent dialysis;
- Are unable to complete clinical history questionnaire due to language or comorbidity

Papendick C, et al. A randomized trial of a 1-hour troponin T protocol in suspected acute coronary syndromes: Design of the Rapid Assessment of Possible ACS In the emergency Department with high sensitivity Troponin T (RAPID-TnT) study. Am Heart J. 2017 Aug;190:25-33. doi: 10.1016/j.ahj.2017.05.004.

RAPID TnT

0/1-HOUR PROTOCOL PERFORMANCE

Death or MI within 30 days



Chew DP, Lambrakis K, Blyth A, Seshadri A, Edmonds MJR, Briffa T, Cullen LA, Quinn S, Karnon J, Chuang A, Nelson AJ, Wright D, Horsfall M, Morton E, French JK, Papendick C. A Randomized Trial of a 1-Hour Troponin T Protocol in Suspected Acute Coronary Syndromes: The Rapid Assessment of Possible ACS In the Emergency Department with High Sensitivity Troponin T (RAPID-TnT) Study. Circulation. 2019 Sep 3. doi: 10.1161/CIRCULATIONAHA.119.042891.

RAPID TnT

RAPID TnT: STATISTICAL CONSIDERATIONS

- **Primary analysis:** Cox proportional hazards model with shared frailty/ robust standard errors to account for within hospital clustering using ITT population
  - **Key Sub-analysis:** patients with ***initial troponin ≤29 ng/L***
- April 2019, DSMB informed the Steering Committee that there is no longer equipoise regarding the event rate in Rule-out MI recommendation (I.e., Discharge base in the 0/1-hour hs-cTnT was safe [<1% rate of Death or MI by 30 days]. Study stopped
- Safety analysis (30-day) presented at ESC Congress 2019 (Paris)
- Effectiveness analysis in 12-month follow-up: database lock late November 2020

RAPID TnT: 12-MONTH OUTCOME MEASURES

The primary outcome: the 12-month composite endpoint of:

- All-cause mortality
- Myocardial infarction adjudicated by the 4th Universal Definition of MI (Types 1-5)

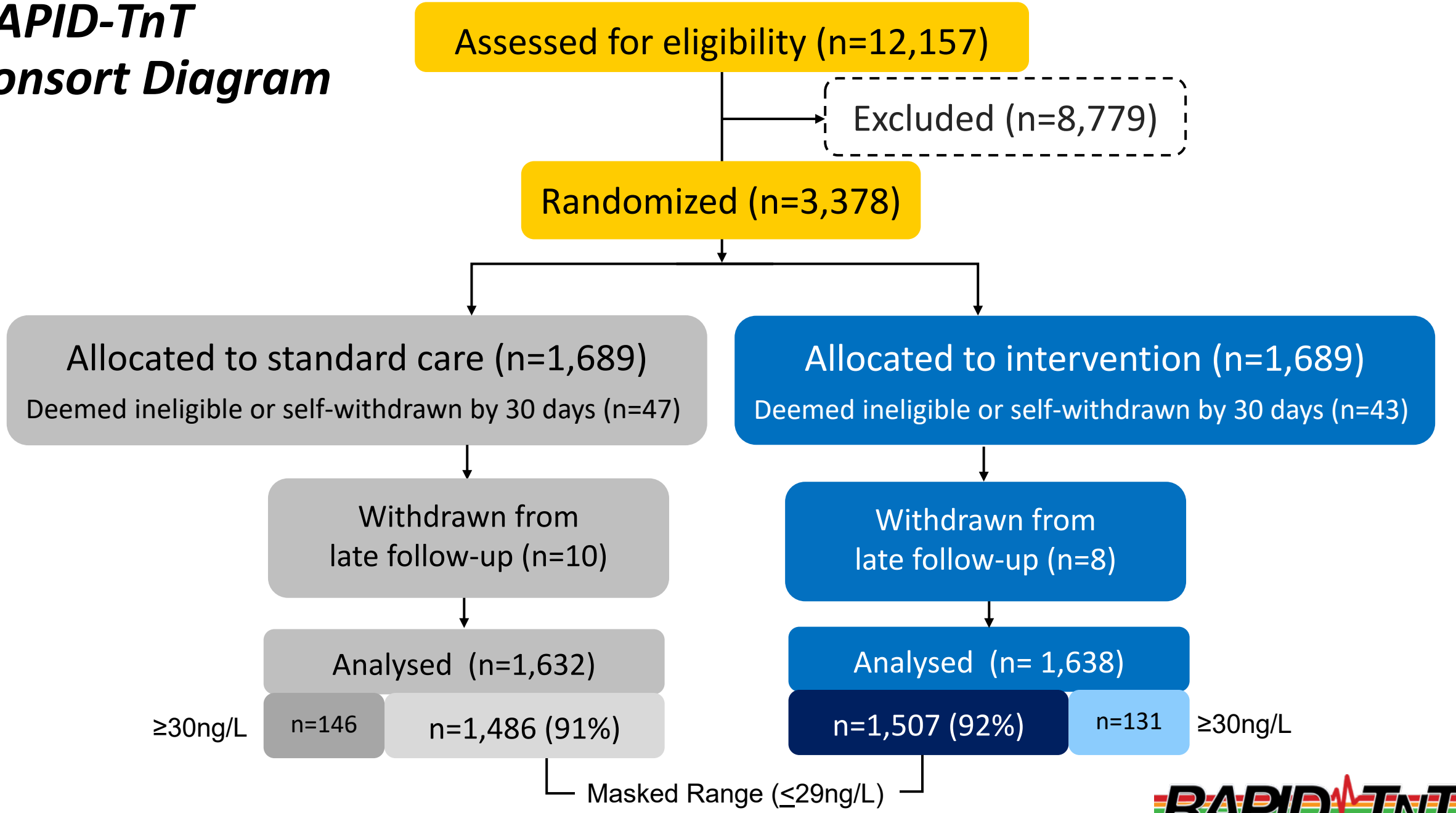
***Excluding Index "presenting" MI**

Major secondary clinical outcomes:

- The occurrence of all-cause mortality or new ACS (MI and unstable angina) at 12 months
- Cardiovascular mortality at 30 days and 12 months
- Unplanned hospital admission for non-coronary cardiovascular diagnoses: CVA; atrial or ventricular arrhythmias; CCF without MI; as documented by a hospital discharge summary within 12 months.

RAPID TnT

RAPID-TnT Consort Diagram



BASELINE CHARACTERISTICS

Characteristic	Standard (*n* = 1632)	0/1-Hour (n = 1638)
Age, median (IQR)	58.6 (48.8, 71.2)	58.7 (48.6, 69.4)
Female sex	46.8 %	46.6 %
Hypertension	20.5 %	19.7 %
Diabetes	17.5 %	15.7 %
Dyslipidaemia	44.1 %	43.4 %
Current smoker	35.7 %	34.6 %
Prior history of CAD	29.0 %	27.8 %
Prior coronary artery bypass grafting	2.8%	3.0 %
Prior percutaneous coronary intervention	8.5%	10.4 %
Glomerular filtration rate, ml/min/1.73m^2, median (IQR)	86.0 (71.1, 98.0)	86.2 (71.6, 98.2)
EDACS, median (IQR)	15.0 (9.0, 21.0)	14.0 (9.0, 20.0)
GRACE score, median (IQR)	75.0 (56.1, 100.8)	74.1 (55.2, 97.2)
HEART score, median (IQR)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)

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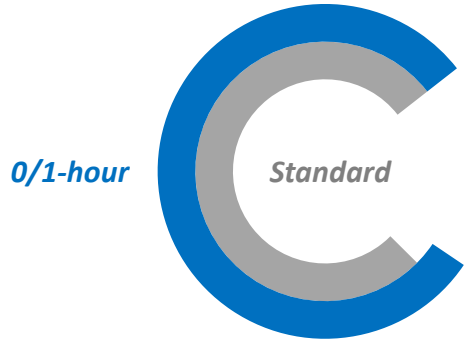
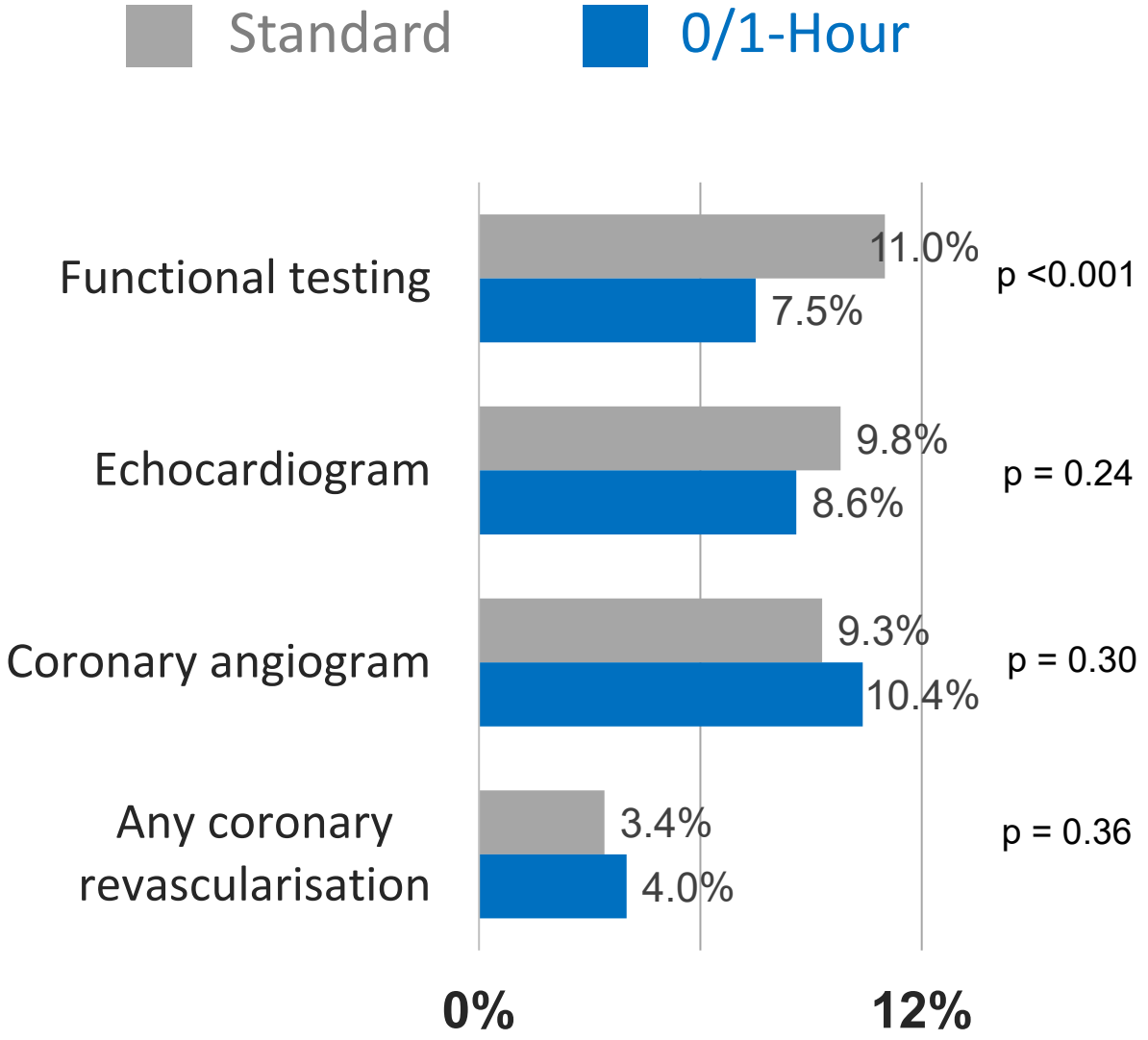
CARDIAC TESTS WITHIN 30 DAYS

All participants

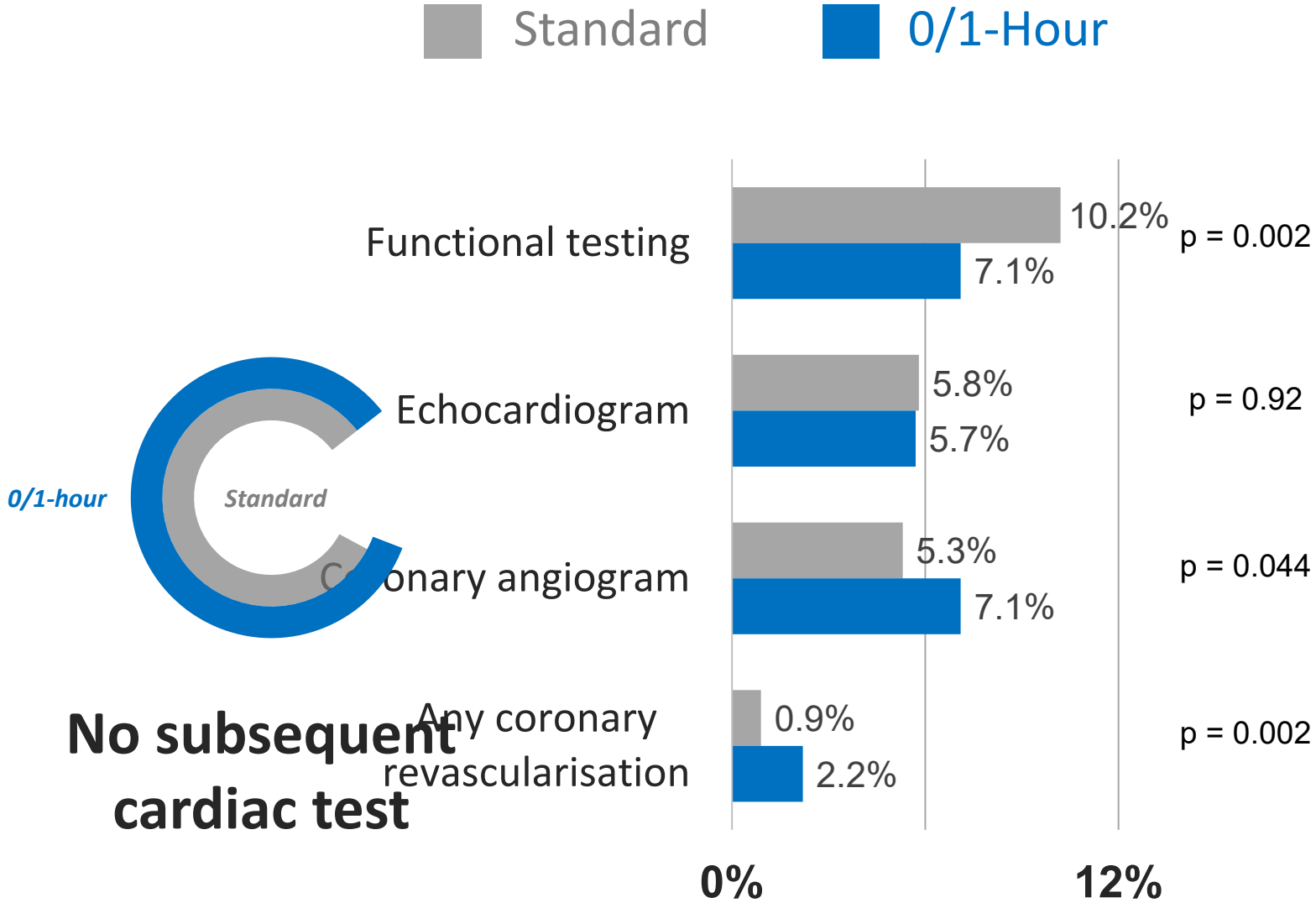


No subsequent cardiac test



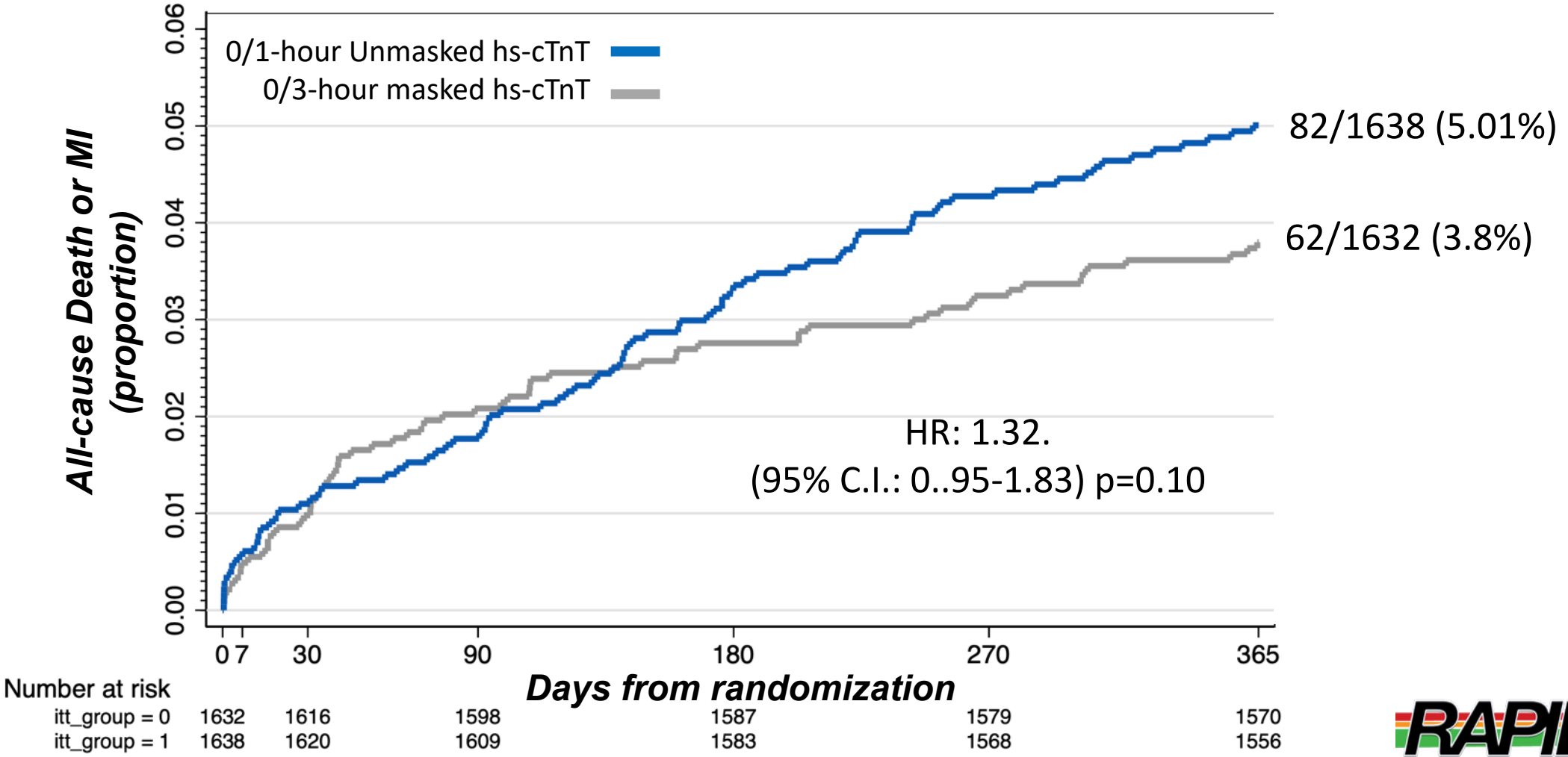
CARDIAC TESTS WITHIN 30 DAYS

≤29 ng/L Troponin T



PRIMARY ENDPOINT:

Death or MI by 12-month follow-up



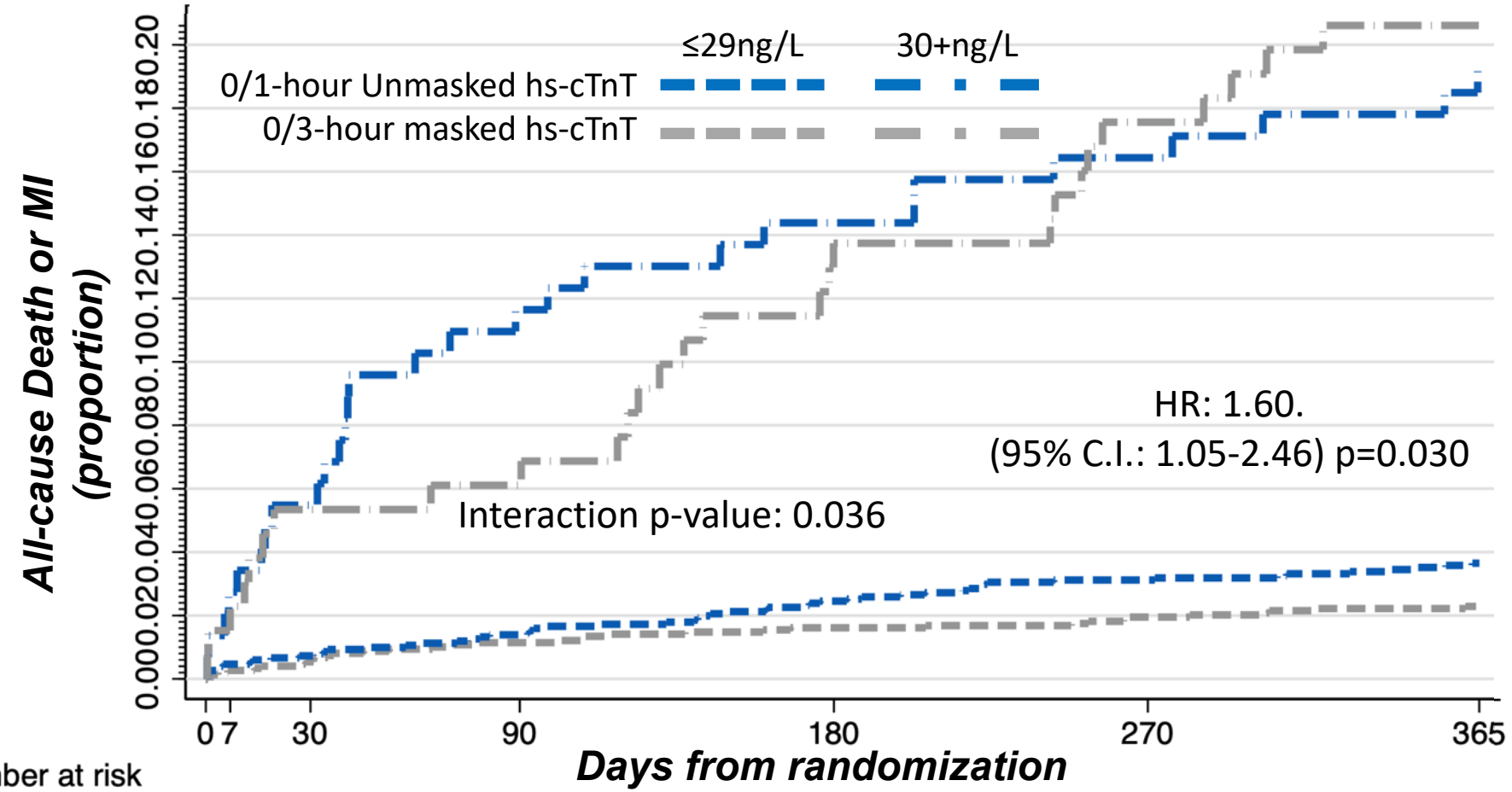
82/1638 (5.01%)

62/1632 (3.8%)

HR: 1.32.
(95% C.I.: 0..95-1.83) p=0.10

PRIMARY ENDPOINT by Troponin ≤29ng/L:

Death or MI by 12-month follow-up



Number at risk

itt_group4 = 0	1486	1478	1469	1462	1457	1452
itt_group4 = 1	146	138	129	125	122	118
itt_group4 = 2	1507	1496	1486	1470	1460	1452
itt_group4 = 3	131	124	123	113	108	104

27/131(20.6%)

28/146 (19.2%)

HR: 1.05.
(95% C.I.: 0..62-1.78) p=0.859

*HR_{adj}: 1.63.
(95% C.I.: 1.15-2.30) p=0.006

55/1486 (3.7%)

34/1507 (2.3%)

*Adjusted for age, diabetes, prior percutaneous coronary intervention, prior atrial fibrillation, prior heart failure and Killip class >1

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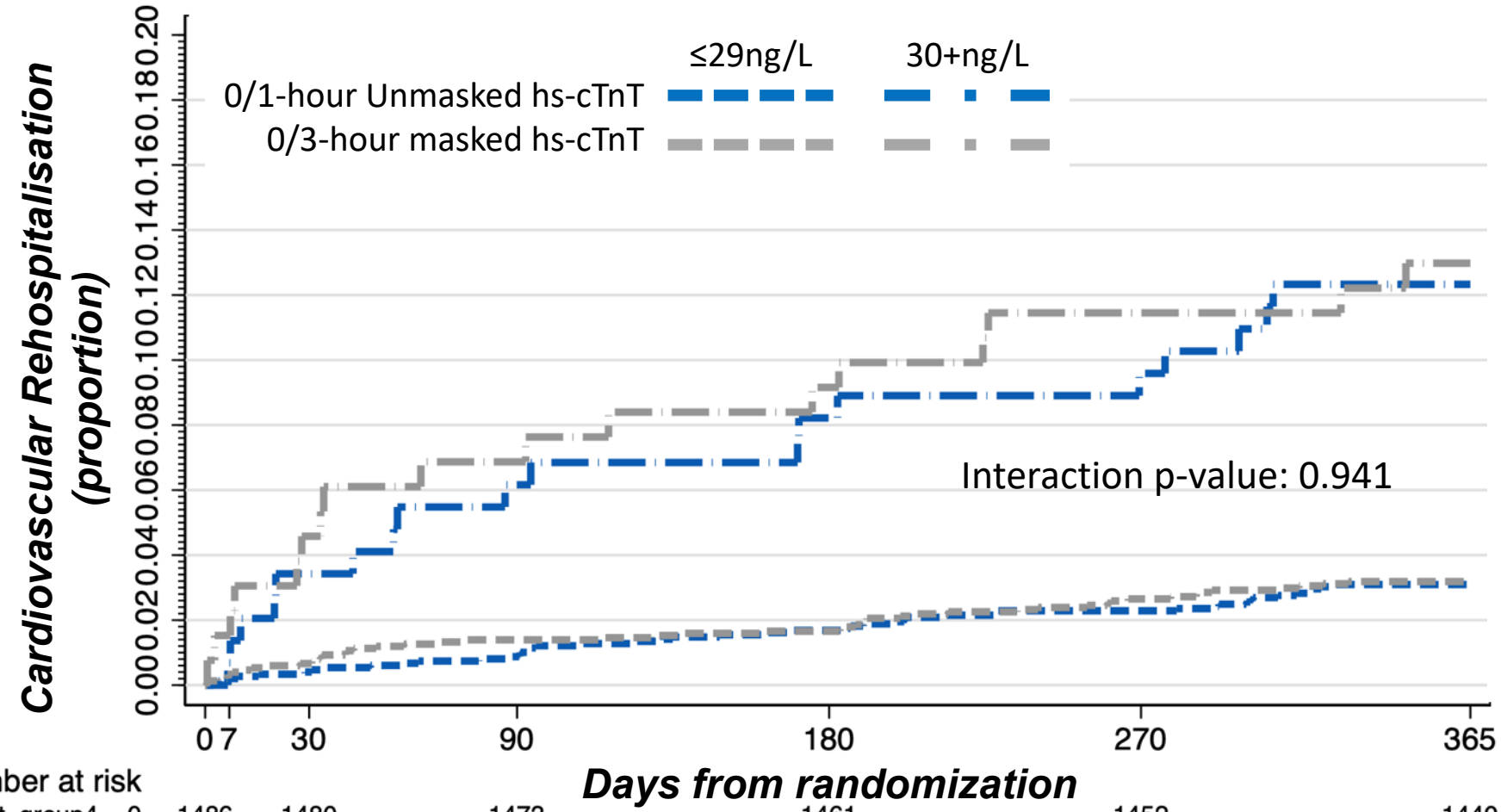
CV Re-hospitalisation by Troponin ≤29ng/L:

Heart Failure, Arrhythmia, CVA/TIA, PVD by 12-months



Number at risk

itt_group4 = 0	1486	1480	1473	1461	1452	1440
itt_group4 = 1	146	141	137	134	132	128
itt_group4 = 2	1507	1497	1486	1482	1467	1459
itt_group4 = 3	131	125	122	119	116	114

HR: 1.07.
(95% C.I.: 0.55-2.06) p=0.855

17/131(12.3%)

18/146 (13.0%)

HR: 1.03.
(95% C.I.: 0.69-1.55) p=0.881

46/1486 (3.1%)

48/1507 (3.2%)

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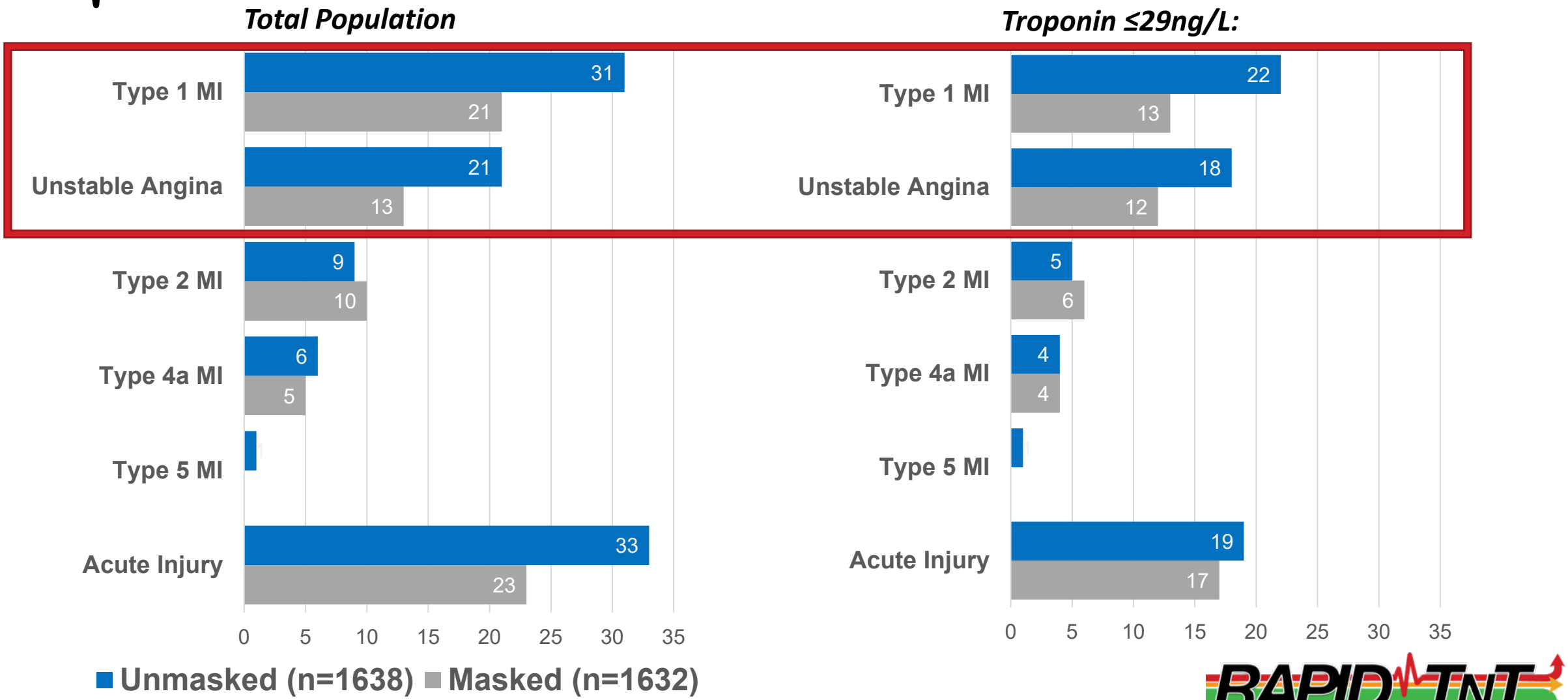
Myocardial Infarction/Injury Classification

Total number of events



Limitations

- No overall difference between study arms using the ITT population. Therefore, observations of excess harm unmasked troponin remains exploratory despite:
  - Representing over 91% of the enrolled participants, and;
  - No significant differences in baseline characteristics between study arms and participants with initial troponin ≤29ng/L
- Subsequent care informed by masked troponin results in both arms may have reduced the diagnosis of subsequent MI
- Clinical interpretation of an “inclusive” definition of MI (Type 1-5) in the primary endpoint will need careful consideration
  - Although this pattern of excess risk is seen across all “coronary” endpoint definitions

CONCLUSIONS

- Among patients with suspected ACS and ischaemia excluded on initial ECG, randomised allocation of unmasked hs-cTnT within a 0/1 hour protocol was associated with
  - A reduction in functional stress testing,
  - An increase in coronary angiography and revascularization.
- Unmasked reporting of hs-cTnT was not associated with a reduction in late death or MI over 12 month follow-up.
- Among those presenting with troponins within the masked range (≤29 ng/L), an increase in death or MI may be evident.
- Optimal strategies for the management of patients with suspected ACS and low concentration troponin elevations requires further study

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Acknowledgements

Steering Committee:
Cynthia Papendick,
Andrew Blyth,
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National Health & Medical Research Council

Roche Diagnostics:
Gesa Albert

SAHMRI South Australian Health & Medical Research Institute

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