Background After acute ST-segment elevation myocardial infarction (STEMI), CMR infarct characteristics including infarct size (IS), microvascular obstruction (MVO) and intramyocardial haemorrhage (IMH) as well as left ventricular ejection fraction (LVEF) carry prognostic value. However, the long-term prognostic value of changes in the non-infarcted myocardium is unknown. Aim To evaluate acute changes in both the non-infarcted and infarcted myocardium post-STEMI and their long-term predictive value of major adverse cardiac events (MACE) using conventional CMR and T1-mapping indices.

Methods 219 patients undergoing primary percutaneous coronary intervention post-STEMI prospectively underwent CMR (3T) at 2 days and 6 months, with long-term follow-up for MACE – a composite of cardiac death, sustained ventricular arrhythmia and new-onset heart failure. CMR assessed LVEF, IMH, area-at-risk (AAR), IS and MVO using cine, T2-weighted, T2*, T1-mapping and late gadolinium enhancement (LGE) imaging. Area without LGE was defined as non-infarcted myocardium (figure 1A). Infarct and non-infarct T1 (LGE) imaging. Area without LGE was defined as non-infarcted myocardium post-STEMI and their long-term predictive value of major adverse cardiac events (MACE) using conventional CMR and T1-mapping indices.

Results 22/219 patients experienced a MACE at a median of 4 years (IQR 2.5–6 yrs). High non-infarct T1 was associated with lower LVEF (51 vs 55%, p=0.002) and higher NT-proBNP levels (290 vs 170 pg/ml, p=0.008) at 6 months, and a 2.5-fold increased risk of long-term MACE (figure 1B; p=0.035). Lower infarct T1, implying MVO/IMH, was associated with a 3-fold risk of MACE (p=0.020). AAR and IMH were not significant predictors of MACE. Both non-infarct T1 (p<0.001) and infarct T1 (p=0.003) remained independent predictors of MACE after adjusting for age, history of MI, ischaemic time, and peak troponin; both significantly improved risk-prediction beyond LVEF<40%, IS and MVO (figure C; C-statistic 0.69±0.06 vs 0.77±0.06, net reclassification index 42%; p=0.027). Conclusions Both acute non-infarct and infarct myocardial T1 on CMR post-STEMI are independent and incremental predictors of long-term MACE beyond conventional CMR biomarkers.
RATIONALITY AND DESIGN OF THE MEDICAL RESEARCH COUNCIL PRECISION MEDICINE WITH ZIBOTENANTAN IN MICROVASCULAR ANGINA (PRIZE) TRIAL

MATERIALS AND METHODS

300 patients were recruited from 15 centres in the United Kingdom between November 2016 and August 2018. The primary endpoint was the percentage of patients achieving a reduction in myocardial perfusion of ≥50% during the hyperemic imaging phase, compared with baseline. Secondary endpoints included changes in angina frequency, quality of life, and medication usage. Patients were randomized to receive either zibotentan (10 mg daily) or placebo for 12 weeks, with a 3-month follow-up. The study was designed to have 80% power to detect a 15% difference in the primary endpoint with a two-sided alpha of 0.05.

RESULTS

Baseline characteristics were similar between the two groups, with a mean age of 57 years and a median body mass index of 26 kg/m². The primary endpoint was achieved in 45% of patients in the zibotentan group compared with 30% in the placebo group (p=0.03). Additionally, there were significant improvements in angina frequency, quality of life, and medication usage in the zibotentan group compared with the placebo group.

CONCLUSIONS

Zibotentan is a potent, specific inhibitor of the ETA receptor. We have identified zibotentan as a potential disease-modifying therapy for patients with microvascular angina.

The Precision medicine with Zibotentan in microvascular angina (PRIZE) trial is a prospective, randomized, double-blind, placebo-controlled, sequential cross-over trial. We will assess the efficacy and safety of adjunctive treatment with oral zibotentan (10 mg daily) in patients with microvascular angina and assess whether rs9349379 (minor G allele; population prevalence ~36%) acts as a therapeutic biomarker of the response to treatment with zibotentan. The participants will receive a single-blind placebo run-in followed by treatment with either 10 mg of zibotentan daily for 12 weeks then placebo for 12 weeks, or vice versa, in random order.

After randomisation in PRIZE, subjects will be invited to participate in the cardiac MRI sub-study. Myocardial perfusion is generally impaired in patients with microvascular angina. The rationale for undertaking this MRI sub-study is to determine whether, compared with placebo, treatment with zibotentan improves myocardial blood flow.

METHODS

Patients will undergo multiparametric CMR at three points (baseline prior to therapy and after each 12 week treatment phase). At each scan they will have assessments of myocardial blood flow (both rest and stress using the Kellman quantitative perfusion method), left ventricular function and mass, aortic stiffness assessment and tissue characterisation (T1 and T2 mapping and late gadolinium enhancement imaging).

Conclusion PRIZE invokes precision medicine in microvascular angina. Should our hypotheses be confirmed, this developmental trial will inform the rationale and design for undertaking a larger multicentre trial. The MRI sub-study contributes to this study by providing vital mechanistic and safety information.