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Original research

Long-term survival benefit of ramipril in patients with acute myocardial infarction complicated by heart failure

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ABSTRACT

Aims ACE inhibition reduces mortality and morbidity in patients with heart failure after acute myocardial infarction (AMI). However, there are limited randomised data about the long-term survival benefits of ACE inhibition in this population.

Methods In 1993, the Acute Infarction Ramipril Efficacy (AIRE) study randomly allocated patients with AMI and clinical heart failure to ramipril or placebo. The duration of masked trial therapy in the UK cohort (603 patients, mean age=64.7 years, 455 male patients) was 12.4 and 13.4 months for ramipril (n=302) and placebo (n=301), respectively. We estimated life expectancy and extensions of life (difference in median survival times) according to duration of follow-up (range 0–29.6 years).

Results By 9 April 2019, death from all causes occurred in 266 (88.4%) patients in placebo arm and 275 (91.1%) patients in ramipril arm. The extension of life between ramipril and placebo groups was 14.5 months (95% CI 13.2 to 15.8). Ramipril increased life expectancy more for patients with than without diabetes (life expectancy difference 32.1 vs 5.0 months), previous AMI (20.1 vs 4.9 months), previous heart failure (19.5 vs 4.9 months), hypertension (16.6 vs 8.3 months), angina (16.2 vs 5.0 months) and age >65 years (11.3 vs 5.7 months). Given potential treatment switching, the true absolute treatment effect could be underestimated by 28%.

Conclusion For patients with clinically defined heart failure following AMI, ramipril results in a sustained survival benefit, and is associated with an extension of life of up to 14.5 months for, on average, 13 months treatment duration.

INTRODUCTION

Survival following acute myocardial infarction (AMI) remains a key objective for healthcare professionals and governments throughout the globe. Despite major advances in the emergency treatment and secondary prevention of AMI, a substantial proportion of patients with AMI develop heart failure,¹ which in turn is associated with high morbidity, mortality and healthcare expenditure.^{2–4}

Moreover, therapeutic inhibition of ACE has become an established strategy in the care of patients with AMI and heart failure.⁵ ACE inhibition reduces death and disease in patients with left ventricular systolic dysfunction, and coronary artery disease.^{6–9} In the Acute Infarction Ramipril

Efficacy (AIRE) study, ACE inhibition at an average follow-up time of 15 months after randomisation significantly reduced all-cause mortality, and continued to confer a survival benefit at 3 years following study closure in the AIRE Extension (AIREX) study.^{10–12} Further placebo-controlled survival studies testing the efficacy of ACE inhibition in patients with AMI and clinical heart failure are unlikely because withholding a treatment of accepted clinical value would be unethical. Therefore, in the AIRE survival (AIRE-S) study, we aimed to assess the long-term (29.6 years after randomisation) magnitude of impact on length of survival observed after treatment with ramipril (target dose 5 mg twice daily) when compared with placebo.

METHODS

Patients and design

The rationale, design, organisation, outcome definitions and results of the AIRE study have been published previously.^{10–12} This was an independent, multinational, multicentre, double-blind, randomised, placebo-controlled, parallel-group investigation into the potential benefits from treatment with the lipophilic ACE inhibitor ramipril (target dose 10 mg/day) following AMI complicated by clinical evidence of heart failure. When the trial was conducted, in 1993, all patients had an ECG and cardiac enzyme confirmation of AMI, and also evidence of transient or persisting heart failure as judged by the attending physician (chest X-ray evidence of left ventricular failure, or auscultatory evidence of pulmonary oedema, or a third heart sound in the presence of persistent tachycardia), usually sufficient to justify diuretic or vasodilator therapy. Patients were excluded if they had evidence of clinical instability, contraindications to the use of ACE inhibitor therapy, heart failure of primary valvular or congenital origin or overt heart failure deemed to require treatment with an open-label ACE inhibitor. After applying these entry criteria to consecutive patients admitted to the UK centres (30 centres), 44% of patients approached declined to give their consent to take part in the study. All 603 of the remaining patients were then randomised by telephone to receive masked treatment with either ramipril (titrated over 4 days to 5 mg twice daily) or a matching placebo. Treatment was started between 2 and 9 days after the onset of AMI. Patients initially received either 1.25 or 2.5 mg ramipril or

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