Reduced exposure to vasopressors through permissive hypotension to reduce mortality in critically ill people aged 65 and over: the 65 RCT

Paul R Mouncey,1* Alvin Richards-Belle,1 Karen Thomas,1 David A Harrison,1 M Zia Sadique,2 Richard D Grieve,2 Julie Camsooksai,3 Robert Darnell,1 Anthony C Gordon,4,5 Doreen Henry,6 Nicholas Hudson,1 Alexina J Mason,4 Michelle Saull,1 Chris Whitman,6 J Duncan Young,7 François Lamontagne,8,9 Kathryn M Rowan1 and the 65 trial investigators†

1Clinical Trials Unit, Intensive Care National Audit & Research Centre, London, UK
2Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London, UK
3Critical Care, Research and Innovation, Poole Hospital NHS Foundation Trust, Poole, UK
4Division of Anaesthetics, Pain Medicine and Intensive Care, Imperial College London, London, UK
5Intensive Care Unit, Imperial College Healthcare NHS Trust, St Mary’s Hospital, London, UK
6Patient representative, UK
7Kadoorie Centre for Critical Care Research and Education, University of Oxford, John Radcliffe Hospital, Oxford, UK
8Department of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada
9Centre de Recherche du Centre Hospitalier, Université de Sherbrooke, Sherbrooke, QC, Canada

*Corresponding author Paul.Mouncey@icnarc.org
†The 65 trial investigators are listed in Appendix 1.

Declared competing interests of authors: Richard D Grieve is a member of the National Institute for Health Research Health Technology Assessment Commissioning Board (2018–present). Anthony C Gordon has received a grant for a National Institute for Health Research Research Professorship; personal fees and non-financial support from Orion Corporation (Espoo, Finland) and Orion Pharma (Newbury, UK); a grant and consulting fees paid to his institution from Tenax Therapeutics (Morrisville, NC, USA); consulting fees paid to his institution from Bristol Myers Squibb (New York, NY, USA); and consulting fees paid to his institution from GlaxoSmithKline plc (Brentford, UK). J Duncan Young was a Consultant Advisor to the National Institute for Health Research/Medical Research Council Efficacy and Mechanism Evaluation programme, a member of the Efficacy and Mechanism Evaluation Strategy Advisory Committee, the Efficacy and Mechanism Evaluation Funding Committee, and the Efficacy and Mechanism Evaluation Funding Committee Sub-Group Remit and Competitiveness Check group, from February 2011 to December 2018. Kathryn M Rowan was a member of the National Institute for Health Research Health Services and Delivery Research Board (2014–19).
Plain English summary

The 65 RCT
Health Technology Assessment 2021; Vol. 25: No. 14
DOI: 10.3310/hta25140

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Low blood pressure is common in patients in intensive care. It is associated with a high risk of death. It can be treated with drugs called vasopressors. These drugs raise blood pressure, but also come with risks and side effects. Usually, a blood pressure target is used to guide how much of the drugs to give to patients.

Two previous clinical trials suggested that using a lower blood pressure target (and therefore giving less of the drugs) might reduce the number of deaths among older patients. However, although these results were promising, more research was needed to find out if they were correct.

The 65 trial was carried out to test if using a lower blood pressure target really did improve outcomes for older patients. The trial also looked at whether or not it would provide value for money for the NHS.

A total of 2600 patients aged ≥ 65 years who had low blood pressure in intensive care joined the trial. Half were randomly assigned to the new lower blood pressure target (less drugs). The other half were assigned to usual care (control group). As we had hoped, patients in the low blood pressure target group received less vasopressor drugs than the usual-care group.

After 90 days, 41% of patients in the new low blood pressure target group had died, compared with 44% in the usual-care group. Although fewer patients died in the low blood pressure target group, the difference was small and may have occurred by chance. On average, the new target saved a small amount of money for the NHS.

Although we could not prove that use of a lower blood pressure target saves lives for older patients in intensive care, our trial suggests that it might. Receiving less vasopressor drugs appeared safe for patients.
Criteria for inclusion in the Health Technology Assessment journal

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HS&DR programme or one of its preceding programmes as project number 15/80/39. The contractual start date was in March 2017. The final report began editorial review in February 2020 and was accepted for publication in November 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HS&DR 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 funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NIHR, NETSCC, the HS&DR programme or the Department of Health and Social Care. 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 HS&DR programme or the Department of Health and Social Care.

© Queen’s Printer and Controller of HMSO 2021. This work was produced by Mouncey et al. under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

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

Professor Ken Stein  Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

Professor John Powell  Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Professor of Digital Health Care, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor André Le May  Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

Professor Matthias Beck  Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin  Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson  Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont  Senior Scientific Adviser (Evidence Use), Wessex Institute, University of Southampton, UK

Dr Catriona McDaid  Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads  Emeritus Professor of Wellbeing Research, University of Winchester, UK

Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross  Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein  Professor of Public Health, University of Exeter Medical School, UK

Professor Jim Thornton  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

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