Study Title:	**"SAH-RISK":** Risk factors for subarachnoid haemorrhage (SAH) - a descriptive and comparative study using electronic health records.
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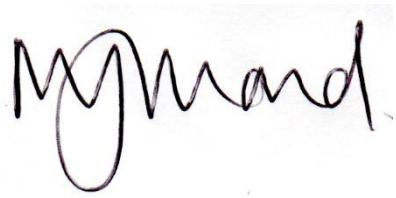
Chief Investigator Signature:	
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CONTENTS

1. SYNOPSIS

Study Title	Risk factors for non-traumatic subarachnoid haemorrhage (SAH): a descriptive and comparative study using electronic health records.
Study Design	Retrospective cohort studies using electronic medical records
Study Participants	Adult patients with data recorded in the TriNetX Analytics Network
Planned Sample Size	Approximately 67.8 million adults in the TriNetX Analytics Network
Planned Study Period	01/01/2021 to 01/07/2021 (6 months)
Objectives	To use electronic health records within the TriNetX database to answer the following research questions: 1. What are the antecedent demographics and characteristics of patients diagnosed with SAH? 2. Is there a difference in risk of SAH between post-menopausal women and men of the same age? 3. Are different antihypertensive classes associated with a differential risk of SAH?

2. ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin 2 receptor blockers
BMI	Body Mass Index
BP	Blood Pressure
CCBs	Calcium channel blockers
HRT	Hormone replacement therapy
ICD-10	International Classification of Diseases, tenth revision
RR	Risk ratio
SAH	Non-traumatic subarachnoid haemorrhage

3. BACKGROUND and RATIONALE

Research questions

1. What are the antecedent demographics and characteristics of patients diagnosed with SAH?
2. Is there a difference in risk of SAH between post-menopausal women and men of the same age?
3. Are different antihypertensive classes associated with a differential risk of SAH?

Background

The incidence of SAH is 7.9/100 000 person-years, with average age of onset of 62 (1). Non-traumatic subarachnoid haemorrhage (SAH) is most commonly caused by rupture of a weakness of an intra-cranial blood vessel (aneurysm). Although it represents only 5% of all strokes, SAH accounts for a similar number of years of life lost as the more common types of stroke (2-4). Despite improvements in clinical management of patients, outcomes after SAH remain poor, with an estimated 26% mortality rate and only 55% of patients regaining independent function (4).

Knowledge of modifiable risk factors for SAH is important in terms of prevention. Prospective population-based studies suggest that women have a 1.24 times greater risk of SAH than men. This becomes apparent after 50 years of age, and increases with each decade (5). An explanation for this observation is lacking, however. Loss of the protective effects of oestrogen in the post-menopausal state has been proposed, but studies comparing hormone replacement therapy (HRT) exposure vs. no HRT exposure on SAH incidence draw conflicting conclusions (6, 7).

Hypertension is an established modifiable risk factor for SAH, approximately doubling the risk of SAH (8, 9). A rise of 10mmHg in systolic blood pressure increases risk of SAH by 21% (10). A recent meta-analysis demonstrates a global decline in blood pressure which parallels a decrease in the global incidence of SAH (1) - highlighting the importance of primary prevention.

Whilst calcium channel blockers are routinely used to prevent secondary ischaemia following SAH, there is no evidence to support the preferential use of specific anti-hypertensives in patients at risk. There is some evidence that certain classes of antihypertensive may offer greater protection against stroke compared to other antihypertensives. One meta-analysis found that calcium channel blockers (CCBs) were associated with a reduced risk ratio (RR) of stroke incidence, compared to other antihypertensive classes (RR 0.83, 95% confidence interval 0.79-0.89)(11). In addition, angiotensin 2 inhibitors (ARBs) may reduce stroke risk compared to angiotensin-converting enzyme inhibitors (ACEis)(12), but the literature is inconsistent (11, 13). These findings are often based on meta-analyses of randomised controlled trials that recorded stroke as a secondary outcome – often not specifying if the stroke was haemorrhagic or ischaemic.

This protocol describes: 1) a descriptive study of the antecedent demographics and characteristics of SAH patients; 2) a comparative study investigating sex-differences and antihypertensive use on the risk of SAH.

4. AIMS and OBJECTIVES.

Descriptive

1. To describe the antecedent demographics and characteristics of SAH patients.

Comparative

1. To explore if the risk of SAH differs between post-menopausal women and age-matched men.
2. To identify if different antihypertensive classes are associated with a differential risk of SAH.

5. STUDY DESIGN

This study has both descriptive and comparative components, described separately.

Data resources underpinning this proposal
This study will use the TriNetX Analytics Network (https://TriNetX.com/). 'TriNetX' is a global federated network capturing anonymized data from electronic health records from 59 healthcare organisations in the USA, totaling 81.0 million patients at the time of writing. Use of TriNetX for research purposes has been described elsewhere (14). Briefly, cohorts of interest can be defined by inclusion and exclusion criteria. These cohorts can then be examined for characteristics and compared for outcomes. Demographics are coded to HL7 version 3 administrative standards. Diagnoses are coded by ICD-10 codes. Measurements are coded to LOINC.

1. What are the antecedent characteristics and demographics of SAH patients?

Definition of patient population
The study population will include all patients in the TriNetX network diagnosed with a non-traumatic subarachnoid haemorrhage (I60) occurring from between the ages of 18-90 years old.

Timeline
We will describe the characteristics and demographics of all SAH patients, as recorded prior to their SAH. The characteristics and demographics of interest are listed in table 1. Characteristics will be described in the lifetime of patients up to the day prior to the index event. Where characteristics could vary, the timeline will be restricted to events occurring from 1 year to 1 day before the index event.

Laboratory measures (blood pressure, body mass index (BMI), serum cholesterol etc.) will use the most recent value, if available, up to the day before the index event.

Table 1: Patient characteristics/demographics of interest

Characteristics	
Demographics	Age (current age and age at index) Sex Race
Diagnoses	Diseases of the circulatory system Hypertensive diseases Essential (primary) hypertension Ischaemic heart diseases Other forms of heart disease Cerebrovascular diseases Cerebral infarction Other cerebrovascular diseases Cerebral aneurysm, non-ruptured Diabetes mellitus Chronic kidney disease Hypertensive chronic kidney disease Overweight and obesity Nicotine dependence Alcohol related disorders Erhlers-Danlos syndromes

	Polycystic kidney, adult type Hormone replacement therapy
Medications	Non-steroidal anti-inflammatory drugs Anticonvulsants Antidepressants Anticoagulants Platelet aggregation inhibitors Angiotensin II inhibitor ACE inhibitors Beta-blockers Calcium channel blockers Diuretics Antihypertensives, other Estrogens Anti-lipaemic agents
Labs	BMI Systolic blood pressure Diastolic blood pressure Serum cholesterol Serum HDL cholesterol Serum LDL cholesterol Triglycerides

Statistical analysis

The aim of the first part of this study is purely descriptive. This will summary the characteristics of all the patients with SAH. Outputs will be presented as means, standard deviations, maximum and minimum range.

2. Is there a difference in risk of SAH between post-menopausal women and men of the same age?

Overview

This component of the study will attempt to identify if there is a difference in SAH risk between women and men aged 55-90, and the change in risk in 5 year categories from 55 to 90.

Definition of patient and comparison groups

We will compare the incidence of SAH occurring aged 55-90, between women and men. We will also make comparisons in 5-year age categories from 55-90 (e.g. women aged 60-64 vs. men aged 60-64) to identify if the risk of SAH changes depending on proximity to menopause.

For each age category, we will calculate the relative risk of SAH, as the ratio of all patients with a new recorded SAH (ICD-10 code: I60) over the total number of patients who had one healthcare visit during this age range.

Propensity score matching

All analysis will be initially run unmatched. If a difference is found between groups, comparisons between propensity-score matched cohorts will be performed.

If required, cohorts will be matched for the following features in their electronic health record up to the day before the index event.

- Demographics: age, race

- Co-morbidities: hypertension, cardiovascular disease (including ischaemic heart disease, arrythmias and heart failure), diabetes mellitus, chronic kidney disease
- Smoking (coded as nicotine dependence)
- Alcohol use (coded as alcohol related disorders)
- Obesity
- BMI (last available reading)
- Blood pressure (last available reading)

Timelines

Our analysis will focus on the incidence of SAH occurring in the specified age category.

Outcomes

The outcome of interest will be occurrence of non-traumatic subarachnoid haemorrhage (I60).

Statistical analysis

If indicated, propensity score matching will be performed as described above. We will report absolute counts, incidence proportion, risk ratios and 95% confidence intervals.

Additional sensitivity analyses to test robustness of results will be performed as required.

3. Are different antihypertensive classes associated with a differential risk of SAH?

Overview

This component of the study will attempt to identify if the risk of SAH differs depending on exposure to specific antihypertensive classes. This will require creating propensity-score matched cohorts and comparing outcomes between matched cohorts.

TriNetX has built-in propensity score matching capabilities. The user selects variables of interest (defined below) to be matched between cohorts, and greedy nearest neighbour matching is used to produce 1:1 matching with a caliper distance of 0.1. Parameters achieving a standard difference < 0.1 will be considered matched.

TriNetX requires each cohort to be less than approximately 1.5 million for propensity score matching. If the cohort sizes are too large, cohorts will be stratified into sex and age specific subcategories to achieve a cohort size that enables propensity score matching.

Definition of patient and comparison groups

Patients aged < 18 will be excluded from our study. Due to the relatively few patients aged > 90 in the TriNetX network, patients aged > 90 are excluded automatically to prevent any risk of identification. The age restrictions imposed will therefore be 18-90, unless otherwise specified.

Due to the suggested beneficial effects of ACEis (15), ARBs (12) and CCBs (11) on stroke, we will make the following comparisons:

- CCB exposure vs. other antihypertensive class exposure
    - CCBs vs. ACEIs/ARBs
    - CCBs vs. Beta-blockers
    - CCBs vs. Diuretics
- Dihydropyridine CCB vs. non-dihydropyridine CCB (diltiazem vs. amlodipine)
- ACEi/ARB exposure vs. other antihypertensive class exposure
    - ACEi/ARB vs. Beta-blockers
    - ACEi/ARB vs. CCBs
    - ACEi/ARB vs. Diuretics

- ACEi vs. ARBs

The exposure group will be selected according to the specific type of antihypertensive in their medical record. Antihypertensive prescription will be defined as requiring two prescriptions separated by at least two years. Patients will be excluded if they had the comparison antihypertensive class noted in their medical record at any time. Patients will also be excluded if they had a SAH occurring prior to commencing antihypertensive treatment. The age restrictions imposed will be 18 – 90. The index event will be the start of the two-year antihypertensive treatment period.

The comparison group will form the inverse of the exposure group. They will be selected as having the comparison antihypertensive in their medical record (again, defined as requiring two prescriptions separated by at least two years). Patients will be excluded if they had the exposure antihypertensive class noted in their medical record at any time. Patients will also be excluded if they had a SAH occurring prior to commencing antihypertensive treatment. The age restrictions imposed will be 18 – 90. The index event will be the start of the two-year antihypertensive treatment period. For example, see table 2.

Table 2: Example of exposure and comparison cohort criteria

	Exposure group, e.g., CCBs	**Comparison group, e.g., diuretics**
Age	18 – 90	18 – 90
Must have	CCB prescription, for minimum 2 years	Diuretic prescription, for minimum 2 years
Must not have	Diuretic prescription SAH occurring before first CCB prescription	CCB prescription SAH occurring before first diuretic prescription

Propensity score matching

All analysis will be initially run unmatched. If a difference is found between groups, comparisons between propensity-score matched cohorts will be performed.

If required, cohorts will be matched for the following features in their electronic health record up to the day before the index event.

- Demographics: age, sex, race
- Co-morbidities: hypertension, cardiovascular disease (including ischaemic heart disease, arrythmias and heart failure), diabetes mellitus, chronic kidney disease
- Smoking (coded as nicotine dependence)
- Alcohol use (coded as alcohol related disorders)
- Obesity
- BMI (last available reading)
- Blood pressure (last available reading)
- Other antihypertensive drugs not forming inclusion/exclusion criteria (ACEi, ARB, beta-blockers, CCBs, diuretics and “other antihypertensives”).

Timelines

Our primary analysis will focus on the timeline occurring from the same day as the index event to 2 years after.

Secondary analyses will use the following timelines:

- 1 month after index event → 2 years
- 6 months after index event → 2 years
- 1 year after index event → 2 years

Outcomes

The primary outcome of interest will be occurrence of non-traumatic subarachnoid haemorrhage (I60).

Secondary outcomes will include;

- Non-traumatic intracerebral haemorrhage (I61) or unspecified non-traumatic intracerebral haemorrhage (I62)
- Cerebral infarction (I63)

The use of negative controls (outcomes for which there are neither mechanistic reasons to expect, nor evidence to indicate a difference between groups) in pharmacoepidemiology is a well-established method to reduce unmeasured confounding (16-18). The following diagnoses will be used as negative controls, as used in similar pharmacoepidemiology studies of antihypertensive classes (19, 20).

- Benign colonic polyp
- Cutaneous abscess
- Ganglion
- Hallux valgus
- Hernia
- In growing nails
- Onycholysis
- Otalgia
- Sebaceous cyst
- Senile keratosis
- Trigger finger
- Viral warts

Statistical analysis

Propensity score matching will be performed as described above. Incidence proportions, absolute counts and risk ratios with 95% confidence intervals will be reported, calculated using the standard methods within the TriNetX platform.

Acknowledging the multiple comparisons to be made in this exploratory study, statistical significance will be defined as $p < 0.001$.

Additional sensitivity analyses to test robustness of results will be performed as required.

Reporting guidelines

Findings will be reported in line with RECORD (the REporting of studies Conducted using Observational Routinely collected health Data) and RECORD-PE guidelines (the REporting of studies Conducted using Observational Routinely collected health Data statement for Pharmacoepidemiology) (21).

6. ETHICAL and REGULATORY CONSIDERATIONS

TriNetX's Analytics network complies with the Health Insurance Portability and Accountability Act (HIPAA). This US federal law that protects the privacy and security of healthcare data. TriNetX is certified to the ISO 27001:2013 standard. TriNetX upholds an Information Security Management System in order to protect the healthcare data it has access to and meet the HIPAA Security Rule requirements.

All data displayed in the TriNetX Platform is de-identified as per Section §164.514(a) of the HIPAA Privacy Rule. The data de-identification process is verified through formal determination by a qualified expert, as specified in Section §164.514(b)(1) of the HIPAA Privacy Rule. As of December 2020, this supersedes the waiver from the Western Institutional Review Board. For more information, see (14).

Potential Conflicts of Interest

TriNetX have granted PJH and CHH unrestricted access to the TriNetX Analytics network for the purposes of performing research, and with no constraints on the analyses or decision to publish.

7. FUNDING

This study requires no formal funding.

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