PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	**UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database**
AUTHORS	Lee, Sally; Shafe, Anna; Cowie, Martin

VERSION 1 - REVIEW

REVIEWER	***Professor Charles Wolfe*** Professor of Public Health and Head of Department Division of Health and Social Care Research King's College London London England No competing interests
REVIEW RETURNED	01-Aug-11

THE STUDY	3) How is 2nd stroke justified after a 56 day period. Toschke et al used a one year period so as not to carry forward the index event? 7) Although treatment rates for hypertension have increased, is this guideline treatment i.e. how effective?
GENERAL COMMENTS	How does this paper add to the evidence of reduced stroke risk and improved survival over and above references cited? The paper does not fully justify the case definition for stroke - important as there is substantial use of non-specific codes and changes in coding over time as outlined by Gulliford MC, Charlton J, Ashworth M, Rudd AG, Toschke AM; eCRT Research Team. Selection of medical diagnostic codes for analysis of electronic patient records. Application to stroke in a primary care database. PLoS One. 2009 Sep 24;4(9):e7168. PubMed PMID: 19777060; PubMed Central PMCID: PMC2744876. Also, results close to this have been reported elsewhere Gulliford MC, Charlton J, Rudd A, Wolfe CD, Toschke AM. Declining 1-year case-fatality of stroke and increasing coverage of vascular risk management: population-based cohort study. J Neurol Neurosurg Psychiatry. 2010 Apr;81(4):416-22. Epub 2010 Feb 22. PubMed PMID: 20176596; PubMed Central PMCID: PMC2921278

REVIEWER	***Craig Anderson*** Professor of Neurology Royal Prince Alfred Hospital, University of Sydney, and The George Institute, Sydney, NSW, Australia
REVIEW RETURNED	05-Aug-2011

REPORTING & ETHICS	No guideline checklist is required for this primarily descriptive study. The authors are employees/consultants for a pharmaceutical company (Boehringer Ingelheim) as stated (which have released a new anticoagulation agent as an alterative to warfarin, which is not stated), but despite this clear COI the analyses, presentation and discussion appears well balanced.

VERSION 1 – AUTHOR RESPONSE

All changes made to the manuscript as detailed below have been highlighted in yellow in the revised document. References have been reformatted to comply with the BMJ Open required format.

Reviewer 1: How is 2nd stroke justified after a 56 day period. Toschke et al used a one year period so as not to carry forward the index event?

Author's Response: The 56 day period was chosen to ensure that the stroke code for the initial stroke was recorded within the GPRD patient record. This was to allow a time delay between a patient being treated in hospital and the GP receiving a letter and entering the data onto the GPRD system. GPRD guidelines state that a GP should enter the event into the system using the first day of the event (i.e. hospital admission date) as the event date. For this reason we can be confident that we have captured initial stroke events correctly.

The reviewer's comment is suggesting that the same stroke event may be entered into a patient's record multiple times during the year following the stroke. In order to ensure that we did not record stroke follow up entries as a secondary stroke, we used a restricted code list which included only acute stroke events, and did not include any of the codes for stroke rehabilitation or stroke monitoring. We assumed that there was a possibility of a GP entering a stroke code more than once in reference to the same stroke event within a limited time frame of 56 days, but beyond this it is more likely that a second coded stroke is a secondary event.

We are aware of the reference suggested by the reviewer, however using the one year gap implies that no second stroke could have happened during the 12 months following the first (initial) stroke and we do not think this assumption is clinically sound.

Reviewer 1: Although treatment rates for hypertension have increased, is this guideline treatment i.e. how effective?

Author's Response: This study investigated the prescribing trends in anti-hypertensives in stroke patients. We were interested in whether this increased prescribing could be one of the factors contributing towards the decrease in the incidence of stroke events and the improvement in post stroke survival. We therefore looked at blood pressure readings from the cohort of patients over time to see whether the anti hypertensive medication was reducing blood pressure. At a population level we found that as the prescribing of anti hypertensives increased the average blood pressure decreased between 1999 and 2009, from (151/84) to (143/81). This pattern was most apparent within the older age groups. Despite the obvious pattern, we cannot ascertain that there is a causal

relationship between higher prescription of anti hypertensives and lower blood pressure. As stated in the limitations of the study, there are other factors which could affect this relationship such as diet and exercise that are not recorded in the database.

Reviewer 1: How does this paper add to the evidence of reduced stroke risk and improved survival over and above references cited?

Author's Response: This paper adds greatly to the evidence of reduced stroke and improved survival. Although the conclusion of the study is the same as the conclusions of other studies on the subject, this study provides evidence that the pattern is consistent across the whole of the UK, whereas earlier studies cited were either conducted in other countries, or used regional data from the UK only. Our study is also the largest study to investigate stroke incidence and survival in the UK, and the most up to date.

Reviewer 1: The paper does not fully justify the case definition for stroke - important as there is substantial use of non-specific codes and changes in coding over time as outlined by

Gulliford MC, Charlton J, Ashworth M, Rudd AG, Toschke AM; eCRT Research Team. Selection of medical diagnostic codes for analysis of electronic patient records. Application to stroke in a primary care database. PLoS One. 2009 Sep 24;4(9):e7168. PubMed PMID: 19777060; PubMed Central PMCID: PMC2744876.

Author's Response: The following statement has been added to the Methods section of the manuscript to better describe the case definition and the code selection for stroke:
Stroke codes used were those which described acute stroke events only- any codes for monitoring or stroke rehabilitation were excluded to ensure that we correctly identified the initial stroke event and did not record follow up of the same stroke as a secondary stroke event.
Reviewer 1: Also, results close to this have been reported elsewhere

Gulliford MC, Charlton J, Rudd A, Wolfe CD, Toschke AM. Declining 1-year case-fatality of stroke and increasing coverage of vascular risk management: population-based cohort study. J Neurol Neurosurg Psychiatry. 2010 Apr;81(4):416-22. Epub 2010 Feb 22. PubMed PMID: 20176596; PubMed Central PMCID: PMC2921278.

Author's Response: The subject of our paper is indeed similar to that conducted by the reviewer, and uses the same data source. Therefore it is reassuring that our results are in agreement, despite the fact that the two groups of authors have used differing rationale to choose the code lists to identify stroke events.

The focus of our paper is different to the Gulliford et al paper, and provides much useful information on stroke patients in the UK over and above the information provided in Gulliford et al. Our paper investigates a greater number of relevant co morbidities of patients who have suffered a stroke, and looks at anticoagulation prescribing before and after stroke as well as anti hypertensives, statins and anti platelets. Our paper also includes a further investigation into the subgroup of patients suffering from atrial fibrillation prior to their initial stroke.

Furthermore, our study used more recent data and shows that the trend in stroke incidence and stroke mortality continues for an additional three year period up to the end of 2008. It also includes a longer follow up period, and we were able to look at 5 year survival following stroke compared to the 1 year mortality in Gulliford et al.

Reviewer 2: No guideline checklist is required for this primarily descriptive study. The authors are employees/consultants for a pharmaceutical company (Boehringer Ingelheim) as stated (which have released a new anticoagulation agent as an alterative to warfarin, which is not stated), but despite this clear COI the analyses, presentation and discussion appears well balanced.

Author's Response: Based on the reviewer's concerns we have added an additional statement to the Conflict of Interest section:

Competing interests
MRC provides consultancy advice to a number of pharmaceutical companies, including Boehringer Ingelheim. He holds no stocks or shares in any such company. SL and AS are employees of Boehringer Ingelheim Ltd. Boehringer Ingelheim Ltd market a number of cardiovascular therapies.

VERSION 2 - REVIEW

REVIEWER	***Charles Wolfe***
REVIEW RETURNED	09-Aug-2011

THE STUDY	Still the issue of how one deals with some codes that mimic stroke is not really detailed. Also the 56 days to recurrence not justified.