SUPPLEMENTARY MATERIAL

Supplementary Methods

Comparative prognostic utility of indices of microvascular function alone or in combination in patients with an acute ST-segment elevation myocardial infarction.

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Setting and study populations

STEMI patients

Screening, enrolment, and data collection were prospectively performed by cardiologists in the cardiac catheterization laboratories of the Golden Jubilee National Hospital, Glasgow, United Kingdom. This hospital is a regional referral center for primary and rescue percutaneous coronary intervention (PCI). The hospital provides clinical services for a population of 2.2 million. A screening log was recorded, including patients who did not participate in the cohort study. Patients were invited to undergo cardiac magnetic resonance imaging (CMR) 2 days and 6 months after hospital admission (1)(2).

Coronary angiogram acquisition

Coronary angiograms were acquired during usual care with cardiac catheter laboratory X-ray (Innova®) and IT equipment (Centricity®) made by GE Healthcare.

Percutaneous coronary intervention

Consecutive admissions with acute STEMI referred for emergency percutaneous coronary intervention (PCI) were screened for the inclusion and exclusion criteria. During ambulance transfer to the hospital, the patients received 300 mg of aspirin, 600 mg of clopidogrel and 5000 IU of unfractionated heparin (3, 4). The initial primary PCI procedure was performed using radial artery access. A conventional approach to primary PCI was adopted in line with usual care in our hospital (3, 4). Conventional bare metal and drug eluting stents were used in line with guideline recommendations and clinical judgement. The standard transcatheter approach for reperfusion involves minimal intervention with aspiration thrombectomy only or minimal balloon angioplasty (e.g. a compliant balloon sized according to the reference vessel

diameter and inflated at 4-6 atmospheres 1-2 times). During PCI, glycoprotein IIbIIIa inhibitor therapy was initiated with high dose tirofiban (25 μg/kg/bolus) followed by an intravenous infusion of 0.15 μg/kg/min for 12 hours, according to clinical judgement and indications for bail-out therapy (3, 4). No reflow was treated according to contemporary standards of care with intra-coronary nitrate (i.e. 200 μg) and adenosine (i.e. 30 – 60 μg) (3, 4), as clinically appropriate. In patients with multivessel coronary disease, multivessel PCI was not recommended, in line with clinical guidelines (3, 4). The subsequent management of these patients was symptom-guided.

Measurement of IMR and CFR at the end of PCI

We adopted a thermodilution technique rather than Doppler, in order to implement a method that is potentially transferable to routine clinical practice. The Doppler measurements are more time-consuming, require considerable experience, may be less reproducible (5), and the guidewire is typically more expensive. The Doppler method less transferrable to every-day practice than the thermodilution method.

A coronary pressure- and temperature-sensitive guidewire (St Jude Medical, Uppsala, Sweden) was used to measure coronary flow reserve (CFR) and the index of microvascular resistance (IMR) in the culprit coronary artery at the end of primary or rescue PCI. The guidewire was calibrated outside the body, equalized with aortic pressure at the ostium of the guide catheter and then advanced to the distal third of the culprit artery. Coronary flow reserve is defined as the mean transit time at rest divided by the mean transit time during hyperemia.

IMR is defined as the distal coronary pressure multiplied by the mean transit time of a 3 ml bolus of saline at room temperature during maximal coronary hyperemia, measured simultaneously (mmHg x s, or units) (6-8).

Hyperemia was induced by 140 μ/kg/min of intravenous adenosine preceded by a 2 ml intracoronary bolus of 200 μg of nitrate. The mean aortic and distal coronary pressures were recorded during maximal hyperemia. We have previously assessed the repeatability of IMR using duplicate measurements 5 minutes apart in a subset of 12 consecutive patients (8).

A priori, based on the prior literature, we pre-specified and examined an IMR>40 and also the following classifications: 1) IMR≤40 and CFR>2.0, 2) IMR>40 and CFR>2.0), 3) IMR≤40 and CFR≤2.0, 4) IMR>40 and CFR≤2.0.

Angiographic analysis

Coronary artery anatomy

The coronary anatomy and disease characteristics of the study participants were described based on the clinical reports of the attending cardiologist. Coronary dominance were assigned as left, right or balanced according to the origin of the posterior descending coronary artery.

Coronary artery disease severity

Quantitative coronary analysis (QCA) of the culprit vessel was performed by two trained observers (J.C., V.Y.T.M) using standard methods (Centricity®, GE Healthcare, Pollards Wood, UK). All coronary angiograms were analysed on a single image analysis software platform using de-identified images. Automatic edge detection algorithms were used to determine the vessel contours by assessing brightness along scan lines perpendicular to the vessel center. Image analysis was performed by two experienced observers supervised by an

expert physician, all of whom were blinded to the other study data. End-diastolic frames were used to assess disease severity using angulations reveal the stenosis at its most severe degree with minimal foreshortening and branch overlap. The coronary artery segments in the culprit artery included all those with a reference diameter ≥1.5 mm.

Definitions

TIMI flow grade

Coronary blood flow can be described based on the visual assessment of coronary blood flow revealed by contrast injection into the coronary arteries (3, 4, 9).

TIMI Coronary Flow Grade	
0	No flow
1	Minimal flow past obstruction
2	Slow (but complete) filling and slow clearance
3	Normal flow and clearance

Myocardial perfusion

Angiographic evidence of myocardial perfusion will be evaluated using the TIMI myocardial perfusion grade (TMP) at the end of the PCI procedure (10).

Grade	
0	No myocardial blush
1	Minimal blush and very slow clearing (e.g. present at

	beginning of next cine)
2	Good blush with slow clearing of myocardial contrast (present at end of cine but gone at beginning of next)
3	Good blush and normal clearing (ie. gone by end of cine)

Assessment by corrected Thrombolysis In Myocardial Infarction Frame Count

Corrected TIMI frame count (cTFC) was calculated as the number of frames for dye to reach a standardised distal landmark in each angiographic territory. The first frame taken for the measurement was the frame in which dye touched both borders of the coronary artery in question and moved forward with at least 70% of the vessel lumen opacified. The standardised distal landmarks were taken as the first branch of the postero-lateral artery for the right coronary artery, the most distal branch of the obtuse marginal for the circumflex, and the distal bifurcation of the left anterior descending (LAD) coronary artery. The number of frames from the first frame to the last frame when the dye entered the standardised distal landmark was counted. A standard image acquisition speed of 30 frames per second was used. The correction factor used to account for the increased length of the LAD compared to the right and circumflex arteries was 1.7 thereby giving a "corrected TIMI frame count".

CMR acquisition and analyses

We used CMR to provide reference data on LV function, pathology and surrogate outcomes, independent of the invasive tests.

CMR acquisition

CMR was performed on a Siemens MAGNETOM Avanto (Erlangen, Germany) 1.5-Tesla scanner with a 12-element phased array cardiac surface coil. T2 maps were acquired in contiguous short axis slices covering the whole ventricle, using an investigational prototype T2-prepared (T2P) TrueFisp sequence (11, 12). Typical imaging parameters were: bandwidth ~947 Hz/pixel; flip angle 70°; T2 preparations: 0 ms, 24 ms, and 55 ms respectively; matrix 160 x 105 pixels; spatial resolution 2.6 x 2.1 x 8.0 mm; slice thickness 8 mm.

T2*-maps were obtained using an investigational prototype T2* map sequence acquired in 3 short-axis slices (basal, mid and apical). Typical imaging parameters were: bandwidth ~814 (x8) Hz/pixel; flip angle 18°; matrix 256x115; spatial resolution 2.6 x 1.6 x 10 mm; slice thickness 8 mm.

In order to assess early microvascular obstruction, early gadolinium enhancement imaging was acquired 1, 3, 5 and 7 minutes post-contrast injection using a TrueFISP readout and fixed inversion time (TI) of 440 ms. Late gadolinium enhancement images covering the entire LV were acquired 10-15 minutes after intravenous injection of 0.15 mmol/kg of gadoterate meglumine (Gd^{2+}-DOTA, Dotarem, Guebert S.A.) using segmented phase-sensitive inversion recovery (PSIR) turbo fast low-angle shot (13). Microvascular obstruction was defined as a dark zone on early delayed enhancement imaging 1, 3, 5 and 7 minutes post-contrast injection and within an area of late gadolinium enhancement. Typical imaging parameters were: matrix = 192 x 256, flip angle = 25°, TE = 3.36 ms, bandwidth = 130 Hz/pixel, echo spacing = 8.7ms and trigger pulse = 2. The voxel size was 1.8 x 1.3 x 8 mm^3. Inversion times were individually adjusted to optimize nulling of apparently normal myocardium (typical values, 200 to 300 ms).

MR image analyses

The images were analysed on a Siemens work-station by observers with at least 3 years CMR experience (N.A., D.C., I.M). All of the images were reviewed by experienced CMR cardiologists (C.B., N.T.). LV dimensions, volumes and ejection fraction were quantified using computer assisted planimetry (syngo MR®, Siemens Healthcare, Erlangen, Germany). All scan acquisitions were spatially co-registered.

T2 and T2 – standardized measurements in myocardial regions of interest*

LV contours were delineated with computer assisted planimetry on the raw T2* image and the last corresponding T2 raw image, with echo time of 55 ms (14). Contours were then copied onto the colour-encoded spatially co-registered maps and corrected when necessary by consulting the SSFP cine images. Apical segments were not included because of partial volume effects. Particular care was taken to delineate regions of interest with adequate margins of separation from tissue interfaces prone to partial volume averaging such as between myocardium and blood. Each T2/ T2* map image was visually assessed for the presence of artefacts relating to susceptibility effects or cardio-respiratory motion. Each map was evaluated against the original images. When artefacts occurred, the affected segments were not included in the analysis.

T2/ T2* values were segmented spatially and regions of interest were defined as (1) remote myocardium, (2) injured myocardium and (3) infarct core. The regions-of-interest were planimetered to include the entire area of interest with distinct margins of separation from tissue interfaces to exclude partial volume averaging. The remote myocardial region-of-interest was defined as myocardium 180º from the affected zone with no visible evidence of infarction, edema or wall motion abnormalities (assessed by inspecting corresponding contrast enhanced T1-weighted, T2-weighted and cine images, respectively). The infarct zone

region-of-interest was defined as myocardium with pixel values (T2) >2 SD from remote myocardium on T2-weighted CMR (11, 12). The infarct core was defined as an area in the center of the infarct territory having a mean T2/ T2* value of at least 2 standard deviations (SDs) below the T2/ T2* value of the periphery of the area-at-risk.

In healthy volunteers, the mid-ventricular T2/T2* map was segmented into 6 equal segments, using the anterior right ventricular-LV insertion point as the reference point (2). T2/T2* was measured in each of these segments, and regions-of-interest were planimetered distinct and separate from blood-pool and tissue interfaces. These segmental values were also averaged to provide one value per subject. Results are presented as average values for segments and slices.

Infarct definition and size

The presence of acute infarction was established based on abnormalities in cine wall motion, rest first-pass myocardial perfusion, and delayed-enhancement imaging. In addition, supporting changes on the ECG and coronary angiogram were also required. Acute infarction was considered present only if late gadolinium enhancement was confirmed on both the axial and long axis acquisitions. The myocardial mass of late gadolinium (grams) was quantified using computer assisted planimetry and the territory of infarction was delineated using a signal intensity threshold of >5 standard deviations above a remote reference region and expressed as a percentage of total LV mass (15). Infarct regions with evidence of microvascular obstruction were included within the infarct area and the area of microvascular obstruction was assessed separately and also expressed as a percentage of total LV mass. The measurements of infarct size were performed by I.M. and N.A.

Microvascular obstruction

Microvascular obstruction was defined as a dark zone on EGE imaging 1, 3, 5 and 7 minutes post-contrast injection that remained present within an area of late gadolinium enhancement at 15 minutes. Identification of microvascular obstruction was performed independently by I.M. and N.A.

Myocardial hemorrhage

Myocardial hemorrhage was scored visually. On the T2* maps, a region of reduced signal intensity within the infarcted area, with a T2* value of <20 ms (16-19), was considered to confirm the presence of myocardial hemorrhage.

Myocardial edema

The extent of myocardial edema was defined as LV myocardium with pixel values (T1/T2) >2 standard deviations from remote myocardium (11, 12, 20-23).

Myocardial salvage

Myocardial salvage was calculated by subtraction of percent infarct size from percent area-at-risk (8, 20, 23). The myocardial salvage index was calculated by dividing the myocardial salvage area by the initial area-at-risk.

Adverse remodeling

Adverse remodeling was defined as an increase in LV end-diastolic volume ≥ 20% at 6 months from baseline (23-25).

Reference ranges

Reference ranges used in the laboratory were 105 – 215 g for LV mass in men, 70 – 170 g for LV mass in women, 77 – 195 ml for LV end-diastolic volume in men, 52 – 141 ml for LV end-diastolic volume in women, 19 – 72 ml for LV end-systolic volume in men and 13 – 51 ml for LV end-systolic volume in women.

Electrocardiogram

A 12 lead electrocardiogram (ECG) was obtained before coronary reperfusion and 60 minutes afterwards with Mac-Lab® technology (GE Healthcare) in the catheter laboratory and a MAC 5500 HD recorder (GE Healthcare) in the Coronary Care Unit. The ECGs were acquired by trained cardiology staff. The ECGs were de-identified and transferred to the local ECG management system. The ECGs were then analysed by the University of Glasgow ECG Core Laboratory which is certified to ISO 9001: 2008 standards as a UKAS Accredited Organization.

The extent of ST-segment resolution on the ECG assessed 60 minutes after reperfusion compared to the baseline ECG before reperfusion (3) was expressed as complete (≥70%), incomplete (30% to < 70%) or none (≤30%). ECG evidence of reperfusion injury was taken as persistence of ST segment elevation resolution post-procedure, and specifically ≤30% ST-segment resolution post-PCI.

Biochemical and hematologic measurements

Blood samples were obtained immediately after reperfusion in the cardiac catheterization laboratory, and subsequently between 0600 - 0700 hrs each day during the initial in-patient stay in the Coronary Care Unit.

Biochemical assessment of infarct size

Troponin T was measured (Elecsys Troponin T, Roche) as a biochemical measure of infarct size. The high sensitive assay reaches a level of detection of 5 pg/ml and achieves less than 10% variation at 14 pg/ml corresponding to the 99th percentile of a reference population. The peak troponin T value for each patient was recorded in the study database.

Biochemical assessment of inflammation

C-reactive protein (CRP) was measured in an NHS hospital biochemistry laboratory using a particle enhanced immunoturbimetric assay method (Cobras C501, Roche) and the manufacturers calibrators and quality control material, as a biochemical measure of inflammation. The high sensitive assay CRP measuring range is 0.1-250 mg/L. The expected CRP values in a healthy adult are < 5 mg/L, and the reference range in our hospital is 0 - 10 mg/L.

Hematological measurement of inflammation

Leucocyte count and leucocyte sub-populations were measured as a hematologic measure of inflammation using sheath flow technology incorporating semi-conductor laser beam, forward and side scattered light (Sysmex XT200i and XT1800i for white blood cell and differential white blood cell counts, respectively). The linearity ranges for white blood cells was 0.00-440.0 x10(9) /L. The following are the normal ranges for full blood count parameters:

	MALE	**FEMALE**
WBC x 10^9/L	4.0 - 11.0	4.0 - 11.0
RBC x 10^12/L	4.50 - 6.50	3.80 - 5.80
Hgb g/L	130 – 180	115 - 165
HCT L/L	0.400 - 0.540	0.370 - 0.470
MCV fL	78 – 99	78 - 99
MCH Pg	27.0 - 32.0	27.0 - 32.0

MCHC g/L	310 – 360	310 - 360
PLATELETS x 10^9/L	150 – 400	150 - 400
NEUTROPHILS x 10^9/L	2.5 - 7.5	2.5 - 7.5
LYMPHOCYTES x 10^9/L	1.5 - 4.0	1.5 - 4.0
MONOCYTES x 10^9/L	0.2 - 0.8	0.2 - 0.8
EOSINOPHILS x 10^9/L	0.0 - 0.4	0.0 - 0.4
BASOPHILS x 10^9/L	0.01 - 0.10	0.01 - 0.10

A blood sample was routinely obtained in the cardiac catheter laboratory, immediately following revascularization and then again at 0700 on the first and second days after admission to hospital.

Pre-specified health outcomes

We pre-specified adverse health outcomes that are pathophysiologically linked with STEMI (26, 27). The primary composite outcome was (1) all-cause death or first heart failure event following the initial hospitalization (Supplementary Methods).

Research staff screened for events from enrolment by checking the medical records and by contacting patients and their primary and secondary care physicians, as appropriate with no loss to follow-up (Figure 2). Each serious adverse event (SAE) was reviewed by a cardiologist who was independent of the research team and blinded to all of the clinical and CMR data. The SAEs were defined according to standard guidelines (26, 27) (Supplementary Methods) and categorized as having occurred either during the index admission or post-discharge. All study participants were followed-up for a minimum of 18 months after discharge. The median duration of follow-up was of 845 days (post-discharge censor duration (range) 598 - 1098 days).

Statistics

Sample size calculation for the whole cohort

With an estimated hemorrhage incidence of 33% at 48 h post-STEMI, 100 subjects would have evidence of myocardial hemorrhage and 200 subjects would not. The study would have 90% power at a 5% level of significance using a two sided two sample t-test to detect a between-group difference in a baseline variable of interest e.g. index of microvascular resistance equivalent to three eighths of a common standard deviation. We also estimated that at least 30 major adverse cardiac events (MACE) would occur based on a conservative estimate of the event rate (10-12%) at 18 months. The sample size calculation was performed using nQuery version 7.0.

Statistical analysis

Categorical variables are expressed as the number and percentage of patients. Most continuous variables followed a normal distribution and are therefore presented as means together with standard deviation. Those variables that did not follow a normal distribution are presented as medians with interquartile range. Differences in continuous variables between groups were assessed by the Student's t-test or ANOVA for continuous data with normal distribution, otherwise the nonparametric Mann-Whitney test or Kruskal-Wallis H test. Differences in categorical variables between groups were assessed using a Fisher's test.

Two raters assessed the angiograms of 30 subjects randomly selected from the whole cohort. Inter-rater reliability for angiographic parameters was assessed using weighted Cohen's kappa and the intra-class correlation coefficient (ICC) with random effects models (Supplementary Results).

Univariable and multivariable associations are assessed using binary logistic regression or linear regression where appropriate. Binary logistic models are compared using

Harrel's C-statistic. Linear regression models are compared using the Bayesian Information Criterion (BIC). The likelihood ratio test was used to compare the binary logistic and linear regression models with IMR, or an IMR>40 and CFR≤2.0. A p-value <0.05 favors including the variable in the model.

Logistic regression (odds ratio, 95% confidence interval) was used to identify potential clinical predictors of all-cause death/heart failure events, including patient characteristics, CMR findings, and IMR and CFR.

All p-values are 2-sided and a p-value > 0.05 indicates the absence of a statistically significant effect. Statistical analyses were performed using R version 2.15.1 or SAS v 9.3, or higher versions of these programs.

Trial Management

The study was conducted in line with Guidelines for Good Clinical Practice (GCP) in Clinical Trials. http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/

Trial management included a Trial Management Group, and an independent Clinical Trials Unit. Day to day study activity was coordinated by the Trial Management Group who was responsible to the Sponsor which was responsible for overall governance and that the trial was conducted according to GCP standards.

Clinical events were assessed and validated by an independent cardiologist (A.M.) who had access to relevant source clinical data. This cardiologist followed an agreed charter and he was blinded to all of the other clinical data.

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