Simvastatin to reduce pulmonary dysfunction in patients with acute respiratory distress syndrome: the HARP-2 RCT

Daniel F McAuley,[1,2,3]* John G Laffey,[4] Cecilia M O'Kane,[1] Gavin D Perkins,[5,6] Brian Mullan,[2] Thomas J Trinder,[7] Paul Johnston,[8] Phillip A Hopkins,[9] Andrew J Johnston,[10] Lynn Murphy,[3] Christine McNally,[3] Ashley M Agus,[3] Clíona McDowell,[3] Colette Jackson[3] and the HARP-2 investigators on behalf of the Irish Critical Care Trials

[1]Wellcome–Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK
[2]Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, UK
[3]Northern Ireland Clinical Trials Unit, Royal Hospitals, Belfast, UK
[4]Department of Anaesthesia, Clinical Sciences Institute, National University of Ireland, Galway, Ireland
[5]Warwick Medical School Clinical Trials Unit, University of Warwick, Coventry, UK
[6]Heart of England NHS Foundation Trust, Coventry, UK
[7]Intensive Care Unit, The Ulster Hospital, Belfast, UK
[8]Intensive Care Unit, Antrim Hospital, Antrim, UK
[9]King's Critical Care Unit, King's College Hospital, London, UK
[10]Intensive Care Unit, Addenbrooke's Hospital, Cambridge, UK

*Corresponding author d.f.mcauley@qub.ac.uk

Declared competing interests of authors: Daniel F McAuley reports grants from the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council and NIHR partnership, Health Research Board, Health and Social Care Research and Development division of the Intensive Care Society of Ireland and REVIVE for the conduct of the study. In addition, Daniel F McAuley reports personal fees from GlaxoSmithKline, Bayer and Peptinnovate Ltd. His institution has received grants from NIHR and other funds were received from GlaxoSmithKline for undertaking bronchoscopy as part of a clinical trial. Daniel F McAuley also holds a patent for a treatment for acute respiratory distress syndrome awarded to Queen's University Belfast and is a member of the Health Technology Assessment (HTA) Commissioning Board. John G Laffey reports grants from the NIHR EME programme, grants from Health Research Award and from the Health Research Board during the conduct of the study. Cecilia M O'Kane reports grants from the NIHR EME programme during the conduct of the study and her spouse has received consultancy fees from GlaxoSmithKline, Peptinnovate Ltd and Bayer. Cecilia M O'Kane has received funds from GlaxoSmithKline for undertaking bronchoscopy as part of a clinical trial, and has received travel and accommodation funding from AstraZeneca for attending a respiratory conference. Gavin D Perkins reports other funds from the Intensive Care Foundation during the conduct of the study, grants and personal fees from GlaxoSmithKline outside the submitted work, is a member of the Health Services and Delivery Research panel and is a NIHR senior investigator.

Published January 2018
DOI: 10.3310/eme05010

Plain English summary

The HARP-2 trial

Efficacy and Mechanism Evaluation 2018; Vol. 5: No. 1
DOI: 10.3310/eme05010

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Plain English summary

The increasing demand for care in an intensive care unit (ICU) currently exceeds supply, leading to a need to explore treatments that may reduce the use of ICU resources and result in increased capacity and improved access to appropriate facilities for critically ill patients. The aim of Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) was to investigate if simvastatin, a drug commonly used to treat high cholesterol, is safe and effective in the treatment of acute lung injury (ALI).

The study was open to patients aged ≥ 16 years who were admitted to specified ICU wards in the UK and who were suffering from ALI. A total of 540 patients were recruited and were randomly allocated to receive either 80 mg of simvastatin or 80 mg of placebo (an identical 'dummy' tablet) for up to 28 days.

To test how simvastatin might work to ease the patient's condition, blood and urine samples were taken to determine the ways in which lung injury develops and to examine how long patients needed assistance with their breathing on a ventilator and how quickly they recovered. Patients were contacted at 3, 6 and 12 months after discharge to fill in a questionnaire to measure the residual effects of the illness on their lives.

The study found that simvastatin was relatively safe with an increase in adverse events but no increase in serious adverse events. The study results show that simvastatin did not significantly improve clinical outcomes for patients and is not of benefit in the management of ALI, but may be used in critically ill patients with a coexisting condition for which a statin is normally prescribed.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal
Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme

The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting 'science driven' studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: http://www.nets.nihr.ac.uk/programmes/eme

This report

The research reported in this issue of the journal was funded by the EME programme as project number 08/99/08. The contractual start date was in September 2010. The final report began editorial review in April 2016 and was accepted for publication in April 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).