

Infective endocarditis following invasive dental procedures: IDEA case-crossover study

Martin H Thornhill,^{1,2*} Annabel Crum,³
Saleema Rex,³ Richard Campbell,³ Tony Stone,³
Mike Bradburn,³ Veronica Fibisan,³ Mark J Dayer,⁴
Bernard D Prendergast,⁵ Peter B Lockhart,²
Larry M Baddour⁶ and Jon Nicholl³

¹Academic Unit of Oral and Maxillofacial Medicine, Surgery and Pathology, School of Clinical Dentistry, University of Sheffield, Sheffield, UK

²Department of Oral Medicine, Atrium Health, Carolinas Medical Center, Charlotte, NC, USA

³School of Health and Related Research, University of Sheffield, Sheffield, UK

⁴Department of Cardiology, Taunton and Somerset NHS Foundation Trust, Taunton, UK

⁵Department of Cardiology, St Thomas' Hospital, London, UK

⁶Division of Infectious Diseases, Mayo Clinic College of Medicine and Science, Rochester, MN, USA

*Corresponding author m.thornhill@sheffield.ac.uk

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/NEZW6709>.

Primary conflicts of interest: Bernard D Prendergast reports unrestricted educational and research grants from Edwards Lifesciences (Irvine, CA, USA) paid to his institution; consulting fees from Anteris Technologies Limited (Toowong, QLD, Australia); and payment or honoraria from Abbott Laboratories (Chicago, IL, USA), Anteris Technologies Limited and Edwards Lifesciences. Larry M Baddour reports royalties or licences from UpToDate, Inc. (Waltham, MA, USA) for authorship duties; consulting fees from Boston Scientific (Marlborough, MA, USA), Botanix Pharmaceuticals (Philadelphia, PA, USA) and Roivant Sciences (Basel, Switzerland); and payment or honoraria from Boston Scientific.

Published May 2022

DOI: 10.3310/NEZW6709

Scientific summary

IDEA case-crossover study

Health Technology Assessment 2022; Vol. 26: No. 28

DOI: 10.3310/NEZW6709

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

Scientific summary

Background

Infective endocarditis (IE) is a life-threatening infection of the endocardial lining of the heart, particularly the heart valves, that has a high morbidity rate and a first-year mortality rate of $\approx 30\%$. Although IE affects only 3–10 per 100,000 people per year, a much larger proportion of individuals with predisposing cardiac conditions are at increased risk of IE. Patients are stratified as at high risk if they have a history of IE, prosthetic heart valves, valve repair with prosthetic material, cyanotic congenital heart disease or congenital heart disease repaired with prosthetic material. Such patients are at high risk for 6 months following the repair, or for life if there is a residual shunt or valvular regurgitation. Moderate-risk patients include those with valvular stenosis or regurgitation, a bicuspid aortic valve or hypertrophic cardiomyopathy.

Infective endocarditis can result from bacteraemia caused by a spectrum of bacterial and fungal organisms entering the circulation. The possibility that some IE cases are linked to invasive dental procedures (IDPs) was first suggested in 1923, and numerous studies have shown that oral viridans group streptococci (OVGS) cause 40–45% of IE cases. In 1953, this recognition led to the first guidelines recommending that patients at increased risk of IE should receive antibiotic prophylaxis (AP) before undergoing IDPs, and this soon became the worldwide standard of care.

Remarkably, to the best of our knowledge, there has never been a randomised controlled trial to demonstrate the efficacy of AP in preventing IE, and there are few data implicating IDPs as the cause of OVGS IE. Many argue that bacteraemia with OVGS as a result of daily activities (including toothbrushing, flossing and chewing) are a more likely cause of IE, particularly in those with poor oral hygiene, than the comparatively rare IDPs. Indeed, because of these uncertainties, the risk of adverse reactions to the antibiotics used in AP, the cost of AP and the potential for promoting antibiotic resistance, the National Institute for Health and Care Excellence (NICE) recommended in 2008 that the use of AP should cease. Despite this, most other countries continue to recommend AP for those at the highest risk of IE, and in 2016 NICE softened its guidance to make AP permissible for patients who still wished to receive it after a full explanation of the risks and benefits.

Objective

There is still considerable uncertainty regarding the benefit of AP in preventing IE. However, AP makes sense only if there is a clear association between IDPs and IE, at least in those at high risk of IE. The aim of this study, therefore, was to investigate if there is a temporal association between IDPs and subsequent IE.

Methods

Between April 2008 and March 2016, NICE recommended against dentists using AP to prevent IE. During this period, the UK was the only place in the world where any association between IDPs and IE was fully exposed. The aim of the Invasive Dentistry–Endocarditis Association (IDEA) study was, therefore, to perform a larger case-crossover study to investigate any temporal association between IDPs and IE. To achieve this, we used NHS Digital data to identify all IE hospital admissions in England between April 2010 and March 2016. These data were then linked to the NHS Business Services

Authority (NHSBSA) data on all NHS courses of dental treatment performed on individuals in the 15 months before IE hospital admission.

The aim was to perform a case-crossover analysis comparing the number of IDPs in the 3 months immediately before IE hospital admission (case period) with that in the preceding 12-month control period.

The case-crossover design eliminates limitations, such as selection bias and confounding for risk of IE, that are implicit in cohort and case-control studies because each case acts as its own control and provides greater statistical power to address these types of cause and effect issue. Furthermore, by linking national IE and dental data, we did not rely on patient recall to determine the timing and nature of any dental procedures that were performed.

Results

If there was a temporal association between IDP and IE, one would expect an increased number of IDPs in the 3-month case period immediately before IE hospital admission compared with that in the 12-month control period. Conversely, if there was no association, one would expect no difference between the case and control periods. To determine the timing of any relationship between IDP and IE, we plotted the monthly number of dental procedures over the 13 months prior to IE hospital admission. This revealed a fall in the number of all types of dental procedures in the few weeks before IE admission. Investigating the reason for this identified that although the NHSBSA require dentists to provide details of the dental procedures they perform during a course of dental treatment, it does not require this for incomplete courses of dental treatment (i.e. those with a start date but not an end date). Unfortunately, one of the most common reasons for a course of dental treatment being incomplete was emergency admission of the patient to hospital for a condition that results in long-term illness or death, such as IE.

Although we investigated different methods for mitigating this data loss, none of them resolved the fact that the data loss focused almost entirely on the case period rather than the control period of the case-crossover study, rendering the case-crossover analysis unreliable and making it difficult to draw any conclusions about the relationship between IDP and IE.

Conclusions

Unfortunately, the loss of critical dental treatment data in the few weeks before a patient was admitted to hospital for IE rendered our case-crossover analysis impossible and meant we were unable to draw any conclusions about the relationship between IDP and IE.

Trial registration

This trial is registered as ISRCTN11684416.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 28. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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 HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. 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 *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 HTA programme as project number 15/57/32. The contractual start date was in September 2016. The draft report began editorial review in July 2021 and was accepted for publication in January 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft 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 and Care 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 NHS, the NIHR, the HTA 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, the HTA programme or the Department of Health and Social Care.

Copyright © 2022 Thornhill *et al.* This work was produced by Thornhill *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed. See: <https://creativecommons.org/licenses/by/4.0/>. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

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 Andrée Le May Chair of NIHR Journals Library Editorial Group (HSDR, PGfAR, PHR journals) and Editor-in-Chief of HSDR, 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 Consultant in Public Health, Delta Public Health Consulting Ltd, UK

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

Ms Tara Lamont Senior Adviser, Wessex Institute, University of Southampton, UK

Dr Catriona McDaid Reader in Trials, 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, Child and Adolescent Mental Health, Palliative Care and Paediatrics Unit, Population Policy and Practice Programme, UCL Great Ormond Street Institute of Child Health, London, 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