High-Sensitivity Cardiac Troponin for Risk Assessment in Patients with Chronic Coronary Artery Disease

ORIGINAL ARTICLE

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Abstract

Background: Cardiac troponin is used for risk stratification of patients with acute coronary syndromes, however the role of testing in other settings remains unclear.

Objective: To evaluate whether cardiac troponin testing could enhance risk stratification in patients with chronic coronary artery disease independent of disease severity and conventional risk measures.

Method: In a prospective cohort of consecutive patients with symptoms suggestive of stable angina attending for outpatient coronary angiography, high-sensitivity cardiac troponin I was measured prior to angiography and clinicians blinded to the results. The primary outcome was myocardial infarction or cardiovascular death during follow-up.

Results: In 4,240 patients (66 [59 to 73] years, 33% female), coronary artery disease was identified in 3,888 (92%) who had 255 (6%) primary outcome events during a median follow-up of 2.4 [1.3-3.6] years. In patients with coronary artery disease, troponin concentrations were two-fold higher in those with an event compared to those without (6.7 [3.2-14.2] *versus* 3.3 [1.7-6.6] ng/L, $p<0.001$). Troponin concentrations were associated with the primary outcome after adjusting for cardiovascular risk factors and coronary artery disease severity (adjusted hazard ratio 2.3, 95%CI 1.7-3.0, $\log_{10}$ troponin, $p<0.001$). A troponin concentration >10 ng/L identified patients with a 50% increase in the risk of myocardial infarction or cardiovascular death.

Conclusion: In patients with chronic coronary artery disease, cardiac troponin predicts risk of myocardial infarction or cardiovascular death independent of cardiovascular risk factors and disease severity. Further studies are required to evaluate whether routine testing could inform the selection of high-risk patients for treatment intensification.

Condensed Abstract

The role of troponin testing in the chronic coronary artery disease remains unclear. To evaluate this, we prospectively measured high-sensitivity cardiac troponin I in consecutive outpatients attending for coronary angiography with symptoms of stable angina. In 3,888 patients with coronary artery disease, troponin was associated with myocardial infarction or cardiovascular death after adjusting for disease severity (adjusted HR 2.3, 95%CI 1.7 to 3.0). A troponin concentration >10 ng/L was associated with a 50% higher risk of major adverse events. Studies are required to evaluate whether routine troponin testing in chronic coronary artery disease to guide management would improve outcomes.

Key words: chronic coronary artery disease, cardiac troponin, risk prediction, coronary angiography, myocardial infarction

Introduction

Risk-stratification is recommended in all patients with a diagnosis of chronic coronary artery disease.[1] Investigation with either functional testing or invasive or computed tomography coronary angiography can identify patients at increased risk of future myocardial infarction or cardiovascular death.[2–4] However, more than half of all myocardial infarctions occur in patients without obstructive coronary artery disease who do not have an ischemic substrate required for reliable risk stratification using these methods.[5,6] There are currently no strategies that can readily be applied to all patients with chronic coronary artery disease to objectively quantify risk and guide treatment. Objective tools to support risk stratification are needed to identify those most likely to benefit from further assessment or treatment intensification.

Cardiac troponin is integral to the assessment and diagnosis of patients with possible acute coronary syndromes,[7] and is the only cardiac biomarker recommended for use in clinical practice in this setting.[8–10] However, routine testing of high-sensitivity cardiac troponin is not currently recommended in the assessment of patients with chronic coronary artery disease. Studies have previously demonstrated the prognostic role of troponin in selected cohorts with asymptomatic coronary artery disease or a prior history of acute coronary syndrome.[11–14] However, the role of routine troponin testing in patients with stable angina and objective evidence of coronary artery disease has not been explored. It remains unclear whether testing would enhance risk stratification in this setting independent of conventional measures of cardiovascular risk and disease severity.

We therefore designed the Myocardial Injury in patients referred for Coronary Angiography (MICA) study to prospectively evaluate the role of high-sensitivity cardiac troponin I testing for

the risk stratification of patients with chronic coronary artery disease (ISRCTN trial registration ISRCTN15620297).

Methods

Study design and population

MICA is a prospective cohort study enrolling all consecutive patients referred from six secondary or tertiary care hospitals to the Royal Infirmary of Edinburgh, Scotland, United Kingdom for outpatient coronary angiography to investigate symptoms suggestive of stable angina. To identify all eligible patients, an electronic form was embedded into the electronic health record system. Patients were included if they were permanently resident in Scotland, were not previously enrolled in the study, and had blood samples taken on the same day as the procedure. Patients were excluded if data from the angiogram was incomplete or missing, or they were previously enrolled in the study. Baseline characteristics and past medical history were determined through linkage with the electronic healthcare record, and regional and national registries as previously described.[15,16] ***(Supplementary Methods I and Supplementary Figure S4)*** The study was conducted in accordance with the Declaration of Helsinki, and registered with International Standard Randomized Controlled Trial Number (ISRCTN) 15620297.

Cardiac troponin testing

Venous blood samples were collected prior to coronary angiography on the day of the procedure as part of routine care and cardiac troponin concentrations measured in real-time using plasma that was surplus to clinical requirements with a high-sensitivity cardiac troponin I (hs-cTnI) assay (ARCHITECT$_{STAT}$ High Sensitivity Troponin-I, Abbott, IL). The responsible cardiologist was blinded to the results and clinical care was not directly altered by cardiac troponin testing. This assay has a sex-specific 99th centile upper reference limit of 34 ng/L in men and 16 ng/L in women,[17] an inter-assay coefficient of variation of 10% at 4.7 ng/L, and a limit of detection of 1.1-1.9 ng/L ***(Supplementary Methods II)***.[18–20]

Coronary angiography

Coronary artery disease severity was determined by the attending interventional cardiologist at the time of angiography and recorded prospectively in a clinical reporting database (TOMCAT, Philips, Netherlands). The maximal diameter stenosis was used to define the severity of coronary artery disease in each major epicardial vessel. Obstructive coronary artery disease was defined by convention as a stenosis ≥70% in one or more major epicardial coronary artery or a stenosis ≥50% in the left main stem. Non-obstructive coronary disease was defined in patients with any evidence of atherosclerotic coronary disease without obstructive disease. Chronic coronary artery disease was defined in patients with non-obstructive or obstructive coronary disease, previous myocardial infarction, or previous revascularization. Coronary artery disease severity was evaluated using the hierarchical Duke Prognostic Index, which categorizes coronary artery disease according to extent, location, and stenosis severity.[21] ***(Supplementary Methods I)***

Clinical outcomes

We used national registries to follow-up the study population as previously deescribed,[15,16,22] until an end of study date of 31st August 2021. ***(Supplementary Methods I and Figure S4)*** The primary outcome was a composite of myocardial infarction or cardiovascular death. Secondary outcomes included myocardial infarction, cardiovascular death, non-cardiovascular death, all-cause death, and index coronary revascularization, defined as percutaneous coronary intervention or coronary artery bypass surgery and within 30 days.

Statistical analysis

Baseline characteristics were summarized for the whole population, and for the population stratified by the presence or absence of chronic coronary artery disease, coronary artery disease severity, and by cardiac troponin concentration. ***(Supplemental Methods III)*** Cardiac troponin concentrations were classified as low (<5 ng/L), intermediate (5 ng/L to the sex-specific 99th centile), or high (above the sex-specific 99th centile) based on previous research.[23,24] In a *post-hoc* analysis cardiac troponin concentrations were also stratified by the limit of detection of the assay using a threshold of <2 ng/L.

Multivariable Cox proportional hazard models were constructed to determine cause-specific hazard ratios for the primary outcome per unit increase in cardiac troponin as a continuous variable in patients with chronic coronary artery disease. ***(Supplemental Methods III)*** Cardiac troponin and creatinine concentrations were included as continuous variables after log transformation. We accounted for the competing risk of all-cause mortality by censoring patients at the point of non-cardiovascular death using previously described methods by Austin *et al*.[25]

The cardiac troponin threshold that identifies patients at increased risk was defined as the lowest cardiac troponin concentration associated with a 50% increase in the risk of the primary outcome. This approach was based on clinical consensus rather than prior research or guidelines. This threshold was then applied in an exploratory analysis of the effect of index revascularization on the primary outcome; calculating the incidence rates of the primary outcome per 100 patient-years in patients above and below this threshold, stratified by index revascularization . Statistical analysis was performed using R (Version 4.2.0).

Results

Between July 31, 2016, and July 31, 2021, a total of 4,917 outpatient procedures were performed for the evaluation of symptoms suggestive of stable angina in patients who met the study inclusion criteria. Following the exclusion of patients where angiography data was incomplete (n=220), and those previously enrolled in the study (n=457), a total of 4,240 unique patients met the study inclusion and exclusion criteria ***(Supplementary Figure S1)***. The study ended after a median follow-up period of 2.4 years (interquartile range [IQR] 1.3 to 3.6).

The median age of participants was 66 (IQR 59 to 73) years, and 33% were female ***(Supplemental Table S1)***. The majority had coronary artery disease on angiography (91.7%, n=3,888/4,240). Of these, 32.2% (n=1,251/3,888) had non-obstructive and 67.8% (n=2,637/3,888) had obstructive disease ***(Supplemental Table S2)***.

Cardiac troponin concentrations were low in the majority of patients (3.3 [IQR 1.7 to 6.8] ng/L) but were higher in patients with chronic coronary artery disease compared to those without (3.4 [1.8 – 7.1] *versus* 1.9 [1.0 – 3.8] ng/L, p<0.001) ***(Supplemental Table S1, Figure 1a)***. In the majority of patients with chronic coronary artery disease, troponin concentrations were above the limit of detection (72.0%, 2,799/3,888) ***(Supplemental Table S11)***. Most had either low (64.5% [2,508/3,888], <5 ng/L) or intermediate (31.3% [1,216/3,888]) concentrations with a minority having cardiac troponin concentrations above the sex-specific 99th centile threshold (4.2% [164/3,888]) ***(Table 1).***

During the follow-up period 255 (6.0%) patients had a primary outcome event of which 183 (4.3%) had myocardial infarction and 89 (2.1%) died of cardiovascular disease **(*Table 2*)**. The

primary outcome was more common in patients with chronic coronary artery disease (6.4% [249/3,888]) than in patients without (1.7% [6/352]). Cardiac troponin concentrations were two-fold higher in those with chronic coronary artery disease and a primary outcome event compared to those with disease who did not have an event (6.7 [3.2 to 14.2], *versus* 3.3 [1.7 to 6.6] ng/L, p<0.001) ***(Figure 2b, Supplemental Table S3)***. In patients with chronic coronary artery disease, the incidence rate of the primary outcome was highest in those with troponin concentrations above the sex-specific 99th centile (6.13 events per 100 patient-years) compared to those with intermediate (4.64 events per 100 patient-years) or low (1.58 events per 100 patient-years) concentrations ***(Figure 2, Table 2)***. In a *post-hoc* analysis, patients with troponin concentrations below the limit of detection (28%, 1,089/3,888) were 5-times less likely to have a primary outcome event than those above the 99th centile (2.8% *versus* 13.4%) (***Supplemental Table S12 and Figure S3)***.

As a continuous measure, troponin concentration was associated with the primary outcome in patients with chronic coronary artery disease (case-specific hazard ratio [HR] 3.3, 95% confidence interval [CI] 2.6 to 4.2, p<0.001, $\log_{10}$ hs-cTnI) ***(Supplemental Table S5)***. After adjusting for age and sex, troponin concentration was an independent predictor of the primary outcome (cause-specific adjusted HR [aHR] 3.3, 95%CI 2.6 to 4.4). Cardiac troponin remained an independent predictor of events in a fully adjusted model Including cardiovascular risk factors, heart failure, renal function, and index revascularization (aHR 2.6, 95%CI 1.9 to 3.4) ***(Supplemental Table S5)***. Compared to patients with cardiac troponin concentrations below 5 ng/L, the hazard ratio for myocardial infarction or cardiovascular death reached 1.5 at concentrations of troponin >10 ng/L. (***Figure 3***). This threshold identified 16.7% [651/3,888] of patients with chronic coronary artery disease as at increased risk of myocardial infarction or cardiovascular death, in whom the absolute risk of a major adverse event was 14.1% [92/651]

after a median of 2.4 years follow up. There was no difference in the risk of myocardial infarction or cardiovascular death associated with an increase in cardiac troponin concentration when stratified by sex ***(Supplemental Table S6).***

Coronary revascularization was performed in 47.2% (n=1,833/3,888) of patients with chronic coronary artery disease and most were prescribed lipid lowering (87.1%, n=3,277/3,888) or anti-platelet (81.3%, n=3,161/3,888) therapy ***(Supplemental Table S7)***. There was no difference in the proportion of patients with or without index revascularization who had a primary outcome event [6.2% *versus* 6.7% respectively, p=0.6] ***(Supplementary Table S8)***. In an exploratory analysis, when stratified by troponin concentration above or below a risk stratification threshold of 10 ng/L, patients with a troponin >10 ng/L tended to have fewer outcome events with index revascularization (5.2 events per 100 patient-years) compared to those without index revascularization (7.7 events per 100 patient-years ***(Figure 4, Supplementary Table S9)***. In contrast, the primary outcome did not differ in patients with and without revascularization when the troponin concentration was ≤10 ng/L.

Coronary artery disease severity as defined using the Duke Prognostic Index was also an important predictor of future myocardial infarction or cardiovascular death. Patients with a Duke Prognostic Index ≥5 were three-times more likely to have a primary outcome as compared to patients with the lowest Duke Prognostic Index (3.56 *versus* 1.04 events per 100 patient-years) ***(Supplemental Table S10)***. After further adjusting for the Duke Prognostic Index in the multivariate Cox model, cardiac troponin remained an independent predictor of the primary outcome (aHR 2.3, 95%CI 1.7 to 3.0) ***(Table 3)***. The incidence rate of the primary outcome was 3-fold higher in patients with a Duke Prognostic Index ≥5 and a troponin concentration >10

ng/L (7.83 events per 100 patient-years), as compared to those with a Duke Index ≥5 and a troponin below this threshold (2.56 events per 100 patient-years) ***(Supplemental Table S10)***. The addition of cardiac troponin concentrations improved discrimination for the primary outcome compared to the Duke Prognostic Index alone (AUC 0.70 *versus* 0.63, p<0.001) ***(Supplemental Figure 2)***.

Discussion

In consecutive patients undergoing coronary angiography to investigate symptoms suggestive of stable angina, we evaluated whether cardiac troponin could identify those patients with chronic coronary artery disease at risk of myocardial infarction or cardiovascular death. We report several observations that are relevant to practice. First, whilst cardiac troponin concentrations are generally low in chronic coronary artery disease, in 1 in 25 patients troponin concentrations were above the 99th centile diagnostic threshold for myocardial infarction. Second, these patients with myocardial injury were four-times more likely to have a subsequent myocardial infarction or cardiovascular death compared to those with troponin concentrations below 5 ng/L. Third, cardiac troponin was an independent predictor of myocardial infarction or cardiovascular death even after adjusting for the severity and extent of chronic coronary artery disease, and other factors that can influence cardiac troponin concentrations, including heart failure and renal dysfunction. Together these findings suggest that routine cardiac troponin testing could provide important additional information to guide the management of patients with chronic coronary artery disease ***(Central Illustration)***.

Current risk stratification strategies for patients with chronic coronary artery disease primarily focus on the identification of obstructive disease and revascularization targets using anatomical and functional imaging. However, half of all myocardial infarctions occur in patients with non-obstructive coronary disease who typically do not have the ischemic substrate on functional testing to effectively guide risk stratification.[5,6] Emerging evidence suggests the identification of low-attenuation plaque using coronary computed topography angiography (CCTA) is a better predictor of subsequent myocardial infarction than the severity of stenosis in patients with chronic coronary artery disease.[4] Despite this, there remain no established strategies for risk

stratification that are widely available in clinical practice to objectively quantify risk or guide treatment decisions in patients with established coronary artery disease.

In recent years there has been a growing interest in the role of cardiac troponin for risk stratification in patients with chronic coronary artery disease. In contrast to the previous generation of assays, high-sensitivity cardiac troponin assays can reliably quantify troponin at concentrations well below the upper reference limit in the majority of people.[9,26] This enhanced precision is widely utilized in accelerated diagnostic pathways for patients with suspected acute coronary syndrome, and these pathways are now recommended by international guidelines.[15,27,28] Although cardiac troponin testing is essential for a diagnosis of myocardial infarction,[9] it also has an important role in assessing infarct size and prognosis following myocardial infarction.[17,24,29–31] In contrast, the role for cardiac troponin testing in patients with chronic coronary artery disease, is still emerging.

In consecutive patients undergoing invasive coronary angiography, we observed that cardiac troponin was a powerful independent predictor of myocardial infarction and cardiovascular death in those with chronic coronary artery disease. Even after accounting for conventional cardiovascular risk factors and comorbidities, the extent and severity of coronary artery disease and the use of revascularization, we found that cardiac troponin was an robust predictor of major adverse cardiovascular events. Unlike studies in the general population or acute coronary syndromes,[32,33] we found the thresholds defining increased risk were similar in men and women.

Our findings support those from other studies that have evaluated cardiac troponin in selected populations.[13,14,34–37] Firstly, in patients with presumed chronic coronary artery disease enrolled in the PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) trial

cardiac troponin was a significant predictor of non-fatal myocardial infarction, heart failure, or cardiovascular death.[35] Investigators in both the PROMISE (Prospective Multicenter Imaging Study for Evaluation of chest pain) and CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) studies demonstrated that troponin concentrations predicted myocardial infarction or cardiovascular death in selected patients undergoing imaging of the coronary or peripheral arteries using a prototype research assay that has now been discontinued.[13,34] Likewise, in patients with stable coronary artery disease undergoing percutaneous coronary intervention, pre-procedural troponin measured using contemporary-sensitive assay has also been shown to be associated with myocardial infarction or all-cause mortality at one year.[38] The more recent INTERCATH study also demonstrated an association between troponin and outcomes.[14] In this study, investigators enrolled patients referred for either emergency or elective coronary angiography, but excluded those with acute coronary syndromes or life-threatening arrythmia. However, in contrast to our analysis, the investigators did not restrict their analysis to those patients with angiographically confirmed coronary artery disease meaning the performance of cardiac troponin to predict outcomes in patients with chronic coronary artery disease remains uncertain. In contrast to prior work, our study is the first to prospectively evaluate this question using a clinically available high-sensitivity cardiac troponin assay in all consecutive patients encountered in routine practice with stable angina and angiographically proven chronic coronary artery disease.

Although we demonstrate cardiac troponin is a powerful predictor of cardiovascular events in patients with chronic coronary artery disease, the mechanisms of troponin release that underpin this observation remain unclear. Irreversible cell necrosis is responsible for cardiac troponin release in acute myocardial infarction.[7,39] Whether irreversible cell necrosis is also responsible for elevated cardiac troponin concentrations in patients with chronic coronary artery disease is

not known, and other release mechanisms may be responsible. The observation that cardiac troponin is transiently increased following moderate exercise has challenged the paradigm that cardiac troponin is always a marker of myocardial ischemia.[40–42] Indeed, in patients with chronic coronary artery disease, cardiac troponin concentrations at rest and after exertion were not reduced despite effective coronary revascularization and resolution of the ischemic substrate.[43,44]

Given the association between cardiac troponin and myocardial infarction in chronic coronary artery disease, it is plausible that small increases in cardiac troponin in some patients may be due to increased plaque activity or vulnerability. Patients with high-risk coronary plaque features identified on 18F-Na positron emission tomography and intra-vascular ultrasound typically have higher cardiac troponin concentrations than those without high risk plaque features.[45] It is possible that the release of pro-inflammatory cytokines in patients with high-risk plaque could induce cardiomyocyte stress in the absence of necrosis.[39,46]

Whilst cardiac troponin testing can improve the detection of functionally relevant coronary disease when compared to clinical assessment alone,[37,47] the role of cardiac troponin testing in the diagnosis of chronic coronary artery disease is likely to be limited. However, cardiac troponin testing could be play an important role following the diagnosis to evaluate risk and guide treatment.[48] A cardiac troponin concentration above 10 ng/L, which is well above the assays limit of quantification, identified 1 in 6 patients in whom the risk of myocardial infarction or cardiovascular death was increased by 50% and in whom the absolute risk was 14.1% after 2.4 years of follow up. This information could help clinicians to identify those patients with chronic coronary artery disease who are most likely to benefit from treatment intensification.

In our study, the majority of patients with chronic coronary artery disease were already established on lipid lowering and antiplatelet therapy, and therefore additional treatment approaches may be required to mitigate risk. Revascularization by percutaneous coronary intervention or coronary artery bypass grafting has a limited role in preventing major adverse cardiovascular events when applied to all patients with chronic coronary artery disease.[44,49–52] However, if cardiac troponin could identify those with unstable or vulnerable plaque, it is plausible that testing could identify those where revascularization could prevent myocardial infarction. Indeed, in our exploratory analysis, we observed that the incidence rate of myocardial infarction or cardiovascular death in patients with troponin concentrations above 10 ng/L was lower when revascularization was performed. In contrast, there was no difference in outcomes between those with and without revascularization where troponin concentrations were below this threshold.

Alternatively, novel approaches to use medical therapies may be required in this population. For example, given that short periods of dual antiplatelet therapy reduce major adverse cardiovascular events in patients after acute plaque rupture and myocardial infarction, it is plausible that a similar approach would be beneficial in selected patients with chronic coronary artery disease and elevated cardiac troponin concentrations. Indeed, investigators in the CHARISMA (The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial demonstrated in patients with coronary artery disease and a previous acute coronary event that the combination of aspirin and clopidogrel reduced the likelihood of adverse cardiovascular events by 17%.[53] Interestingly, the greatest benefit was seen in patients with the shortest period from the acute event, suggesting that unstable plaque was prerequisite to therapeutic benefit from intensified antiplatelet therapy.

In our study patients with the greatest burden of disease using the Duke Prognostic Index were at the highest risk of adverse cardiovascular events, with this association augmented in patients who also had an elevated cardiac troponin concentration above 10 ng/L. The use of cardiac troponin testing alongside assessment of disease severity could help identify those patients who would benefit from intensified treatment. Randomized trials are needed to evaluate whether routine cardiac troponin testing to guide the management of patients with chronic coronary artery disease can reduce major adverse cardiovascular events.

Study limitations

Our study has several limitations. First, we recognize our cohort comprises of patients with suspected anginal symptoms that were sufficiently limiting to warrant invasive coronary angiography. Therefore, it may not represent the full spectrum of chronic coronary artery disease. Also, we did not collect data on symptom frequency or severity in this study, precluding an evaluation or risk stratified by symptom burden. Nonetheless, patients with limiting anginal symptoms requiring coronary angiography are encountered frequently in practice, and this selection bias does not negate the potential for cardiac troponin to guide management in this setting. Second, we recognize our study is limited to a single country and the severity and extent of coronary artery disease will be dependent on the selection of patients for angiography. As such, external validation in other healthcare settings is needed to ensure our findings are generalizable. Third, cardiac troponin was measured using a single high-sensitivity cardiac troponin I assay, and the thresholds evaluated here are likely to differ for other assays. Finally, cardiac troponin was only measured on a single occasion, and it would be important to evaluate whether changes in cardiac troponin over time can further inform risk prediction.

Conclusion

In conclusion, cardiac troponin predicts myocardial infarction or cardiovascular death in patients with chronic coronary artery disease independently of traditional measures of cardiovascular risk or disease severity. Further studies are required to evaluate if routine cardiac troponin testing could guide the management of patients with chronic coronary artery disease and reduce adverse cardiovascular events.

Perspectives

Competency in Patient Care and Procedural Skills:

In patients with chronic coronary artery disease, high-sensitivity cardiac troponin can identify those at higher risk of major adverse events.

Translational Outlook:

Randomized trials are needed to evaluate the role of routine cardiac troponin testing to guide the management of patients with chronic coronary artery disease.

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Figure titles and legends

Central Illustration. Myocardial Injury in patients referred for Coronary Angiography.

In 3,888 consecutive outpatients attending for coronary angiography with symptoms of stable angina and coronary artery disease, high-sensitivity cardiac troponin I was associated with myocardial infarction or cardiovascular death after adjusting for disease severity and extent (adjusted HR 2.3, 95%CI 1.7 to 3.0). A troponin concentration >10 ng/L was associated with a 50% higher risk of major adverse events. Routine cardiac troponin testing identifies patients with chronic coronary artery disease at increased risk of major adverse events. Studies are now required to evaluate whether routine troponin testing in chronic coronary artery disease to guide management would improve outcomes.

Figure 1. Density plots of cardiac troponin concentrations

Density plot of cardiac troponin concentrations in: **[A]** patients with (red) or without (green) chronic coronary artery disease (red); **[B]** patients with chronic coronary artery disease with (red) or without (blue) myocardial infarction or cardiovascular death.

Figure 2. Cumulative incidence of MI or cardiovascular death stratified by troponin.

Cumulative incidence of myocardial infarction or cardiovascular death using the Kaplan-Meier method in patients with chronic coronary artery disease stratified by cardiac troponin concentration (low [<5 ng/L], intermediate [5 ng/L to sex-specific 99th centile], and high [> sex-specific 99th centile]).

Figure 3. Hazard of cardiac troponin for myocardial infarction or cardiovascular death

Unadjusted cause-specific hazard ratio of increasing cardiac troponin concentrations as continuous marker for myocardial infarction or cardiovascular death in patients with chronic coronary artery disease. Reference level below 5 ng/L.

Figure 4. MI or cardiovascular death stratified by revascularization and troponin.
Cumulative incidence of myocardial infarction or cardiovascular death using the Kaplan-Meier method in patients with chronic coronary artery disease and cardiac troponin concentrations above (red) or below (green) the risk stratification threshold of 10 ng/L, with (solid) or without (dashed) coronary revascularization during the index procedure.

Table 1**.** Baseline characteristics of patients with chronic coronary disease stratified by troponin concentration.

	All patients	**Low troponin**	**Intermediate troponin**	**High troponin**
No. of participants (%)	*3,888 (100)*	*2,508 (64)*	*1,216 (31)*	*164 (4)*
Age (years), median [IQR]	67 [59, 73]	65 [58, 71]	70 [62, 77]	72 [61, 78]
Sex (male)	2706 (69.6)	1622 (64.7)	988 (81.2)	96 (58.5)
Past medical history				
Coronary artery disease	3028 (77.9)	1924 (76.7)	978 (80.4)	126 (76.8)
Cerebrovascular disease	180 (4.6)	97 (3.9)	68 (5.6)	15 (9.1)
Hyperlipidemia	3385 (87.1)	2229 (88.9)	1024 (84.2)	132 (80.5)
Diabetes mellitus	729 (18.8)	418 (16.7)	274 (22.5)	37 (22.6)
Previous myocardial infarction	907 (23.3)	489 (19.5)	362 (29.8)	56 (34.1)
Heart failure	250 (6.4)	102 (4.1)	122 (10.0)	26 (15.9)
PCI	1603 (41.2)	1022 (40.7)	516 (42.4)	65 (39.6)
CABG	181 (4.7)	83 (3.3)	87 (7.2)	11 (6.7)
High-sensitivity cardiac troponin I				
Median concentration, ng/L [IQR]	3.4 [1.8, 7.1]	2.2 [1.3, 3.3]	9.0 [6.4, 13.1]	38.8 [28.0, 55.2]
Other laboratory results				
Creatinine, median [IQR]	78 [70, 93]	75 [69, 88]	84 [73, 101]	82 [70, 107]
Hemoglobin, mean (SD)	138.1 (14.9)	138.9 (14.1)	137.2 (16.0)	132.7 (17.7)
LDL cholesterol, mean (SD)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)	2.3 (0.9)

Figures are shown as number (%) unless otherwise stated. Primary outcome is a composite of non-fatal myocardial infarction or cardiovascular death. Troponin concentration categorized as low (<5 ng/L), intermediate (5 ng/L to sex-specific 99th centile), and high (greater than 99th centile)

Table 2. Clinical outcomes and incidence rates stratified by troponin concentration

	Chronic coronary artery disease			No coronary artery disease
	low troponin	**intermediate troponin**	**high troponin**	
No. of participants	*2,508*	*1,216*	*164*	*352*
Primary outcome	99 (1.58)	128 (4.64)	22 (6.13)	6 (0.66)
Myocardial infarction	83 (1.33)	85 (3.08)	12 (3.34)	<5
Cardiovascular death	22 (0.35)	53 (1.92)	11 (3.06)	<5
Non-cardiovascular death	80 (1.28)	65 (2.36)	12 (3.34)	9 (0.98)
All-cause death	102 (1.63)	118 (4.28)	23 (6.41)	13 (1.31)

Figures are shown as number (incidence-rate per 100 patient-years). Primary outcome is a composite of non-fatal myocardial infarction or cardiovascular death. Cardiac troponin concentrations categorized as low (<5 ng/L), intermediate (5 ng/L to sex-specific 99th centile), and high (greater than sex-specific 99th centile). Due to data minimization procedures all values less than 5 are reported as <5.

.

Table 3. Predictors of myocardial infarction or cardiovascular death in patients with chronic coronary disease

	Cause-specific Hazard ratio (95%CI)	**P value**
Cardiac troponin I (log_{10})	2.3 (1.7 to 3.0)	<0.001*
Age per 10 years	1.04 (0.9 to 1.2)	0.594
Male sex	0.6 (0.5 to 0.8)	0.001*
Cardiovascular risk factors	2.1 (1.5 to 3.0)	
Previous myocardial infarction	1.3 (1.0 to 1.8)	<0.001*
Hyperlipidemia	1.7 (1.3 to 2.2)	0.048*
Heart failure	1.0 (0.7 to 1.0)	<0.001*
Diabetes mellitus	1.4 (0.8 to 2.6)	0.862
Previous stroke	2.3 (1.6 to 3.2)	0.220
Creatinine concentration (log)	2.29 (1.7 to 3.0)	<0.001*
Duke Prognostic Index		
1	*Reference*	-
2	0.7 (0.2 to 1.9)	0.454
3	1.2 (0.6 to 2.4)	0.661
4	1.8 (1.1 to 3.0)	0.017*
5	1.8 (1.0 to 3.1)	0.035*
6	2.6 (1.5 to 4.3)	<0.001*
7	2.1 (1.2 to 3.7)	0.008*

Cause-specific hazard ratios with 95% confidence intervals adjusted for all other covariates in the model. * p-value <0.05.

Central Illustration. Myocardial Injury in patients referred for Coronary Angiography.

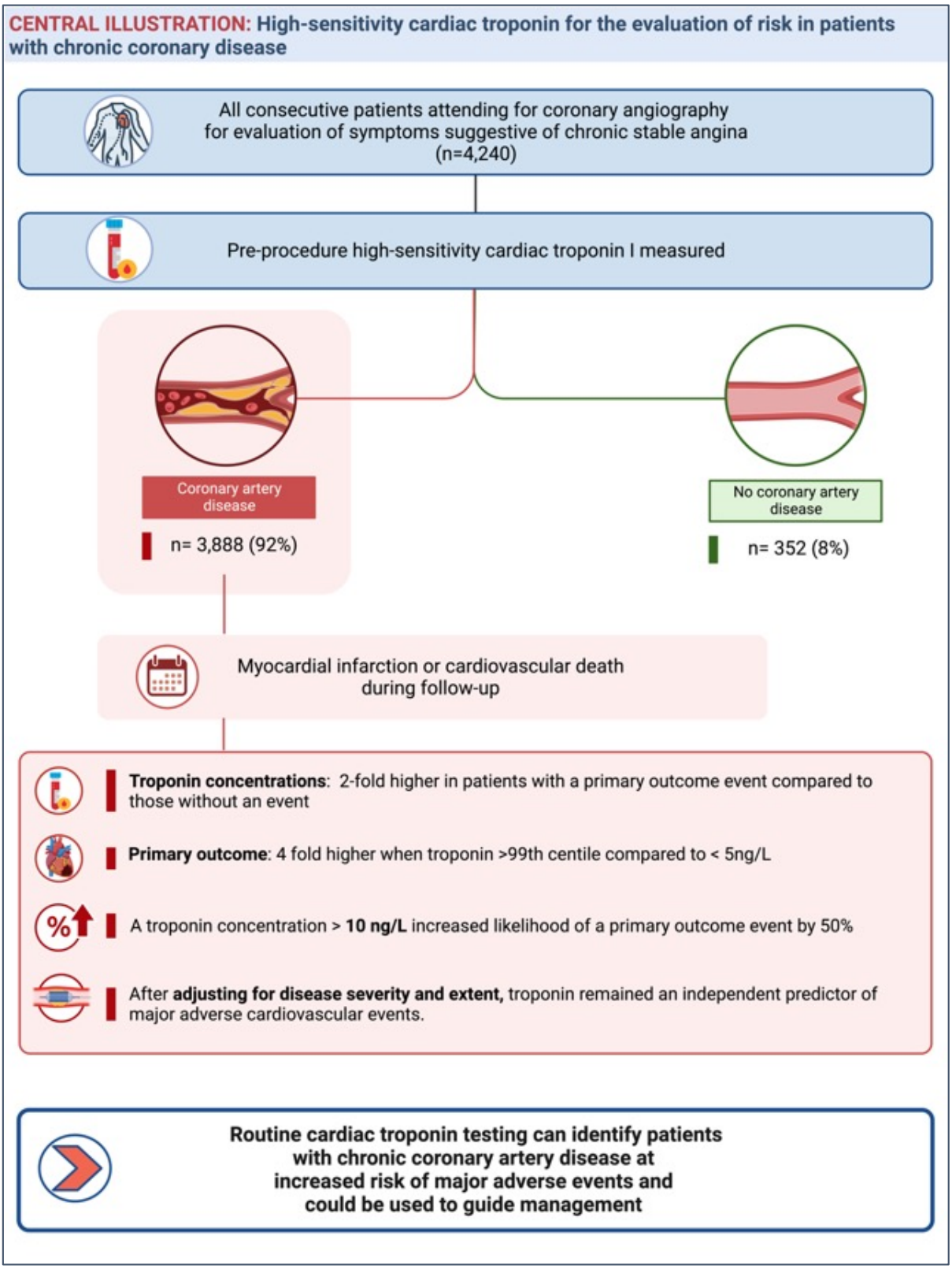


Figure 1. Density plots of cardiac troponin concentrations

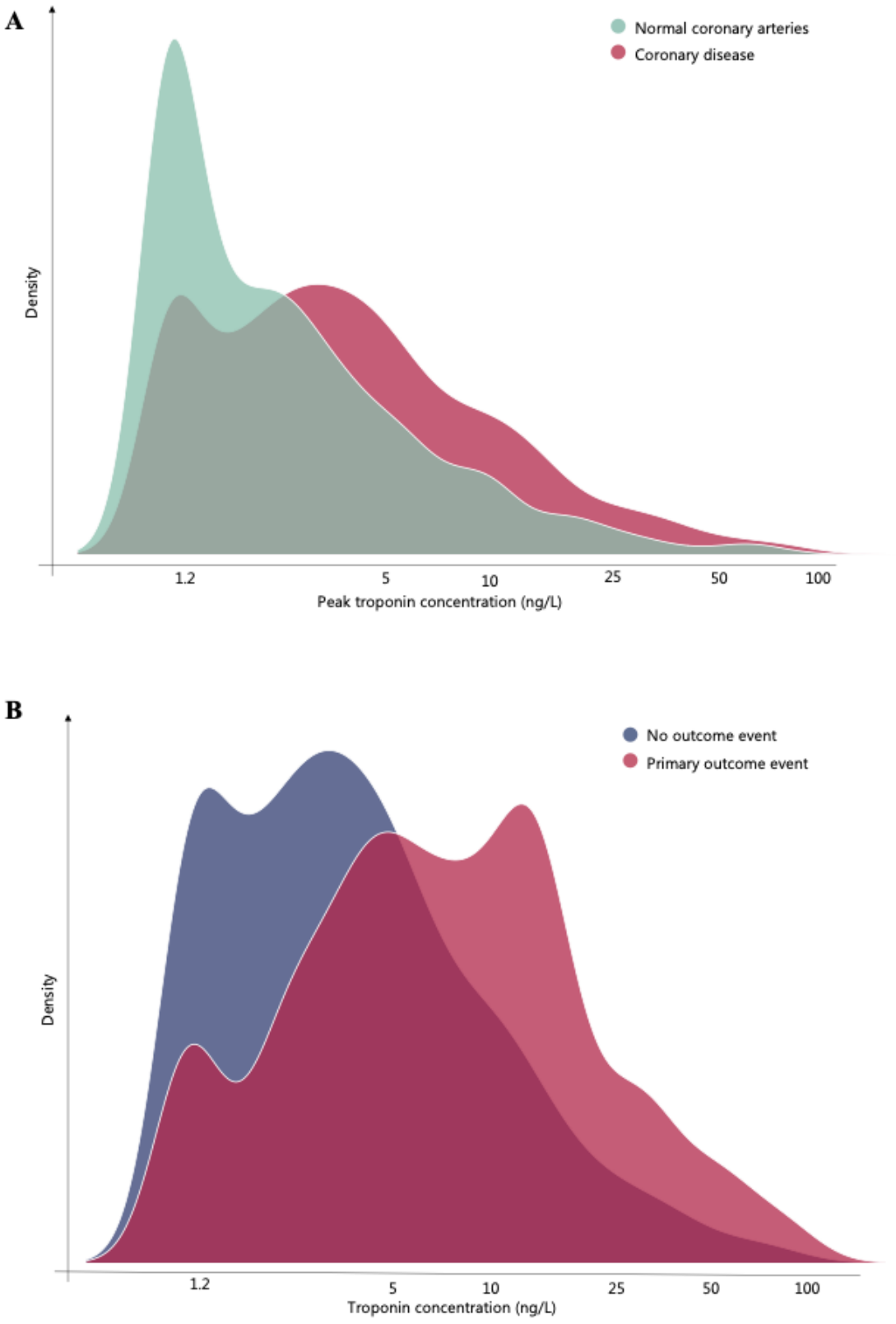
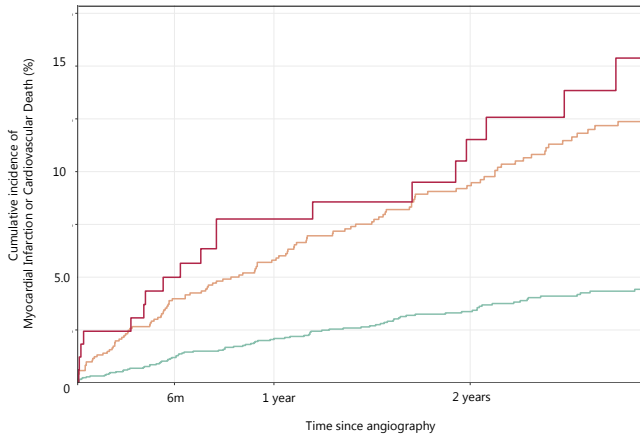


Figure 2. Cumulative incidence of MI or cardiovascular death stratified by troponin.



	Number at risk				
Troponin category	**0**	**6 months**	**1 year**	**2 years**	**3 years**
Low	2,508	2,307	2,046	1,546	993
Intermediate	1,216	1,073	914	647	405
High	164	144	120	86	49

Figure 3. Hazard of cardiac troponin for myocardial infarction or cardiovascular death

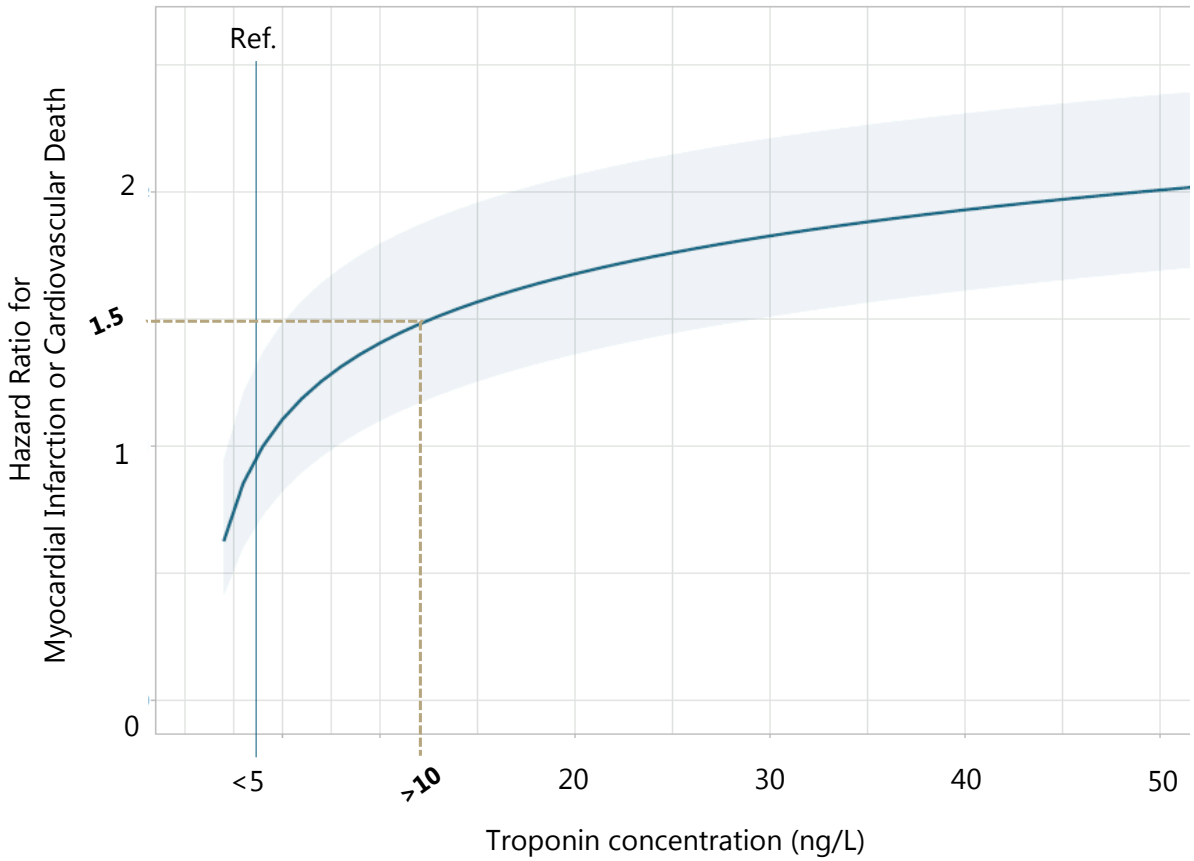
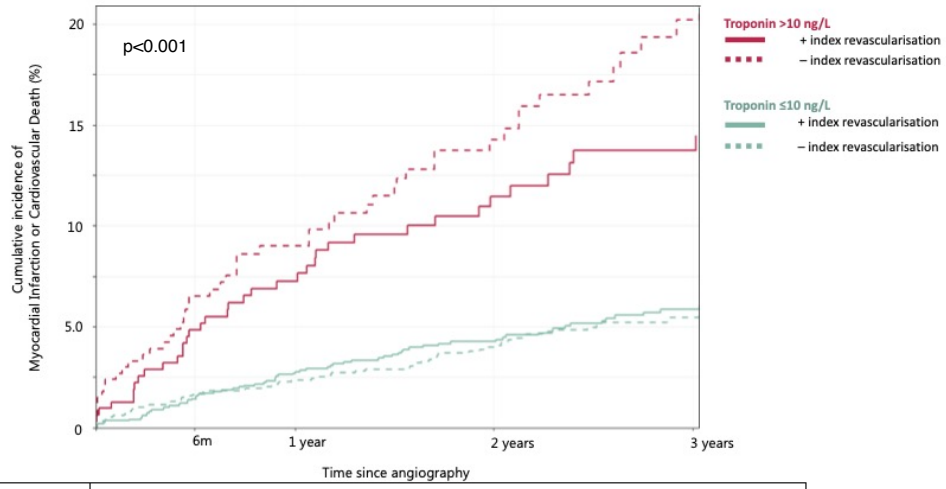


Figure 4. MI or cardiovascular death stratified by revascularization and troponin.



		Number at risk				
	Category	**0**	**6 months**	**1 year**	**2 years**	**3 years**
Troponin ≤10 ng/L	***+ revascularization***	1,517	1399	1,231	907	595
	- revascularization	1,720	1554	1,383	1,040	645
Troponin >10 ng/L	***+ revascularization***	316	288	244	175	118
	- revascularization	335	284	233	157	90

SUPPLEMENTAL APPENDIX

High-Sensitivity Cardiac Troponin for Risk Assessment in Patients with Chronic Coronary Artery Disease

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Supplemental Methods I

The study was approved by National Health System (NHS) Lothian Bioresource Regional Tissue Bank (East of Scotland Research Ethics Committee, reference 20/ES/0061), the Caldicott Guardian and Research Ethics Committee (reference DL21016), and the Public Benefit and Privacy Panel for Health and Social Care (reference 2021-0131). Individual patient consent was not required as no additional procedures were required for the research study and all data was collected from the electronic patient record and registries, deidentified and linked within a Secure Data Environment (DataLoch, Edinburgh, United Kingdom). The study was registered with International Standard Randomized Controlled Trial Number (ISRCTN) 15620297.

Baseline characteristics, past medical history, and clinical outcomes were determined using linked local electronic healthcare records, regional and national registry data ***(Supplementary Figure S4)***. These were defined using the International Classification of Disease (ICD)-10 and the Classification of Interventions and Procedures Version 4 (OPCS4) codes below.[1]

In Scotland, all permanent residents have a unique 10-digit Community Health Index (CHI) number which facilitates accurate and reliable linkage for the follow-up of individuals across multiple health boards and regions. All hospital care episodes, community prescribing records, and death certificates are held centrally by Public Health Scotland and can be linked using CHI in individual patients. This ensures data capture is complete in all patients even when moving from one region to another, but as in all clinical studies there is a small risk of loss to follow-up if patients emigrate from Scotland. We excluded patients who were not permanent residents in Scotland to minimise this risk of loss to follow-up. In our previous trials that have applied the same methodology, loss to follow-up due to emigration was 0.6% at 5 years. [2]

[1] Anand A, Lee KK, Chapman AR, *et al.* High-Sensitivity Cardiac Troponin on Presentation to Rule out Myocardial Infarction: A Stepped-Wedge Cluster Randomized Controlled Trial. *Circulation* 2021; **143**: 2214–24.

[2] Shah ASV, Anand A, Sandoval Y, *et al.* High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: A cohort study. *Lancet* 2015; **386**: 2481–8.

Diagnostic and procedural codes used to inform baseline characteristics:

Condition/Procedure	**ICD/OPCS4**
Coronary artery disease	I20-I25
Cerebrovascular disease	I60-I68
Hyperlipidemia	E78
Diabetes mellitus	E11-14
Previous myocardial infarction	I21,I22
Heart failure	I50
PCI	K49,K50,K75
CABG	K40-48

Diagnostic codes used to inform clinical outcomes:

Condition	**ICD**
All-cause death	A00-Z99
Cardiovascular death	I01, I02, I05 – I09, I10-I15, I20-28, I30-I52, I60-I69, I70-I79, I80-I89, I95-I99
Myocardial infarction	I21, I22

Disease severity was calculated using the modified Duke Prognostic Index as previously described.[1] This hierarchical index categorizes CAD according to its anatomical location, stenosis severity, and overall extent.

Duke Score	**Description**
7	Left main coronary artery ≥50%
6	2-vessel severe stenosis (>70%) including severe disease in proximal LAD
6	3-Vessel severe stenosis
5	1 vessel severe proximal LAD
5	2-Vessel severe stenosis (excluding pLAD)
5	3-Vessel moderate stenosis (≥50-70%)
4	2-Vessel moderate stenosis
4	1 vessel severe stenosis (excluding pLAD)
3	1-Vessel moderate stenosis
2	1 vessel mild proximal LAD (<50%)
1	Mild disease (excluding pLAD)

[1] Reynolds HR, Shaw LJ, Min JK, et al. Outcomes in the ISCHEMIA Trial Based on Coronary Artery Disease and Ischemia Severity. *Circulation*. 2021:1024-1038.

Supplemental Methods II

Sample collection and analysis

Cardiac troponin I concentrations were prospectively measured by a UKAS accredited central hospital laboratory in plasma collected for clinical purposes in 4.5 mL Lithium Heparin Sarstedt monovette tubes (SARSTEDT AG & Co. Nümbrecht, Germany) as per local hospital procedure. Samples were analyzed in real time using the Abbott ARCHITECT$_{STAT}$ high-sensitivity troponin I assay on the Abbott Architect i2000 platform (Abbott Diagnostics, Illinois, United States).

This assay has a sex-specific 99th centile upper reference limit of 34 ng/L in men and 16 ng/L in women, an inter-assay coefficient of variation of 10% at 4.7 ng/L and 20% at 1.3 ng/L. The limit of detection for this assay is reported as between 1.1 – 1.9 ng/L from the product package insert (Abbott ARCHITECT$_{STAT}$ high-sensitive troponin-I package insert G1-0139/R02). For the purpose of our analysis the limit of detection was defined as 2 ng/L. Troponin concentrations were reported as absolute numbers to one decimal place.

Troponin was measured in blood sample remaining after clinical tests had been performed and troponin results were not revealed to clinicians. Troponin was not routinely measured in this setting as part of normal clinical care.

Baseline clinical variables for the models were selected based on their clinical relevance.[25–29] Cardiac troponin and creatinine concentrations were included as continuous variables after log transformation.

Supplemental Methods III

Continuous variables are presented as mean (SD) or median (IQR), as appropriate. Categorical variables are presented as absolute numbers (%). Group-wise comparisons were performed using χ^2, Kruskal-Wallis or one-way analysis of variance tests as appropriate. Data was assessed for systematic missingness. Missing creatinine values were estimated using multivariable imputation with chained equations. Subsequent analyses were conducted using a single imputed value for each missing value.

Density plots were constructed to graphically evaluate the frequency of troponin concentrations firstly stratified by angiographic findings, and then in patients with coronary artery disease stratified by whether or not a primary outcome event occurred.

Incidence rates for primary and secondary outcomes were calculated per 100 patient-years in patients with chronic coronary artery disease stratified by cardiac troponin concentration category, and in those without chronic coronary artery disease.

The Kaplan-Meier method was applied to estimate the cumulative incidence of the primary outcome during follow-up. Non-cardiovascular death was considered as a competing risk.

Multivariable Cox proportional hazard models were constructed to determine cause-specific hazard ratios for the primary outcome. Baseline clinical variables for the models were selected based on their clinical relevance.[1] We examined for nonproportional hazards graphically and by calculating deviation from linearity over time using Schoenfeld residuals.

[1] Wereski R, Kimenai DM, Bularga A, et al. Risk factors for type 1 and type 2 myocardial infarction. EHJ 2022; 43: 127–35.

Supplemental Tables

Table S1**.** Baseline characteristics in patients with and without chronic coronary artery disease

	All	**Coronary artery disease**	**No coronary artery disease**
No. of participants	*4,240*	*3,888*	*352*
Age (years), median [IQR]	66.0 [59.0, 73.0]	67.0 [59.0, 73.0]	62.0 [55.0, 70.0]
Sex (male)	2,854 (67.3)	2,706 (69.6)	148 (42.0)
Past medical history			
Coronary artery disease	3,134 (73.9)	3,028 (77.9)	106 (30.1)
Cerebrovascular disease	186 (4.4)	180 (4.6)	6 (1.7)
Hyperlipidemia	3,634 (85.7)	3,385 (87.1)	249 (70.7)
Diabetes mellitus	758 (17.9)	729 (18.8)	29 (8.2)
Previous myocardial infarction	907 (21.4)	907 (23.3)	352 (100.0)
Heart failure	267 (6.3)	250 (6.4)	17 (4.8)
PCI	1603 (37.8)	1603 (41.2)	352 (100.0)
CABG	181 (4.3)	181 (4.7)	352 (100.0)
High-sensitivity cardiac troponin I			
Median [IQR], ng/L	3.3 [1.7, 6.8]	3.4 [1.8, 7.1]	1.9 [1.0, 3.8]
Low (<5 ng/L)	2,792 (65.8)	2,508 (64.5)	284 (80.7)
Intermediate	1,275 (30.1)	1,216 (31.3)	59 (16.8)
High (>99th centile)	173 (4.1)	164 (4.2)	9 (2.6)
Other laboratory results			
Creatinine, median [IQR]	77.0 [69.0, 92.0]	78.0 [70.0, 93.0]	71.0 [64.0, 82.0]
Hemoglobin, mean (SD)	138.0 (14.8)	138.1 (14.9)	136.7 (13.7)
LDL cholesterol, mean (SD)	2.2 (0.9)	2.2 (0.9)	2.4 (0.9)

Figures are number (%) unless otherwise stated. Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; IQR = inter-quartile range; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.

Table S2**.** Baseline characteristics and outcomes stratified by coronary artery disease status as obstructive, non-obstructive or normal at angiography.

	All patients	**Obstructive coronary disease**	**Non-obstructive coronary disease**	**Normal**
No. of participants	*4,240*	*2,637 (62.2)*	*1,216 (28.7)*	*352 (8.3)*
Age (years), median [IQR]	66.0 [59.0, 73.0]	67.0 [60.0, 74.0]	67.0 [60.0, 74.0]	62.0 [55.0, 70.0]
Sex (male)	2,854 (67.3)	1,979 (75.0)	1979 (75.0)	148 (42.0)
Past medical history				
Coronary artery disease	3,134 (73.9)	2,637	894 (71.5)	106 (30.1)
Cerebrovascular disease	186 (4.4)	67.0 [60.0, 74.0]	51 (4.1)	6 (1.7)
Hyperlipidemia	3,634 (85.7)	1,979 (75.0)	1,054 (84.3)	249 (70.7)
Diabetes mellitus	758 (17.9)	2,637	198 (15.8)	29 (8.2)
Previous myocardial infarction	907 (21.4)	67.0 [60.0, 74.0]	230 (18.4)	0 (0.0)
Heart failure	267 (6.3)	1,979 (75.0)	67 (5.4)	17 (4.8)
PCI	1603 (37.8)	2,637	310 (24.8)	0 (0.0)
CABG	181 (4.3)	181 (6.9)	0 (0.0)	0 (0.0)
High-sensitivity cardiac troponin I				
Median concentration, ng/L [IQR]	3.3 [1.7, 6.8]	3.9 [2.1, 8.3]	2.7 [1.4, 5.1]	1.9 [1.0, 3.8]
Low (<5 ng/L)	2,792 (65.8)	1577 (59.8)	931 (74.4)	284 (80.7)
Intermediate	1,275 (30.1)	930 (35.3)	286 (22.9)	59 (16.8)
High (>99th centile)	173 (4.1)	130 (4.9)	34 (2.7)	9 (2.6)
Other laboratory results				
Creatinine, median [IQR]	77.0 [69.0, 92.0]	79.0 [71.0, 94.0]	76.0 [68.0, 90.0]	71.0 [64.0, 82.0]
Hemoglobin, mean (SD)	138.0 (14.8)	138.5 (15.1)	137.3 (14.5)	136.7 (13.7)
LDL cholesterol, mean (SD)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)	2.4 (0.9)
Outcome events				
Primary outcome	255 (6.0)	207 (7.8)	42 (3.4)	6 (1.7)
Myocardial infarction	183 (4.3)	152 (5.8)	28 (2.2)	3 (0.9)
Cardiovascular death	89 (2.1)	70 (2.7)	16 (1.3)	3 (0.9)
Non-cardiovascular death	166 (3.9)	110 (4.2)	47 (3.8)	9 (2.6)
All-cause death	255 (6.0)	180 (6.8)	63 (5.0)	12 (3.4)

Figures are number (%) unless otherwise stated. Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; IQR = inter-quartile range; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation. Primary outcome is a composite of non-fatal myocardial infarction or cardiovascular death.

Table S3**.** Baseline characteristics stratified by primary outcome in patients with chronic coronary artery disease

	Primary outcome	
	No	**Yes**
No. of participants	*3,639*	*249*
Age (years), median (IQR)	67 [59, 73]	69.0 [60, 76]
Sex (Male)	2,532 (69.6)	174 (69.9)
Past medical history		
Coronary artery disease	2,819 (77.5)	209 (83.9)
Cerebrovascular disease	158 (4.3)	22 (8.8)
Hyperlipidemia	3,170 (87.1)	215 (86.3)
Diabetes mellitus	661 (18.2)	68 (27.3)
Previous myocardial infarction	808 (22.2)	99 (39.8)
Heart failure	205 (5.6)	45 (18.1)
PCI	1,490 (40.9)	113 (45.4)
CABG	157 (4.3)	24 (9.6)
High-sensitivity cardiac troponin I		
Median concentration, ng/L (IQR)	3.3 [1.7, 6.6]	6.7 [3.2, 14.2]
Low (<5ng/L)	1,711 (47.0)	122 (49.0)
Intermediate (5ng/L to 99th centile)	2,409 (66.2)	99 (39.8)
High (>99th centile)	1,088 (29.9)	128 (51.4)
	142 (3.9)	22 (8.8)
Other laboratory results		
Creatinine, median (IQR)	78 [70, 92]	85 [73, 107]
Hemoglobin, mean (SD)	138.6 (14.6)	131.9 (18.5)
LDL cholesterol, mean (SD)	2.2 (0.9)	2.3 (1.0)

Figures are shown as number (%) unless otherwise stated. Primary outcome is a composite of non-fatal myocardial infarction or cardiovascular death.

Table S4. Outcomes in patients with and without chronic coronary artery disease

	All	**Coronary artery disease**	**No coronary artery disease**
No. of participants	*4,240*	*3,888*	*352*
Primary outcome	255 (6.0)	249 (6.4)	6 (1.7)
Myocardial infarction	183 (4.3)	180 (4.6)	3 (0.9)
Cardiovascular death	89 (2.1)	86 (2.2)	3 (0.9)
Non-cardiovascular death	166 (3.9)	157 (4.0)	9 (2.6)
All-cause death	255 (6.0)	243 (6.2)	12 (3.4)

Figures are shown as number (%) unless otherwise stated. Primary outcome is a composite of non-fatal myocardial infarction or cardiovascular death.

Table S5. Hazards of cardiac troponin as a continuous measure for myocardial infarction or cardiovascular death

	Model 1	**Model 2**	**Model 3**	**Model 4**
Cardiac troponin I (log_{10})	**3.2 (2.5 to 4.2)***	**3.3 (2.6 to 4.4)***	**2.4 (1.8 to 3.1)***	**2.6 (1.9 to 3.4)***
Age per 10 years	-	1.1 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)
Male sex	-	0.8 (0.6 to 1.04)	1.0 (0.9 to 1.2)	0.7 (0.5 to 0.9)*
Angiographic findings				
Obstructive coronary disease (Yes/No)		-	1.9 (1.3 to 2.6)*	-
Index revascularization	-	-	-	1.0 (0.8 to 1.3)
Cardiovascular risk factors				
Previous myocardial infarction	-	-	1.7 (1.3 to 2.2)*	1.8 (1.4 to 2.3)*
Hyperlipidemia	-	-	1.0 (0.7 to 1.4)	1.0 (0.7 to 1.4)
Heart failure	-	-	2.1 (1.5 to 3.0)*	2.1 (1.5 to 3.0)*
Diabetes mellitus	-	-	1.4 (1.0 to 1.8)*	1.4 (1.0 to 1.8)*
Previous stroke	-	-	1.4 (0.8 to 2.6)	1.4 (0.8 to 2.5)
Creatinine concentration (log)	-	-	2.3 (1.6 to 3.2)*	2.3 (1.6 to 3.2)*

Unadjusted (Model 1) and adjusted (Models 2-4) hazard ratios with 95% confidence intervals. Adjustment is made for all other covariates in the individual model column where hazard ratios are presented. * denotes a p-value <0.05.

Table S6. Hazards for myocardial infarction or cardiovascular death across a range of cardiac troponin thresholds compared to a referent group (<5 ng/L) stratified by sex

High-sensitivity cardiac troponin I risk thresholds (ng/L)	Hazard Ratio (95% Confidence Interval)	
	Female	Male
<5	Ref	Ref
5	1.1 (0.6 to 2.0)	1.1 (0.8-1.6)
6	1.2 (0.7-2.1)	1.2 (0.9-1.7)
7	1.3 (0.8-2.1)	1.3 (0.9-1.7)
8	1.3 (0.8-2.2)	1.3 (1.0-1.8)
9	1.4 (0.9-2.2)	1.4 (1.0-1.9)
10	1.4 (0.9-2.3)	1.4 (1.1-1.9)
11	1.5 (0.9-2.3)	1.5 (1.1-1.9)
12	1.5 (1.0-2.4)	1.5 (1.1-2.0)
13	1.5 (1.0-2.4)	1.5 (1.2-2.0)
14	1.6 (1.0-2.4)	1.6 (1.2-2.0)
15	1.6 (1.0-2.5)	1.6 (1.2-2.1)
16	1.6 (1.1-2.5)	1.6 (1.3-2.1)
17	1.7 (1.1-2.5)	1.6 (1.3-2.1)
18	1.7 (1.1-2.5)	1.7 (1.3-2.1)
19	1.7 (1.1-2.5)	1.7 (1.3-2.2)
20	1.7 (1.2-2.6)	1.7 (1.3-2.2)

Table S7. Medical therapy and index revascularization in the study population

	All	**Coronary artery disease**	**No coronary artery disease**
No. of participants	*4,240*	*3,888*	*352*
Baseline medical therapy			
Any antiplatelet	3,385 (79.8)	3,161 (81.3)	224 (63.6)
Aspirin	2,839 (67.0)	2,647 (68.1)	192 (54.5)
$P2Y_{12}$ inhibitor	1,830 (43.2)	1,739 (44.7)	91 (25.9)
Lipid lowering therapy	3,634 (85.7)	3,385 (87.1)	249 (70.7)
Index revascularization	1,833 (43.2)	1,833 (47.2)	0
Subsequent medical therapy			
Any anti-platelet	3,468 (81.8)	3,328 (85.6)	140 (39.8)
Aspirin	2,882 (68.0)	2,765 (71.1)	117 (33.2)
$P2Y_{12}$ inhibitor	2,313 (54.6)	2,278 (58.6)	35 (9.9)
Lipid lowering therapy	3,684 (86.9)	3,484 (89.6)	200 (56.8)

Figures are shown as number (%) unless otherwise stated. Index revascularization was defined as percutaneous coronary intervention or coronary artery bypass surgery and within 30 days.

Table S8. Baseline characteristics and clinical outcomes in patients with chronic coronary artery disease stratified by index revascularization.

		Index revascularization	
	All patients	**No**	**Yes**
No. of participants	*3,888*	*2,055*	*1,833*
Age (years), median [IQR]	67 [59, 73]	67.0 [60, 74]	66.0 [59, 73]
Sex (Male)	2,706 (69.6)	1330 (64.8)	1376 (75.1)
Past medical history			
Coronary artery disease	3,028 (77.9)	1552 (75.5)	1476 (80.5)
Cerebrovascular disease	180 (4.6)	101 (4.9)	79 (4.3)
Hyperlipidemia	3,385 (87.1)	1759 (85.6)	1626 (88.7)
Diabetes mellitus	729 (18.8)	379 (18.4)	350 (19.1)
Previous myocardial infarction	907 (23.3)	424 (20.6)	483 (26.4)
Heart failure	250 (6.4)	142 (6.9)	108 (5.9)
PCI	1603 (41.2)	529 (25.7)	1074 (58.6)
CABG	181 (4.7)	96 (4.7)	85 (4.6)
High-sensitivity cardiac troponin I			
Median concentration, ng/L (IQR)	3.4 [1.8, 7.1]	3.4 [1.7, 7.0]	3.5 [1.9, 7.3]
Low (<5 ng/L)	2,508 (64.5)	1339 (65.2)	1169 (63.8)
Intermediate	1,216 (31.3)	634 (30.9)	582 (31.8)
High (>99th centile)	164 (4.2)	82 (4.0)	82 (4.5)
Other laboratory results			
Creatinine, median (IQR)	78.0 [70.0, 93.0]	77.0 [69.0, 92.0]	78.0 [71.0, 93.0]
Hemoglobin, mean (SD)	138.1 (14.9)	137.1 (15.2)	139.3 (14.6)
LDL cholesterol, mean (SD)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)
Clinical outcomes			
Primary outcome	249 (6.4)	127 (6.2)	122 (6.7)
Myocardial infarction	180 (4.6)	86 (4.2)	94 (5.1)
Cardiovascular death	86 (2.2)	52 (2.5)	34 (1.9)
Non-cardiovascular death	157 (4.0)	93 (4.5)	64 (3.5)
All-cause death	243 (6.2)	145 (7.1)	98 (5.3)

Figures are shown as number (%) unless otherwise stated. Primary outcome is a composite of non-fatal myocardial infarction or cardiovascular death.

Table S9. Incidence rates per 100 person-years, in patients with chronic coronary artery disease, stratified by index revascularization and troponin concentration above and below the risk-stratification threshold of 10 ng/L

Incidence event rate per 1,000 person-years	**Troponin ≤10 ng/L**		**Troponin >10 ng/L**	
	No revascularization	Revascularization	No revascularization	Revascularization
Primary outcome	1.8	2.2	7.7	5.2
Myocardial infarction	1.4	1.9	4.1	3.2
Cardiovascular death	0.6	0.5	4.2	2.3
Non-cardiovascular death	1.6	1.4	4.1	1.6
All-cause death	2.1	1.8	8.3	3.9

Primary outcome is a composite of non-fatal myocardial infarction or cardiovascular death.

Table S10. Incidence rates for myocardial infarction or cardiovascular death per 100 patient-years, stratified by Duke Index and troponin concentration above and below the risk-stratification threshold of 10 ng/L

	Incidence rate for myocardial infarction or cardiovascular death per 100 patient-years		
Duke Prognostic Index	**All**	**Troponin ≤10 ng/L**	**Troponin >10 ng/L**
1 - 2	1.04	0.64	5.60
3 - 4	2.50	2.07	4.93
5 - 7	3.56	2.56	7.83

Table S11**.** Baseline characteristics of patients with chronic coronary artery disease stratified by cardiac troponin concentration using the limit of detection.

		Troponin category		
	All patients	**Below limit of detection***	**Intermediate**	**Above sex-specific 99th-centile**
No. of participants (%)	*3,888 (100)*	*1,089 (28)*	*2,635 (68)*	*164 (4)*
Age (years), median [IQR]	67 [59, 73]	63 [56, 69]	68 [61, 75]	72 [61, 78]
Sex (male)	2,706 (69.6)	601 (55.2)	2,009 (76.3)	96 (58.5)
Past medical history				
Coronary artery disease	3,028 (77.9)	822 (75.5)	2,080 (78.9)	126 (76.8)
Cerebrovascular disease	180 (4.6)	34 (3.1)	131 (5.0)	15 (9.1)
Hyperlipidemia	3,385 (87.1)	969 (89.0)	2,284 (86.7)	132 (80.5)
Diabetes mellitus	729 (18.8)	165 (15.2)	527 (20.0)	37 (22.6)
Previous myocardial infarction	907 (23.3)	176 (16.2)	675 (25.6)	56 (34.1)
Heart failure	250 (6.4)	24 (2.2)	200 (7.6)	26 (15.9)
PCI	1,603 (41.2)	426 (39.1)	1,112 (42.2)	65 (39.6)
CABG	181 (4.7)	15 (1.4)	155 (5.9)	11 (6.7)
High-sensitivity cardiac troponin I				
Median concentration, ng/L [IQR]	3.4 [1.8, 7.1]	1.2 [0.5, 1.6]	4.7 [3.0, 8.5]	38.8 [28.0, 55.2]
Other laboratory results				
Creatinine, median [IQR]	78 [70, 93]	73 [67,83]	81 [72,95]	82 [70, 107]
Hemoglobin, mean (SD)	138.1 (14.9)	138.6 (13.5)	138.3 (15.2)	132.7 (17.7)
LDL cholesterol, mean (SD)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)	2.3 (0.9)

*Figures are shown as number (%) unless otherwise stated. Primary outcome defined in patients with non-fatal myocardial infarction or cardiovascular death during follow-up. *Troponin concentration categorized as below the assay's limit of detection (<2 ng/L), intermediate (2 ng/L to sex-specific 99th centile), and high (greater than sex-specific 99th centile)*

Table S12**.** Outcomes in patients with chronic coronary artery disease stratified by cardiac troponin category and the assay's limit of detection.

	All	**Below limit of detection***	**Intermediate**	**Above sex-specific 99th-centile**
No. of participants	*3,888*	*1,089 (28)*	*2,635 (68)*	*164 (4)*
Primary outcome	249 (6.4)	31 (2.8)	196 (7.4)	22 (13.4)
Myocardial infarction	180 (4.6)	26 (2.4)	142 (5.4)	12 (7.3)
Cardiovascular death	86 (2.2)	6 (0.6)	69 (2.6)	11 (6.7)
Non-cardiovascular death	157 (4.0)	18 (1.7)	127 (4.8)	12 (7.3)
All-cause death	243 (6.2)	24 (2.2)	196 (7.4)	23 (14.0)

*Figures are shown as number (%) unless otherwise stated. Primary outcome is a composite of non-fatal myocardial infarction or cardiovascular death. *Troponin concentration categorized as below the assay's limit of detection (<2 ng/L), intermediate (2 ng/L to sex-specific 99th centile), and high (greater than sex-specific 99th centile)*

Table S13**.** Cox regression model evaluating independent predictors of myocardial infarction or cardiovascular death in patients with chronic coronary artery disease when troponin is used as a categorical variable

	Adjusted Cause-specific Hazard Ratio (95%CI)	**P value**
Cardiac troponin category		
Low (<5 ng/L)	*Reference*	-
Intermediate (5 ng/L to 99th centile)	2.85 (2.16 – 3.76)	<0.001
High (> 99th centile)	3.59 (2.25 – 5.74)	<0.001
Age per 10 years	1.08 (0.95 – 1.23)	0.232
Male sex	0.86 (0.65 – 1.14)	0.304

Supplemental Figures

Figure S1. Study population and exclusions

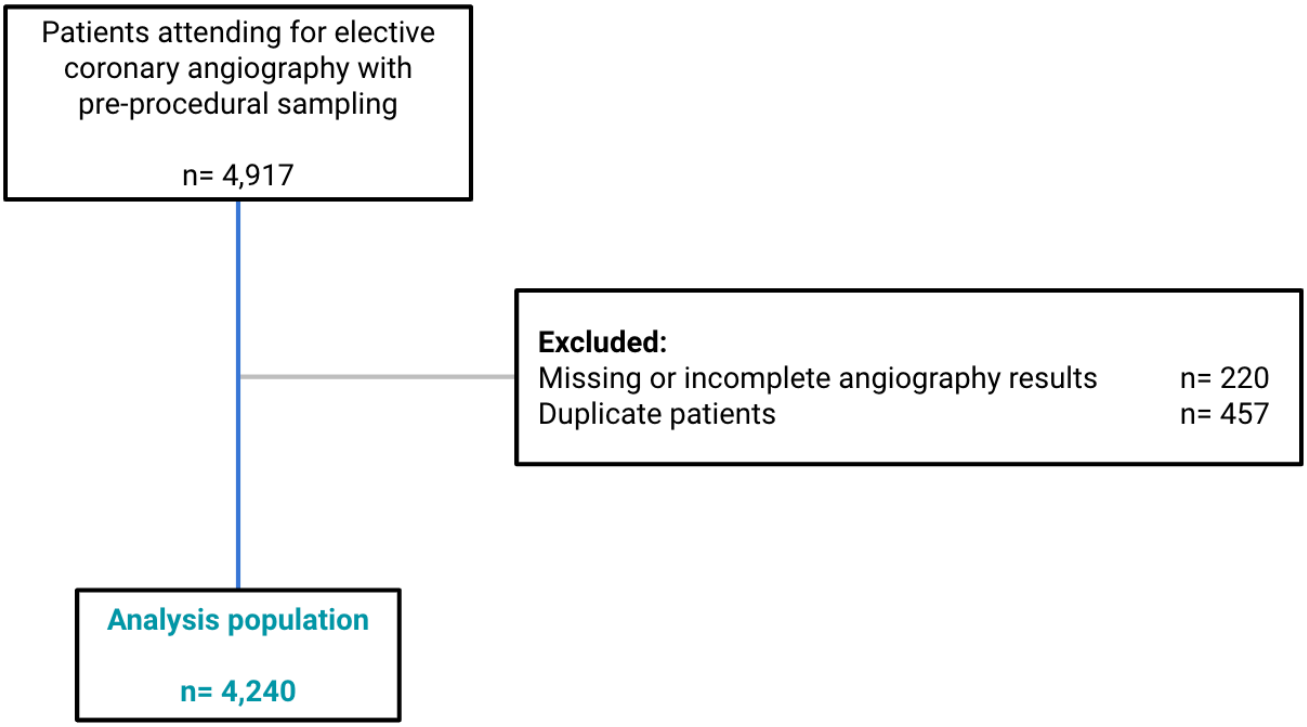


Figure S2. Discrimination for myocardial infarction or cardiovascular death

Area Under the Receiver Operating Curve for myocardial infarction or cardiovascular death based on Duke Prognostic Index alone (blue), or the Duke Prognostic Index and high-sensitivity cardiac troponin (red)

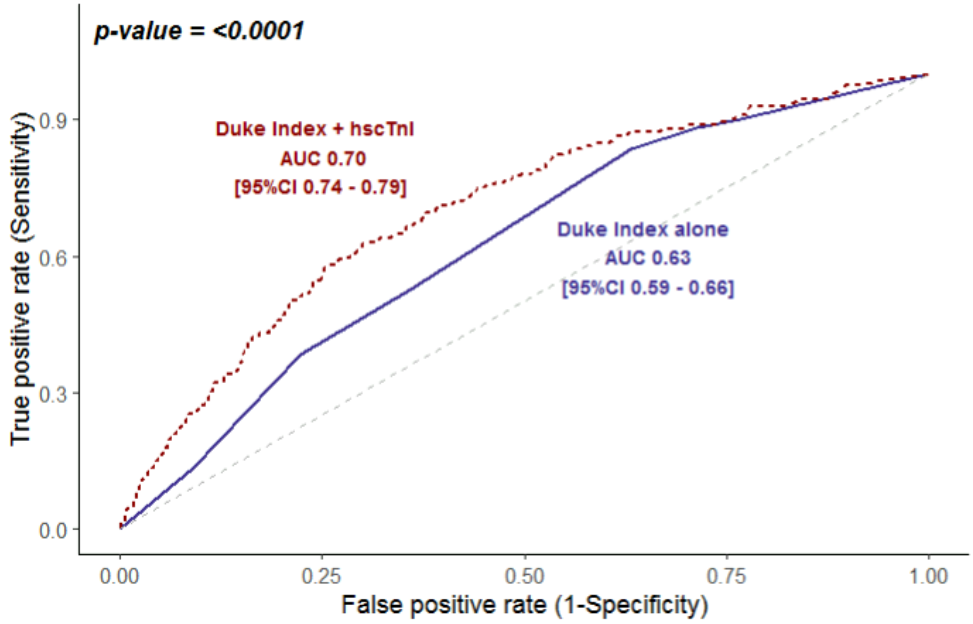
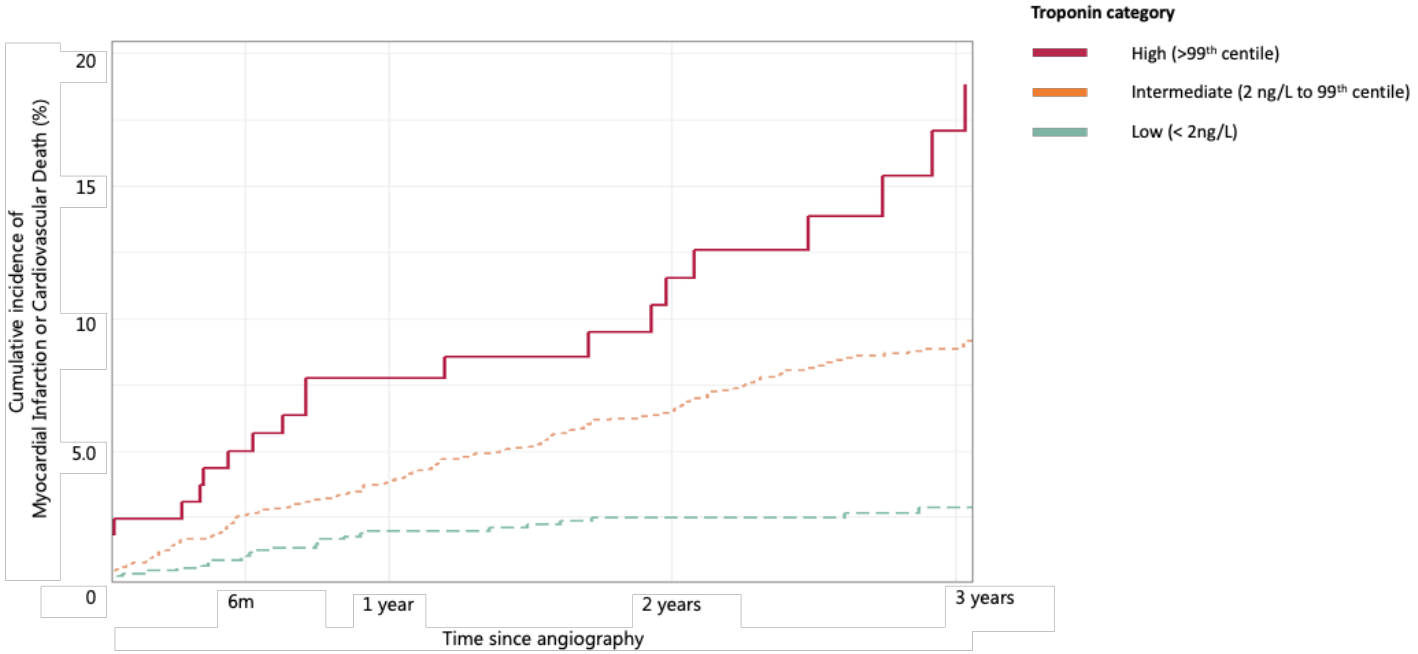


Figure S3. Cumulative incidence of myocardial infarction or cardiovascular death stratified by troponin category.
Troponin categories derived from the assay limit of detection: low, concentration troponin <2 ng/L (green); intermediate, troponin concentration 2 ng/L to the sex-specific 99th-centile (orange); high, troponin concentration > sex-specific 99th centile (red)



	Number at risk				
Troponin category	**0**	**6 months**	**1 year**	**2 years**	**3 years**
Low/below limit of detection	1,089	1,001	894	681	438
Intermediate	2,635	2,379	2,071	1,512	960
High/above sex-specific 99th-centile	164	144	120	86	49

Figure S4. Study data linkage process.

Process of linking study data from local, regional, and national registry databases to determine study outcomes