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Association between clinical presentations before myocardial infarction and coronary mortality: a prospective population-based study using linked electronic records

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Background Ischaemia in different arterial territories before acute myocardial infarction (AMI) may influence post-AMI outcomes. No studies have evaluated prospectively collected information on ischaemia and its effect on short- and long-term coronary mortality. The objective of this study was to compare patients with and without prospectively measured ischaemic presentations before AMI in terms of infarct characteristics and coronary mortality.

Methods and results As part of the CALIBER programme, we linked data from primary care, hospital admissions, the national acute coronary syndrome registry and cause-specific mortality to identify patients with first AMI ($n = 16{,}439$). We analysed time from AMI to coronary mortality ($n = 5283$ deaths) using Cox regression (median 2.6 years follow-up), comparing patients with and without recent ischaemic presentations. Patients with ischaemic presentations in the 90 days before AMI experienced lower coronary mortality in the first 7 days after AMI compared with those with no prior ischaemic presentations, after adjusting for age, sex, smoking, diabetes, blood pressure and cardiovascular medications [HR: 0.64 (95% CI: 0.57–0.73) $P < 0.001$], but subsequent mortality was higher [HR: 1.42 (1.13–1.77) $P = 0.001$]. Patients with ischaemic presentations closer in time to AMI had the lowest seven day mortality (P-trend = 0.001).

Conclusion In the first large prospective study of ischaemic presentations prior to AMI, we have shown that those occurring closest to AMI are associated with lower short-term coronary mortality following AMI, which could represent a natural ischaemic preconditioning effect, observed in a clinical setting.

Clinical trials registration Clinicaltrials.gov identifier NCT01604486.

Keywords Myocardial infarction • Epidemiology • Ischaemia

Introduction

Roughly half of patients with acute myocardial infarctions (AMIs) have been previously diagnosed with atherosclerotic disease or have reported chest pain to their physician.[1] Myocardial ischaemia occurring shortly prior to AMI has been associated with smaller infarct sizes.[2–4] This effect has been attributed to ischaemic preconditioning, the phenomenon by which brief episodes of ischaemia prior to a prolonged ischaemic insult can improve outcomes.[5,6] There has also been growing interest in the use of remote ischaemic

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preconditioning as an intervention in experimental studies[7] and randomized trials to improve outcomes after coronary interventions.[8–10] However, there is also evidence that patients with prior atherosclerotic disease diagnoses in one or more arterial territory are likely to have more advanced atherosclerotic disease and therefore poorer outcomes.[11] The effect of myocardial or remote ischaemia at different times prior to a first AMI on subsequent coronary mortality is unclear, especially in the longer term (Supplementary material online, *Table S1*).[3,12–14]

No studies have evaluated prospectively collected information on pre-AMI ischaemia and the effects on short- and long-term coronary mortality. Using prospective data to define exposure to ischaemia is important because in experimental models the time course of ischaemia is critical.[15] We have identified three other major limitations of the epidemiological evidence to date. First, previous studies have been restricted to myocardial ischaemia despite interest in the conditioning effects of remote ischaemia occurring in other arterial beds.[7,9] Second, most previous studies have been in hospitalized patients only and with further selection criteria (e.g. patients aged ≥75,[12] who met screening criteria for trial entry,[16] or were able to provide a clear history of angina[3]), which means that the extent of ischaemic presentations prior to AMI in general populations is unclear. Third, previous studies have been unable to assess whether the apparent protective effect was confounded by receipt of risk-lowering medications.

We sought to address these limitations by performing a large, prospective study of the occurrence, timing and associated outcomes of ischaemic presentations, including atherosclerotic disease in different arterial beds and chest pain before non-fatal and fatal AMI, both in and out of hospital. The first objective was to compare patients with and without pre-AMI ischaemic presentations in terms of AMI characteristics including type [ST-elevation MI (STEMI) and non ST-elevation MI (NSTEMI)] and severity. The second objective was to examine the association between pre-AMI ischaemic presentations and short- and long-term coronary mortality, and the third to determine whether cardiovascular medications given in response to these ischaemic presentations are associated with coronary heart disease mortality.

Methods

Study design

The prospectively collected medical records of a cohort of AMI patients were reviewed to assess the occurrence of chest pain and ischaemic atherosclerotic disease in any arterial bed in the 90 days prior to AMI. Those with and without these presentations were compared in terms of their AMI characteristics and subsequent coronary mortality.

Data sources

As part of the CALIBER research programme (Cardiovascular disease research using Linked Bespoke studies and Electronic health Records),[17] the records of patients in the Myocardial Ischaemia National Audit Project (MINAP, the national registry of acute coronary syndrome[18]), and Hospital Episode Statistics (HES, hospital discharge data set[19]) were linked to longitudinal electronic health records from primary care in the General Practice Research Database (GPRD[20]) and to Office for National Statistics (ONS[21]) cause-specific mortality data (for details, see Supplementary material online, *Table S2*). Linkage was performed by a trusted third party and was based on National Health Service (NHS) number, date of birth, gender and postcode. Around 40% of the general practices in GPRD (all English) permitted linkage.[22]

Definition of acute myocardial infarction

Patients with non-fatal and fatal AMI were identified based on a record in any one of the four data sources; in MINAP using cardiac markers and electrocardiogram findings, Read codes in GPRD, ICD-10 codes in HES and ONS mortality data (full definitions in Supplementary material online, *Table S2*). We excluded those with a recorded history of AMI ($n = 6337$), under the age of 18 at AMI ($n = 2$), not registered with the primary care practice for at least 1 year before AMI ($n = 8516$), whose AMIs occurred outside the period where all databases were collecting data (outside 1 January 2003 to 31 December 2008, $n = 23\,804$), and patients without any primary care consultations in their record prior to AMI ($n = 12$).

Categorization of ischaemia before acute myocardial infarction

Patients were initially categorized into three groups based on their pre-AMI experience of ischaemic atherosclerotic disease (coronary, cerebrovascular, and peripheral arterial disease, see Supplementary material online, *Table S3*) and chest pain, according to the scheme in *Figure 1*.

Patients with 'no prior ischaemic presentations' had no atherosclerotic disease in their electronic health record and no consultations for chest pain in the 90 days before AMI. Patients with 'new ischaemic presentations' had either a new atherosclerotic disease diagnosis in the 90 days before AMI (either first ever diagnosis or diagnosis in a new arterial bed, e.g. new coronary disease diagnosis in the presence of longer-term cerebrovascular disease) or a chest pain consultation in the 90 days before AMI. Patients with 'existing ischaemic diseases' had no new atherosclerotic disease diagnoses or chest pain consultations in the 90 days before AMI but had long-standing atherosclerotic disease (>90 days' duration). The timing of the onset of atherosclerotic disease was taken as the date of the first code indicating disease in the patient's record.

In the second part of the analysis, the timing of the closest ischaemic presentation prior to AMI was split into categories (1–2, 3–7, 8–30, and 31–90 days before AMI) based on the time periods used in previous studies of prodromal angina.[14,16,23–27]

Cardiovascular risk factors and risk-lowering medication prior to acute myocardial infarction

Age, sex, ethnicity, deprivation (based on the Index of Multiple Deprivation 2007, a measure of socio-economic status),[28] risk factors and primary care consultation rate were taken from primary care or hospital records. Risk factors included smoking, hypertension, total serum cholesterol, HDL cholesterol, and diabetes (Supplementary material online, *Table S3*). Blood pressure lowering, lipid lowering, and antiplatelet medication prescriptions in the 6 months prior to AMI were determined based on prescriptions issued in primary care and use of these drugs at hospital admission.

Follow-up after acute myocardial infarction and primary outcome

Patients with AMI were followed up for a median of 2.6 years (range 0–7.7 years) after AMI. The primary outcome was coronary heart disease death (ICD-10 codes I20-I25).

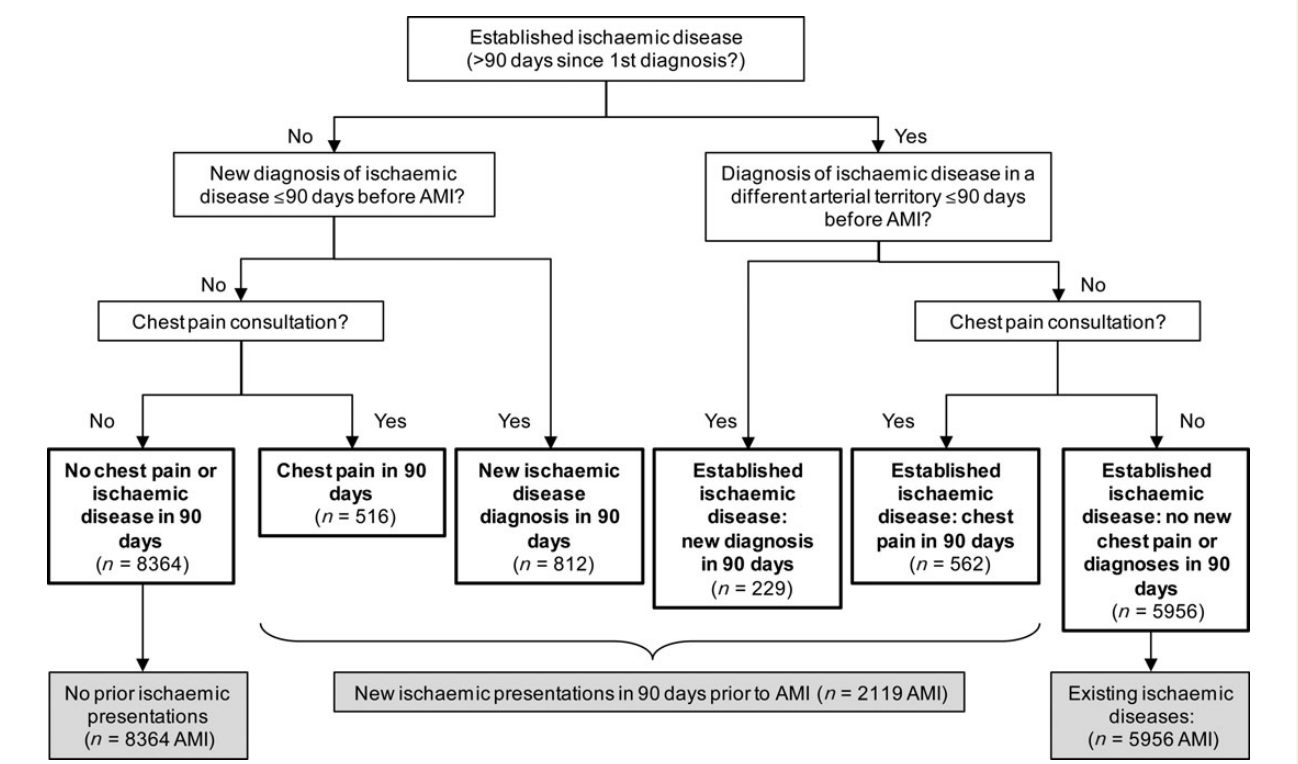


Figure 1 Use of prospectively collected data to categorize patients who subsequently went on to experience acute myocardial infarction ($n = 16\,439$), according to prior atherosclerotic disease and chest pain consultations. Note: Atherosclerotic disease, defined as myocardial ischaemia (stable or unstable angina, percutaneous coronary ischaemia, coronary artery bypass graft), cerebral ischaemia (ischaemic stroke, transient ischaemic attack), and new peripheral arterial disease diagnoses including intermittent claudication (Supplementary material online, *Table S3*). New ischaemic presentations in patients with established ischaemic disease represent new chest pain in the context of existing cerebrovascular or peripheral arterial disease, or a diagnosis of ischaemic disease in a new arterial territory.

Statistical analysis

Characteristics of MINAP AMI patients in each exposure group were compared using χ^2 tests for categorical variables, Kruskal–Wallis tests for medians, and *t*-tests for means. Cox regression analysis was used to compare post-AMI coronary mortality. Tests for proportional hazards were performed on all models and interactions with time were fitted where there was non-proportionality. In the first instance, interactions with time were fitted based on follow-up time categories of 0–7, 8–30, 31–90, 91 days to 1 year and 1–2 years, which we considered to be the time points at which the mortality effects may change. The 0–7 day category is approximately concordant with average duration of hospital stay, making it akin to in-hospital mortality, which is an outcome in the majority of studies of this type. We then combined the time periods where the effect of previous ischaemic presentations was similar, based on similar effect measures and assessed using likelihood ratio tests. Regression analyses were adjusted for age, sex, cardiovascular risk factors and medications. Details of *post hoc* and sensitivity analyses are described in the Supplementary material online.

All analyses were performed in Stata version 11. The study details are registered online at clinicaltrials.gov (NCT01604486, May 2012) and a time-stamped detailed analytic protocol is available on request. CALIBER has received ethics approval (ref 09/H0810/16) for creation of linked pseudoanonymized data encompassing GPRD, HES, MINAP, and ONS.

Results

We identified 16 439 patients with first AMI who met all inclusion criteria. Over one-fifth of these patients were fatal AMI with no hospital record; 2119 (12.9%) patients presented to their family physician with *new ischaemic presentations* (as defined in methods, *Figure 1*) in the 90 days before AMI, 8364 (50.9%) had *no prior ischaemic presentations*, and 5956 (36.2%) had *existing ischaemic diseases* with no new presentations in the 90 days before AMI. Patients with existing ischaemic disease had the highest pre-AMI Framingham risk (for hard coronary endpoints), those with new ischaemic presentations before AMI had intermediate risk, and those with no prior ischaemic presentations had the lowest risk (*Table 1*, $P < 0.001$).

Timing of ischaemic presentations before acute myocardial infarction

Of the 2119 patients who had ischaemic presentations in the 90 days prior to AMI, 452 (2.7%) patients first presented in the 1–2 days prior to AMI, 405 (2.5%) in 3–7 days, 676 (4.1%) in 8–30 and 586 (3.6%) in the 31–90 days. A full description of the diagnoses made during these periods is shown in Supplementary material online, *Table S4*. Chest pain, stable angina, and coronary disease of unspecified type were

Table 1 Prospectively collected patient characteristics of patients with and without ischaemic presentations in the 90 days before acute myocardial infarction (n = 16 439 acute myocardial infarction)

	No new ischaemic presentations	New ischaemic presentations in 90 days before AMI	Existing ischaemic diseases[a]
n patients with AMI	8364	2119	5956
Age, median (IQR)	68 (57–79)	72 (61–81)	79 (70–85)
Women, *n* (%)	3030 (36.2)	803 (37.9)	2652 (44.5)
Most deprived IMD quintile	1603 (19.2)	399 (18.9)	1281 (21.5)
Smoking, *n* (%)			
Non-smoker	1225 (14.6)	282 (13.3)	792 (13.3)
Ex-smoker	4055 (48.5)	1262 (59.6)	3876 (65.1)
Current smoker	2830 (33.8)	554 (26.1)	1186 (19.9)
Unknown	254 (3)	21 (1)	102 (1.7)
Hypertension, *n* (%)	3725 (44.5)	1264 (59.7)	4320 (72.5)
Total serum cholesterol in mmol/L, mean (SD)	5.6 (0.8)	5.6 (0.9)	5.3 (1)
HDL cholesterol in mmol/L, mean (SD)	1.3 (0.3)	1.3 (0.3)	1.4 (0.3)
Diabetes, *n* (%)	1026 (12.3)	377 (17.8)	1505 (25.3)
Framingham 10 year CHD risk, *n* (%)			
<10%	1940 (22.9)	390 (17.7)	639 (11.1)
10–20%	4776 (56.3)	1181 (53.6)	2973 (51.7)
>20%	1763 (20.8)	633 (28.8)	2134 (37.1)
Blood pressure lowering drugs, *n* (%)			
First prescription in 90 days	82 (1)	130 (6.1)	51 (0.9)
Any prescription in 90 days	2,867 (34.3)	1,220 (57.6)	4,261 (71.5)
Lipid-lowering drugs, *n* (%)			
First prescription in 90 days	103 (1.2)	158 (7.5)	132 (2.2)
Any prescription in 90 days	918 (11)	668 (31.5)	2,601 (43.7)
Antiplatelet drugs, *n* (%)			
First prescription in 90 days	79 (0.9)	253 (11.9)	72 (1.2)
Any prescription in 90 days	825 (9.9)	883 (41.7)	3,283 (55.1)

IQR, inter-quartile range; SD, standard deviation; IMD, index of multiple deprivation; HDL, high-density lipoprotein; CHD, coronary heart disease .
[a]Patients in the 'existing ischaemic diseases' group had no new ischaemic presentations in the 90 days prior to AMI.

the most common presentations in the period before AMI both in patients with and without established atherosclerotic disease.

Myocardial infarction characteristics

Among 6695 MINAP patients, those who presented with new ischaemia in the 90 days before AMI or with existing ischaemic diseases were more likely to have a NSTEMI compared with patients who did not present (68.1% and 68.3 vs. 46.4%, respectively, $P < 0.001$). Acute myocardial infarction size, measured by peak troponin values, was lower ($P < 0.001$) in those with new ischaemic presentations (median 1.3 μg/L, IQR: 0.3–6.9), and in patients with existing ischaemic diseases (1.4 μg/L, 0.3–7.5) compared with those without prior ischaemic presentations (2.6 μg/L, 0.6–12.8), but systolic blood pressure was similar in the three groups. The median heart rate at admission was similar in those with new ischaemic presentations to those without any prior disease but higher in those with existing ischaemic diseases (*Table 2*). Both STEMI and NSTEMI patients who had presented with new ischaemic presentations in the 90 days prior to AMI had smaller infarct sizes than patients who did not present (Supplementary material online, *Table S6*).

Post-acute myocardial infarction coronary mortality

Crude 1 week mortality rates for patients in each of the three analytic groups are described in *Figure 2*, which shows that patients with new ischaemic presentations prior to AMI had lower mortality than those with no prior ischaemic presentations or patients with existing ischaemic diseases.

Patients with ischaemic presentations in the 90 days before AMI had lower coronary mortality in the first 7 days after AMI compared with patients with no prior ischaemic presentations, even after adjustment for age, sex, cardiovascular risk factors and cardiovascular medication prescriptions in the 6 months before AMI [HR: 0.64 (95% CI: 0.57–0.73), $P < 0.001$]. This analysis included deaths prior to and during hospital admission. In this first week after AMI, there was borderline evidence of an effect of existing ischaemic

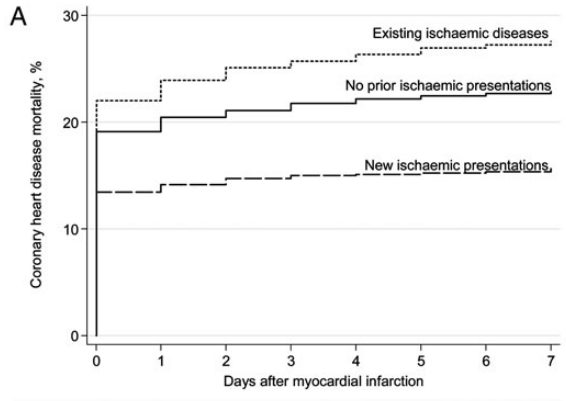
Table 2 Myocardial infarction characteristics among acute myocardial infarction patients recorded in the MINAP registry, in those with and without ischaemic presentations in the 90 days before acute myocardial infarction ($n = 6695$)

	No prior ischaemic presentations	New ischaemic presentations in 90 days before AMI	Existing ischaemic diseases[a]
n AMI	3796	681	2218
AMI type, *n* (%)			
STEMI	2192 (57.7)	257 (37.7)***	786 (35.4)***
NSTEMI	1604 (42.3)	424 (62.3)	1432 (64.6)
ECG record, *n* (%)			
ST segment elevation	2094 (55.2)	237 (34.8)***	719 (32.4)***
Left bundle branch block	91 (2.4)	23 (3.4)	134 (6)
ST segment depression	385 (10.1)	110 (16.2)	414 (18.7)
T-wave changes only	437 (11.5)	97 (14.2)	283 (12.8)
other abnormality	288 (7.6)	79 (11.6)	283 (12.8)
Normal ECG	209 (5.5)	45 (6.6)	139 (6.3)
Unknown	292 (7.7)	90 (13.2)	246 (11.1)
Peak troponin in μg/L, median (IQR)	2.6 (0.6–13)	1.3 (0.3–6.9)***	1.4 (0.3–7.5)***
Unknown, *n* (%)	655 (17.3)	85 (12.5)	261 (11.8)
Raised markers, *n* (%)	3408 (89.8)	610 (89.6)	2006 (90.4)
Unknown, *n* (%)	388 (10.2)	71 (10.4)	212 (9.6)
Heart rate at admission (b.p.m.), median (IQR)	77 (64–91)	77 (65–90)	80 (68–98)***
Unknown, *n* (%)	857 (22.6)	156 (22.9)	487 (22)
Systolic BP at admission (mmHg), median (IQR)	140 (122–160)	138 (122–157)	140 (120–159)
Unknown, *n* (%)	861 (22.7)	158 (23.2)	481 (21.7)
Reperfusion, *n* (%)			
Thrombolysis	1662 (43.8)	180 (26.4)***	526 (23.7)***
PCI or CABG	274 (7.2)	23 (3.4)***	88 (4)***
Reperfusion NOS	10 (0.5)	1 (0.2)	5 (0.3)
Time to admission in minutes, median (IQR)	144.2 (80.8–360.4)	175.9 (89.6–500.3)**	159.5 (85.2–356.1)
Unknown, *n* (%)	905 (23.8)	235 (34.5)	681 (30.7)
Admission to reperfusion in minutes, median (IQR)	24 (13.1–50.2)	28.4 (17.5–61.2)**	28.4 (15.3–61.2)***
Unknown, *n* (%)	1936 (51)	482 (70.8)	1634 (73.7)
Symptom onset to reperfusion in minutes, median (IQR)	146.4 (96.1–281.8)	172.6 (104.9–345.2)*	170.4 (111.4–290.5)**
Unknown, *n* (%)	2,166 (57.1)	511 (75)	1704 (76.8)

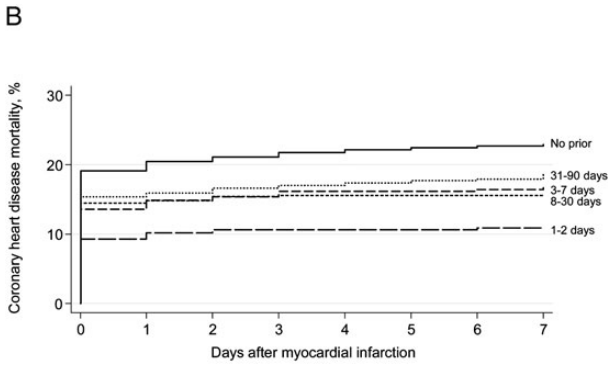
AMI, acute myocardial infarction; MINAP, Myocardial Ischaemia National Audit Project; STEMI, ST-elevation MI; NSTEMI, non ST-elevation MI; BP, blood pressure; IQR, inter-quartile range; b.p.m., beats per minute; ECG, electrocardiogram; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NOS, not otherwise specified.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared with patients with no prior ischaemic presentations, from the χ^2 test for categorical variables, the Kruskal–Wallis test for comparing medians, T-test for comparing means.
[a]Patients in the 'existing ischaemic diseases' group had no new ischaemic presentations in the 90 days prior to AMI.

diseases on coronary mortality [HR: 0.92 compared with no prior ischaemic presentations (95% CI: 0.85–1.00) $P = 0.05$] (*Figure 3*). There was no evidence that these associations were modified by age, sex, previous hypertension, or reperfusion strategy ($P > 0.05$ in each case). Among all patients with AMI, the risk of dying before hospitalization was lower for those with new ischaemic presentations (where the fully adjusted odds ratio for death before hospitalization in those with new ischaemic presentations was 0.64 (95% CI: 0.55–0.74), $P < 0.001$ compared with those with no prior ischaemic presentations).

During the 7–90 days after AMI, the protective effect seen in the first week was lost [adjusted HR for new ischaemic presentations 0.88 (95% CI: 0.65–1.20), $P = 0.421$]. For patients with existing ischaemic diseases, this time period saw an increase in the rate of mortality [adjusted HR: 1.24 (1.01–1.51), $P = 0.038$] (*Figure 3*). From 90 days after AMI, there was evidence for higher mortality risk in those with new ischaemic presentations prior to AMI [adjusted HR: 1.42 (95% CI: 1.13–1.77) $P = 0.001$]. There was also a stronger effect of existing ischaemic diseases during this period [adjusted HR: 2.24 (95% CI: 1.91–2.64) $P < 0.001$].



Number at risk at start of risk period							
No prior ischaemic presentations	8364	6646	6521	6463	6399	6358	6329
New ischaemic presentations	2119	1768	1753	1738	1732	1726	1724
Existing ischaemic diseases	5956	4488	4367	4295	4255	4212	4174



Number at risk at start of period							
No prior	8364	6646	6521	6463	6399	6358	6329
1-2 days	452	403	399	397	397	397	397
3-7 days	405	334	329	327	324	324	324
8-30 days	676	563	560	556	555	554	554
31-90 days	586	468	465	458	456	451	449

Note: "No prior" indicates no prior ischaemic presentations, "1-2 days" indicates new ischaemic presentations 1-2 days prior to MI, "3-7 days" indicates new ischaemic presentations 3-7 days prior to MI, etc.

Figure 2 Crude Kaplan–Meier-based cumulative incidence curves for 7 day coronary heart disease mortality following acute myocardial infarction (*A*) in patients with no prior ischaemic presentations ($n = 8364$), with new ischaemic presentations in the 90 days before acute myocardial infarction ($n = 2119$) and with existing ischaemic diseases ($n = 5956$), and (*B*) in patients with no prior ischaemic presentations ($n = 8364$) and patients with new ischaemic presentations at different times prior to acute myocardial infarction.

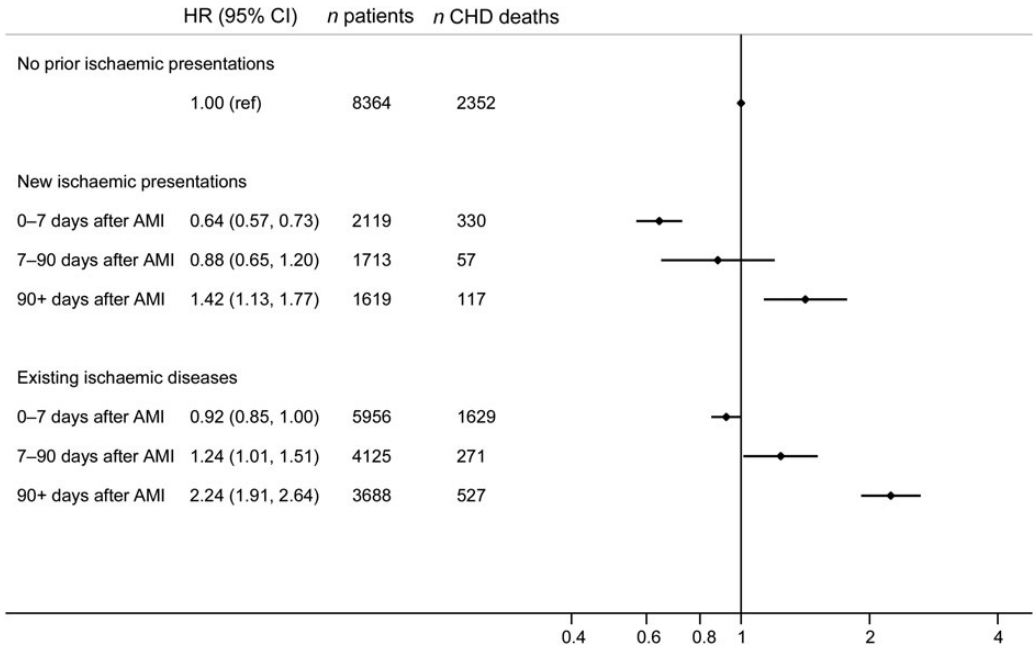


Figure 3 Association of new ischaemic presentations and coronary heart disease mortality at 7 , 7–90, and 90+ days (up to 7.6 years) after acute myocardial infarction. Note: Hazard ratios are adjusted for age, sex, smoking, hypertension, diabetes, total cholesterol, anti-anginal, blood pressure lowering, lipid lowering, and antiplatelets in the 6 months before acute myocardial infarction. HR, hazard ratio; AMI, acute myocardial infarction.

There was a strong effect of the timing of clinical presentation prior to AMI on coronary mortality in the week after AMI (test for trend $P = 0.001$). Patients who presented in the 1–2 days before AMI had the lowest rate of coronary mortality [adjusted HR: 0.53 (95% CI: 0.40–0.71) $P < 0.001$], with an intermediate level for those presenting in the 3–7 and 8–30 days before, and with a persistent effect in patients presenting 31–90 days before AMI [adjusted HR: 0.80 (95% CI: 0.64–0.99) $P = 0.042$] (*Figure 4*).

Possible explanations for improved short-term mortality

We undertook several *post hoc* and sensitivity analyses to explain the results found in the main analysis. These analyses are detailed in the Supplementary material: in brief we noted that (i) on stratifying our analysis by AMI type (where available), the effect of new ischaemic presentations in the 90 days prior to AMI on 7 day coronary mortality in NSTEMI was similar to the main effect HR = 0.61 (0.30–1.23), but the effect in STEMI was 0.83 (0.48–1.41) (*P*-value for interaction 0.69), though given limited power, the observed differences could reflect chance variation; (ii) time from symptom onset to hospital admission and time to reperfusion were longer in the group with new ischaemic presentations in the 90 days before AMI; (iii) neither use of cardiovascular medications nor coronary (Framingham) risk score appeared to confound the observed associations between prior presentations and mortality, (iv) the protective association was retained on adjusting for infarct size, but there were few patients with infarct size recorded and this reduced the power of the analysis to detect an effect.

Discussion

Summary

The current study provides new insight into the epidemiology of ischaemic presentations before AMI and their associations with coronary mortality by utilizing prospectively collected data prior to AMI. In this analysis of fatal and non-fatal AMI patients, those with ischaemic presentations in the 90 days preceding AMI had a lower rate of coronary mortality in the week following AMI compared with those with no prior ischaemic presentations. This effect was largest in patients who consulted in the 2 days before their infarct. Over the following

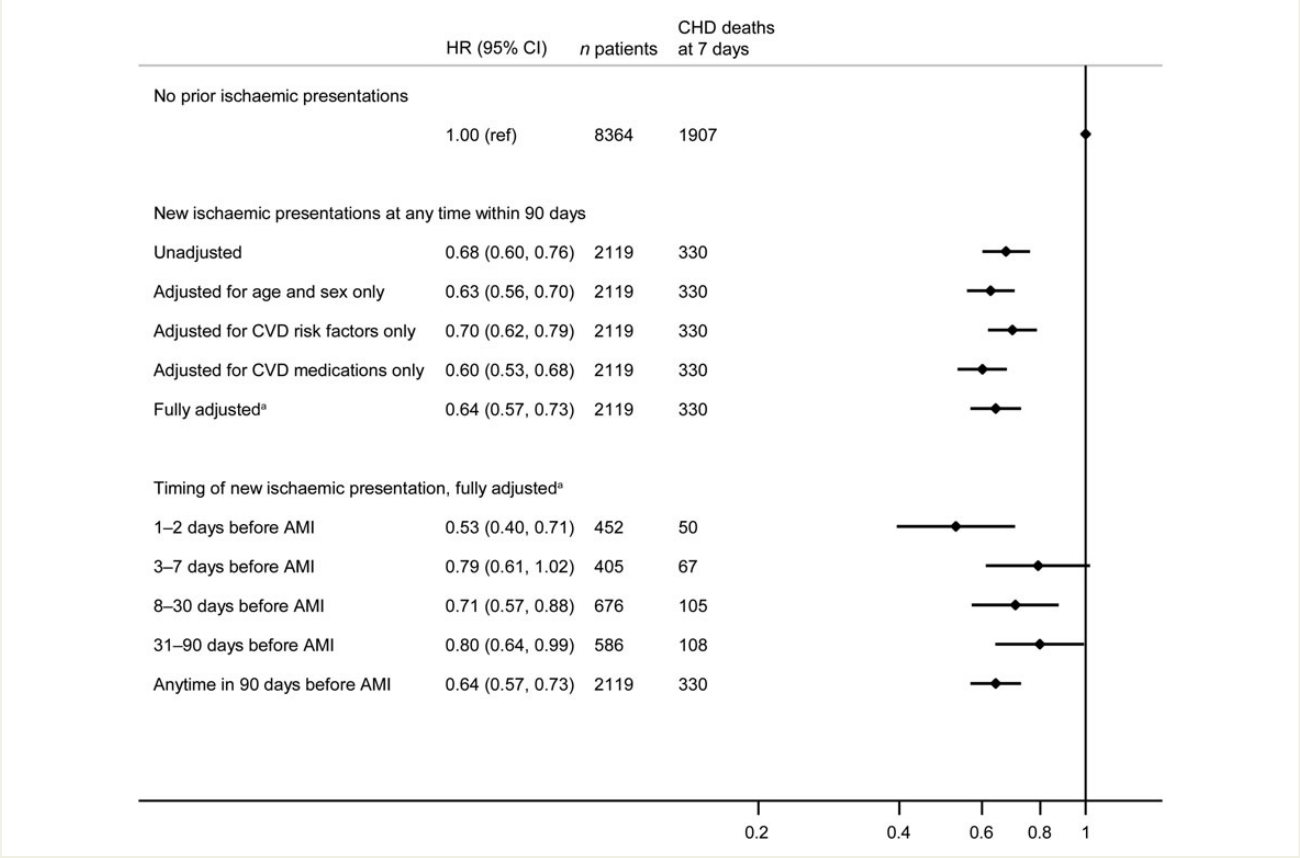


Figure 4 Association of new ischaemic presentations and coronary heart disease mortality at 7 days after acute myocardial infarction, and the effect of new ischaemic presentations at different times prior to acute myocardial infarction. [a]Fully adjusted model includes age, sex, cardiovascular disease risk factors, cardiovascular disease medications. Cardiovascular disease risk factors included smoking, hypertension, diabetes, total cholesterol. Cardiovascular disease medications included anti-anginal, blood pressure lowering, lipid lowering, and antiplatelets in the 6 months before acute myocardial infarction. HR, hazard ratio; AMI, acute myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease.

months, the effect transitioned and for patients surviving past 90 days, previous ischaemia was associated with an increased rate of coronary mortality. We suggest that the early beneficial associations of ischaemic presentations in the 2 days prior to AMI with mortality may be a result of ischaemic preconditioning, and that the later poorer mortality in this group is attributable to a higher atherosclerotic disease burden.

To our knowledge, no other studies have examined the onset of atherosclerotic disease or chest pain consultations prospectively in the period leading to AMI. Other studies of retrospectively measured pre-infarction angina have shown that it is associated with fewer in-hospital outcomes including smaller infarct size[3,29] and lower in hospital coronary mortality[3,24] and more rapid coronary thrombolysis,[30] which is consistent with our findings. A number of studies investigating the effect of remote preconditioning in various settings have described similar beneficial associations with short- and long-term non-fatal coronary outcomes.[31,32]

The current analysis showed that after 90 days of follow-up, the rate of coronary mortality was higher in the group with ischaemic presentations compared with those without any presentations. This was not explained by pre-AMI coronary risk, AMI type, or by cardiovascular medication use prescribed in response to ischaemic presentations. Other studies investigating longer-term coronary mortality have shown contradictory results for local ischaemia, perhaps due to variation in the definition and timing of ischaemia,[3,24,33] or their methods to examine changes in the effect over time. Those investigating longer-term outcomes in trials of remote ischaemic preconditioning have shown beneficial effects on all-cause and coronary mortality after percutaneous coronary intervention (PCI)[8,10] and coronary artery bypass graft (CABG)[32] which is discrepant with our findings. However, the results of these trials are unlikely to be concordant with our findings due to the different exposures (natural ischaemia in the current study vs. inflated blood pressure cuff in the trials, which is controlled in terms of timing, duration, and location), different patient populations (all AMI patients in the current study vs. patients undergoing PCI and CABG[32] in the trials) and different outcomes (coronary mortality here vs. all-cause mortality in many of the trials). We are unaware of any other studies investigating the effect of remote and local pre-AMI ischaemia on longer-term outcomes.

Few studies have investigated the effect of angina at different times prior to AMI: Kloner *et al.*[34] showed that patients who reported angina in the 24 h before infarct had a lower event rate and smaller infarcts, but found no effect of angina occurring >24 h before infarct. The detail of exposure definition in our study, the follow-up data on cause and time of death and size of our study provide sufficient power to clarify the effect of exposures at different time points on both short- and longer-term coronary mortality.

We have shown that the overall exposure of ischaemia in any arterial bed prior to AMI is associated with lower short-term coronary mortality. However, further analysis of our data showed that the effect was restricted to patients with myocardial ischaemia rather than with spatially remote ischaemia. The number of patients with non-myocardial ischaemia in the 90 days prior to AMI was low and the associations require further consideration given studies showing evidence for a remote preconditioning effect on post-AMI survival.[8,10,32]

Possible explanations

Although this study was not designed to investigate mechanisms for differences in survival, various factors were examined to explain the observed associations. Similar to another study,[25] we found that differences in rates of coronary mortality between groups were not explained by faster time to hospital admission or reperfusion. They were also not explained by health-seeking behaviour, cardiovascular medications (despite increased prescriptions in patients with ischaemia in the 90 days prior to AMI) or differences in baseline cardiovascular risk.

As described here and elsewhere, previous manifestations of atherosclerotic disease are associated with NSTEMI rather than STEMI.[1,35,36] However, whether ischaemic symptoms are causally related to subsequent AMI type, or whether patients with NSTEMI are simply more likely to experience an intermittent, stuttering onset of AMI cannot be determined from these data. On stratifying by AMI type, the effect of ischaemic presentations on 7 day coronary mortality appeared larger in patients with NSTEMI, though we did not have enough power among those with known AMI type to exclude the possibility that this reflected chance variation. The majority of previous studies have been in STEMI patients and we therefore suggest that there may also be an effect in NSTEMI.

The associations seen in our analysis may be attributable to a natural ischaemic preconditioning effect, particularly in the group presenting in the 1–2 days prior to AMI.[37] The associations seen at times further removed from AMI (between 7 and 90 days) are unlikely to be related to a direct ischaemic preconditioning effect. Instead, these may reflect a continuation of symptoms after physician consultation, or collateral channel formation.[38]

The protection against early but not late mortality was also described in the French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction. In this observational study, users of the antidiabetic drug glibenclamide, which is used to inhibit ischaemic preconditioning experimentally, had poorer in hospital outcomes compared with users of other antidiabetic medications.[39]

Strengths

This study was in a population-based sample. Inclusion of fatal AMI patients who did not reach hospital is unique, as other studies drew their samples from hospitals or trial populations. The prospective data from primary care allowed detailed measurement of chest pain and atherosclerotic disease presentations prior to AMI without errors in recall, and ONS mortality data are near complete and allowed us to examine long-term follow-up for all patients.

As the gatekeeper for healthcare in the UK, the general practitioner is likely to see patients with chest pain or ischaemic presentations, who might then be referred on to a cardiologist or chest pain clinic. Angina is also managed by the general practitioner in primary care, and any discharges from secondary care should also be coded in the general practice record. Therefore, we hope to have captured the majority of symptoms reported to the healthcare system.

Weaknesses

We are inferring that chest pain or atherosclerotic disease presentations recorded by GPs are ischaemic, as our measures were not based on ST segment monitoring or myocardial perfusion imaging.

We also acknowledge that not all patients with ischaemic symptoms will report these to a physician, and that many patients will have ischaemia in the hours prior to AMI, which our study did not have the resolution to measure. Indeed, the proportion of patients who presented with ischaemia here is lower than the reported proportions in studies that retrospectively assess ischaemia after AMI.[4,14,16] However, any underestimation of ischaemia is unlikely to account for the observed association; misclassification of patients who failed to report their symptoms in the days before AMI, or who had symptoms in the hours before AMI is likely to have led to an underestimate of the effect of previous ischaemic presentations. Finally, the timing of the ischaemia exposure in this study reflects the time when treatment was sought, rather than the true timing of symptoms. In UK primary care, patients with chest pain should be seen with little delay, but there may still have been some time lag into our reported estimates.

Our primary outcome of coronary heart disease mortality may not have captured all of the effect of prior ischaemic presentations; there is increasing evidence to suggest that there may be an effect on non-coronary mortality.[32,40] However, since ours was a study of patients with AMI, we anticipated that the majority of the effect would be on coronary outcomes.

Implications

If the lower short-term mortality in those with ischaemic presentations 1–2 days prior to AMI were due to preconditioning, and the higher longer-term risk due to more vulnerable disease (and not causally related to the earlier presentation), then it would suggest that patients with a suspected AMI and no previously reported chest pain may warrant more aggressive early treatment, for example, with aspirin, beta-blockers or thrombolytic drugs, though such a strategy would need to be properly evaluated in a trial setting. There may also be implications for the longer-term management of patients.

Additionally, there may be a role for intervention with ischaemic preconditioning. If we had a better understanding of the triggers of AMI (e.g. influenza[41]) and were able to identify patients at high short-term risk of AMI, then an option for intervention might be remote ischaemic preconditioning with a blood pressure cuff, shown in randomized trials to be beneficial prior to vascular surgery on subsequent myocardial damage.[9] Research priorities are therefore to investigate the mechanisms underlying our findings for ischaemic presentations at various times prior to AMI, to clarify the role of early treatment, to further investigate potential triggers of AMI and patients at high short-term risk, and also to characterize the role of AMI type.

Conclusion

In the first large study using prospectively collected information on ischaemic presentations prior to AMI, symptoms of ischaemia prior to AMI recorded by a physician are associated with a lower rate of short term but a higher rate of longer-term coronary mortality. We observed the strongest associations in patients with ischaemia closest in time to AMI, but there was still an effect of ischaemia occurring up to 90 days prior to AMI. These observations are consistent with a natural ischaemic preconditioning effect, observed in 'real-world' clinical practice.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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