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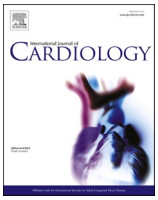

# Impacts of high sensitivity troponin T reporting on care and outcomes in clinical practice: Interactions between low troponin concentrations and participant sex within two randomized clinical trials

Kristina Lambrakis [a,b,*], Ehsan Khan [a,b], Anke van den Merkhof [a,e], Cynthia Papendick [b,c], Anthony Chuang [a,b], Yuze Zhai [a], Joanne Eng-Frost [b], Simon Rocheleau [b], Sam J. Lehman [a,b], Andrew Blyth [a,b], Tom Briffa [f], Stephen Quinn [j], John K. French [d], Louise Cullen [g,h,i], Derek P. Chew [a,b]

[a] College of Medicine & Public Health, Flinders University of South Australia, Adelaide, Australia
[b] South Australian Department of Health, Adelaide, Australia
[c] School of Medicine, University of Adelaide, Adelaide, Australia
[d] Department of Cardiology, Liverpool Hospital, University of New South Wales, Sydney, Australia
[e] Faculty of Medical Sciences, University of Groningen, the Netherlands
[f] School of Population and Global Health, University of Western Australia, Perth, Australia
[g] Emergency and Trauma Centre, Royal Brisbane and Women's Hospital, Brisbane, Australia
[h] School of Public Health, Queensland University of Technology, Brisbane, Australia
[i] School of Medicine, University of Queensland, Brisbane, Australia
[j] Department of Statistics, Data Science and Epidemiology, Swinburne University of Technology, Melbourne, Australia

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ABSTRACT

*Background:* The impacts of high sensitivity cardiac troponin (hs-cTn) reporting on downstream interventions amongst suspected acute coronary syndrome (ACS) in the emergency department (ED), especially amongst those with newly identified hs-cTn elevations and in consideration of well-established sex-related disparities, has not been critically evaluated to date. This investigation explores the impact of hs-cTnT reporting on care and outcomes, particularly by participant sex.

*Methods:* Two similarly ED-based randomized controlled trials conducted between July 2011 to March 2013 ($n$ = 1988) and August 2015 to April 2019 ($n$ = 3378) were comparatively evaluated. Clinical outcomes were adjudicated to the Fourth Universal Definition of MI. Changes in practice were assessed at 30 days, and death or MI were explored to 12 months.

*Results:* The HS-Troponin study demonstrated no difference in death or MI with unmasking amongst those with hs-cTnT <30 ng/L, whereas the RAPID TnT study demonstrated a significantly higher rate. In RAPID TnT, there was significant increase in death or MI associated with unmasking for females with hs-cTnT <30 ng/L (masked: 11[1.5%], unmasked: 25[3.4%],HR: 2.27,95%C.I.:1.87–2.77,$P$ < 0.001). Less cardiac stress testing with unmasking amongst those <30 ng/L was observed in males in both studies, which was significant in RAPID TnT (masked: 92[12.0%], unmasked: 55[7.0%], $P$ = 0.008). In RAPID TnT, significantly higher rates of angiography in males were observed with unmasking, with no such changes amongst females <30 ng/L (masked: 28[3.7%], unmasked: 51[6.5%],$P$ = 0.01).

*Conclusion:* Compared with males, there were no evident impacts on downstream practices for females with unmasking in RAPID TnT, likely representing missed opportunities to reduce late death or MI.

* Corresponding author at: Flinders University, Flinders Drive, Bedford Park, South Australia 5042, Australia.
*E-mail address:* Kristina.Lambrakis@flinders.edu.au (K. Lambrakis).

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## 1. Introduction

Cardiac troponin has long been the cornerstone of suspected acute coronary syndrome (ACS) evaluation [1]. Advancements in troponin assays over time have led to the development of assays which can now accurately detect very low levels of myocardial damage, with regulatory approvals for their clinical use attained in most countries, globally. Accordingly, high sensitivity cardiac troponin (hs-cTn) assays are being increasingly deployed in clinical practice with the promise of enhancing the diagnostic assessment of suspected acute myocardial infarction (MI) [2,3].

Underpinned by the Fourth Universal Definition of MI, hs-cTn had been anticipated to refine risk stratification and provide improved diagnostic discriminatory capability, particularly for the abundant low- and intermediate-risk patients who present to emergency departments (EDs) with suspected ACS [3,4]. Early adopters of hs-cTn assays have implemented rapid serial testing protocols alongside these novel assays in an effort to yield operational benefits such as reduced ED length of stay and hospital admissions in addition to anticipated clinical benefits such as reduced missed MI [5,6]. Whilst the adoption of hs-cTn has provided opportunity for earlier detection of evolving MI as well as the ability to rule-out evolving MI with increased certainty, their ability to improve clinical outcomes has not been demonstrated [7,8].

Utilization of more sensitive troponin assays, which come at the cost of reduced specificity for acute myocardial infarction, may have impacts on downstream cardiac investigations, particularly amongst those with newly identified elevations in troponin. In particular, how the refined discrimination of risk offered by high-sensitivity troponin reporting interacts with the well described sex-based differences in risk perception and investigative practices has not been well evaluated. Utilising two similarly designed and implemented large patient-level randomized controlled trials evaluating the deployment hs-cTnT reporting in clinical practice, we conducted a comparative investigation to explore the impact on patterns of clinical investigation, care and outcomes as well as their interaction with participant sex, principally amongst the cohort with hs-cTnT elevations that were previously undetected.

## 2. Methods

### 2.1. Study design and population

Two randomized clinical trials investigating the unmasked deployment of hs-cTnT reporting in practice were included for this investigation, with ethical approval for this analysis granted by the Southern Adelaide Clinical and Human Research Ethics Committee (ID: 152.19) in Adelaide, Australia. These studies have been described in detail elsewhere, with the key difference between the studies being the unguided unmasking of hs-cTnT in the first study and use of a 0/1-h hs-cTnT repeat testing protocol with suggested management pathways provided in the second [9,10]. In both studies, patients were screened and enrolled in EDs of metropolitan public hospitals in South Australia (SA). Enrolment occurred before the first troponin sample was available to ensure troponin result reporting was consistent with the randomization arm for each participant. Eligibility for both studies required patients to be presenting to the ED with a primary clinical concern of suspected ACS, without definitive evidence of coronary ischemia on ECG. Patients had to be at least 18 years of age and be willing to give written informed consent to participate. They were not eligible if they required permanent dialysis or where there was a language barrier or comorbidity present where they could not provide informed consent or complete clinical history questionnaires. Those with chest pain or suspected ACS symptoms thought to be secondary to other non-cardiac conditions at initial assessment were also not eligible.

### 2.2. Patient and public involvement

There was no patient and public involvement sought for this retrospective investigation of two randomized controlled trials.

### 2.3. System-level masking of troponin T

Whilst the Roche Diagnostics Elecys 5th generation hs-cTnT assay (LoB: 3n/L, LoD: 5 ng/L, 99th percentile: 14 ng/L) was implemented in all SA metropolitan public hospitals in July 2011, troponin T reporting in clinical practice remained aligned with the 4th generation assay (i.e. upper reference range: 30 ng/L) and therefore clinicians remained blinded in practice to troponin results <30 ng/L. As such, robust investigations of care and outcomes associated the release of hs-cTnT results below 30 ng/L in the health system were able to be conducted.

### 2.4. Study protocols

The first hs-cTnT study, referred to henceforth as HS-Troponin, was conducted in 5 metropolitan public hospitals from July 2011 to March 2013, enrolling 1988 participants (Fig. 1). Participants were randomized 1:1 to receive standard masked hs-cTnT results (i.e. blinded to values <30 ng/L) versus unmasked hs-cTnT results (i.e. actual values down to the LoD; 5 ng/L). Repeat test timing in both arms was guided by standard state-wide ACS pathways at that time, which suggested repeat testing at 3- and 6-h, though this timing was ultimately at clinician discretion. Subsequent care was at clinician discretion in both arms, and participants were followed up for 12 months [11] (ACTRN12611000879965).

The second hs-cTnT study, known as RAPID TnT, was conducted in four metropolitan public hospitals from August 2015 to April 2019, enrolling 3378 participants (fig. 2). Participants were randomized 1:1 to receive standard masked hs-cTnT results in a 0/3 h repeat testing protocol with discretionary 6-h testing as per standard state-wide ACS pathways at the time versus unmasked hs-cTnT results within an accelerated 0/1-h repeat testing protocol where participants were classified based on hs-cTnT results and guidance for subsequent care was provided. Classifications were MI 'rule out', 'observe' and 'rule in' as shown in Supplemental Table 1. Whilst recommendations for subsequent care were provided in the 0/1-h hs-cTnT arm, subsequent care ultimately remained at clinician discretion. All participants were followed up for 12 months [12] (ACTRN12615001379505).

### 2.5. Data collection and outcomes measures

Systematic data-linkage of hospital and administrative data, including pathology, in conjunction with medical record review and participant follow up were used to identify downstream cardiac investigations and procedures, health system operational metrics and potential adverse clinical events in both studies. Subsequent cardiac testing including stress testing (ECG, echocardiographic, nuclear, cardiac magnetic resonance imaging), echocardiography, invasive coronary angiography and coronary revascularization were ascertained, in addition to admission and discharge rates, ED length of stay (LOS), total hospital LOS and outpatient health service utilization. In this study, downstream testing and interventions were reported to 30 days, as it is within this timeframe that such assessments would be expected to be conducted for ED presentations consistent with suspected ACS.

The primary endpoint in the HS-Troponin study was the composite of all-cause mortality and ACS (i.e. MI and unstable angina) at 12 months whilst the primary endpoint in the RAPID TnT study was the composite of all-cause mortality and MI at 30 days, with secondary endpoints exploring these outcomes at 12 months. For the purposes of this investigation, the primary endpoint was the composite all-cause mortality and MI at 12 months, however the composite of all-cause mortality and ACS was also assessed. New or re-current MI was defined as a rise and/or

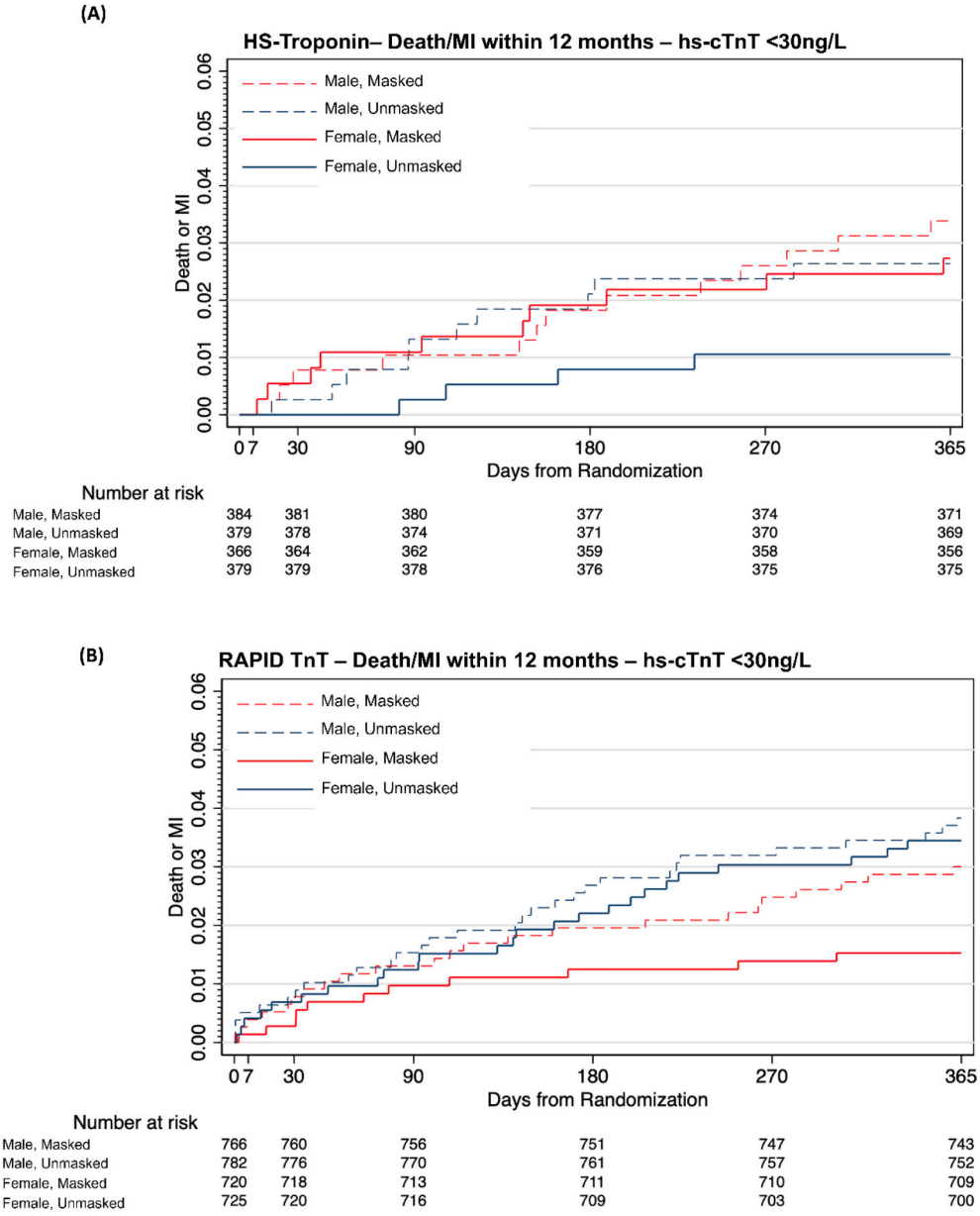


**Fig. 1.** 12-Month Kaplan Meier Event Survival Curves for (a) death or MI in HS-Troponin amongst those with hs-cTnT <30 ng/L and (b) death or MI in RAPID TnT amongst those with hs-cTnT <30 ng/L.

fall in cardiac troponin in addition to at least one qualifying criterion of acute myocardial ischemia as defined by the Fourth Universal Definition of MI [4]. Where an MI was diagnosed within the first 12 h of the index presentation (i.e. enrolling presentation) and the participant remained in hospital, this was not included as endpoint as it was considered a presenting MI. If a participant was discharged from hospital and re-presented within 12 h however, this was considered an endpoint as it reflected a missed MI. Key secondary endpoints included individual components of the primary endpoint, composite of all-cause mortality and ACS (i.e. including unstable angina), cardiovascular mortality, acute and chronic myocardial injury as well as non-coronary cardiovascular rehospitalization, specifically heart failure, atrial and ventricular arrhythmias, cerebrovascular and peripheral vascular events.

### 2.6. Clinical adjudication

Clinical outcomes were originally adjudicated in both studies by clinical event committees (CECs) consisting of a team of independent cardiologists led by a senior cardiologist. Each case was adjudicated independently by two adjudicators according to a CEC charter which defined criteria to be met for a diagnosis. Agreement by both clinical adjudicators on the diagnosis was considered final. Where the diagnosis differed between the clinical adjudicators, the case was provided to a third adjudicator or taken to a CEC meeting where disagreements were settled by the majority. Importantly, given the HS-Troponin study predated the Fourth Universal Definition of MI, all index admissions and re-presentations with documented troponin elevations were re-adjudicated using these criteria to ensure consistency. For the re-adjudication of the HS-Troponin study to the latest iteration of the Universal Definition of MI, clinical experts utilized the same definition which was used in the RAPID TnT to ensure outcomes were evaluated equivalently. No sex-specific hs-cTnT thresholds were used. This re-adjudication process remained blinded to randomized allocation. Index presentations were previously adjudicated in the RAPID TnT study. For the purposes of this investigation, the index presentations in the HS-Troponin study were also retrospectively adjudicated, with oversight from a senior

cardiologist. Index events were clinically adjudicated into diagnostic classifications of type 1 MI, type 2 MI, acute myocardial injury and chronic myocardial injury as per the Fourth Universal Definition of MI in addition to 'other cardiac' which was defined by a troponin rise which was clearly due to an alternative cardiac diagnosis such as arrhythmia or heart failure (not included in myocardial injury diagnostic classification), 'chest pain' which was defined as chest pain without a troponin rise and no distinguishable alternative diagnosis, as well as 'non-cardiac' which was defined as a presentation with no elevation in troponin and a clear alternative non-cardiac diagnosis.

### 2.7. Statistical analysis

Baseline characteristics, investigations within 30 days, prescription of discharge medication and outcomes to 12 months are presented by enrolling study, masked/unmasked study arm, initial troponin level < 30 ng/L and by participant sex. These characteristics are reported as medians (interquartile ranges) for continuous variables and count (%) for categorical variables and were compared with Kruskal-Wallis testing and Chi -squared testing respectively. To assess the validity of pooling these studies, the interaction between the randomization to unmasking, the enrolling study, and 12-month death or MI was examined in the overall cohort and those with troponin concentrations <30 ng/L using a Cox proportional hazards model. Using logistic regression, further interactions between enrolling study, unmasking by sex were performed to explore possible differences in clinical practice patterns by participant sex in the two studies. Kaplan-Meier event curves were plotted by study and by sex, in the overall population and those with an initial troponin level < 30 ng/L. All analyses were undertaken using STATA 17 (College Station, TX) and a $p$ value of <0.05 was considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics

Cumulatively, there were a total of 5207 participants between the two studies at 12 months in consideration of those who withdrew, with 2596 in the standard masked hs-cTnT arm and 2611 in the unmasked hs-cTnT arm. Of those, 4501 participants had index hs-cTnT results <30 ng/L, with 2236 in masked arm and 2265 in the unmasked arm. Upon analysis of the randomized allocation, the primary endpoint suggested a differing effect of unmasking by enrolling study in the overall population ($P_{interaction} = 0.082$) and those with hs-cTnT <30 ng/L ($P_{interaction} = 0.006$), therefore the studies are not pooled but presented comparatively.

In the HS-Troponin study, there were a total of 1937 participants enrolled with a median age of 61 years (interquartile range [IQR]: 49–74 years) and 46.3% of participants were female. In the RAPID TnT study, there were a total of 3270 participants enrolled with a median age of 59 years (IQR:49–71 years) and 46.8% of participants were female. There were 1508 and 2993 participants with hs-cTnT results <30 ng/L in HS-Troponin and RAPID TnT, respectively.

Comparing HS-Troponin with RAPID TnT amongst all participants, differences in baseline characteristics were predominantly in cardiovascular risk factors and prior cardiovascular history, with a higher median HEART score of 4 (IQR:2–5). Those in the RAPID TnT study however had higher rates of smoking, family history of coronary artery disease (CAD) and known CAD with an overall HEART score of 3 (IQR:2–4) as shown in Supplemental Table 2. When exploring baseline characteristics by participant sex, males in the HS-Troponin study had a higher prevalence of diabetes, hyperlipidemia, smoking, known CAD, prior MI, prior heart failure, prior coronary revascularization in addition to poorer renal function and a higher maximum hs-cTnT concentration however median HEART score was similar (males: 4, IQR:3–5; females: 4, IQR:2–5). Similar characteristics were observed in males compared to females in the RAPID TnT study, with a median HEART score of 3 for both males (IQR:2–4) and females (IQR:2–4). Few differences were observed in each study between masked and unmasked cohorts within sex-specific groups (Table 1). The rate of Type 1 MI diagnosed at index presentation was higher in the RAPID TnT study (HS-Troponin: 2.3% vs RAPID TnT: 3.8%, $P = 0.003$). There was no difference in the rate of diagnosis of index Type 1 associated with the unmasking of troponin results observed in either study. While women had a lower rate of Type 1 MI diagnosed at admission, (males: 4.5% vs females: 1.7%, $P < 0.001$), unmasking of troponin results did not significantly change the diagnosis of Type 1 MI amongst men or women in either study.

### 3.2. Clinical outcomes

In the HS-Troponin study, clinical outcomes at 12 months amongst all participants were not different between masked and unmasked hs-cTnT arms, with numerically lower rates of all outcomes including the composite of death or MI in the unmasked arm, aside from cardiovascular re-hospitalization (Supplemental Table 3). Conversely, whilst 12-month event rates were also not different between masked and unmasked arms in the RAPID TnT study, there were slightly higher rates of all outcomes including the composite of death or MI in the unmasked arm (Supplemental Fig. 3). These observations persist when confining the analyses to those with hs-cTnT concentrations <30 ng/L, with the HS-Troponin study demonstrating numerically lower rates of death or MI with unmasking whilst the RAPID TnT study demonstrated a significantly higher rate of death or MI with unmasking (masked: 34 [2.3%], unmasked: 55 [3.6%], hazard ratio [HR]:1.60, 95% confidence interval [C.I.]:1.21–2.12, $P = 0.001$) (Table 2). When exploring outcomes by participant sex in the HS-Troponin study, particularly amongst those with a hs-cTnT concentration < 30 ng/L, males had higher rates of death or MI overall compared to females, with unmasking of hs-cTnT associated with a no difference in outcomes. In the RAPID TnT study however, higher rates of death or MI were seen overall, with females having a significant increase in death or MI associated with unmasking (masked: 11 [1.5%], unmasked: 25 [3.4%], HR: 2.27, 95% C.I.:1.87–2.77, $P < 0.001$) (Fig. 3). This association persisted after adjusting for GRACE score captured at baseline (HRadj for unmasking 2.25 95%C.I.:1.84–2.76,P < 0.001).

### 3.3. Downstream cardiac investigations and procedures

Within the HS-Troponin study, unmasking appears to have no impact on whether participants were discharged directly from the ED amongst all enrolled participants and those with hs-cTnT <30 ng/L. In the RAPID TnT study, given the clinical recommendations, unmasking was associated with increased rates of direct discharge from ED at index presentation amongst all enrolled participants and those with hs-cTnT <30 ng/L (masked: 511 [34.4%], unmasked: 723 [48.0%], $P < 0.001$) (Supplemental Table 4). When exploring by participant sex, amongst all participants in the HS-Troponin study there was no difference in ED discharge rates, however when confining to hs-cTnT <30 ng/L, greater rate of discharge directly from ED was observed in males (masked: 175 [45.6%], unmasked: 202 [53.3%], $P = 0.033$) which was not observed in females. Amongst those with hs-cTnT <30 ng/L in the RAPID TnT study however, females were just as likely discharged from ED (masked: 242 [33.6%], unmasked: 363 [50.1%], $P < 0.001$) compared to males (masked: 269 [35.1%], unmasked: 360 [46.0%], P < 0.001)($P_{interaction} = 0.129$). Investigation patterns within 30 days from enrolment in the HS-Troponin study was similar between masked and unmasked arms, whereas in RAPID TnT a numerical decrease in functional cardiac testing was observed with unmasking. Amongst those with hs-cTnT concentrations <30 ng/L, a significant decrease in functional cardiac testing as well as a significant increase in coronary angiography and coronary revascularization driven by PCI with unmasking was observed in the RAPID TnT study, that was not seen with the HS-Troponin study

**Table 1**
Baseline characteristics disaggregated by study, randomized arm and participant sex amongst those with hs-cTnT <30 ng/L.

| Baseline Characteristics < 30 ng/L | HS-Troponin ($n$ = 1508) | | RAPID TnT ($n$ = 2993) | |
|---|---|---|---|---|
| Randomization arm | Masked | Unmasked | Masked | Unmasked |
| Total number, n | 750 | 758 | 1486 | 1507 |
| Females | 366 | 379 | 720 | 725 |
| Males | 384 | 379 | 766 | 782 |
| Median age, years (IQR) | 58.8 (47.3, 71.7)* | 59.7 (47.6, 71.4) | 57.8 (48.0, 70.3) | 58.0 (47.9, 68.2) |
| Females | 61.0 (49.4, 74.6) | 60.4 (48.3, 74.5) | 59.3 (49.5, 71.7) | 58.4 (48.8, 69.8) |
| Males | 57.3 (44.7, 68.5)* | 58.2 (45.1, 69.5) | 56.2 (46.4, 68.4) | 57.5 (47.3, 66.6) |
| Known hypertension, no. (%) | 372 (49.6%) | 368 (48.5%) | 280 (18.8%) | 260 (17.3%) |
| Females | 182 (49.7%) | 185 (48.8%) | 133 (18.5%) | 130 (17.9%) |
| Males | 190 (49.5%) | 183 (48.3%) | 147 (19.2%) | 130 (16.6%) |
| Known diabetes mellitus, no. (%) | 109 (14.5%) | 126 (16.6%) | 238 (16.0%) | 213 (14.1%) |
| Females | 57 (15.6%) | 65 (17.2%) | 116 (16.1%) | 94 (13.0%) |
| Males | 52 (13.5%) | 61 (16.1%) | 122 (15.9%) | 119 (15.2%) |
| Known hyperlipidemia, no. (%) | 370 (49.3%) | 375 (49.5%) | 635 (42.7%) | 642 (42.6%) |
| Females | 191 (52.2%) | 178 (47.0%) | 286 (39.7%) | 295 (40.7%) |
| Males | 179 (46.6%) | 197 (52.0%) | 349 (45.6%) | 347 (44.4%) |
| Current smoker, no. (%) | 140 (18.7%) | 146 (19.3%) | 525 (35.3%) | 510 (33.8%) |
| Females | 59 (16.1%) | 52 (13.7%) | 217 (30.1%) | 211 (29.1%) |
| Males | 81 (21.1%) | 94 (24.8%) | 308 (40.2%) | 299 (38.2%) |
| Family history of coronary artery disease, no. (%) | 414 (55.2%) | 400 (52.8%) | 860 (58.9%) | 909 (61.2%) |
| Females | 218 (59.6%) | 211 (55.7%) | 436 (61.8%) | 462 (64.7%) |
| Males | 196 (51.0%) | 189 (49.9%) | 424 (56.1%) | 447 (58.0%) |
| Known coronary artery disease, no. (%) | 86 (14.0%) | 106 (16.6%) | 405 (27.3%) | 392 (26.0%) |
| Females | 32 (10.5%) | 39 (12.3%) | 169 (23.5%) | 153 (21.1%) |
| Males | 54 (17.4%) | 67 (20.9%) | 236 (30.8%) | 239 (30.6%) |
| Prior myocardial infarction, no. (%) | 59 (9.6%) | 67 (10.5%) | 132 (8.9%) | 137 (9.1%) |
| Females | 22 (7.2%) | 26 (8.2%) | 44 (6.1%) | 40 (5.5%) |
| Males | 37 (11.9%) | 41 (12.8%) | 88 (11.5%) | 97 (12.4%) |
| Prior heart failure, no. (%) | 42 (6.8%) | 40 (6.3%) | 71 (4.8%) | 51 (3.4%) |
| Females | 20 (6.5%) | 17 (5.3%) | 33 (4.6%) | 32 (4.4%) |
| Males | 22 (7.1%) | 23 (7.2%) | 38 (5.0%) | 19 (2.4%) |
| Prior atrial fibrillation, no. (%) | 64 (10.4%) | 81 (12.7%) | 129 (8.7%) | 104 (6.9%) |
| Females | 37 (12.1%) | 42 (13.2%) | 54 (7.5%) | 48 (6.6%) |
| Males | 27 (8.7%) | 39 (12.1%) | 75 (9.8%) | 56 (7.2%) |
| Prior chronic obstructive pulmonary disease, no. (%) | 62 (8.3%) | 68 (9.0%) | 55 (3.7%) | 59 (3.9%) |
| Females | 30 (8.2%) | 41 (10.8%) | 25 (3.5%) | 39 (5.4%) |
| Males | 32 (8.4%) | 27 (7.1%) | 30 (3.9%) | 20 (2.6%) |
| Prior stroke, no. (%) | 15 (2.0%) | 12 (1.6%) | 43 (2.9%) | 42 (2.8%) |
| Females | 8 (2.2%) | 3 (0.8%) | 19 (2.6%) | 21 (2.9%) |
| Males | 7 (1.8%) | 9 (2.4%) | 24 (3.1%) | 21 (2.7%) |
| Prior coronary artery bypass grafting, no. (%) | 23 (3.7%) | 33 (5.2%) | 32 (2.2%) | 41 (2.7%) |
| Females | 8 (2.6%) | 9 (2.8%) | 19 (2.6%) | 21 (2.9%) |
| Males | 15 (4.8%) | 24 (7.5%) | 24 (3.1%) | 21 (2.7%) |
| Prior percutaneous coronary intervention, no. (%) | 48 (7.8%) | 60 (9.4%) | 118 (7.9%) | 145 (9.6%) |
| Females | 15 (4.9%) | 23 (7.2%) | 32 (4.4%) | 40 (5.5%) |
| Males | 33 (10.6%) | 37 (11.5%) | 86 (11.2%) | 105 (13.4%) |
| Killip class II or above, no. (%) | 50 (6.7%) | 67 (8.8%) | 39 (2.6%) | 21 (1.4%) |
| Females | 26 (7.1%) | 32 (8.4%) | 20 (2.8%) | 13 (1.8%) |
| Males | 24 (6.2%) | 35 (9.2%) | 19 (2.5%) | 8 (1.0%) |
| Median eGFR, mL/min/1.73$^2$ (IQR) | 85.5 (67.7, 103.2) ‡ | 85.7 (65.4, 103.3) ‡‡ | 87.3 (73.4, 98.9) ‡‡‡ | 87.1 (73.9, 99.0) † |
| Females | 102.4 (89.3, 112.3)** | 101.2 (87.8, 111.3)^ | 85.1 (72.0, 97.5)*** | 86.6 (72.0, 99.9)^ |
| Males | 72.7 (58.9, 83.2)*** | 69.9 (57.4, 83.2)** | 89.1 (75.6, 99.9)^^ | 87.5 (74.9, 98.8)^^^ |
| Median maximum troponin T, ng/L (IQR) | 6.0 (3.0, 10.0) | 5.5 (3.0, 11.0) | 6.0 (4.0, 11.0) | 6.0 (4.0, 10.0) |
| Females | 5.0 (3.0, 10.0) | 4.0 (3.0, 10.0) | 5.0 (3.0, 9.0) | 5.0 (3.0, 9.0) |
| Males | 7.0 (3.0, 11.0) | 7.0 (3.0, 12.0) | 8.0 (5.0, 12.0) | 7.0 (5.0, 12.0) |
| Median HEART score (IQR) | 3.0 (2.0, 4.0)* | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) |
| Females | 3.5 (2.0, 5.0) | 3.0 (2.0, 5.0) | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) |
| Males | 3.0 (2.0, 4.0)* | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) | 3.0 (2.0, 4.0) |

* = missing data for n = 1, ** = missing data for $n$ = 8, *** = missing data for 4; ^ = missing data for 9, ^^ = missing data for 10, ^^^ = missing data for 7, ‡ = missing data for 12, ‡‡ = missing data for 17, ‡‡‡ = missing data for 14, † = missing data for 16.

(Table 3). Exploring the change in investigational practice amongst patients with hs-cTnT <30 ng/L, both studies observed a lower rate of stress testing amongst males with unmasking, with this difference being statistically significant in the RAPID TnT study. Similarly, there was an increase in coronary angiography amongst male participants, that was statistically significant in the RAPID TnT study. In contrast, there was no change in practice amongst female participants in RAPID TnT as a result of unmasking. In the HS-Troponin study, there were no changes in risk-modifying pharmacotherapies at ED discharge amongst all participants with unmasking, nor amongst those with hs-cTnT <30 ng/L. Similar findings were observed in these cohorts within the RAPID TnT study.

## 4. Discussion

This comparative analysis of two randomized controlled trials which prospectively explored the impacts of implementing hs-cTnT reporting in the ED suggests hs-cTnT, particularly within a guided 0/1-h protocol in RAPID TnT, has an impact on subsequent clinical management of suspected ACS patients. This shift in practice, however, did not lead to improved clinical outcomes in either study. While no benefit was observed in the HS-Troponin study, worse outcomes with unmasking were observed in the RAPID TnT study amongst those with low level

**Table 2**
Clinical outcomes disaggregated by study, randomized arm and participant sex amongst those with hs-cTnT <30 ng/L.

| Clinical Outcomes - <30 ng/L | HS-Troponin (*n*=1508) | | | | RAPID TnT (*n*=2993) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Randomization arm | Masked | Unmasked | P Value | HR (95% CI) | Masked | Unmasked | P Value | HR (95% CI) | Interaction P |
| Total number, n | 750 | 758 | – | – | 1486 | 1507 | – | – | – |
| Females | 366 | 379 | – | – | 720 | 725 | – | – | – |
| Males | 384 | 379 | – | – | 766 | 782 | – | – | – |
| All-cause mortality & myocardial infarction, no. (%) | 23 (3.1%) | 14 (1.8%) | 0.146 | 0.60 (0.30–1.20) | 34 (2.3%) | 55 (3.6%) | 0.001 | 1.60 (1.21–2.12) | 0.006 |
| Females | 10 (2.7%) | 4 (1.1%) | <0.001 | 0.38 (0.24–0.61) | 11 (1.5%) | 25 (3.4%) | <0.001 | 2.27 (1.87–2.77) | <0.001 |
| Males | 13 (3.4%) | 10 (2.6%) | 0.645 | 0.78 (0.27–2.25) | 23 (3.0%) | 30 (3.8%) | 0.174 | 1.28 (0.90–1.83) | 0.356 |
| All-cause mortality & acute coronary syndrome, no. (%) | 30 (4.0%) | 21 (2.8%) | 0.177 | 0.69 (0.40–1.18) | 44 (3.0%) | 70 (4.6%) | <0.001 | 1.58 (1.30–1.92) | 0.003 |
| Females | 10 (2.7%) | 5 (1.3%) | 0.071 | 0.48 (0.22–1.07) | 14 (1.9%) | 30 (4.1%) | <0.001 | 2.15 (1.79–2.58) | <0.001 |
| Males | 20 (5.2%) | 16 (4.2%) | 0.519 | 0.81 (0.42–1.55) | 30 (3.9%) | 40 (5.1%) | 0.074 | 1.31 (0.97–1.77) | 0.158 |
| All-cause mortality, no. (%) | 18 (2.4%) | 8 (1.1%) | 0.115 | 0.44 (0.16–1.22) | 12 (0.8%) | 25 (1.7%) | 0.003 | 2.06 (1.27–3.34) | 0.005 |
| Females | 8 (2.2%) | 2 (0.5%) | <0.001 | 0.24 (0.13–0.46) | 5 (0.7%) | 11 (1.5%) | 0.012 | 2.19 (1.19–4.04) | <0.001 |
| Males | 10 (2.6%) | 6 (1.6%) | 0.576 | 0.61 (0.11–3.49) | 7 (0.9%) | 14 (1.8%) | 0.091 | 1.98 (0.90–4.32) | 0.203 |
| Myocardial infarction, no. (%) | 5 (0.7%) | 7 (0.9%) | 0.629 | 1.39 (0.37–5.22) | 23 (1.5%) | 32 (2.1%) | 0.001 | 1.38 (1.14–1.66) | 0.992 |
| Females | 2 (0.5%) | 2 (0.5%) | 0.966 | 0.97 (0.20–4.74) | 7 (1.0%) | 14 (1.9%) | 0.119 | 2.00 (0.84–4.75) | 0.404 |
| Males | 3 (0.8%) | 5 (1.3%) | 0.568 | 1.69 (0.28–10.30) | 16 (2.1%) | 18 (2.3%) | 0.586 | 1.10 (0.77–1.58) | 0.631 |
| Acute myocardial injury, no. (%) | 10 (1.3%) | 10 (1.3%) | 0.954 | 0.99* (0.67–1.45) | 17 (1.1%) | 19 (1.3%) | 0.376 | 1.10 (0.89–1.37) | 0.608 |
| Females | 8 (2.2%) | 5 (1.3%) | 0.129 | 0.60 (0.31–1.16) | 3 (0.4%) | 7 (1.0%) | <0.001 | 2.32 (1.45–3.73) | 0.001 |
| Males | 2 (0.5%) | 5 (1.3%) | 0.106 | 2.54 (0.82–7.88) | 14 (1.8%) | 12 (1.5%) | 0.270 | 0.84 (0.61–1.15) | 0.05 |
| Chronic myocardial injury, no. (%) | 61 (8.1%) | 78 (10.3%) | 0.267 | 1.28* (0.83–1.98) | 95 (6.4%) | 98 (6.5%) | 0.905 | 1.02 (0.76–1.36) | 0.363 |
| Females | 29 (7.9%) | 43 (11.3%) | 0.014 | 1.45 (1.08–1.96) | 31 (4.3%) | 42 (5.8%) | 0.081 | 1.36 (0.96–1.91) | 0.737 |
| Males | 32 (8.3%) | 35 (9.2%) | 0.772 | 1.12 (0.52–2.39) | 64 (8.4%) | 56 (7.2%) | 0.298 | 0.85 (0.63–1.15) | 0.489 |
| Cardiovascular re-presentation to hospital, no. (%) | 41 (5.5%) | 57 (7.5%) | 0.327 | 1.40 (0.72–2.74) | 46 (3.1%) | 48 (3.2%) | 0.894 | 1.03 (0.66–1.62) | 0.431 |
| Females | 25 (6.8%) | 29 (7.7%) | 0.748 | 1.14 (0.52–2.46) | 17 (2.4%) | 18 (2.5%) | 0.818 | 1.06 (0.67–1.67) | 0.867 |
| Males | 16 (4.2%) | 28 (7.4%) | 0.145 | 1.81 (0.81–4.02) | 29 (3.8%) | 30 (3.8%) | 0.966 | 1.01 (0.52–1.97) | 0.242 |

troponin elevations (i.e., <30 ng/L). This excess risk appears to be borne by female participants in this study. Examination of the changes in practice patterns between the two studies by participant sex suggested no observable impact on investigation or prescribing patterns in female participants, in contrast to clear reductions in functional testing and increase in angiography in men. While this shift in practice in response to unmasking hs-cTnT in men was not associated with reductions in 12-month death or MI, a lack of change in practice and high rates of discharge amongst female participants may indicate missed opportunities to reduce late death or MI. Optimal investigative strategies for patients with low concentration troponin elevations needs further refinement with careful consideration of patient sex.

Although no sex-specific hs-cTnT thresholds or clinical pathways were utilized in either of these studies and median HEART score were the same between females and males within each study, the higher incidence of death or MI amongst women with low level hs-cTnT elevations in the RAPID TnT study may be, in part, explained by the observed sex-specific changes in practice associated with unmasking. With clinical management ultimately remaining at clinician discretion, it is possible that unconscious clinician bias contributed to sex-specific differences in practice, where women received less subsequent cardiac investigations than men who, although received less functional cardiac testing, underwent coronary angiography more frequently when hs-cTnT was unmasked. Perceived risk in women has been demonstrated as often underestimated, which may have contributed to differences in practice and subsequent clinical outcomes observed in this investigation and may suggest a need for a targeted approach to risk assessment and communication in women [13,14].

Overall, this study supports previous findings that confirm the safety of deploying hs-cTn assays into clinical practice, with no significant differences observed in clinical outcomes by 12 months [7,11,15]. The practice changes in downstream cardiac testing observed in this study at 30 days, particularly observed in men, reinforces other observational studies which also noted reductions in functional testing and increases in angiography and PCI [16], however are inconsistent with other hs-cTn implementation investigations which observed either no changes or decreases in coronary angiography and revascularization alongside decreases in functional testing [17–19]. Few studies have explored the impact of participant sex on subsequent cardiac testing in the context of hs-cTnT implementation, however the sex-based differences in practice and the overall lower rates of risk-modifying pharmacotherapies in women at ED discharge is consistent with existing evidence suggesting

**Table 3**
Downstream cardiac testing disaggregated by study, randomized arm and participant sex amongst those with hs-cTnT <30 ng/L.

| Downstream testing - <30 ng/L | HS-Troponin (*n*=1937) | | | RAPID TnT (*n*=3270) | | | |
|---|---|---|---|---|---|---|---|
| Randomization arm | Masked | Unmasked | P Value | Masked | Unmasked | P Value | Interaction P |
| Total number, n | 750 | 758 | – | 1486 | 1507 | – | – |
| Females | 366 | 379 | – | 720 | 725 | – | – |
| Males | 384 | 379 | – | 766 | 782 | – | – |
| Discharged from ED, no. (%) | 360 (48.0%) | 378 (49.9%) | 0.47 | 511 (34.4%) | 723 (48.0%) | <0.001 | <0.001 |
| Females | 185 (50.5%) | 176 (46.4%) | 0.26 | 242 (33.6%) | 363 (50.1%) | <0.001 | <0.001 |
| Males | 175 (45.6%) | 202 (53.3%) | 0.033 | 269 (35.1%) | 360 (46.0%) | <0.001 | 0.416 |
| Cardiac stress test, no. (%) | 179 (23.9%) | 162 (21.4%) | 0.25 | 150 (10.1%) | 106 (7.0%) | 0.003 | 0.164 |
| Females | 81 (22.1%) | 86 (22.7%) | 0.85 | 58 (8.1%) | 51 (7.0%) | 0.46 | 0.501 |
| Males | 98 (25.5%) | 76 (20.1%) | 0.072 | 92 (12.0%) | 55 (7.0%) | 0.0008 | 0.261 |
| Coronary angiography, no. (%) | 31 (4.1%) | 34 (4.5%) | 0.74 | 47 (3.2%) | 70 (4.6%) | 0.037 | 0.324 |
| Females | 15 (4.1%) | 12 (3.2%) | 0.50 | 19 (2.6%) | 19 (2.6%) | 0.98 | 0.612 |
| Males | 16 (4.2%) | 22 (5.8%) | 0.30 | 28 (3.7%) | 51 (6.5%) | 0.010 | 0.530 |
| Percutaneous coronary intervention, no. (%) | 5 (0.7%) | 7 (0.9%) | 0.57 | 13 (0.9%) | 30 (2.0%) | 0.010 | 0.455 |
| Females | 1 (0.3%) | 3 (0.8%) | 0.33 | 1 (0.1%) | 5 (0.7%) | 0.10 | 0.735 |
| Males | 4 (1.0%) | 4 (1.1%) | 0.99 | 12 (1.6%) | 25 (3.2%) | 0.036 | 0.367 |
| Coronary artery bypass graft, no. (%) | 1 (0.1%) | 2 (0.3%) | 0.57 | 1 (0.1%) | 4 (0.3%) | 0.18 | 0.677 |
| Females | 1 (0.3%) | 0 (0.0%) | 0.31 | 0 (0.0%) | 1 (0.1%) | 0.32 | – |
| Males | 0 (0.0%) | 2 (0.5%) | 0.15 | 1 (0.1%) | 3 (0.4%) | 0.33 | – |
| Coronary revascularization, no. (%) | 6 (0.8%) | 9 (1.2%) | 0.45 | 14 (0.9%) | 34 (2.3%) | 0.004 | 0.430 |
| Females | 2 (0.5%) | 3 (0.8%) | 0.68 | 1 (0.1%) | 6 (0.8%) | 0.059 | 0.317 |
| Males | 4 (1.0%) | 6 (1.6%) | 0.51 | 13 (1.7%) | 28 (3.6%) | 0.021 | 0.641 |
| Discharged on a statin, no. (%) | 278 (37.1%) | 292 (38.5%) | 0.56 | 517 (34.8%) | 519 (34.4%) | 0.84 | 0.555 |
| Females | 128 (35.0%) | 129 (34.0%) | 0.79 | 220 (30.6%) | 196 (27.0%) | 0.14 | 0.499 |
| Males | 150 (39.1%) | 163 (43.0%) | 0.27 | 297 (38.8%) | 323 (41.3%) | 0.31 | 0.749 |
| Discharged on an antiplatelet, no. (%) | 81 (10.8%) | 80 (10.6%) | 0.87 | 135 (9.1%) | 168 (11.1%) | 0.061 | 0.127 |
| Females | 31 (8.5%) | 35 (9.2%) | 0.71 | 50 (6.9%) | 56 (7.7%) | 0.57 | 0.951 |
| Males | 50 (13.1%) | 45 (11.9%) | 0.62 | 85 (11.1%) | 112 (14.3%) | 0.057 | 0.135 |
| Discharged on an ACE inhibitor or ARB, no. (%) | 269 (35.9%) | 259 (34.2%) | 0.49 | 537 (36.1%) | 547 (36.3%) | 0.93 | 0.537 |
| Females | 125 (34.2%) | 124 (32.7%) | 0.68 | 243 (33.8%) | 228 (31.4%) | 0.35 | 0.843 |
| Males | 144 (37.5%) | 135 (35.6%) | 0.59 | 294 (38.4%) | 319 (40.8%) | 0.33 | 0.320 |
| Discharged on a beta-blocker, no. (%) | 159 (21.2%) | 171 (22.6%) | 0.52 | 305 (20.5%) | 312 (20.7%) | 0.90 | 0.656 |
| Females | 63 (17.2%) | 82 (21.6%) | 0.13 | 122 (16.9%) | 113 (15.6%) | 0.48 | 0.102 |
| Males | 96 (25.0%) | 89 (23.5%) | 0.62 | 183 (23.9%) | 199 (25.4%) | 0.48 | 0.419 |

women presenting with suspected ACS receive less guideline-recommended management [20–22].

### 4.1. Study limitations

There are weaknesses in this investigation that necessitate consideration. Although these studies were designed to enroll similar cohorts in similar environments, the interventions differed for each patient-level randomized clinical trial, with RAPID TnT not only providing unmasked hs-cTnT reporting but doing so within in a 0/1-h repeat testing protocol which provided clinicians with MI rule out, rule in and observe recommendations and guidance on subsequent acute care. This may have led to differences in practice between studies, however not within studies. Additionally, as these studies were targeting low to intermediate risk participants, the volume of participants receiving subsequent cardiac investigations and interventions is relatively low with cohorts becoming smaller also when disaggregating by participant sex, therefore conclusions drawn must be carefully considered in light of this.

## 5. Conclusion

The key findings of comparing these two large RCTs investigating the implementation of hs-cTnT are that hs-cTnT reporting does lead to changes in practice, particularly amongst those with low level troponin elevations, however these changes are not associated with improvements in clinical outcomes. This investigation highlights that these shifts in practice appear to be influenced by participant sex, with excess risk of adverse clinical outcomes observed in women despite no differences in baseline risk of men and women. This suggests a need for re-evaluation of downstream cardiac testing, particularly for the newly identified cohort with low level troponin elevations often not due to type 1 MI, and with a specific focus on improving disparate care and outcomes for females. Critically, this investigation demonstrates the needs for clinical decision-masking to evolve alongside clinical innovation, also highlighting the need for well-considered implementation strategies of such advancements in practice.

## Contributions

Study design and development: KL, DPC.
Analysis: DPC.
First Drafting of Manuscript: KL, DPC.
Final Approval of Manuscript: All.

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## Declaration of Competing Interest

KL: None.
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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131396.

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