

# Outcomes in terms of morbidity and mortality among elderly head injury patients on pre-injury anticoagulation: A systematic review protocol

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## Research Article

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# Abstract

**Background:** The global burden of traumatic brain injuries continues to remain grossly underestimated and is thought to cost about US\$400 billion annually. Elderly individuals have the highest age-specific rates of TBIs and are more likely to take anticoagulant medication than other age groups and are therefore theoretically at a higher risk of morbidity and mortality following head injuries. However, the evidence for these worse outcomes is at best unclear, and this has a significant impact on decision-making in clinical settings, sometimes resulting in unnecessary delays to treatment.

**Methods:** This protocol has been developed using the PRISMA-P guidelines. We will search the main clinical indexing databases (including PubMed/MEDLINE, EMBASE, Cochrane reviews, and ClinicalTrials.gov) for studies that evaluated outcomes in terms of morbidity and mortality among anticoagulated individuals aged over 65, to identify all English language studies published between the years 2000 and 2021. The identified studies will then be screened using pre-determined eligibility criteria detailed in the body of this work. Finally, two independent reviewers will screen, select, evaluate the included studies for quality, and extract data related to the use of anticoagulants in the elderly from all relevant sources.

A logically sound analytic framework will then be employed to determine the impact of the use of anticoagulation on outcomes as outlined.

**Discussion:** This study aims to identify the existing evidence for outcomes in this population, contribute to the current body of knowledge, and provide more explicit guidance for clinical practice. We envisage that the findings surrounding outcomes in the head-injured, anticoagulated elderly population will guide clinicians towards better decision-making in both the in-patient and out-patient setting and contribute to the development of clinical guidelines.

**Systematic review registration:** This systematic review is registered on the PROSPERO database with registration number: CRD42021220974

## Background

Traumatic brain injuries (TBIs) are a significant public health problem worldwide (1). There are an estimated 262 head injuries per 100,000 population occurring annually in Europe (1), and brain injuries count among the top 15 causes of death worldwide (2). The rates of head injuries have also continued to increase with a 3.6% increase in the number of head injuries recorded annually worldwide between 1990 and 2016 (3). Furthermore, with about 50% of road traffic accidents involving some form of head injury (4), the focus of objective 3.6[1] of the 2030 Sustainable Development Goals only serves to emphasise the growing public health importance of head injuries and the increasing need for evidence (5).

The burden of head injuries is reflected in high costs for governments worldwide, with direct costs[2] for traumatic brain injuries averaging \$13 billion a year and indirect productivity costs averaging \$67 billion

a year in the United States alone (6). These indirect costs are usually a result of lifelong biological impairment such as cognitive impairment or paraplegia, limiting the individual's functional ability and impacting the society on which they may become dependent (7). It has also been noted that the Disability-Adjusted Life Years (DALY) losses for road-traffic injuries (which account for approximately 60% of all traumatic brain injuries) are the highest among all other diseases (2).

Especially important is the trimodal distribution of head injuries, with the first peak in childhood, the second in adolescence, and the third in the elderly, with the incidence of intracranial injuries being the highest in the older population (2). Falls are the most frequent cause of head injuries in the ageing population and account for 20-30% of the burden of this condition. In contrast, although interpersonal violence and workplace/sport-related injuries are also frequent causes of head injuries, they account for 20% of the cases (2). Intracranial injuries are typically associated with some form of vascular disruption and resultant bleeding into the intracranial space, resulting in a myriad of neurological outcomes (8). The risk of intracranial bleeding could be increased by the use of anticoagulant medication (9). This risk is significant as the use of anticoagulant and antiplatelet medication is higher in older individuals as part of a trend towards higher life expectancies (10).

Only one systematic review has been published on the relationship between peri-injury anticoagulation and outcomes in trauma patients (11). There is little evidence to demonstrate how this relationship might have been affected by head injuries sustained. Two uncompleted systematic reviews regarding anticoagulant use and head trauma were commenced (one in 2012, the second in 2016). Still, none of these is completed to date, despite being past their respective deadlines (10). While some studies have suggested worsening outcomes with the use of anticoagulants in head injuries (12,13), some others have posited that this relationship is non-existent and probably confounds the relationship between age and mortality (14,15).

Considering the weight of the burden of head injuries and the prevailing lack of evidence, there must be a synthesis of the existing research on outcomes in head injuries. This synthesis aims to properly guide the development of policy, especially concerning considerations around anticoagulation in managing head injuries and will also contribute to improving healthcare decision-making in the older population. This study will thus be focused on outcomes (as defined by morbidity and mortality), specifically in the anticoagulated older population of individuals  $\geq 65$  years with head injuries.

[1] "By 2020, to halve the number of global deaths and injuries from road traffic injuries"

[2] Direct costs refer to the direct costs of treatment/hospital care and long-term rehabilitation/social and other forms of care while indirect costs refer to the economic losses incurred due to reduced/lack of productivity as a result of disabilities secondary to head injuries

## Methods

# Objectives

## Primary objective

To synthesise the existing evidence on the impact of pre-injury anticoagulation on outcomes (as defined by morbidity and mortality) in head-injured patients  $\geq 65$  years old.

## Sub-objectives

- To measure and compare the impact of anticoagulant use on outcomes stratified by the severity of the head injury experienced, and class of anti-coagulants
- To add to the existing body of knowledge on the utilisation of anticoagulants in head-injured patients
- To contribute to defining public policy and guidelines on the use of anticoagulants in the older population

## Study design

The study will be a systematic review of all eligible studies that have described the outcomes in older head-injury patients on anticoagulants. These studies will be obtained from the sources listed in Table 1. A flow chart outlining the study methodology is shown in Fig. 1.

This paper contains the systematic review protocol, which was developed as per PRISMA-P guidelines for systematic review protocols (16). In addition, a completed checklist for the PRISMA-P guidelines has been completed and provided as a supplementary file. The systematic review has been registered on PROSPERO[3], and the complete study will be reported in line with the PRISMA statement (17).

Table 1  
Sources of information

Category	Name of index
Databases	MEDLINE, EMBASE, COCHRANE reviews (including CENTRAL databases), MedOne Neurosurgery.
Other selected indexes	PubMed, ResearchGate, Google Books, Google Scholar
Research registers	National Institute of Health Research, UK; guidelines relevant to head injuries, e.g. NICE, ACS TQIP, and The Brain Trauma Foundation
Unpublished research	British National Bibliography for Report Literature, Dissertation Abstracts, Index to Scientific and Technical Proceedings, System for Information on Grey Literature, key individuals in the research field.

The search strategy will include keywords that have been derived from scoping research[4] in the subject field. These keywords are listed in Appendix 1.

## Study selection

Two reviewers will select studies based on the eligibility criteria outlined in Box 1. These criteria are based on the standard PICOS format recommended in the PRISMA and AMSTAR checklists (17–19). Full-text studies will be reviewed and considered potentially relevant when it is not possible to completely exclude them simply based on title/abstract (20). The planned process of study selection is shown in the flowchart in Fig. 2

### Box 1

#### Eligibility Criteria

##### Inclusion criteria

Population: studies that cover individuals  $\geq 65$  years diagnosed with a traumatic brain injury/head injury, irrespective of its severity. This will also include studies that examine other forms of trauma in addition to head injuries (as long as the outcomes under study were documented)

- Intervention/Exposure: Individuals  $\geq 65$  years who have experienced a head injury while on pre-injury/pre-event anticoagulation (irrespective of whether these treatments have been stopped)
- Comparisons: Individuals  $\geq 65$  years who have experienced head injuries that WERE not on pre-injury anticoagulants
- Outcomes: Prevalence of short/long-term morbidity and mortality between the uncoagulated and coagulated groups, and between the different classes of anticoagulants. Primary outcome will be mortality (in hospital, and 30-day mortality). Secondary outcomes are outlined in appendix 2
- Setting: Hospital admissions, emergency admissions (secondary care in any of its forms) worldwide (focusing on studies in English)
- Study design: The focus will be on quantitative studies
- Studies published in or after the year 2000

##### Exclusion criteria

- Individuals  $< 65$  years old
- Individuals who have experienced other forms of trauma without a head injury component
- Studies that examined head injuries but did not look at the outcomes under study as listed in appendix 2
- Individuals with any other co-existing neurological deficit that may confound outcomes
- Studies published in any other language but the English language.

Following study selection, both reviewers will compare findings from the study search. In cases of disagreements, we will moderate these with a third reviewer (21). We will also search the references of the identified studies for other relevant sources. Experts who have conducted applicable or similar research

will also be contacted to identify unpublished sources. Additionally, I will hand-search specific public health, trauma, and neurosurgery journals for other relevant studies.

## **Study selection and data management**

Study records will be managed using Mendeley – a referencing/bibliography software, and Covidence, an online systematic review tool used for study selection and data collection. Covidence will also be used for study screening, full-text review, as the second risk-of-bias assessment, and study characteristics and outcomes extraction. Data collected will be exported to Excel and RevMan for further analysis. During the search process, I may revise my inclusion and exclusion criteria to help ensure that essential studies are not excluded and eliminate irrelevant studies. Any changes to the protocol will be tracked on PROSPERO and a personal reflective journal.

## **Risk of bias/quality control**

Sensitivity analysis will be used to examine each of the studies selected for the possible risk of bias using RevMan 5. In addition, the Cochrane risk of bias tool (RoB2) and the ROBINS-1/robvis tools will be used to evaluate the risk of bias for randomised controlled trials and non-randomised studies, respectively (22, 23). In the presence of bias, the studies will be excluded from the systematic review as per the AMSTAR protocol (19).

## **Data collection**

Data will be collected from the selected studies and grouped based on sample characteristics (such as age, sex, ethnicity, socio-economic status, type of anticoagulant, mechanism, and severity of injury), sample size, and outcomes using piloting forms. The corresponding author (Ogbu, I.) will collect this data collection once studies have been selected. The data items to be collected have been listed in Appendix 2 and will be kept in a Microsoft Excel spreadsheet.

## **Data analysis and study reporting**

The data will be presented in a spreadsheet to allow easy semi-qualitative comparison of the various population demographics, intervention types, and outcomes. The data will subsequently be grouped by intervention type and outcome to evaluate across studies.

The discussion will be based on the analysis of the outcome measures. Additionally, a meta-analysis will be conducted based on the data collected during the review process. The systematic review (& meta-analysis) will be reported in line with PRISMA recommendations. At the end of the study, the strength of the overall body of evidence will be assessed using GRADE criteria (24).

Outcomes will be compared using ORs. In addition to a narrative synthesis, the outcomes will be synthesised using pooled effect estimates (using weighted effects estimates). These estimates will be considered in the context of the level of heterogeneity between the effect estimates of the studies identified. The heterogeneity of studies will be evaluated using the  $I^2$  statistic. Some heterogeneity is expected considering that we will be examining various quantitative study types.

Following the study, a meta-analysis is planned, which will compare outcomes with low to moderate heterogeneity using a fixed-effects model. Outcomes with high heterogeneity will be analysed using a random-effects model. All of this will be done using RevMan 5.

Additionally, subgroup analysis will be conducted for the various anticoagulant groups to compare outcomes between these. Our ability to run a meta-analysis here will depend on the results of the study, especially regarding the heterogeneity of the identified studies.

Sub-group analysis will be conducted to compare outcomes across various anticoagulant groups - NOACs versus non-NOACs to observe differences in outcome between the two groups. Similarly, further sub-group analysis will be conducted to determine the association between the use of LMWH, NOACs, and Warfarin/Coumarin and the various outcomes to be tested to observe any differences between the three groups. If possible, I will also evaluate the difference in outcomes between studies in different geographical locations.

Comparing outcomes in the NOAC and non-NOAC groups will be through the use of ORs and mean differences for the continuous outcomes. In comparing the various anticoagulant sub-groups, multivariate inferential statistical tests, including ANOVA, will be used to determine the difference between outcomes in the three groups of anticoagulated patients.

Sub-group analysis will also be further driven by the heterogeneity found among the various studies sampled during the systematic review (which will also be explored using sensitivity analysis).

[3] the International prospective register of systematic reviews. Registration number CRD42021220974

[4] done prior to commencing the systematic review

## Discussion

This systematic approach will allow us to evaluate the existing evidence and synthesise the current evidence regarding the association between anticoagulant use and clinical outcome (as defined in Appendix 2) in head-injured patients aged > 65 years. We seek to determine if there is a clear association between the use of anticoagulants and worse outcomes in this group of patients. We aim to provide a framework with which to guide out-patient and in-patient clinical practice and a body of evidence for the development of future guidance for the judicious use of anticoagulant medication in specific at-risk groups. In the event of the amendment of this protocol—in whole or part, the date of each amendment and the description of the particular change made and its rationale will be documented and tracked on PROSPERO.

While this research can guide decisions in clinical practice and policy-making processes, one of the main limitations would be the lack of evidence considering the extent of findings of my preliminary search with

610 results as shown in appendix 1. Also, the level of skill of the researcher may affect the quality of the study. To mitigate this, I will engage in a continuous feedback process with my other authors and supervisor and engage in iterative learning using available material on systematic reviews and the Cochrane website throughout the study.

There is also subjectivity during the study screening process, which the extra reviewers will mitigate. Also, there is a likelihood that non-database studies may be missed. To minimise this, I will use adapted search strings on specific journal websites. We will also recognise any other further limitations encountered during the study in the final synthesis of results.

The dissemination of findings of this systematic review will follow PRISMA recommendations and will eventually include a publication of the final results of the review in a scientific journal and this may also include presentation of the study findings at scientific conferences at various levels—national and international. Additionally, stakeholders involved during the study will be apprised of the study results.

## Declarations

**Ethical approval and consent to participate:** The systematic review intends to use data from pre-existing retrospective studies. Ethical approval for the study has been waived by the University of Edinburgh MPH Ethics Group (MPHEG) due to the absence of foreseeable ethical risks. The application number for the ethics application was MPH202125, and the final letter waiving approval can be provided on request from the corresponding author

**Consent for publication:** Not applicable. The study does not contain individualized data

**Availability of data and materials:** Data sharing does not apply to this article as no datasets were generated or analysed during the current study.

**Competing interests:** Not applicable

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**Author's contributions:**

IO wrote the protocol from start to finish, running all research

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**Author's information:** Not applicable. This systematic review is to be undertaken as my final year dissertation for the award of an MPH degree at the University of Edinburgh.

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## Appendices

### Appendix 1: Search terms

The search terms in table A.1 have been adapted from existing literature. They have been grouped by the standard PICOS format and will be linked by Boolean terms during the search itself (as shown in the table A.1 below).

Table A.1

Index of search terms to be used in the identification of studies for inclusion in the planned systematic review.

Category	Search terms
Population	"Elderly" ">65" "Older" OR "Head injur*" OR "Traumatic brain injur*" OR "brain injur*" OR "head trauma" OR "brain trauma" OR "cranial bleed" OR "cranial haemorrhage" OR "cranial hemorrhage" OR "brain hemorrhage" OR "brain haemorrhage" OR "cerebral bleed" OR "cerebellar bleed" OR "TBI" OR "GCS" OR "penetrating" OR "skull fracture" OR "craniocerebral trauma" OR "Extraaxial."
Intervention	"Anticoagula*" OR "Anticoag*" OR "Warfarin" OR "Dabigatran" OR "Apixaban" OR "Dalteparin" OR "Aspirin" OR "Clopidogrel" OR "Coumarin" OR "heparin" OR "NOAC" OR "LMWH" OR "fondaparinux" OR "edoxaban" OR "betrixaban" OR "rivaroxaban" OR "tinzaparin" OR "enoxaparin" OR "danaparoid" OR "lepirudin" OR "thrombin inhibitor" OR "bivalirudin" OR "desirudin" OR "Xa inhibit*" OR "coumarin"
Comparison	Already covered by the search terms listed in 'intervention' and population
Outcomes	"DALYs" OR "long-term disability" OR "disability" OR "length of stay" OR "length of admission" OR "duration of admission" OR "duration of hospital stay" OR "neurological impairment" OR "paralysis" OR "palsy" OR "neurological deficit" OR "post-traumatic disability" OR "death" OR "dead"

## Appendix 2: Data items to be collected

### Data items

#### A. Clinical information of study participants

- a. Age
- b. Gender
- c. GCS (on admission)
- d. Type of head injury
- e. Mechanism of head injury
- f. Anticoagulation status
- g. Primary outcome data
- h. Secondary outcome data

### Study-related data

- a. First author
- b. Publication year
- c. Country of the corresponding author
- d. Publishing journal
- e. Study design
- f. Sample size
- g. Description of study participants

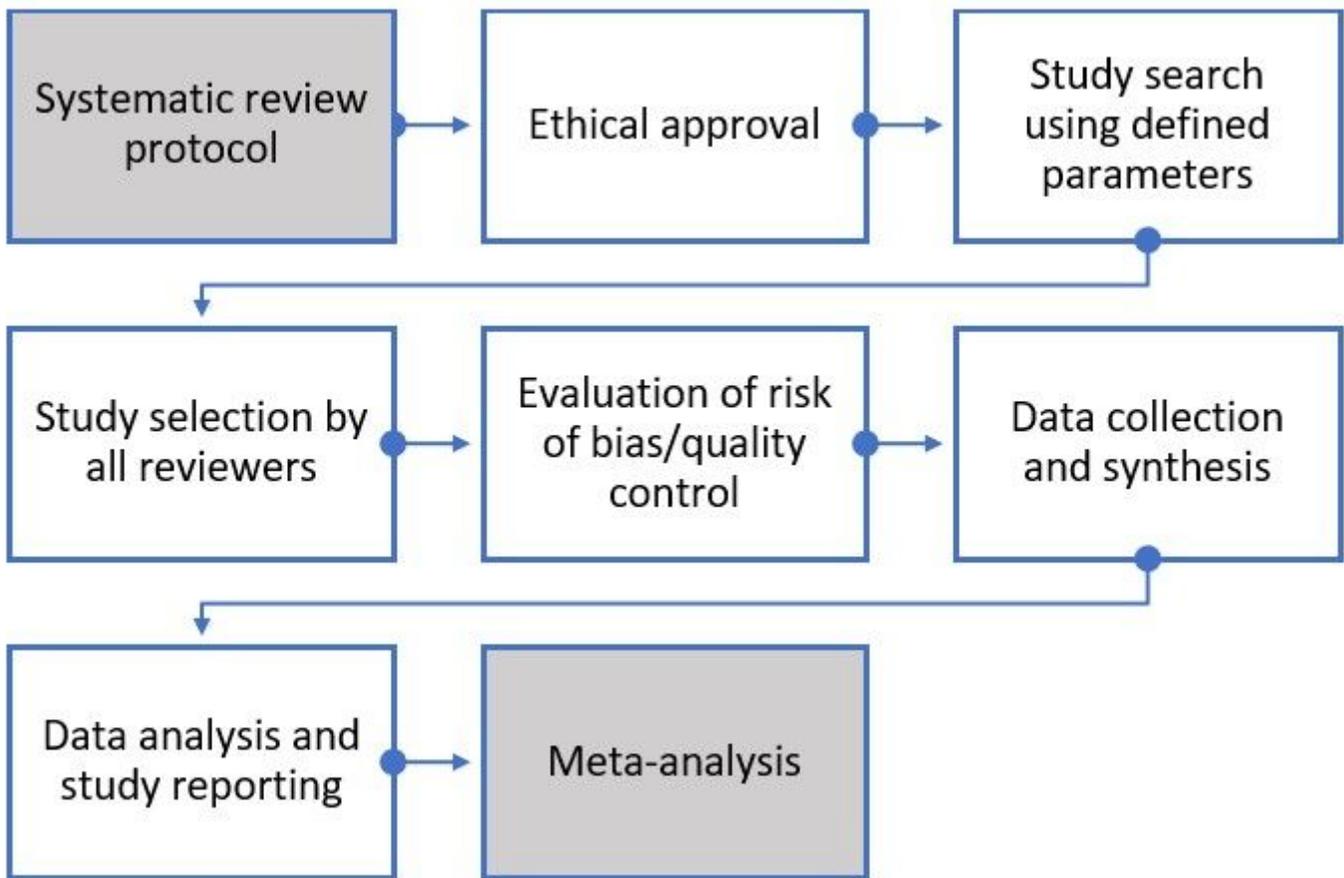
### **Primary outcome**

- In-hospital mortality and 30-day mortality

### **Secondary outcomes**

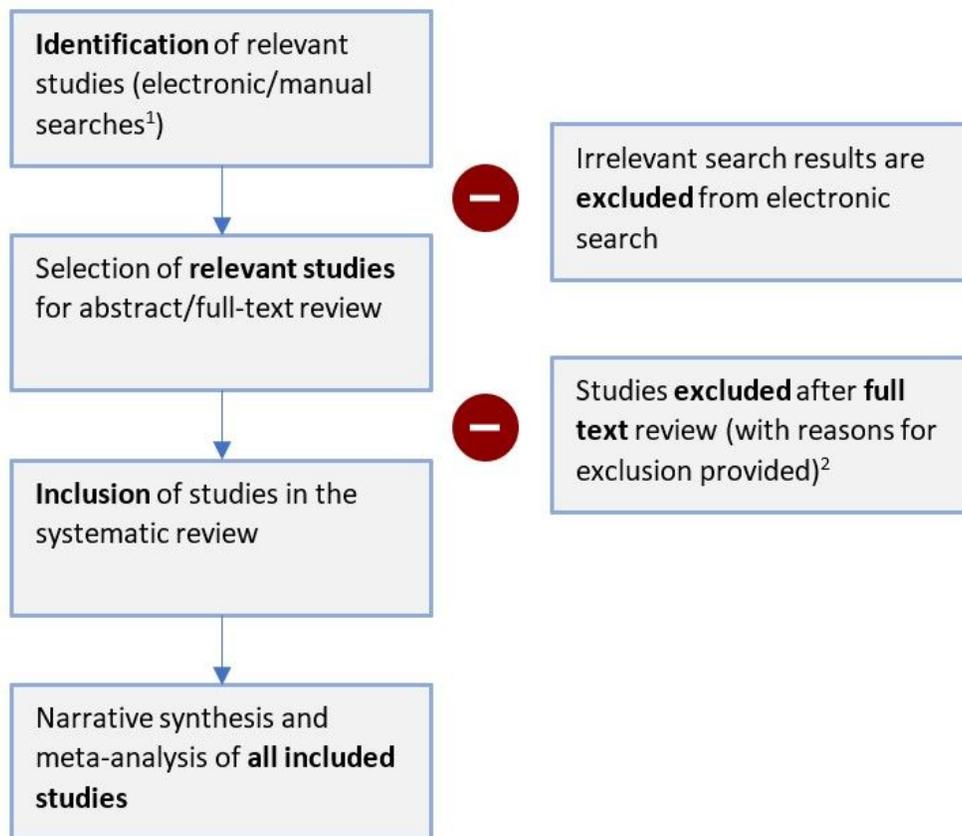
- Long/short term morbidity (viz subsequent neurological deficit/neurological impairment)
- Length of hospital stay
- Length of ICU stay
- Secondary ICH
- Need for operation

## **Figures**



**Figure 1**

Flowchart outlining the study methodology/process



<sup>1</sup>Experts in the field contacted; searches within the references of relevant studies conducted

<sup>2</sup>Studies including those from electronic and manual searches

## Figure 2

Flow chart outlining the study selection process

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMAPchecklist.doc](#)