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Long Term Outcomes in Patients with Type 2 Myocardial Infarction and Myocardial Injury

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Abstract

Background—Type 2 myocardial infarction and myocardial injury are common in clinical practice, but long-term consequences are uncertain. We aimed to define long-term outcomes and explore risk stratification in patients with type 2 myocardial infarction and myocardial injury.
Methods—We identified consecutive patients (n=2,122) with elevated cardiac troponin I concentrations (≥0.05 µg/L) at a tertiary cardiac center. All diagnoses were adjudicated as per the Universal Definition of Myocardial Infarction. The primary outcome was all-cause death. Secondary outcomes included major adverse cardiovascular events (MACE; non-fatal myocardial infarction or cardiovascular death) and non-cardiovascular death. To explore competing risks, cause-specific hazard ratios were obtained using Cox regression models.
Results—The adjudicated index diagnosis was type 1 or type 2 myocardial infarction or myocardial injury in 1,171 (55.2%), 429 (20.2%) and 522 (24.6%) patients, respectively. At five years, all-cause death rates were higher in those with type 2 myocardial infarction (62.5%) or myocardial injury (72.4%) compared with type 1 myocardial infarction (36.7%). The majority of excess deaths in those with type 2 myocardial infarction or myocardial injury were due to non-cardiovascular causes (HR 2.32, 95%CI 1.92-2.81, *versus* type 1 myocardial infarction). Despite this, the observed crude MACE rates were similar between groups (30.6% *versus* 32.6%), with differences apparent after adjustment for co-variates (HR 0.82, 95%CI 0.69-0.96). Coronary heart disease was an independent predictor of MACE in those with type 2 myocardial infarction or myocardial injury (HR 1.71, 95%CI 1.31-2.24).
Conclusions—Despite an excess in non-cardiovascular death, patients with type 2 myocardial infarction or myocardial injury have a similar crude rate of major adverse cardiovascular events to those with type 1 myocardial infarction. Identifying underlying coronary heart disease in this vulnerable population may help target therapies that could modify future risk.

Key Words: acute coronary syndrome; myocardial infarction; survival; type 2 myocardial infarction

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Clinical Perspective

What is new?

- We report long term outcomes at 5 years in consecutive patients with type 1 or type 2 myocardial infarction, or myocardial injury.
- Two-thirds of patients with type 2 myocardial infarction or myocardial injury are dead at 5 years, with a similar rate of future non-fatal myocardial infarction or cardiovascular death as those with type 1 myocardial infarction.
- The presence of coronary artery disease is an independent predictor of future cardiovascular risk in patients with type 2 myocardial infarction or myocardial injury.

What are the clinical implications?

- Clinicians should consider risk stratification in patients with type 2 myocardial infarction or myocardial injury for the likelihood of coronary artery disease.
- Prospective clinical trials are needed to define the efficacy and safety of secondary prevention therapies in patients with type 2 myocardial infarction or myocardial injury, which have the potential to modify future outcomes.

The diagnostic criteria for acute myocardial infarction were updated to accommodate the introduction of more sensitive cardiac troponin assays, and in recognition of the wide range of conditions that are associated with myocardial injury.[1] The third universal definition of myocardial infarction recommends a classification based on etiology, where type 1 myocardial infarction is due to plaque rupture or erosion with atherothrombotic consequences, and type 2 myocardial infarction due to myocardial oxygen supply-demand imbalance in the absence of atherothrombosis. Patients with elevated cardiac troponin concentrations who do not have overt myocardial ischemia are classified as having myocardial injury.[2] Whilst these diagnostic categories are considered distinct in guidelines, implementation in clinical practice has been challenging due to similarities between patients with type 2 myocardial infarction and myocardial injury, with the implications of these diagnoses uncertain.

The Global Task Force is reviewing the classification of myocardial infarction, and recognizes the need to provide greater clarity for clinicians in practice.[3] Whilst patients with type 2 myocardial infarction and myocardial injury have higher crude rates of all-cause death compared with those with type 1 myocardial infarction,[4-9] differences do not always persist in adjusted analyses,[10,11] and few studies report cause of death or risk of future cardiovascular events.[12] If patients with type 2 myocardial infarction are at increased risk of cardiovascular events attributable to atherosclerotic disease, then targeted investigation and preventative therapies have the potential to modify outcomes.

In consecutive patients with elevated cardiac troponin concentrations measured using a sensitive assay, we previously observed that the diagnosis of type 2 myocardial infarction or myocardial injury was as common as type 1 myocardial infarction.[4] Here we report outcomes for these patients, and determine the clinical features associated with major adverse cardiovascular events, with the aim of improving risk stratification in patients with type 2 myocardial infarction or myocardial injury.

Methods

Transparency and openness promotion

The analysis code for this study has been made available online ***(Supplemental Appendix 1).*** The data will not be made available to other researchers for the purposes of reproducing the results due to lack of data sharing approval.

Study population

Consecutive hospital inpatients with elevated cardiac troponin I concentrations (≥0.05 μg/L) were identified at a tertiary cardiac center (Royal Infirmary of Edinburgh, Scotland, UK) during the validation (January 19th to July 31st 2008) and implementation (January 19th to July 31st 2009) phases of a contemporary sensitive cardiac troponin I assay.[4,13] We included all patients in whom cardiac troponin was requested by the attending clinician, regardless of suspected etiology or hospital department. All clinical details were obtained using an electronic patient record (TrakCare, InterSystems, Cambridge, MA). We excluded patients admitted for elective procedures, those with incomplete electronic hospital records, and patients who were not residents to ensure follow up was complete.

Cardiac troponin assay

Plasma cardiac troponin concentrations were measured using a contemporary sensitive cardiac troponin I assay (ARCHITECT$_{STAT}$, Abbott Laboratories, Abbott Park, IL). The study was divided into validation and implementation phases.[4,13] Only cardiac troponin concentrations above the diagnostic threshold of the previous generation assay (≥0.20 μg/L) were reported to clinicians during the validation phase, whereas concentrations above a revised diagnostic threshold (≥0.05 μg/L) were reported during the implementation phase. The 99th centile of this assay is 0.028 μg/L; however, a diagnostic threshold of ≥0.05 μg/L was implemented as this was the minimum concentration where the coefficient of variation was <10% under local laboratory conditions. All troponin results were available to the research team irrespective of study phase.

Diagnostic classification

All diagnoses were classified as per the third universal definition of myocardial infarction.[2,4] Patients were classified as having a type 1 myocardial infarction when myocardial necrosis occurred in the context of a presentation with suspected acute coronary syndrome with symptoms of myocardial ischemia, or evidence of myocardial ischemia on the electrocardiogram. Patients with symptoms or signs of myocardial ischemia that were thought to be due to increased oxygen demand (e.g. tachyarrhythmia or hypertrophy) or decreased supply (e.g. hypotension, hypoxia or anaemia) and myocardial necrosis in the context of an alternative clinical diagnosis were classified as having a type 2 myocardial infarction. Myocardial injury was defined as evidence of myocardial necrosis in the absence of any symptoms or signs of myocardial ischemia. For this analysis, we excluded patients classified as having type 3, type 4a or 4b, or type 5 myocardial infarction. Each case was reviewed and classified independently by two cardiologists, and any discrepancies were resolved by consensus through in-depth review of source data. Further information on the adjudication process is provided in ***Supplemental Appendix 2***.

Clinical outcomes

Clinical outcomes were identified using local and national population registries. We determined death using TrakCare (InterSystems, Cambridge, MA) and the National Register of Scotland

(NRS), with future hospitalization for myocardial infarction or heart failure identified using an extract from the Scottish Morbidity Record (SMR01). We defined death from a cardiovascular cause where one of the following ICD10 codes were listed as primary cause of death: I20-25, I34-37, I42-43, I46, I48-51 and I60-69 ***(Supplemental Appendix 3)*****.** The primary outcome was all cause death. Secondary outcomes included major adverse cardiovascular events (MACE; defined as cardiovascular death or subsequent myocardial infarction), non-fatal myocardial infarction, fatal myocardial infarction, hospitalization with heart failure, and non-cardiovascular death. We obtained follow up for all patients until the primary outcome or date of censoring (16th November 2015).

Ethical considerations

The parent study protocol evaluated the implementation of a sensitive cardiac troponin assay, and was deemed to fall under the remit of audit and service evaluation by the NHS Lothian Regional Ethics Committee, therefore formal ethical approval was not required. For this study, we received approval from the Caldicott guardian to obtain long term follow up through local and national registries.

Statistical analysis

Baseline characteristics were summarized as mean (SD) or median (IQR) as appropriate, with patients grouped based on the classification of myocardial infarction. Crude incidence rates for primary and secondary outcomes were calculated, with risk ratios obtained using a generalized linear model with a log link, Poisson error distribution and robust variance estimates.[14] We adjusted for clinically relevant covariates including age, sex, renal function (estimated glomerular filtration rate, eGFR), hemoglobin (g/L), diabetes mellitus, hypertension, coronary heart disease (defined as previous myocardial infarction, coronary revascularization or known angina pectoris), stroke, peripheral vascular disease or cigarette smoking. The study period included a lowering of the upper reference limit for cardiac troponin from 0.20 µg/L (validation phase) to 0.05 µg/L (implementation phase), and we therefore included study phase in all models. We repeated these analyses among only those patients who survived 30 days after presentation, defining the start of the follow-up period as 30 days post presentation. To explore competing risks, cause-specific hazard ratios were obtained using Cox regression models for type 1 myocardial infarction *versus* type 2 myocardial infarction or myocardial injury for MACE and non-cardiovascular death. Penalised splines were used to accommodate departures from linearity. We examined for non-proportional hazards graphically and via the method proposed by Grambsch and Therneau.[15] In patients who survived to 30 days, we explored associations between covariates and future risk of MACE. Cumulative incidence plots were produced for secondary cardiovascular outcomes, which also illustrate the competing risk of non-cardiovascular death. We report 95% confidence intervals for all estimates, with all analyses performed using R (Version 3.2.2) using the *survival* and *cmprsk* packages.[16]

Results

We identified 2,929 consecutive patients with elevated cardiac troponin concentrations (≥0.05 µg/L) of whom 807 met our exclusion criteria (***Supplemental Figure 1***). In the study population (n=2,122), the adjudicated diagnosis was type 1 myocardial infarction in 1,171 patients (55.2%), type 2 myocardial infarction in 429 patients (20.2%) and myocardial injury in 522 patients (24.6%; ***Table 1***).

Clinical characteristics

Patients with type 2 myocardial infarction or myocardial injury were older, and there were a higher proportion of women than men compared to patients with type 1 myocardial infarction. Anaemia or renal impairment was more common in patients with type 2 myocardial infarction or myocardial injury. A history of previous coronary revascularization was more frequent in those with type 1 myocardial infarction. At presentation, the prescription of anti-platelet, anti-hypertensive and lipid lowering therapies was similar across all patients (***Table 1***)**.** The most common diagnoses in patients with type 2 myocardial infarction or myocardial injury were cardiac arrhythmia, decompensated left ventricular failure, pneumonia or long bone fracture, with variation in prevalence by classification ***(Supplemental Table 1).***

Clinical outcomes at five years in all patients

During 8,809 person years follow up (median 4.9 years), death from any cause occurred in 1,231 patients (58%). In patients with type 2 myocardial infarction, at five years, the observed risk of death was higher compared to those with type 1 myocardial infarction (62.5% *versus* 36.7%, unadjusted relative risk (RR) 2.15, 95% confidence intervals (95%CI) 1.82-2.55 . After incorporating age, sex, renal function, hemoglobin and other clinically relevant co-variates, the adjusted RR fell to 1.51, (95%CI 1.21-1.87, ***Table 2, Figure 1***).

The five-year risk of non-fatal myocardial infarction or cardiovascular death (MACE) was similar in patients with type 2 compared to type 1 myocardial infarction (30.1% *versus* 32.6%, unadjusted RR 0.92, 95% CI 0.77-1.09, ***Figure 2***), but lower after adjustment for age, sex and other co-variates (adjusted RR 0.74, 95%CI 0.62-0.88). Adjusting for the same co-variates, the cause-specific hazard ratio for MACE (with non-cardiovascular mortality as the competing outcome) was similar to the relative risk (HR 0.82 95%CI 0.69-0.96, ***Table 3, Supplemental Table 2***).

For the individual components of MACE, the risk of non-fatal myocardial infarction was lower in those with type 2 myocardial infarction compared to type 1 myocardial infarction (10.0% *versus* 17.8%, adjusted RR 0.58, 95%CI 0.44-0.77). Whilst the crude rates of cardiovascular death were higher for type 2 myocardial infarction compared to type 1 myocardial infarction (24.2% *versus* 21.6%) the adjusted relative risk was lower at 0.85 (95%CI 0.70-1.03). Risks of fatal-myocardial infarction and hospitalization with heart failure were comparable across groups **(*Table 2*).** Non-cardiovascular death was higher in patients with type 2 myocardial infarction compared to type 1 myocardial infarction (35.7% *versus* 13.2%, adjusted RR 1.66, 95%CI 1.40-1.98, ***Figure 2****)*.

We found similar relative risks for patients with myocardial injury compared to type 1 myocardial infarction for most primary and secondary outcomes, but a lower risk of non-fatal myocardial infarction and higher risk of non-cardiovascular death were observed. Patients with myocardial injury had a higher risk of all-cause death and heart failure hospitalization than patients with type 2 myocardial infarction (***Supplemental Table 3***).

Clinical outcomes at five years in those who survive to 30 days

In patients who survived from their initial presentation to 30 days, death from any cause occurred in 31% (333/1,074) of patients with type 1 myocardial infarction, 56.1% (207/368) of patients with type 2 myocardial infarction and 67% (293/437) of patients with myocardial injury (***Supplemental Table 4***). The adjusted relative risk of death for patients with type 2 myocardial infarction versus type 1 myocardial infarction was similar to that observed in the total population (adjusted RR 1.52, 95%CI 1.21-1.92). For all but one of the secondary outcomes, the relative risks were similar to those obtained in the main analysis. However, the association between type of myocardial infarction and risk of MACE was weaker than was observed in the whole population, occurring in 27.4% (101/368) of patients with type 2 myocardial infarction and 27.7% (298/1,074) of patients with type 1 myocardial infarction, with an adjusted RR of 0.80 (95%CI 0.65-0.98).

In patients with type 2 myocardial infarction or myocardial injury, age, declining renal function, a history of diabetes mellitus, peripheral vascular disease and coronary artery disease were independent predictors of MACE at five years (***Supplemental Table 5***). The presence of coronary artery disease was associated with an increase in the cause-specific hazard ratio for MACE at five years (HR 1.71, 95%CI 1.31-2.24), compared to those without coronary artery disease. When compared to patients with type 1 myocardial infarction, patients with type 2 myocardial infarction or myocardial injury with coronary artery disease had a higher risk of MACE (RR 1.56, 95%CI 1.29-1.88). The adjusted cause-specific hazard ratio for MACE, which accounts for competing risk from non-cardiovascular death, was 1.05 (95%CI 0.85-1.30, ***Figure 3***). On discharge from hospital, patients with type 2 myocardial infarction or myocardial injury and a history of coronary artery disease were less likely than those with type 1 myocardial infarction to be prescribed aspirin (66.2% *versus* 90.7%), a statin (69.2% *versus* 86.0%) or an ACE inhibitor (52.9% *versus* 71.3%, P<0.001 for all, ***Table 4***).

Discussion

In a cohort of consecutive hospitalized patients with elevated cardiac troponin concentrations, we classified the diagnosis of myocardial infarction according to the universal definition and report outcomes after five years follow up. We make several observations that have implications for clinical practice. First, over two-thirds of patients with type 2 myocardial infarction or myocardial injury are dead at five years. This mortality rate was twice that of patients with type 1 myocardial infarction, with differences primarily due to an excess in non-cardiovascular deaths. Second, major adverse cardiovascular events occurred in one-third of patients, and rates were similar irrespective of diagnostic classification. In those patients with type 2 myocardial infarction or myocardial injury, the presence of coronary heart disease was one of the strongest predictors of MACE. Those patients with type 2 myocardial infarction or myocardial injury with known coronary artery disease were less likely to receive secondary prevention therapies compared to those with type 1 myocardial infarction. Identifying patients with elevated cardiac troponin concentrations in the context of an acute illness who have underlying coronary heart disease may provide an opportunity for clinicians to improve the targeting of preventative therapies and reduce the risk of cardiovascular events.

Several studies demonstrate that the diagnosis of type 2 myocardial infarction is common in clinical practice, responsible for between 2% and 37% of all elevations in cardiac troponin in unselected hospitalized patients and between 5% to 71% in unselected patients attending the Emergency Department.[17-21] Myocardial injury has been reported in up to 70% of unselected patients,[5,22] but as the frequency of diagnosis is not reported by the majority of studies, failure to classify patients according to the criteria set out in the universal definition may inflate the incidence of type 2 myocardial infarction.[23] Both type 2 myocardial infarction and myocardial injury increase the risk of all-cause death at up to three years.[5-9,21,23-25] We now provide outcome data at five years demonstrating that two-thirds of patients with type 2 myocardial infarction or myocardial injury are dead with twice the event rate of patients with type 1 myocardial infarction.

One of the key limitations of prior analyses is the majority have not reported the specific cause of death, and therefore estimates of the proportion of events which may be attributable to cardiovascular disease, are lacking.[26,27] We found the excess in all-cause death in patients with type 2 myocardial infarction or myocardial injury was largely attributable to a three-fold increase in non-cardiovascular death. As patients with type 2 myocardial infarction or myocardial injury are older, and have a higher prevalence of anaemia, renal impairment, and other co-morbidities, this is perhaps unsurprising. Nonetheless, it is notable that the crude risk of MACE in patients with type 2 myocardial infarction or myocardial injury was similar to that in patients with type 1 myocardial infarction. In models taking into account the differences in age, sex and other characteristics between patients with different index diagnoses, the risk of subsequent cardiovascular events was around 25% lower in patients with type 2 myocardial infarction or myocardial injury than in patients with type 1 myocardial infarction. This may in part be attributable to competing risks, with the much higher rates of non-cardiovascular death reducing the pool of patients at risk of having a cardiovascular event. However, competing risks are not the only explanation for the lower rates of MACE in patients with type 2 myocardial infarction or myocardial injury, as in an adjusted analysis taking into account competing risks and other clinical variables, a difference in the cause-specific hazard ratio was still apparent between the groups.

The diagnostic distinction between patients with type 2 myocardial infarction and myocardial injury is challenging, but worthwhile if the diagnosis conveys important prognostic information, or influences treatment decisions.[7,28-30] In our analysis, the recommended classification of type 2 myocardial infarction or myocardial injury did not differentially identify those patients at risk of MACE. This observation is consistent with previous studies and suggests alternate strategies for risk stratification may be required. In patients with type 2 myocardial infarction, the presence of obstructive coronary artery disease may influence prognosis. Outcomes from the SWEDEHEART registry of 41,817 patients with type 1 or 2 myocardial infarction demonstrated an increased risk of all-cause death in patients with type 2 myocardial infarction with obstructive coronary artery disease compared to those without.[21] Similarly, in a recent analysis of the APACE cohort, Nestelberger et al found patients with type 2 myocardial infarction and coronary artery disease had a 90 day cardiovascular mortality of 3.6%, with no deaths observed in those without coronary artery disease.[31] Our analysis supports these findings, with coronary artery disease one of the strongest predictors of MACE in patients with type 2 myocardial infarction or myocardial injury. The prevalence of coronary artery disease in patients with type 2 myocardial infarction or myocardial injury was 42% in our cohort, and varies between 36% to 78% in previous reports.[7,11,21,22,32] However, estimates obtained from registry studies are hindered by selection bias as those who undergo angiography will have a higher pre-test probability of coronary artery disease, and the true prevalence of coronary artery disease in this group of patients remains uncertain. [33]

Importantly, patients with type 2 myocardial infarction or myocardial injury receive fewer prescriptions for preventative therapies compared to those with type 1 myocardial infarction.[9,10,20-23] To date, there have been no randomized controlled trials evaluating secondary prevention in this population, and there are no formal recommendations for risk assessment or treatment.[30] Given the current heterogeneity in application of the Universal Definition of Myocardial Infarction, the feasibility of delivering such a study with comparable observations across multiple healthcare settings is uncertain. Primary prevention guidelines recommend statin therapy where the predicted ten year risk of adverse cardiovascular events exceeds 10%.[34] In our study, patients who survive their initial presentation with type 2 myocardial infarction and are not already known to have coronary artery disease, the rate of MACE exceeds 10% at one year. Whilst this may be partially attributable to age and the presence of co-morbidities, a significant proportion may have unrecognized coronary artery disease and may benefit from further investigation or preventative therapies.

We believe clinicians should adopt a pragmatic approach, and risk stratify individual patients based on their likelihood of coronary artery disease.[29,30] There are no risk assessment tools validated for use in this setting, therefore clinicians must review the presenting symptoms, medical history, cardiovascular risk factors, serial 12-lead electrocardiograms and any available imaging findings and apply clinical judgement. Where the probability of coronary disease is high, it may be reasonable to commence secondary prevention with aspirin and a statin in the absence of contraindications. If patients with type 2 myocardial infarction are found to have obstructive coronary artery disease, revascularization could plausibly reduce the risk of future cardiac events, but this strategy has not been evaluated. Where the probability of coronary disease is intermediate or low, further investigation (invasive or CT coronary angiography) should be considered to identify patients with underlying coronary artery disease, where the benefits of secondary prevention are well recognized. The optimal timing for investigation in this group of patients is also uncertain. Where the probability of type 1 myocardial infarction is high, invasive assessment should be considered on an urgent basis in line with standard practice. In those patients where myocardial injury or infarction is secondary to oxygen supply-demand imbalance, further assessment may need to be deferred until the patient has recovered from their primary illness. Furthermore, a recognition that these patients are at increased risk of non-cardiovascular events may lead to an improvement in outcomes, through better monitoring or intensification of treatment of the primary presenting condition.

There are important limitations to the data presented. The study population was identified on the basis of an elevated troponin I concentration measured using a contemporary sensitive assay with a diagnostic threshold of 0.05 μg/L, and the true prevalence of myocardial injury and infarction could be higher using a lower threshold or a high-sensitivity cardiac troponin assay. Whilst two cardiologists adjudicated all index diagnoses using all available clinical information, with excellent intra-observer agreement, there remains potential for misclassification, particularly for type 2 myocardial infarction and myocardial injury. There is likely to be variation in the in-hospital treatments received which we could not adjust for, nor could we adjust for illness severity. As previously reported, a low proportion of patients with type 2 myocardial infarction or myocardial injury underwent inpatient coronary angiography.[4] We therefore defined coronary artery disease based on a diagnosis of angina, previous myocardial infarction or previous coronary revascularization, which is likely to significantly underestimate the prevalence of coronary artery disease. Finally, subsequent hospitalizations and cardiovascular or non-cardiovascular death were determined using ICD-10 coding obtained from regional and national registry data, where there is the potential for both diagnostic and coding error. We were therefore not able to determine the incidence of subsequent type 1 or type 2 myocardial infarction.

Conclusions

Over two-thirds of patients admitted to hospital with type 2 myocardial infarction or myocardial injury die within five years, with the majority of deaths due to non-cardiovascular causes. Nonetheless, major adverse cardiovascular events occur in one-third of patients with elevated cardiac troponin concentrations, irrespective of whether myocardial necrosis was spontaneous or secondary to another acute illness. Whilst patients with type 1 myocardial infarction were at highest risk, there was no separation of risk between those with a diagnosis of type 2 myocardial infarction or myocardial injury. In contrast, those patients with type 2 myocardial infarction or myocardial injury known to have coronary artery disease are at highest risk of cardiovascular events, and efforts to diagnose coronary artery disease may provide opportunities to target preventative therapies and improve patient outcomes.

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Disclosures

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Table 1. Baseline characteristics of the study population

	Type 1 Myocardial Infarction (n=1,171)	Type 2 Myocardial Infarction (n=429)	Myocardial Injury (n=522)	P value
Baseline Characteristics				
Age	68 (14)	75 (14)	76 (13)	<0.001
Male (%)	709 (60.5)	222 (51.7)	260 (49.8)	<0.001
Past Medical History				
Diabetes Mellitus (%)	185 (16.7)	93 (21.7)	96 (18.7)	0.072
Hypertension (%)	533 (48.2)	254 (59.3)	303 (58.9)	<0.001
Hyperlipidaemia (%)	539 (48.6)	177 (41.5)	202 (39.5)	0.001
Family History (%)	193 (18.1)	14 (3.3)	10 (2.0)	<0.001
Ischaemic Heart Disease (%)	497 (44.7)	191 (44.6)	186 (36.3)	0.004
Previous MI (%)	231 (23.9)	109 (26.0)	107 (20.9)	0.183
Previous Stroke (%)	92 (8.3)	48 (11.2)	86 (16.8)	<0.001
Peripheral Vascular Disease (%)	85 (7.7)	29 (6.8)	39 (7.6)	0.831
Previous PCI (%)	153 (14.7)	17 (4.0)	23 (4.5)	<0.001
Previous CABG (%)	62 (6.3)	30 (7.1)	32 (6.2)	0.849
Smoker (%)	380 (34.0)	62 (14.5)	73 (14.0)	<0.001
Admission Medication				
Aspirin (%)	413 (49.7)	175 (44.1)	207 (45.9)	0.141
Clopidogrel (%)	100 (12.2)	25 (6.3)	26 (5.8)	<0.001
Beta-blocker (%)	257 (31.2)	101 (25.7)	111 (24.6)	0.022
ACE Inhibitor (%)	300 (36.4)	136 (34.4)	158 (35.1)	0.782
Statin (%)	384 (46.5)	156 (39.5)	191 (42.4)	0.054
Long Acting Nitrate (%)	124 (15.1)	48 (12.2)	43 (9.6)	0.017
Calcium Channel Blocker (%)	165 (20.1)	65 (16.5)	67 (14.9)	0.050
GTN Spray (%)	250 (30.3)	76 (19.3)	63 (14.0)	<0.001
Diuretic (%)	230 (27.9)	170 (43.0)	196 (43.6)	<0.001
Warfarin (%)	35 (4.5)	38 (9.7)	52 (11.6)	<0.001
Baseline Investigations				
Haemoglobin (g/L)	133.9 (20.4)	121.4 (25)	120.2 (22.1)	<0.001
Urea (mmol/L)	8.2 (9.4)	10 (7.1)	12.02 (11.5)	<0.001
Creatinine (mmol/L)	106.8 (59.8)	132.5 (108.9)	155 (172.2)	<0.001
Corrected eGFR (ml/min)	69 (26)	58 (28)	54 (32)	<0.001
Cholesterol (mmol/L)	4.8 (1.3)	4.3 (1.2)	4.3 (1.4)	<0.001
Troponin I (µg/L)	2.42 (0.27-15.23)	0.14 (0.07-0.66)	0.13 (0.06-0.39)	<0.001

Values are mean (SD),median (IQR) or n(%). MI – myocardial infarction. PCI – percutaneous coronary intervention. CABG – coronary artery bypass grafting. ACE – angiotensin converting enzyme. GTN – glyceryl trinitrate, eGFR – estimated glomerular filtration rate, Ischaemic Heart Disease – previous myocardial infarction or angina pectoris. P values obtained from group-wise comparisons using Chi-square, Kruskal Wallis or one way analysis of variance tests as appropriate.

Table 2. Death and major cardiovascular events at 5 years stratified by diagnosis

	Type 1 MI (n=1,171)	Type 2 MI (n=429)	Myocardial injury (n=522)	Type 2 MI versus Type 1 MI		Myocardial Injury versus Type 1 MI	
				Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Death from any cause	430 (36.7%)	268 (62.5%)	378 (72.4%)	2.15 (1.82-2.55)	1.51 (1.21-1.87)	2.88 (2.43-3.40)	2.09 (1.72-2.55)
MACE	382 (32.6%)	129 (30.1%)	162 (31.0%)	0.92 (0.77-1.09)	0.74 (0.62-0.88)	0.95 (0.81-1.11)	0.77 (0.66-0.89)
Non-fatal MI	209 (17.8%)	43 (10.0%)	35 (6.7%)	0.60 (0.45-0.79)	0.58 (0.44-0.77)	0.43 (0.31-0.58)	0.44 (0.32-0.60)
Cardiovascular death	253 (21.6%)	104 (24.2%)	145 (27.8%)	1.11 (0.92-1.34)	0.85 (0.70-1.03)	1.25 (1.07-1.46)	0.92 (0.79-1.07)
Fatal MI	32 (2.7%)	9 (2.1%)	18 (3.4%)	0.81 (0.45-1.46)	0.64 (0.37-1.11)	1.17 (0.81-1.71)	0.93 (0.64-1.34)
Heart failure hospitalization	103 (8.8%)	25 (5.8%)	48 (9.2%)	0.71 (0.50-1.02)	0.77 (0.54-1.12)	1.03 (0.81-1.32)	1.08 (0.86-1.35)
Non-cardiovascular death	155 (13.2%)	153 (35.7%)	218 (41.8%)	2.33 (1.99-2.71)	1.66 (1.40-1.98)	2.54 (2.33-2.89)	1.84 (1.61-2.11)

Event rates (number, %) for primary and secondary outcomes with adjusted relative risk (RR) and 95% confidence intervals (95% CI) at five years. MACE = major adverse cardiovascular events (non-fatal type 1 myocardial infarction or cardiovascular death), MI = myocardial infarction. For the composite of MACE, patients who experienced non-fatal myocardial infarction and subsequent cardiovascular death are counted once. Cause of death was not determined in 48 patients due to missing data.

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Table 3. Cause-specific hazard ratio for MACE and non-cardiovascular death in patients with type 2 myocardial infarction *or* myocardial injury versus type 1 myocardial infarction in unadjusted and fully adjusted Cox-regression models.

	Major Adverse Cardiovascular Events	
	csHR (95% CI)	P value
Model 1	1.16 (1.00-1.34)	0.052
Model 2	0.84 (0.72-0.98)	0.024
Model 3	0.74 (0.63-0.87)	<0.001
Model 4	0.82 (0.69-0.96)	0.016
	Non-Cardiovascular Death	
	csHR (95% CI)	P value
Model 1	3.73 (3.15-4.41)	<0.001
Model 2	2.63 (2.21-3.12)	<0.001
Model 3	2.27 (1.90-2.72)	<0.001
Model 4	2.32 (1.92-2.81)	<0.001

Model 1 – Unadjusted. Model 2 – Adjusted for Age and Sex. Model 3 – As per Model 2 with adjustment for estimated glomerular filtration rate. Model 4: As per Model 3 with adjustment for haemoglobin, smoking, diabetes, hypertension, coronary artery disease, stroke, peripheral vascular disease and study phase. csHR- cause specific hazard ratio. Type 1 myocardial infarction as the referent group. P-value for inclusion of index diagnosis term.

Table 4. Recommended therapies at discharge in patients with type 1 myocardial infarction, type 2 myocardial infarction and myocardial injury who survive to 30 days, stratified by the presence of coronary artery disease.

	Type 1 Myocardial Infarction (n=1,074)	*Type 2 Myocardial Infarction or Myocardial Injury* *Known coronary artery disease* (n=325)	*Type 2 Myocardial Infarction or Myocardial injury* *No known coronary artery disease* (n=467)	*P value*
Aspirin	896 (90.7%)	190 (66.2%) *	148 (37.7%)	<0.001
Clopidogrel	823 (80.7%)	52 (17.6%) *	31 (7.6%)	<0.001
Beta-blocker	651 (64.2%)	126 (42.6%) *	97 (23.7%)	<0.001
ACE Inhibitor	724 (71.3%)	156 (52.9%) *	124 (30.2%)	<0.001
Statin	872 (86.0%)	204 (69.2%) *	120 (29.3%)	<0.001
Long acting nitrates	143 (14.1%)	77 (26.1%) *	12 (2.9%)	<0.001
GTN Spray	671 (66.0%)	121 (41.0%) *	23 (5.6%)	<0.001
Calcium Channel Blockers	165 (16.3%)	67 (22.7%)	43 (10.5%)	<0.001
Warfarin	33 (3.4%)	44 (15.0%) *	64 (15.6%)	<0.001

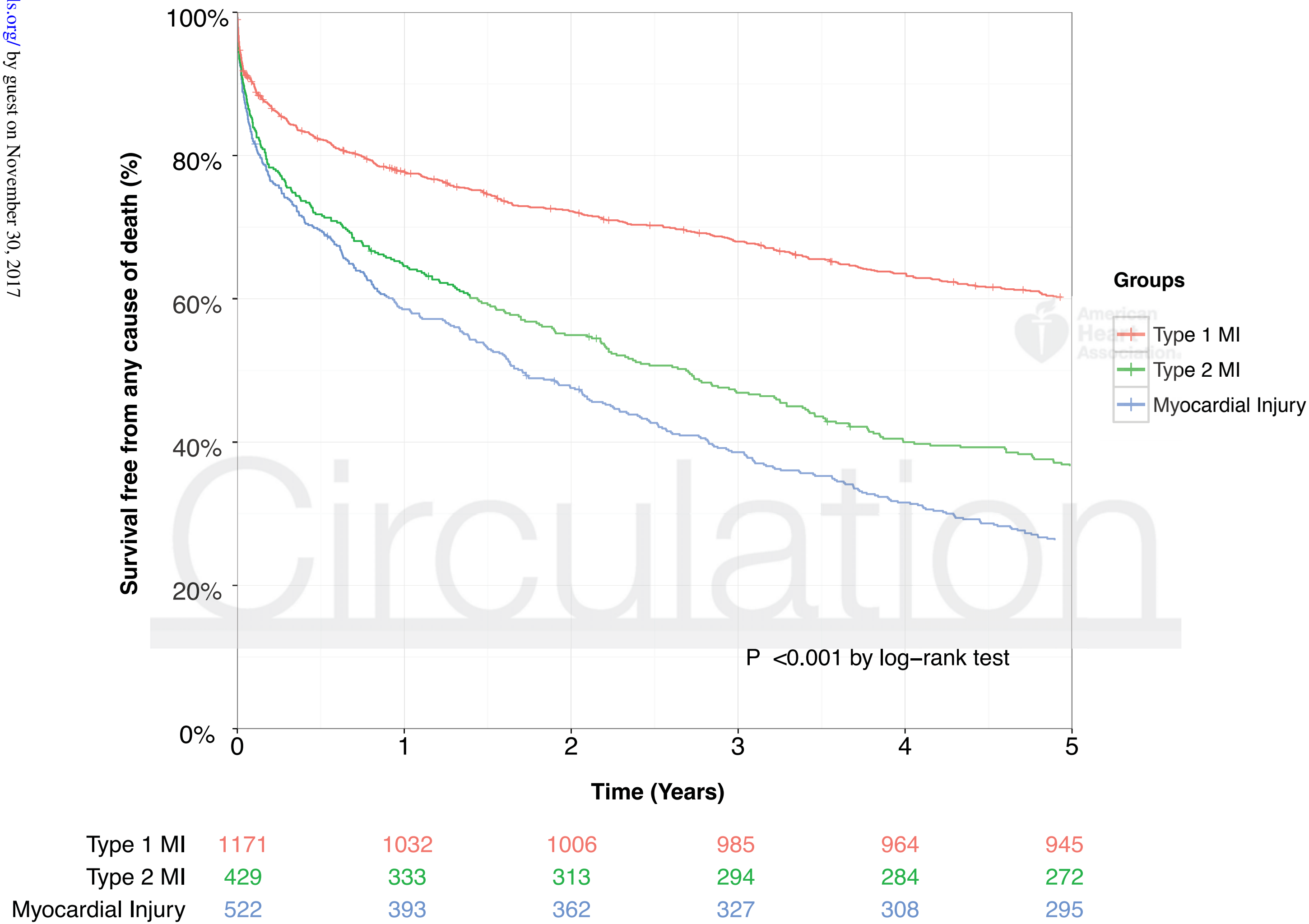
P values obtained from group-wise comparison using Chi-square test. *P<0.001 in post hoc analysis comparing patients with type 2 myocardial infarction or myocardial injury with coronary artery disease versus patients with type 1 myocardial infarction.

Figure Legends

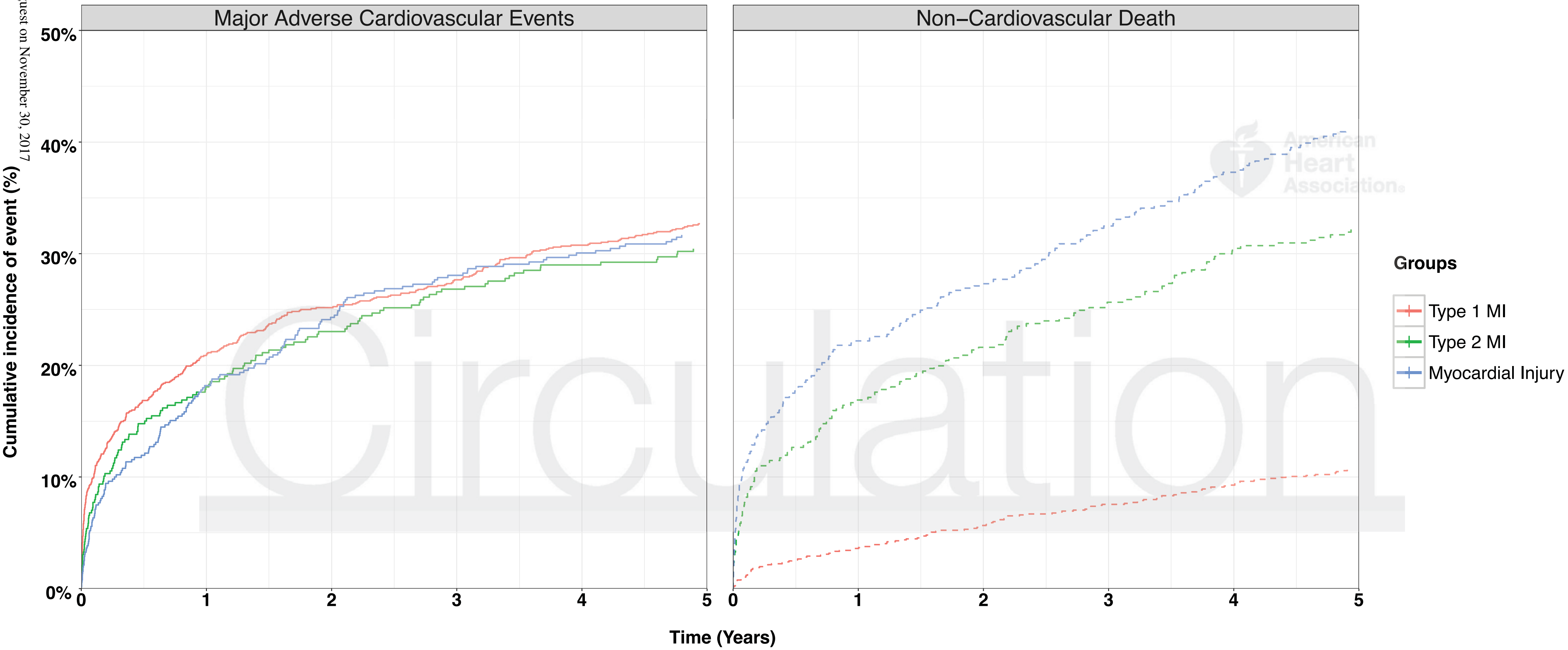
Figure 1. Kaplan-Meier curves illustrating risk of death from any cause at five years stratified by index diagnosis, with table of number at risk. Pair-wise comparison of groups obtained using the log-rank test.

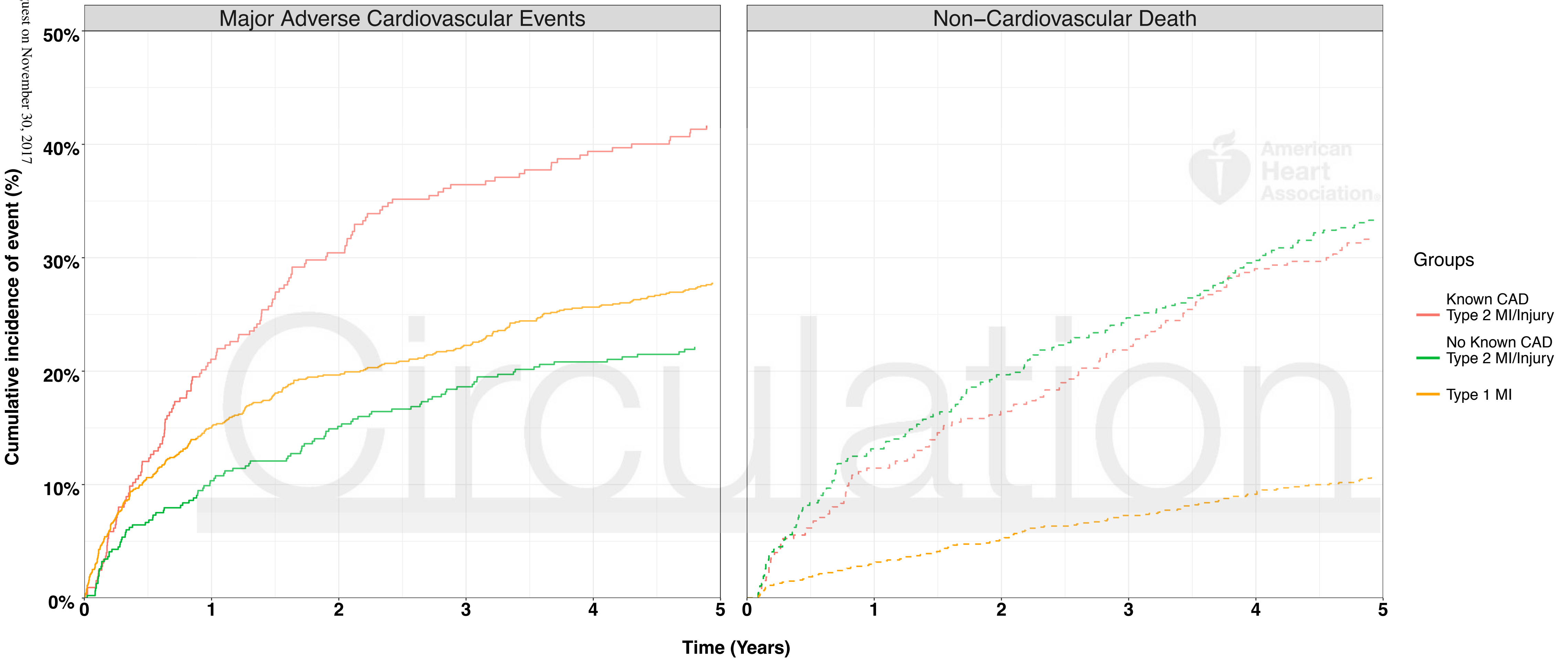
Figure 2. Cumulative incidence curves illustrating risk of major adverse cardiovascular events (MACE; type 1 myocardial infarction or cardiovascular death) and competing risk of non-cardiovascular death at five years stratified by index diagnosis.

Figure 3. Cumulative incidence curves illustrating risk of major adverse cardiovascular events (MACE; type 1 myocardial infarction or cardiovascular death) and competing risk of non-cardiovascular death in those who survive to 30 days in patients with type 1 myocardial infarction, and in those with type 2 myocardial infarction or myocardial injury stratified by known coronary artery disease (CAD).



100%
80%
60%
40%
20%
0%
Survival free from any cause of death (%)
0
1
2
3
4
5
Time (Years)
Groups
Type 1 MI
Type 2 MI
Myocardial Injury
P <0.001 by log−rank test
Type 1 MI 1171 1032 1006 985 964 945
Type 2 MI 429 333 313 294 284 272
Myocardial Injury 522 393 362 327 308 295


Major Adverse Cardiovascular Events
Non−Cardiovascular Death
Cumulative incidence of event (%)
0%
10%
20%
30%
40%
50%
0
1
2
3
4
5
Time (Years)
Groups
Type 1 MI
Type 2 MI
Myocardial Injury


Major Adverse Cardiovascular Events
Non−Cardiovascular Death
Cumulative incidence of event (%)
0%
10%
20%
30%
40%
50%
0
1
2
3
4
5
Time (Years)
Groups
Known CAD
Type 2 MI/Injury
No Known CAD
Type 2 MI/Injury
Type 1 MI
American Heart Association
Circulation

Circulation

Long Term Outcomes in Patients with Type 2 Myocardial Infarction and Myocardial Injury

Andrew R. Chapman, Anoop S. V. Shah, Kuan Ken Lee, Atul Anand, Oliver Francis, Philip Adamson, David A. McAllister, Fiona Strachan, David E. Newby and Nicholas L. Mills

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SUPPLEMENTAL MATERIAL

Long term outcomes in patients with type 2 myocardial infarction and myocardial injury

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Running title: *Long term outcomes of type 2 myocardial infarction*

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Supplemental Table 1. Most common primary discharge diagnoses in patients with an adjudicated diagnosis of type 2 myocardial infarction or myocardial injury.

Type 2 Myocardial Infarction	*Myocardial Injury*
Arrhythmia (19.1%, 82/429)	Heart Failure (12.8%, 67/522)
Pneumonia (13.5%, 58/429)	Arrhythmia (10.9%, 57/522)
Heart Failure (12.4%, 53/429)	Pneumonia (9.6%, 50/522)
Fracture (4.2%, 18/429)	Fracture (8.0%, 42/522)

Supplemental Table 2 – Cause-specific hazard ratios for major adverse cardiovascular events in all patients.

	Major Adverse Cardiovascular Events (MACE)	
	Unadjusted HR (95% CI)	***Adjusted HR (95% CI)***
Age (per 10-year increase)	1.60 (1.50-1.70)	-
Sex (male)	0.85 (0.73-0.98)	1.09 (0.93-1.28)
Haemoglobin (per 10 g/L reduction)	1.18 (1.14-1.21)	1.07 (1.03-1.11)
eGFR (per 10 ml/min reduction)	1.20 (1.17-1.24)	-
Smoking	0.66 (0.55-0.79)	1.26 (1.02-1.56)
Diabetes Mellitus	1.77 (1.49-2.10)	1.36 (1.14-1.64)
Hypertension	1.66 (1.42-1.93)	1.05 (0.89-1.24)
Coronary Artery Disease	2.52 (2.16-2.94)	1.80 (1.52-2.14)
Stroke	1.88 (1.53-2.31)	1.10 (0.89-1.38)
Peripheral Vascular Disease	2.07 (1.65-2.59)	1.45 (1.14-1.86)
Validation phase	1.21 (1.04-1.40)	1.16 (0.99-1.35)
Type 1 Myocardial Infarction	1.00	1.00
Type 2 Myocardial Infarction / Myocardial Injury	1.16 (1.00-1.34)	0.82 (0.69-0.96)

Penalised smoothing splines used for age and eGFR (estimated glomerular filtration rate) in multivariate model. Type 1 Myocardial Infarction as referent group.

Supplemental Table 3 – Adjusted relative risks of primary and secondary outcomes for patients with myocardial injury versus type 2 myocardial infarction

	Myocardial Injury versus Type 2 MI **Adjusted RR (95% CI)**
Death from any cause	1.27 (1.08-1.48)
MACE	0.99 (0.87-1.13)
Non-fatal MI	0.80 (0.61-1.03)
Cardiovascular death	1.07 (0.94-1.22)
Fatal MI	1.18 (0.87-1.58)
Heart failure hospitalization	1.23 (1.03-1.46)
Non-cardiovascular death	1.12 (0.99-1.26)

Models adjusted for age, gender, renal function, haemoglobin and history of hypertension, stroke, peripheral vascular disease, diabetes mellitus, smoking, coronary artery disease and study phase.

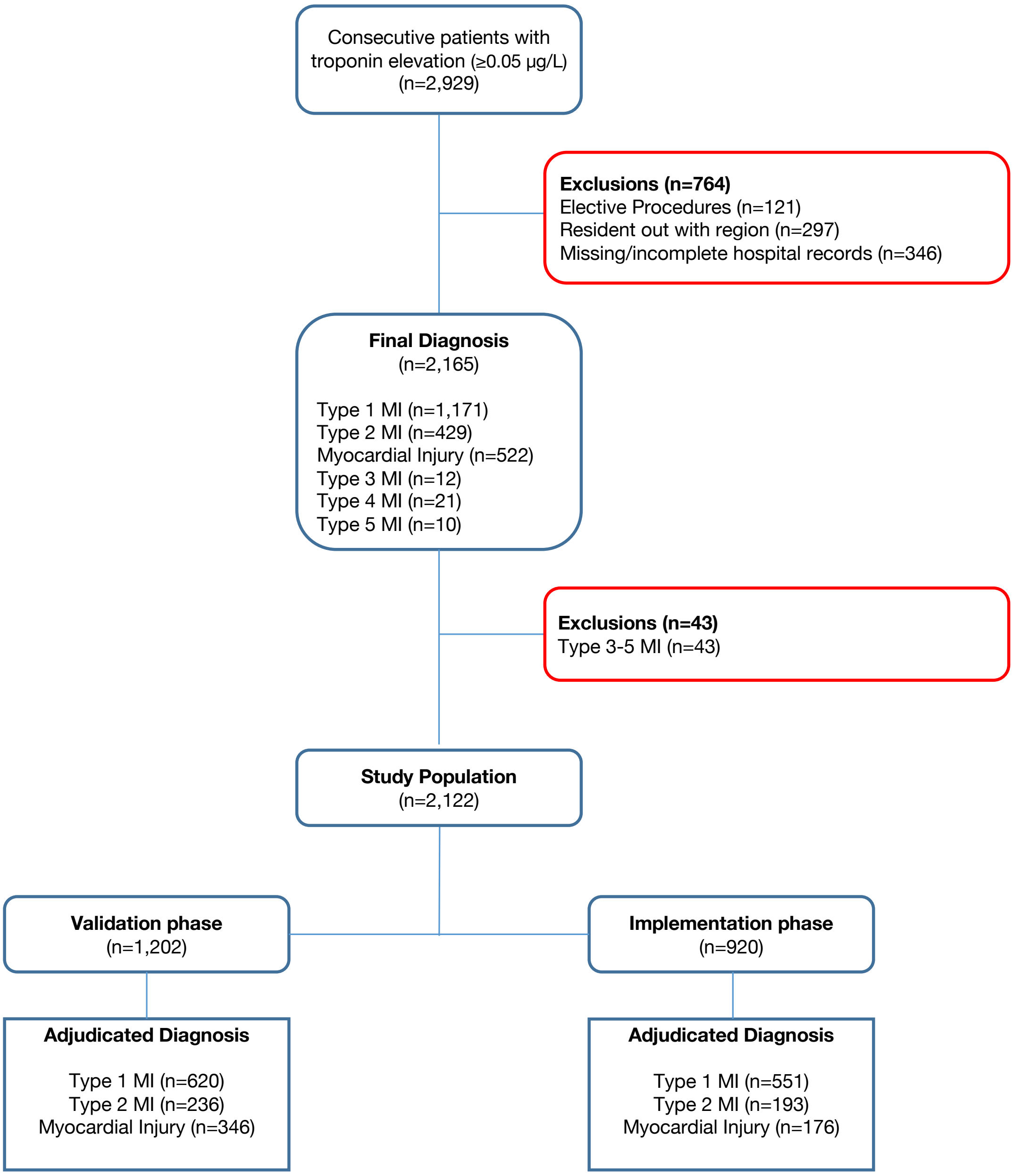
Supplemental Table 4. Death and major cardiovascular events at 5 years stratified by diagnosis in those who survived index hospitalization

	Type 1 MI (n=1,074)	Type 2 MI (n=368)	Myocardial injury (n=437)	Type 2 MI versus Type 1 MI Adjusted RR (95% CI)	Myocardial Injury versus Type 1 MI Adjusted RR (95% CI)
Death from any cause	333 (31.0%)	207 (56.1%)	293 (67.0%)	1.52 (1.21-1.92)	1.95 (1.60-2.39)
MACE	298 (27.7%)	101 (27.4%)	135 (30.9%)	0.80 (0.65-0.98)	0.87 (0.73-1.02)
Non-fatal MI	198 (18.4%)	41 (11.1%)	34 (7.8%)	0.60 (0.45-0.81)	0.46 (0.34-0.64)
Cardiovascular death	172 (16.0%)	77 (20.9%)	118 (27.0%)	0.95 (0.76-1.18)	1.07 (0.90-1.27)
Fatal MI	32 (3.0%)	9 (2.4%)	17 (3.9%)	0.65 (0.38-1.14)	0.90 (0.61-1.31)
Heart failure hospitalization	92 (8.6%)	22 (6.0%)	39 (8.9%)	0.86 (0.58-1.26)	1.18 (0.91-1.52)
Non-cardiovascular death	145 (13.5%)	121 (32.8%)	162 (37.1%)	1.55 (1.28-1.88)	1.61 (1.38-1.88)

Supplemental Table 5. – Cause-specific hazard ratios for major adverse cardiovascular events in patients with type 2 myocardial infarction *or* myocardial injury alone *who survive from their initial presentation to 30 days*; unadjusted and fully adjusted cox-regression models.

	Major Adverse Cardiovascular Events (MACE)	
	Unadjusted HR (95% CI)	***Adjusted HR (95% CI)***
Age (per 10-year increase)	1.56 (1.39-1.75)	1.53 (1.34-1.75)
Sex (male)	1.08 (0.84-1.38)	1.26 (0.97-1.64)
Haemoglobin (per 10 g/L reduction)	1.10 (1.04-1.16)	1.04 (0.99-1.10)
eGFR (per 10 ml/min reduction)	1.16 (1.10-1.21)	1.11 (1.05-1.17)
Smoking	0.86 (0.60-1.23)	1.39 (0.94-2.05)
Diabetes Mellitus	1.79 (1.36-2.35)	1.50 (1.12-2.01)
Hypertension	1.61 (1.24-2.10)	1.02 (0.76-1.36)
Stroke	1.54 (1.12-2.13)	1.12 (0.80-1.55)
Peripheral Vascular Disease	2.43 (1.68-3.50)	1.82 (1.21-2.74)
Validation phase	1.19 (0.92-1.53)	1.25 (0.96-1.63)
Coronary Artery Disease	2.21 (1.73-2.83)	1.71 (1.31-2.24)

eGFR = estimated glomerular filtration rate. Patients without coronary artery disease as referent group.



Supplemental Figure 1. – CONSORT Diagram with identification of the study population. Consecutive patients with elevation in cardiac troponin concentration were identified (≥0.05 µg/L). We excluded patients who underwent elective procedures, residents not local to our region or with missing or incomplete records. After adjudication, we excluded those with Type 3-5 myocardial infarction.

Supplemental Appendix 1. Analysis code

All analysis was performed using R (version 3.2.2) using the *survival* and *cmprsk* packages. For transparency, the analysis code is available open source via GitHub.[3]

Available at https://github.com/a-r-chapman/type_2_outcomes

Supplemental Appendix 2. Additional information on diagnostic adjudication

Criteria for adjudication of patients with myocardial necrosis

Type 1 myocardial infarction	Myocardial necrosis (any cardiac troponin I [cTnI] concentration above the upper reference limit) with rise and or fall in cTnI concentration where serial testing was available AND symptoms OR signs of myocardial ischaemia
Type 2 myocardial infarction	Myocardial necrosis (any cTnI concentration above the upper reference limit) with rise and or fall in cTnI concentration where serial testing was available AND symptoms OR signs of myocardial ischaemia AND evidence of increased oxygen demand (e.g. tachyarrhythmia, hypertrophy) or reduced supply (e.g. hypotension, hypoxia or anaemia) in context of alternative clinical diagnosis
Myocardial injury	Myocardial necrosis (any cTnI concentration above the upper reference limit) without symptoms OR signs of myocardial ischaemia in context of alternative clinical diagnosis

The process of adjudication was conducted by two cardiologists independently. Both had access to the electronic patient record. The adjudicated diagnosis was reached by evaluating the attending clinicians documentation of the presenting complaint, past medical history, cardiovascular risk factors and clinical examination findings including routine observations (pulse, blood pressure, pulse oximetry, temperature and conscious level). All investigation results undertaken by the attending clinician were available for review, including biochemistry and haematology results, the 12 lead electrocardiogram, echocardiogram, chest X-ray and invasive coronary angiography findings when performed. Both adjudicating cardiologists had access to the final discharge letter documenting the attending clinicians' final diagnosis. We did not apply specific criteria to define supply or demand imbalance,[1] but adjudicated myocardial supply or demand imbalance on an individual patient basis, in line with most studies in this area.[2]

Upper reference limit = 0.05 µg/L

Supplemental Appendix 3. Additional information on classification of cardiovascular death

ICD Code	Definition
Ischaemic heart diseases	
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications from acute myocardial infarction
I24	Other acute ischaemic heart diseases
I25	Chronic ischaemic heart disease
Other forms of heart disease	
I34	Non-rheumatic mitral valve disorders
I35	Non-rheumatic aortic valve disorders
I36	Non-rheumatic tricuspid valve disorders
I37	Pulmonary valve disorders
I42	Cardiomyopathy
I43	Cardiomyopathy in diseases classified elsewhere
I46	Cardiac arrest
I48	Atrial fibrillation and flutter
I49	Other cardiac arrhythmias
I50	Heart failure
I51	Complications and ill-defined descriptions of heart disease
Cerebrovascular diseases	
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracerebral haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction

I65	Occlusion and stenosis of precerebral arteries, not resulting in infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease

Supplemental References

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