The Rapid Assessment of Possible ACS In the emergency Department with high sensitivity Troponin T (RAPID-TnT) Study

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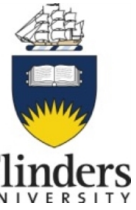


Declaration of interest

- Others (Grant in Aid Roche Diagnostics)

BACKGROUND

- Suspected ACS in the Emergency Department
  - one of the most common presentations to emergency services
  - very resource intensive
  - equivocal benefit for the traditional ‘liberal’ approach to further testing

- High sensitivity troponins have the potential to improve the early diagnosis of myocardial infarction
  - High negative predictive value effective in ruling out MI.

- Increased sensitivity could lead to more downstream cardiac testing
  - Uncertain benefit and even potential harm.

KEY STUDY QUESTION

- What is the clinical impact of the ***improved diagnostic precision*** of hs-cTnT assay incorporated into a rapid 0/1-hour protocol in terms of ***patient outcomes*** *and/*or ***greater emergency department efficiency*** when embedded within practice?
  - **Conditions needed to address this question**:
    1. No prior access to hs-cTnT results to influence clinical decision-making
    2. Clinical practice where 0/1-hour protocols are not standard of care

- **Primary Hypothesis:** Compared with our current standard practice, clinical care based on a 0/1-hour hs-cTnT protocol will provide non-inferior clinical outcomes at 30 days
- **Secondary hypothesis:** Suspected ACS patients discharged from the ED under the 0/1-hour hs-cTnT protocol is safe *(30-day death or new/recurrent MI of <1%)*

RAPID TnT

STUDY DESIGN

- Prospective “in practice” patient-level randomized non-inferiority evaluation of a **0/1-hour protocol** using a **hs-cTnT** reporting format (LoD 5ng/L) compared with a **0/3-hour protocol** using **masked hs-cTnT** reporting (≤29ng/L) in participants with suspected ACS

- Conducted in four metropolitan public emergency departments in Adelaide, Australia from August 2015-April 2019

- **Funding:** National Health and Medical Research Council of Australia (APP 1224471) and restricted educational grant from Roche Diagnostics International (Rotkreuz, Switzerland)

RAPID TnT

RAPID TnT: OUTCOME MEASURES

The primary outcome: the 30-days composite endpoint of:

- All-cause mortality
- Myocardial infarction adjudicated by the 4th Universal Definition of MI

***Excluding Index "presenting" MI**

Major secondary clinical outcomes:

- The occurrence of all-cause mortality or new ACS at 12 months
- Cardiovascular mortality at 30 days and 12 months
- Unplanned hospital admission: non-elective coronary revascularization; CVA; atrial or ventricular arrhythmias; CCF without MI; as documented by a hospital discharge summary at 30 days and 12 months.

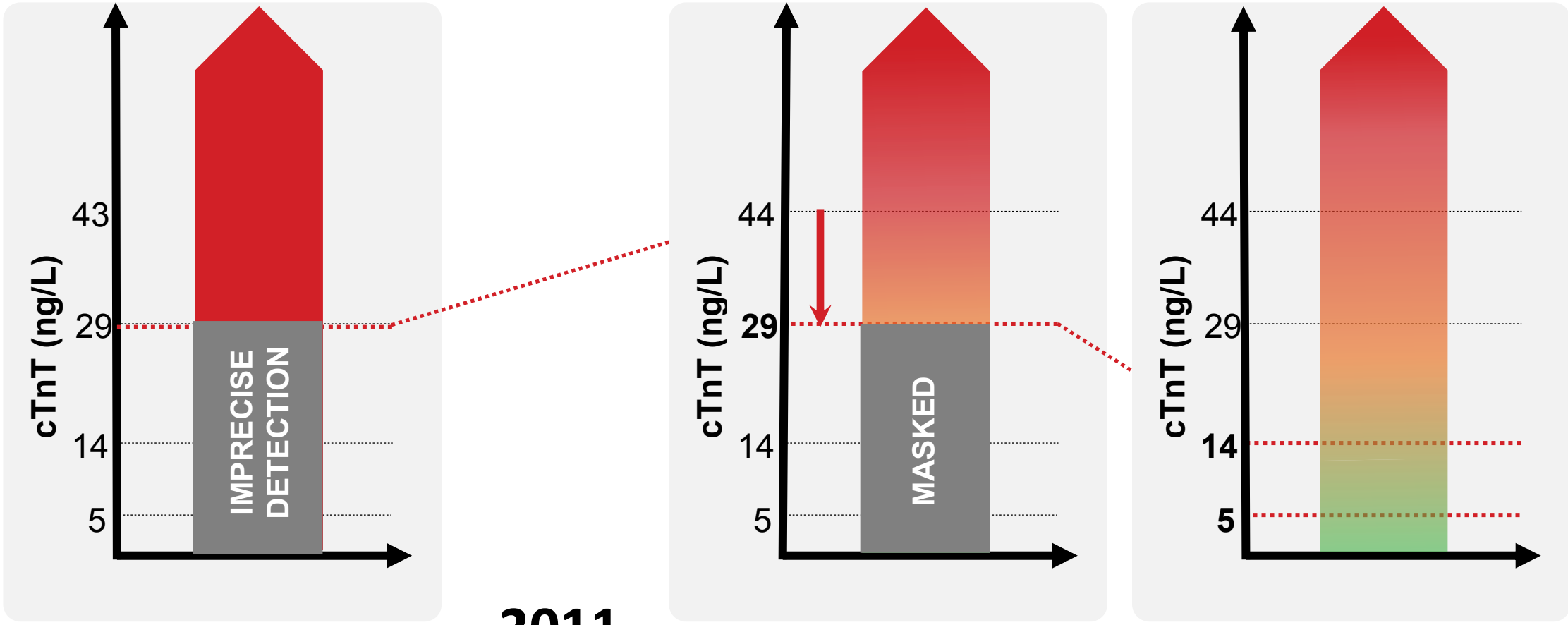
LOCAL IMPLEMENTATION OF TROPONIN T

- In 2011 Roche Diagnostics 5th generation hs-cTnT assay was introduced as the sole troponin assay in public hospitals in South Australia

- Due to concerns regarding a higher rate of abnormal troponin results and increased invasive testing, the reported lower limit was aligned to the 4^{th} generation level of ≤29 ng/L.
  - (N.B: an improvement in test performance recognized)

- Local EDs remained masked to troponin T concentration below 29 ng/L; and clinicians had no prior clinical experience with hs-cTnT results below this level

Staged Implementation of cTnT to hs-cTnT



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

2011

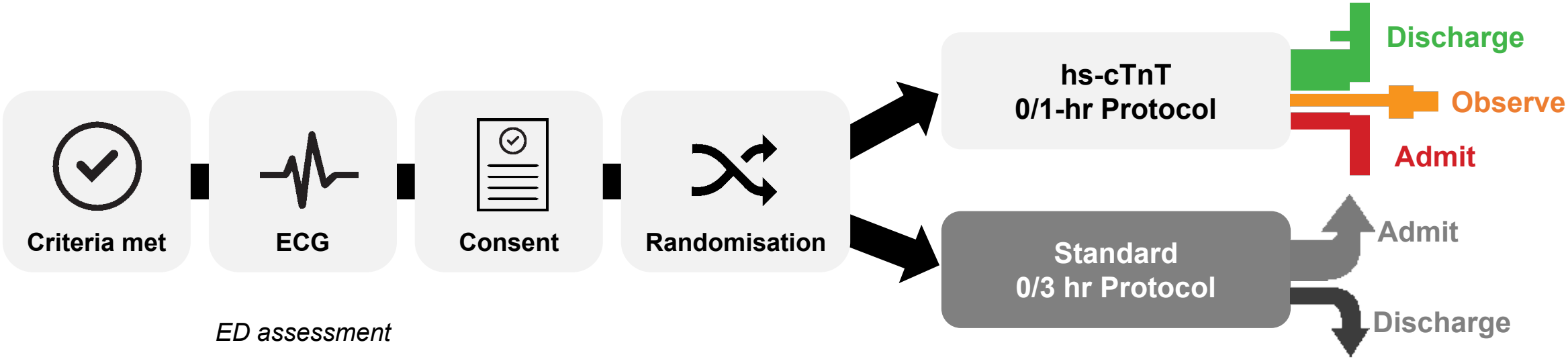
hs-cTnT
(ULN: <29ng/L, below 29ng/L masked)

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

RAPID TnT: STUDY SCHEMATIC



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: ELIGIBILITY CRITERIA

Inclusion Criteria

Patients presenting to the ED were eligible if they had:

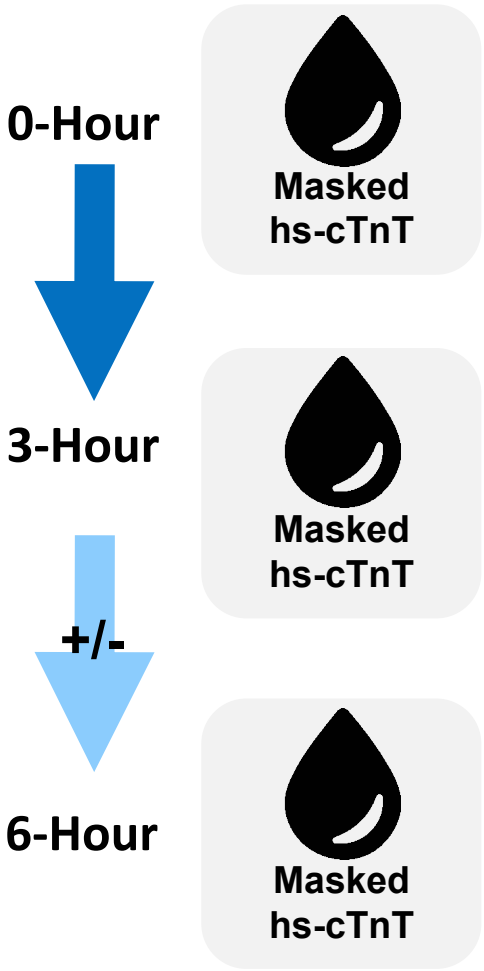
- Clinical features of chest pain or suspected ACS as the principal cause for investigation;
- Baseline electrocardiogram (ECG) interpreted as not definitive for coronary ischemia;
- Age greater than 18 years of age or older;

Exclusion Criteria

Patients were considered ineligible if they:

- Require admission for non-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;

STANDARD 0/3-HOUR masked hs-cTnT PROTOCOL



Troponin >29ng/L on any sample
Prior Known CAD
Ongoing Chest Pain

Admit

Suggested Management:

- General Medicine or Cardiology Consult

Troponins ≤29ng/L
No ongoing chest pain

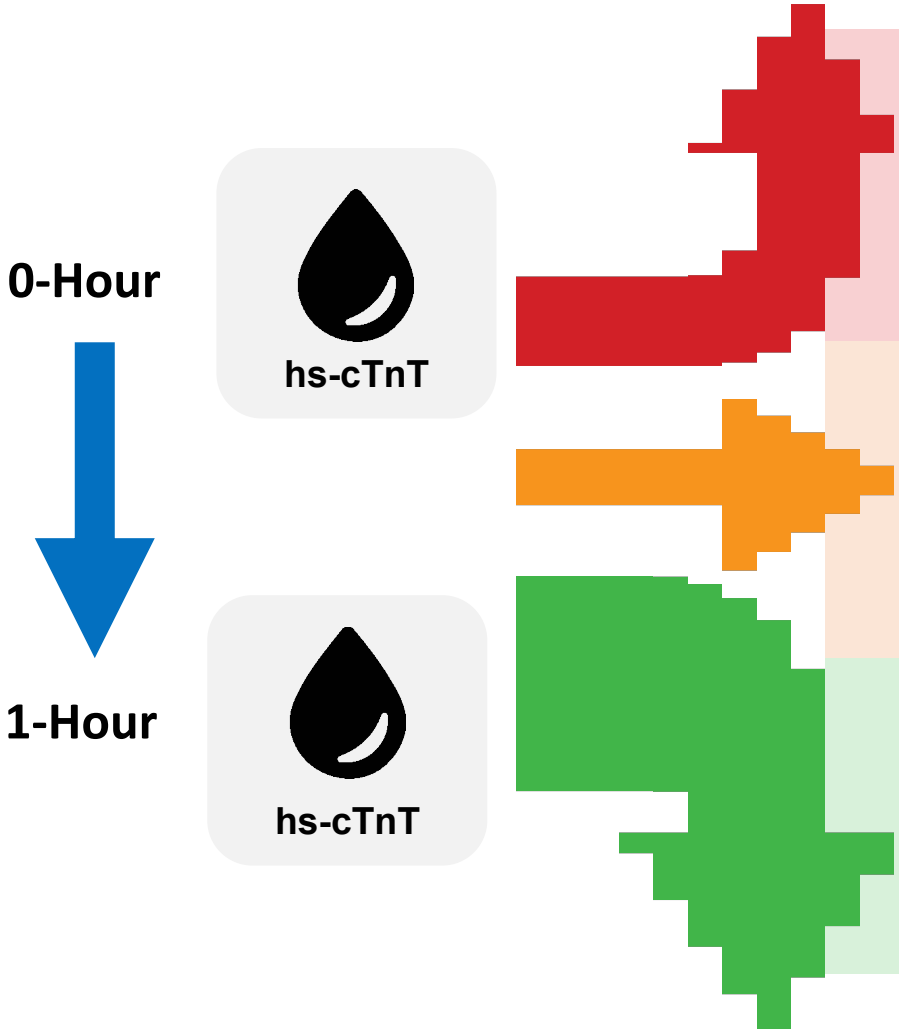
Discharge

Suggested Management:

- Risk stratify based on age >65 years and 3 or more Cardiac Risk factors
- Discretion and discussion with cardiology
- Intermediate risk: Discharge with early outpatient stress testing
- Low risk: Discharge for review in primary care

RAPID TnT

0/1-HOUR hs-cTnT PROTOCOL



Baseline hsTnT ≥52ng/L
OR
Delta hsTnT ≥5ng/L at 1hr

Rule In (Treat as ACS)

Suggested Management:

- Consult Cardiology for admission

Baseline hsTnT 13-51ng/L
OR
Delta hsTnT 3-4ng/L at 1 hr

Observe (ACS Probability: 25%)

Suggested Management:

- Requires further troponin testing in 4h
  Discuss further testing with ED Consultant or Registrar
- Consider extended care in ED admission

Baseline hsTnT <5ng/L
OR
Baseline hsTnT ≤12 ng/L AND
Delta hsTnT <3ng/L at 1 hr

Rule Out (ACS Probability: <1%)

Suggested Management:

- Patient able to be discharged immediately
- Follow-up (GP or Cardiac Clinic) determined by cardiovascular risk factors

Roffi M, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2015 Aug 29. pii: ehv320.

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RAPID TnT: SYSTEMATIZED DATA COLLECTION

- Leverage single state-wide patient administration system and pathology systems through data-linkage
  - All hs-cTnT results (index and subsequent) sourced from the pathology service
  - All representations to the ED/hospitals interrogated
  - All ECG, cardiac investigation reporting systems interrogated
- Index admission and subsequent event adjudication:
  - All episodes of care with at least 1 hs-cTnT result >14ng/L examined
  - All episodes of care with targeted ICD-10AM and DRG codes examined

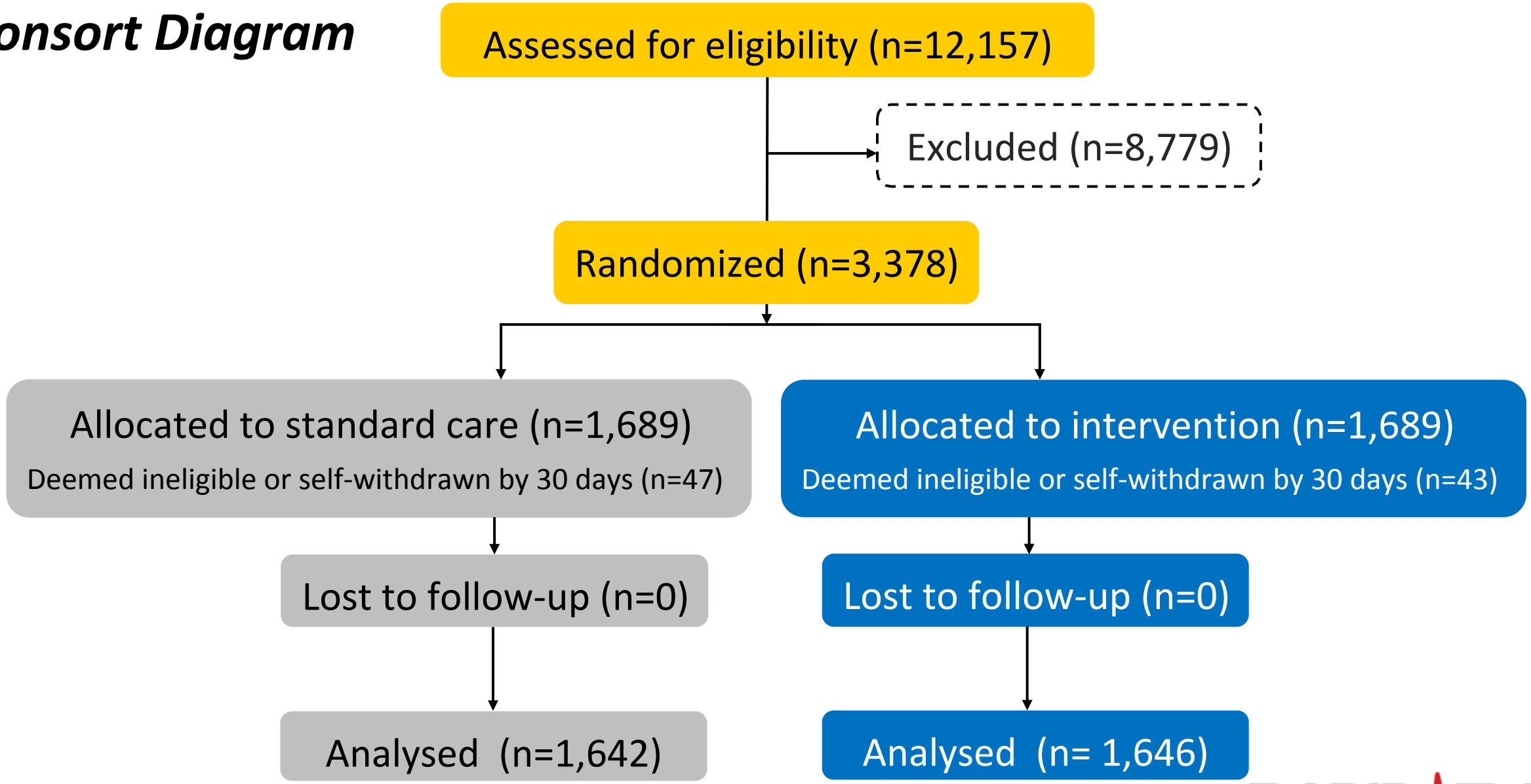
RAPID TnT

RAPID TnT: STATISTICAL CONSIDERATIONS

- **Sample size** targeted 1212 patients receiving a rule out-MI/discharge recommendation in the 0/1 hour arm to assess primary endpoint (97.5% C.I.) event rate of <1%
  - Anticipated rate of rule out MI recommendation was 60% (observed 72%)
  - Anticipated rate of initial troponin >29ng/L was 25% (observed rate 9%). Planned sample n=5400
- **Non-inferiority margin** defined as upper 97.5% C.I. of 0/1 hour hs-cTnT arm not 0.5% worse than 0/3-hour masked hs-cTnT arm i.e. Number needed to harm with new protocol >200
- **Primary analysis:** Poisson regression with robust standard errors using ITT population
  - **Key Sub-analysis:** patients with ***initial troponin ≤29 ng/L***
- **Sensitivity analysis:** Poisson regression using PP population, defined as troponin reported as randomized and care aligned with recommendation
- April 2019, DSMB informed the Steering Committee that there is no longer equipoise regarding the event rate in patients with Rule-out MI recommendation. Study stopped

RAPID TnT

RAPID-TnT Consort Diagram

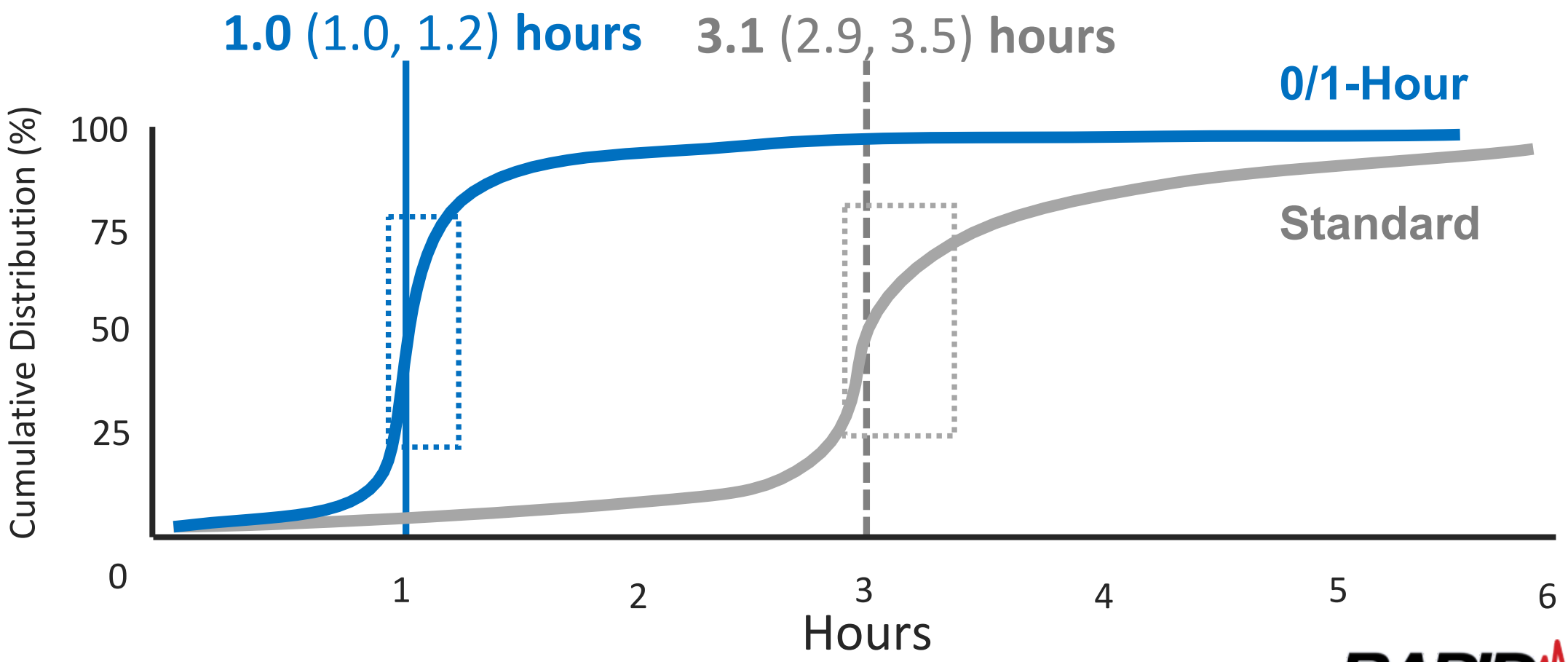


BASELINE CHARACTERISTICS

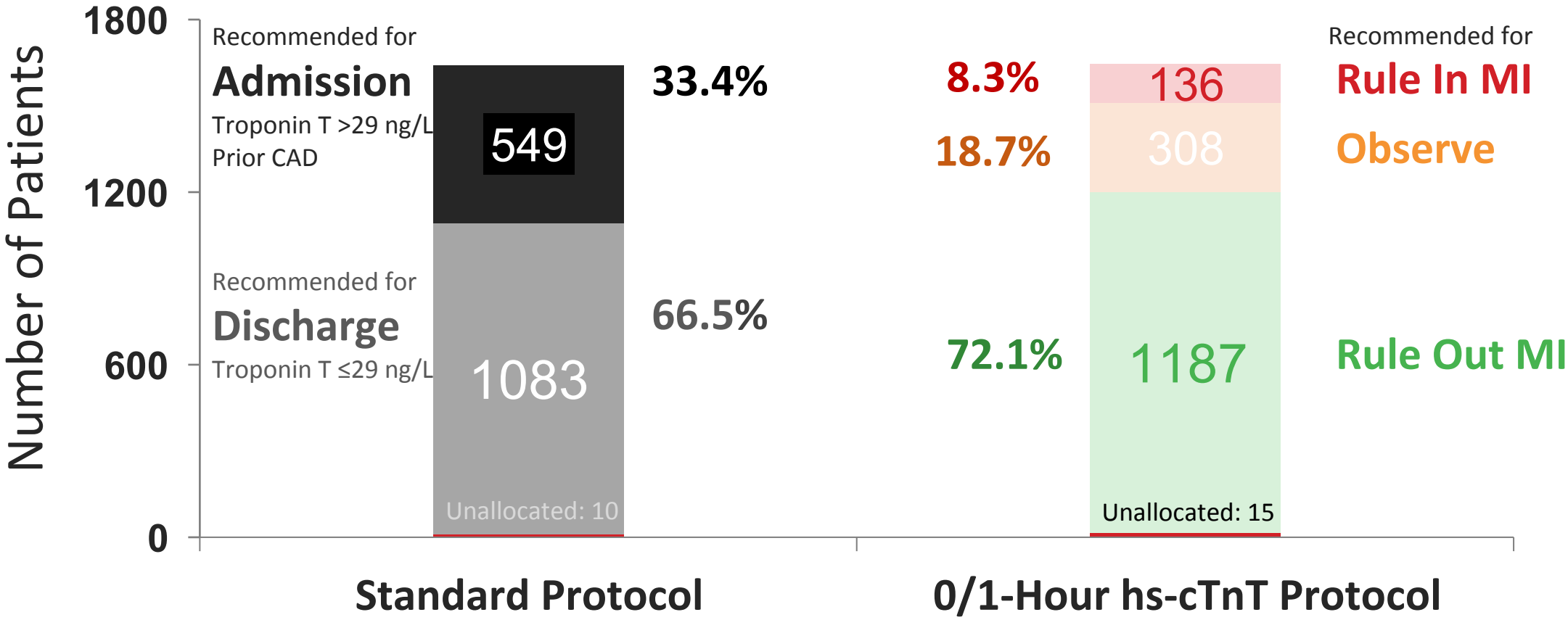
Characteristic	Standard (*n* = 1642)	0/1-Hour (n = 1646)
Age, median (IQR)	58.6 (48.8, 71.2)	58.7 (48.6, 69.4)
Female sex	46.8 %	46.8 %
Hypertension	20.5 %	19.7 %
Diabetes	17.4 %	15.8 %
Dyslipidaemia	44.0 %	43.3 %
Current smoker	35.6 %	34.6 %
Prior history of CAD	29.0 %	27.8 %
Prior coronary artery bypass grafting	2.8%	3.0 %
Prior percutaneous coronary intervention	8.4%	10.4 %
Glomerular filtration rate, ml/min/1.73m^2, median (IQR)	86.0 (71.1, 98.1)	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)

RAPID TNT

TIME BETWEEN TROPONIN T TESTING



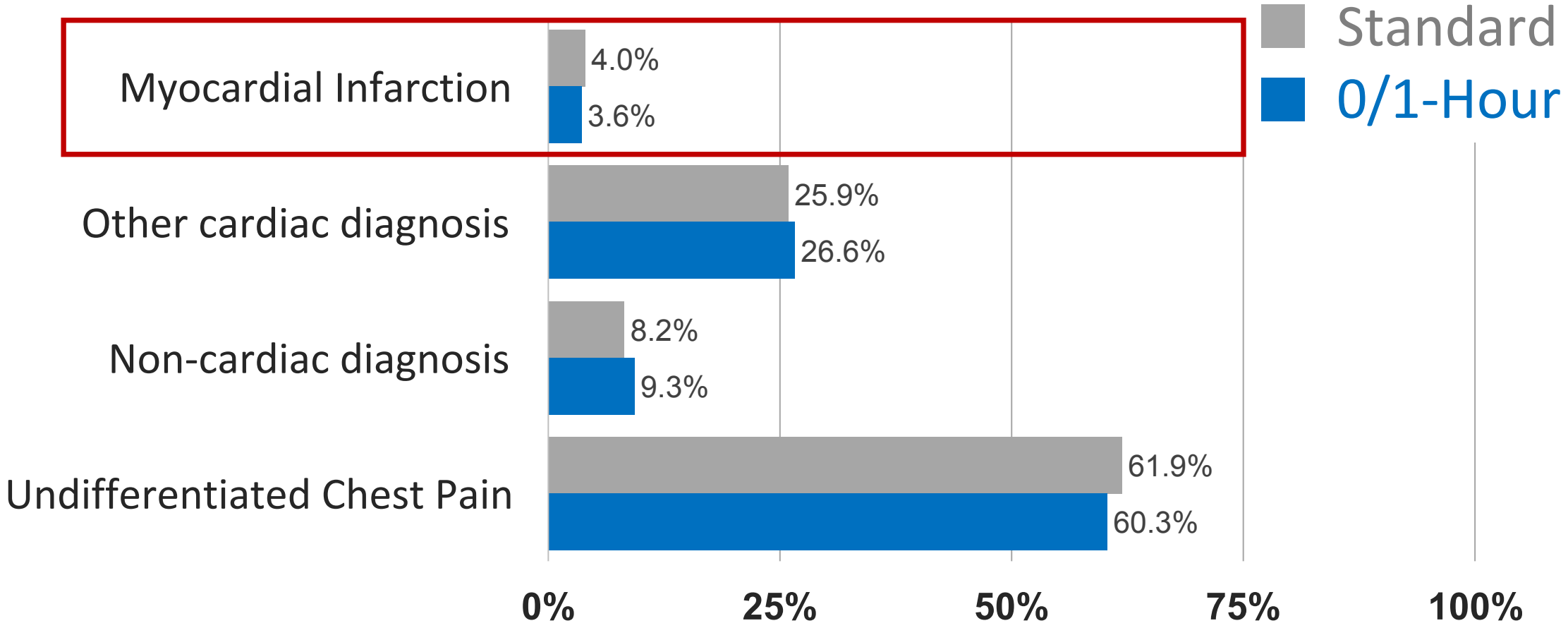
TRIAGE RECOMMENDATION



N.B.: Actual management based on clinical discretion

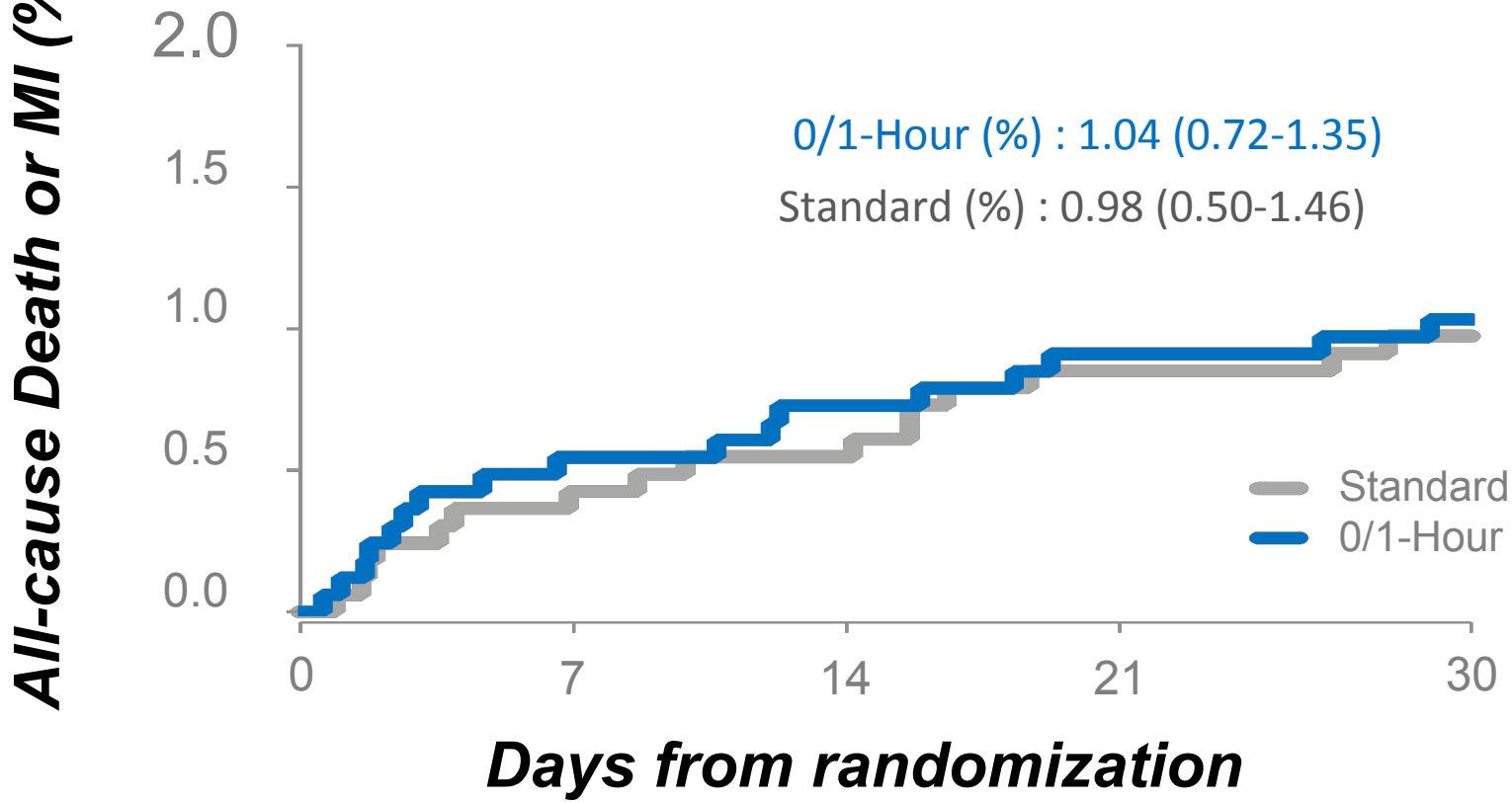
INDEX CLINICAL DIAGNOSIS

All participants



PRIMARY ENDPOINT:

30-day Death or MI



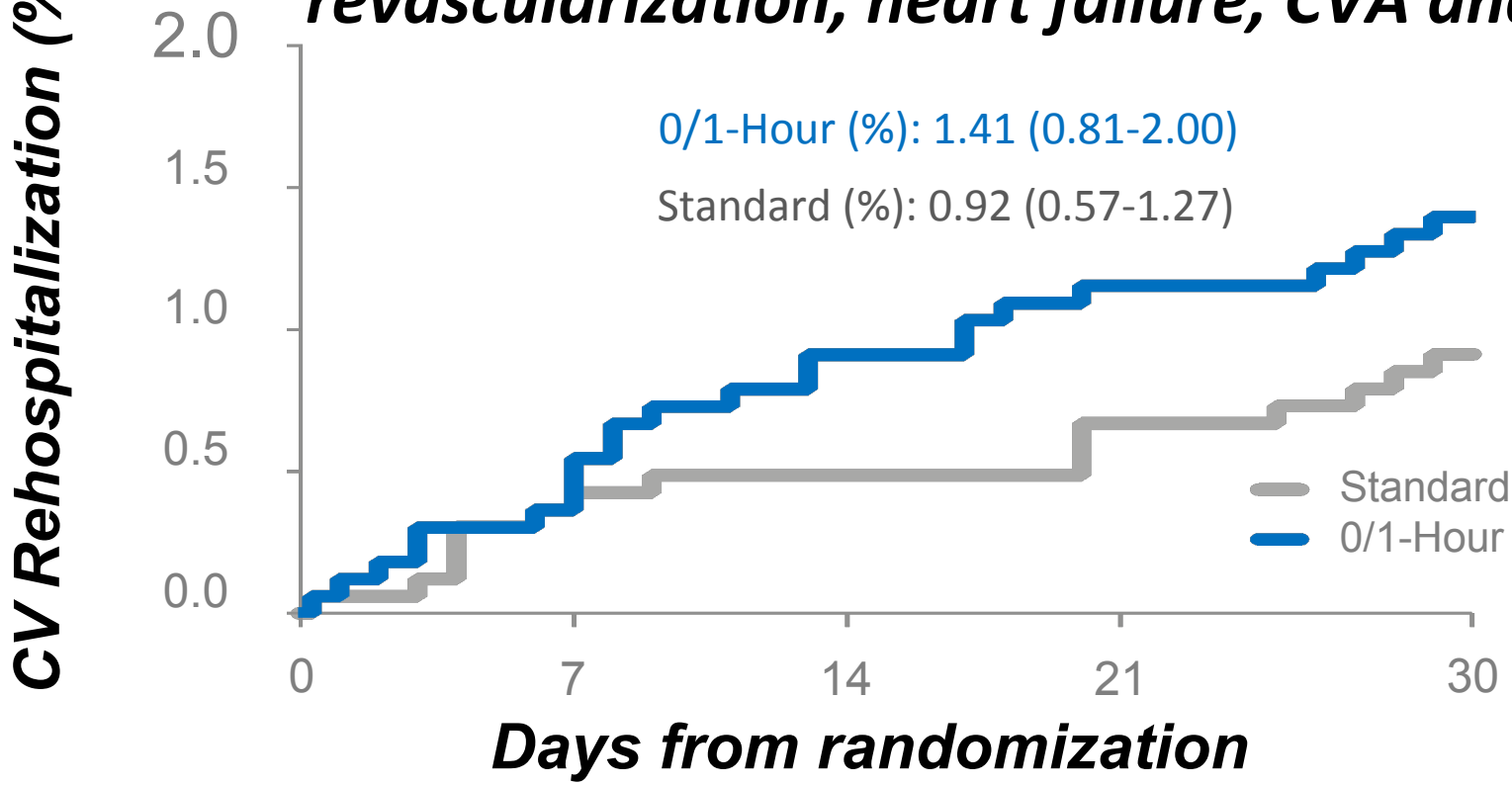
IRR: 1.06 (95% C.I.: 0.53-2.11)
Non-inferiority p=0.006
Log-rank p-value =0.886

*IRR=Incident rate ratio
Poisson confidence intervals

Standard	1642	1635	1633	1628	1626
0/1-Hour	1646	1637	1634	1631	1629

CV RE-HOSPITALIZATION

30-day rehospitalization for non-elective coronary revascularization, heart failure, CVA and arrhythmias



IRR: 1.53 (95% C.I.: 1.12-2.10)
Log-rank p-value: 0.194

*Poisson confidence intervals

Standard	1642	1636	1634	1631	1627
0/1-Hour	1646	1640	1631	1627	1623

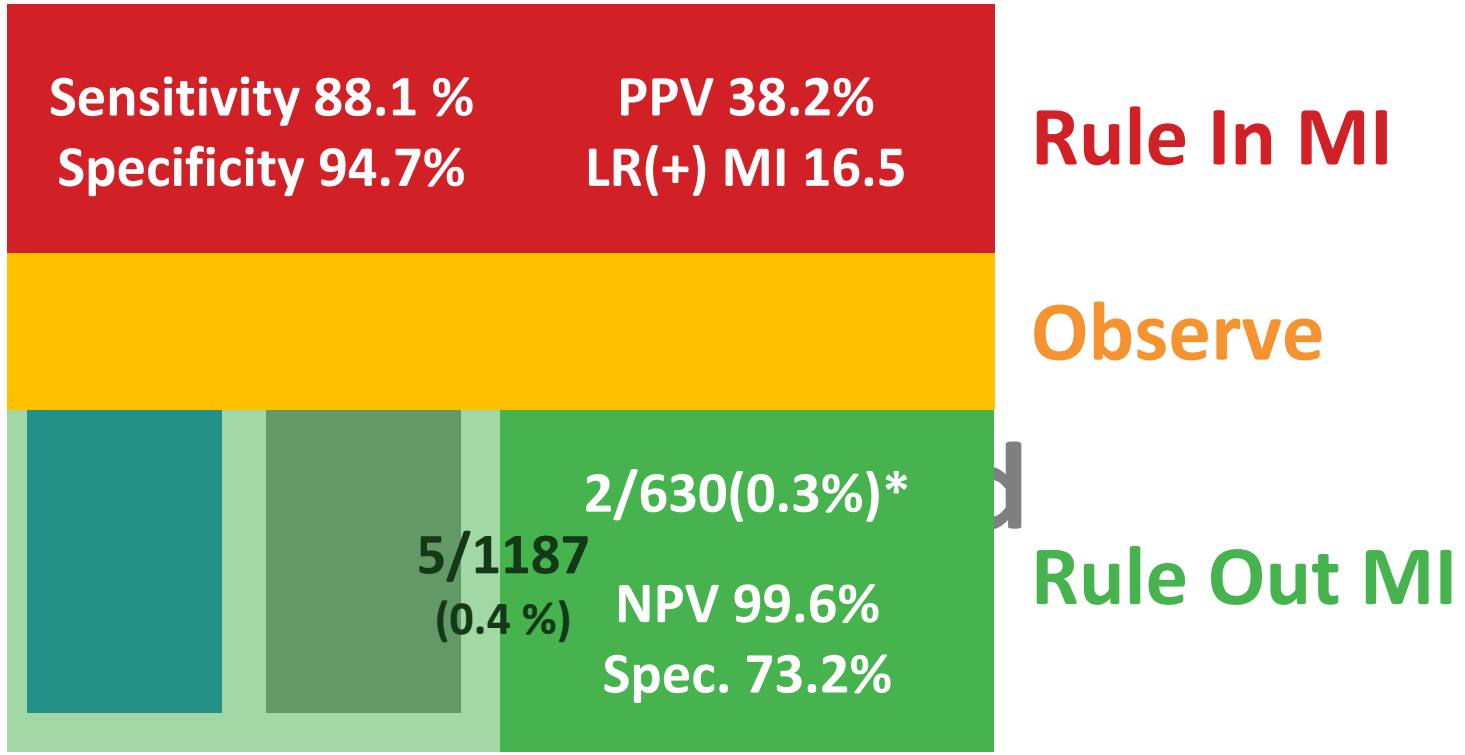
RAPID TNT

0/1-HOUR PROTOCOL PERFORMANCE

Death or MI within 30 days

0/1-Hour

1 %



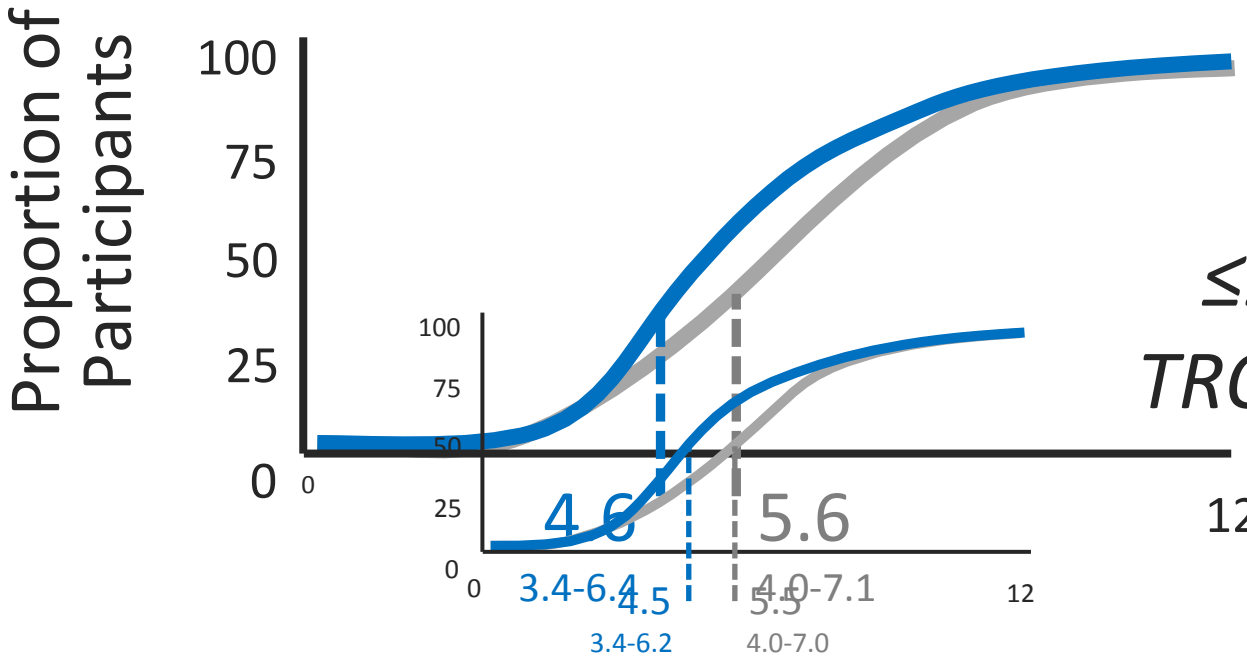
*Basis for DSMB Recommendation

CUMULATIVE DISTRIBUTION OF TIME

First 12 hrs

ALL PATIENTS

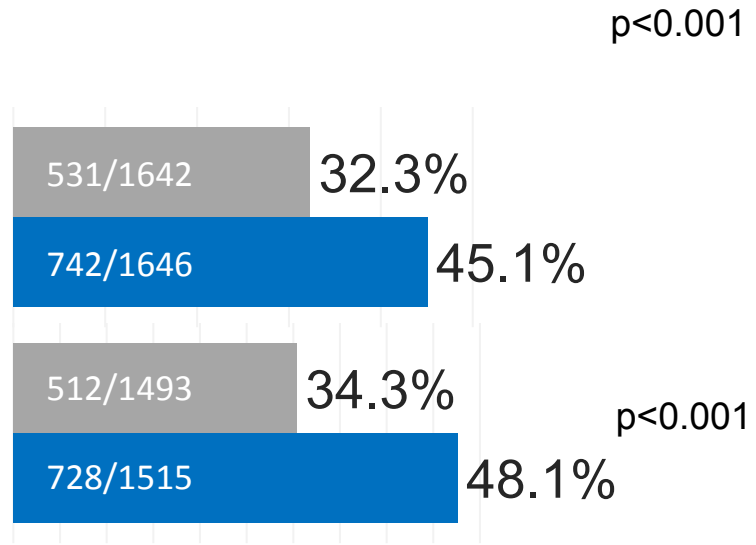
≤29 ng/L TROPONIN T



Hours in ED

Standard

0/1-Hour

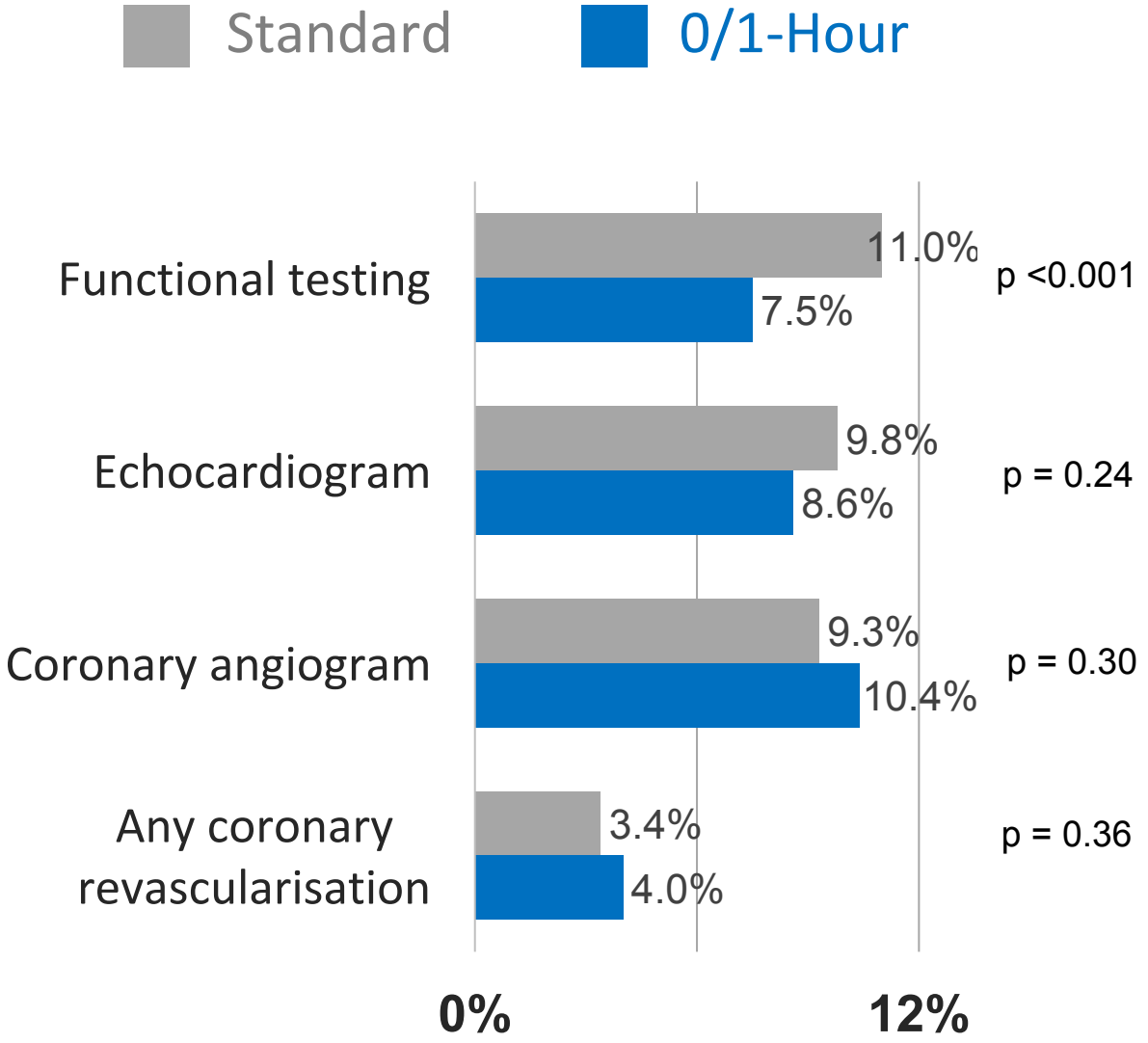


Discharged from the ED

CARDIAC TESTS WITHIN 30 DAYS

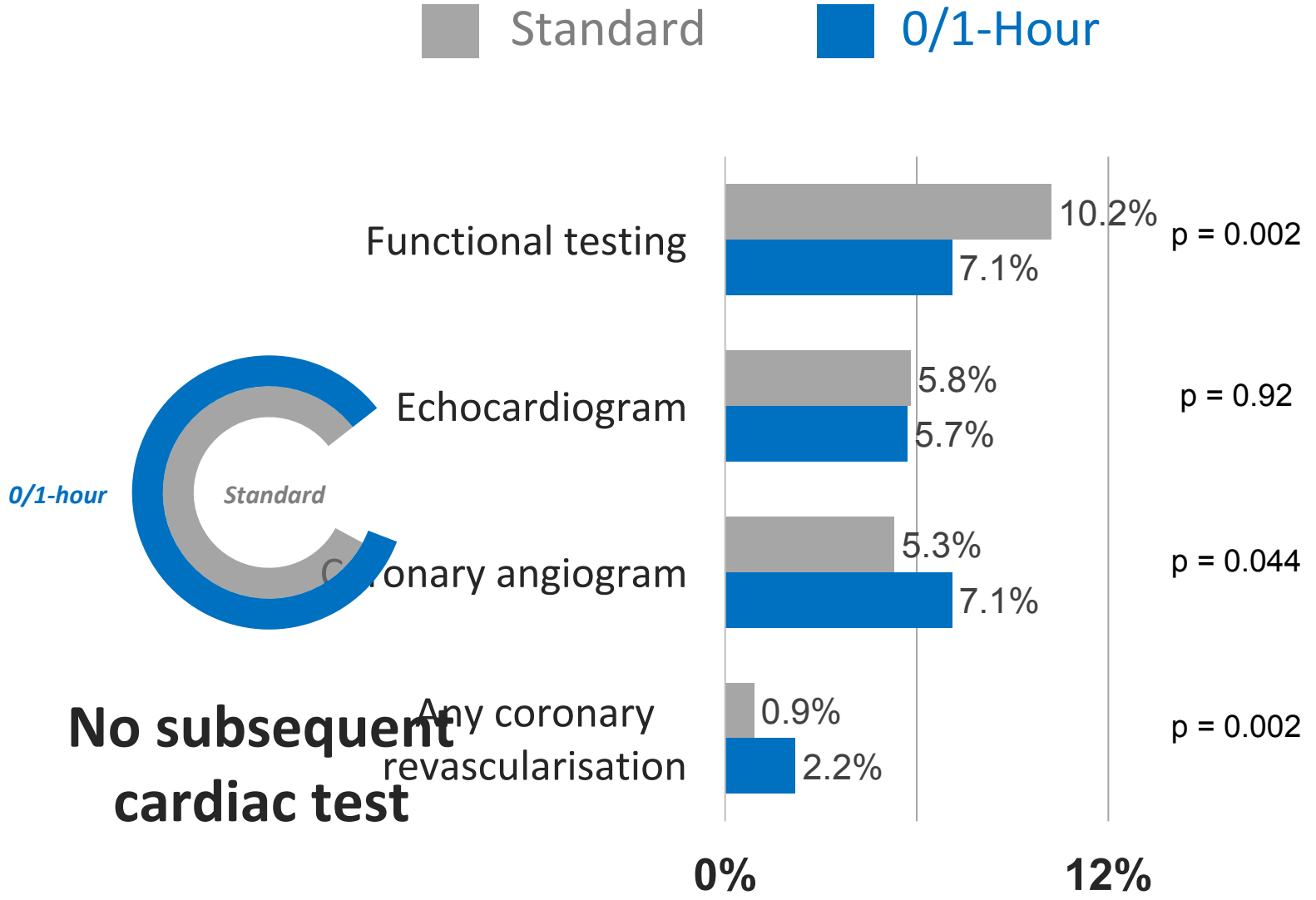
All participants

No subsequent cardiac test



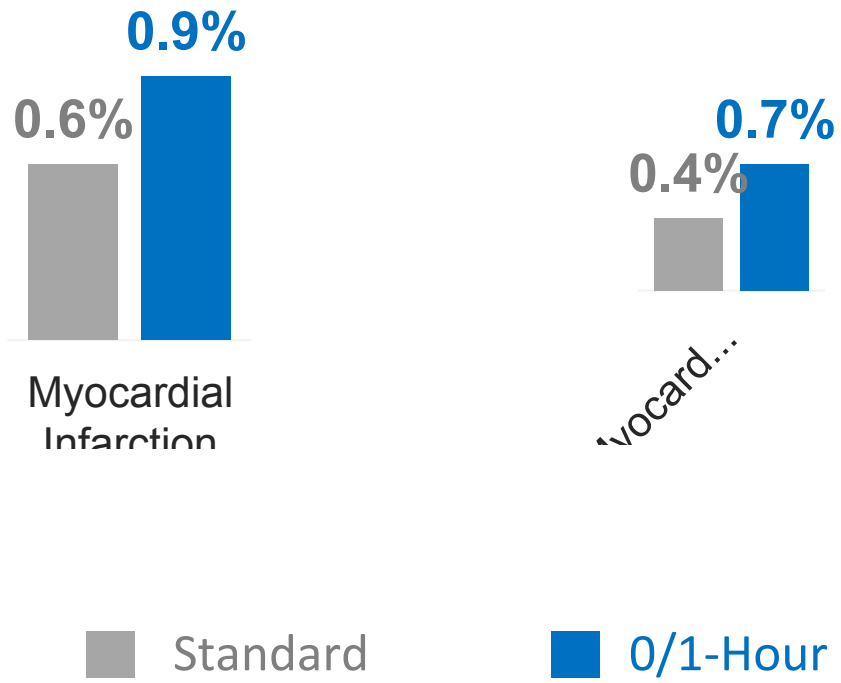
CARDIAC TESTS WITHIN 30 DAYS

≤29 ng/L Troponin T

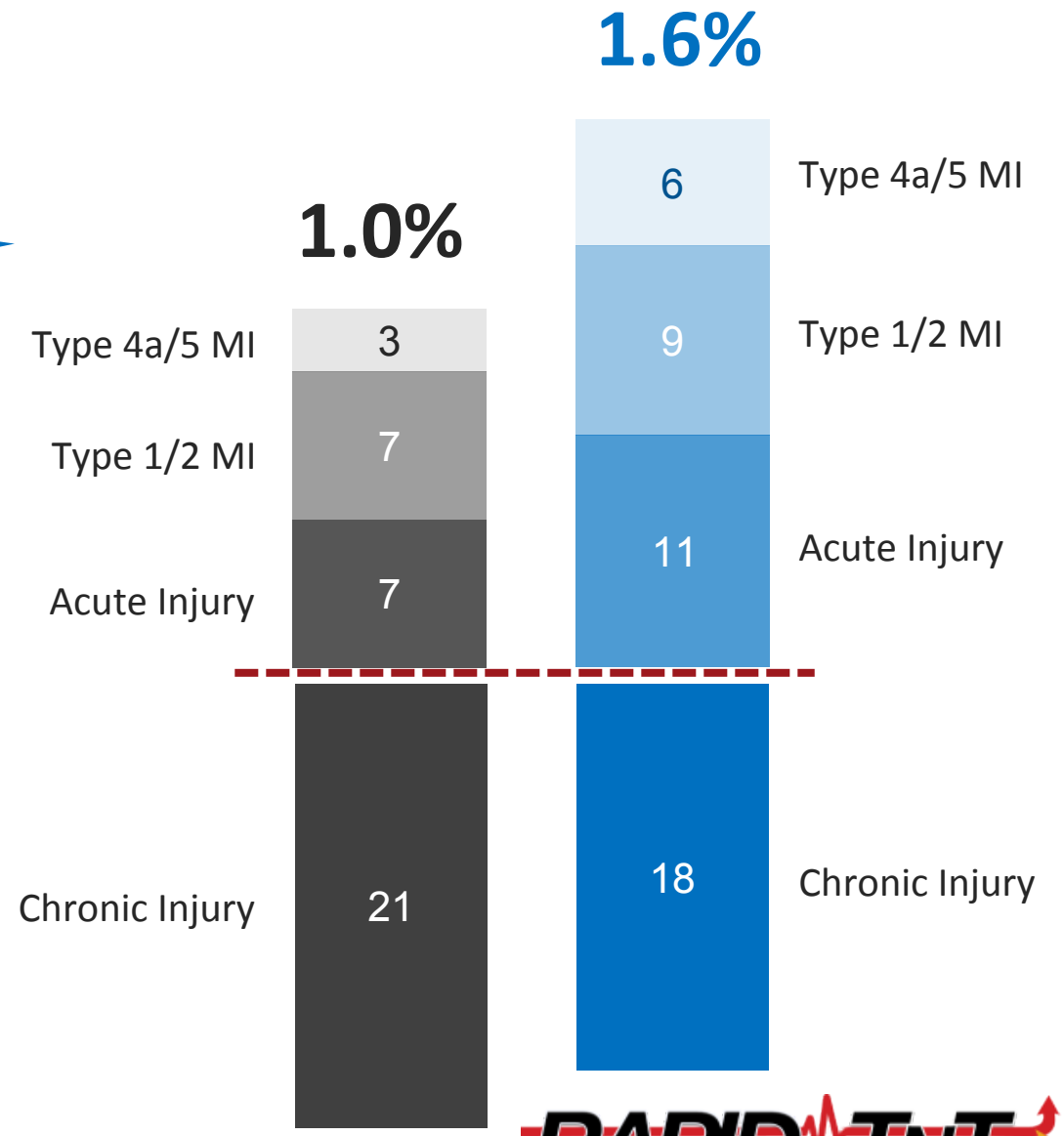


MYOCARDIAL INFARCTION AND INJURY

All patients



p = 0.004



RAPID TnT

CONCLUSIONS

- Patients classified as “Rule-out MI” are **safe for early discharge** and have low rate of death or MI within 30 days supporting the **routine implementation of a 0/1-hour hs-cTnT protocol**
- Implementing high-sensitivity troponin in routine practice **does not appear to “improve” the diagnosis of MI**, although the impact on late outcomes and cost-effectiveness await the 12-month analysis
- However, use of **invasive coronary investigation is increased** among patients with **newly identified low-concentration** troponin elevations and strategies to mitigate associated cardiac injury may require further refinements in acute coronary syndrome care.

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