STUDY PROTOCOL

Risk of intracranial hemorrhage in users of oral antithrombotic drugs: Study protocol for a nationwide study [version 1; peer review: 2 approved]

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Abstract

Background A wide range of antithrombotic medications can be used in the prevention and treatment of thrombosis. Among hemorrhagic complications of antithrombotic drugs, intracranial hemorrhage may have particularly devastating consequences with high morbidity, disability and mortality rates. The incidence and risks of intracranial hemorrhage in patients on antithrombotic treatments from regular clinical practice outside clinical trials remain largely unknown. It is not known if results from clinical trials can be extrapolated to everyday clinical practice. We will conduct a nationwide study to investigate the risks and incidence rates of intracranial hemorrhage in users oral antithrombotic drugs in Norway from 2008 through 2014.

Methods and design The aim of this nationwide study is to investigate the incidence rates of intracranial hemorrhage requiring hospitalization in users of oral antithrombotic drugs. The study will be conducted within the approximately 4.7 million inhabitants of Norway from January 1st, 2008, to December 31st, 2014. Treatment and outcome data are obtained from the Norwegian patient registry and the Norwegian prescription database.

Trial registration number Clinicaltrials.gov (NCT02481011)
Keywords
Stroke, Hematoma, Drug-Related Side Effects and Adverse Reactions, Hematoma, Subdural, Intracranial

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Background

According to the World Health Organization (WHO) the disorders caused by thrombosis are collectively the most frequent cause of death and disability in the developed world\(^1\). A wide range of antithrombotic medications can be used in the prevention and treatment of thrombosis. There are two main groups of antithrombotic therapy: anticoagulants which limit activity of the coagulation cascade, and antiplatelet agents which limit activation or activity of blood platelets\(^2\). Certain disorders are best managed with antiplatelet medications, others with anticoagulants, and some with both\(^3\).

The challenge is to prevent thrombosis while maintaining hemostasis, namely the capacity to preclude hemorrhage. The most serious adverse effect of antithrombotic therapy is bleeding. Combinations of antithrombotic agents are now frequently used, and this may lead to an increased frequency of significant bleeding complications\(^4-6\).

Among hemorrhagic complications of antithrombotic drugs, intracranial hemorrhage (ICH) may have particularly devastating consequences with high morbidity, disability and even mortality rates\(^7,8\). Intracerebral hemorrhage is generally associated with a higher risk for death and incurs greater loss of health over a lifetime than ischemic stroke\(^9-11\).

Although a certain risk for bleeding may be acceptable in the context of even greater protection against ischemic events, it is important to quantify the magnitude of bleeding risk. So far the efficacy and safety profile of antithrombotic agents are generally assessed in randomized controlled trials (RCT). However, extrapolating the results from RCTs to the general patient population in this context is challenging. Patients who participate in clinical trials are frequently highly selected and may therefore not be representative of users in everyday clinical practice. Clinical follow-up and drug compliance are often better in clinical trials and polypharmacy is less common than in clinical practice. In addition, the primary endpoint of RCTs is usually not complications, and complication numbers are limited as treatment period is often much shorter than in routine management of a chronic disease or condition. In everyday practice there is a risk of drifts in indications, inclusion criteria, exclusion criteria, and stop-criteria suggested by RCTs. Specifically, in the context of antithrombotic drugs this may potentially lead to treating patients with lesser risk of thromboembolic events but with higher risk of hemorrhage. Collectively these factors may lead to other incidence rates in the general clinical population than what is frequently reported in the literature.

The incidence of intracranial hemorrhage due to antithrombotic therapy could theoretically be monitored by post-marketing surveillance by including spontaneously reported events. Unfortunately, it seems this does not provide more reliable estimates. A recent study from Finland showed that bleeding complications due to oral anticoagulation with Warfarin are underreported in daily clinical practice\(^12\). Further, it has been shown that reporting rates of side effects following medical therapy tend to decrease over time indicating that it is more likely that adverse events to a newer drug are reported compared to a drug that has been available for many years\(^13,14\). This is why we need population-based large-scale pharmaco-epidemiological studies, i.e. real world data, in which cohorts of patients exposed to antithrombotic medications are monitored to estimate a valid and reliable risk of the treatment.

The incidence rates of intracranial hemorrhage in patients on antithrombotic treatments in the general population remain unknown. We will conduct a nationwide study to investigate the incidence rates of ICH in users oral antithrombotic drugs in Norway from 2008 through 2014.

Methods and design

Reporting will be consistent with the strengthening the reporting of observational studies in epidemiology (STROBE) statement.

Aims of the study

The primary aim of this nationwide study is to investigate the incidence rates of ICH requiring hospitalization (inpatient treatment) in users of different oral antithrombotic drugs. Secondary aims are assessments of case-fatality rates following ICH and proportion of patients undergoing neurosurgical procedures in users and non-users of antithrombotic drugs.

Study population

The study will be conducted within the approximately 4.7 million inhabitants of Norway (2008 census, Statistics Norway) from January 1\(^{st}\), 2008, to December 31\(^{st}\), 2014. All residents included in the Norwegian patient registry (NPR) and/or Norwegian prescription database (NorPD) aged 18 years or older at the start of the study are eligible for inclusion. According to NPR, the expected number of eligible patients with ICH during the study period is in the range of 50,000 to 60,000. The National Registry provides information to NPR and NorPD on vital status (dead or alive). Information about public specialist health care (both inpatient and outpatient treatment) and any dispensed prescription in Norway can be linked to residents by using a unique 11-digit personal identifier.

Inclusion criteria

1. Hospitalization due to ICH (Table 1)
2. Residential address in Norway in the entire study period
3. Age ≥18 years on January 1\(^{st}\) 2008

Exclusion criteria

1. Traumatic (high-energy) intracranial injury
2. Parenteral (high-energy) intracranial injury

The Norwegian health care system

Norway has a public health care system with quite evenly distributed resources and uniform training and licensing for medical professionals. Only public hospitals provide health care to patients with ICH. The health authorities cover all inpatient treatment for patients with intracranial hemorrhage, and costs concerning established treatment options are generally not a concern for the individual patients or their doctors. Further, the government covers a variable proportion of the costs of antithrombotic drugs prescribed by physicians. Preapproved medicines available for general reimbursement
Table 1. The ICD-10 and ICPC-2 groups of ICH and comorbidity screened in this study.

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>ICD-10</th>
<th>ICPC-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>I60.0–I60.9</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>I61.0–I61.9</td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>I62.0–I62.9</td>
<td></td>
</tr>
<tr>
<td>Nontraumatic intracranial</td>
<td>I60.0–I60.9</td>
<td></td>
</tr>
<tr>
<td>hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial injury</td>
<td>S06.3–S06.9</td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>I48</td>
<td>K78</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>I63–I68, I20–125, I74, G45.8, G45.9</td>
<td>K93, K94</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>I21, I22, I70.0, I70.2–I70.9, F01</td>
<td>K74, K75, K76, K89, K90, K91, K92, K99</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, T51, Z71.4, Z72.1</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>B15–19, C22, D68.4, K70–K77, Z94.4</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>M19</td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>K25–K29</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>E10–E14</td>
<td>T89, T90</td>
</tr>
<tr>
<td>Hypertension</td>
<td>I10–I15</td>
<td>K85, K86, K87</td>
</tr>
<tr>
<td>Heart failure</td>
<td>I11.0, I42, I50, J81</td>
<td>K77, K82, K83, K84</td>
</tr>
<tr>
<td>Bleeding</td>
<td>I69.0–I69.2, J94.2, K25.0, K25.4, K26.0, K26.4, K27.0, K28.0, K92.0–K92.2, N02, R04, R31</td>
<td></td>
</tr>
<tr>
<td>Accidents</td>
<td>V0n–Y3n, S06.0–S06.3, S10–T19</td>
<td></td>
</tr>
</tbody>
</table>

ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICPC-2 = version 2 of the International Classification of Primary Care

ensure that patients get part of the medicine expenses covered by the government when having a chronic, prolonged or severe illness. This ensures access to medicines regardless of financial situation. There are in general few disparities in access to health care in the Norwegian population and insurance policies do not influence the treatment of intracranial hemorrhage. Antithrombotic medicine in Norway is only available at pharmacies if the patient has a prescription from a physician.

The Norwegian prescription database (NorPD)
NorPD was initiated on January 1st 2004, and contains important information on prescriptions for medications dispensed from all pharmacies throughout the country. All pharmacies are required to register each drug dispensing in NorPD, ensuring complete registration. NorPD registers the unique personal identification number of the patient, type of drug according to the Anatomical Therapeutic Chemical (ATC) classification system, number of Defined Daily Doses as defined by WHO, date of dispensing, quantity dispensed, and drug strength and formulation. NorPD does not include the prescribed daily dose. In addition, diagnoses are registered for medications with reimbursement according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) or version 2 of the International Classification of Primary Care (ICPC-2). The 11-digit personal identification number, which is encrypted in NorPD, ensures that a complete prescription history can be established for each individual. The oral antithrombotic drugs included in the present study are presented in Table 2. The number of patients on oral antithrombotic drugs, either single agent or combined regimens) during the decade-long study period will be retrieved from NorPD.

The Norwegian patient registry (NPR)
NPR automatically receives information regarding diagnoses and procedures when patients receive both inpatient and outpatient
Comorbidity and concomitant medication

We will identify comorbidities from both NPR and NorPD, including atrial fibrillation, congestive heart failure, thromboembolism, vascular disease, hypertension, diabetes mellitus, peptic ulcer, liver disease, alcohol abuse, osteoarthritis, previous bleeding, and chronic renal failure. Dispensed prescriptions for renin–angiotensin system inhibitors, antiarrhythmic drugs (beta-blockers, digoxin, class 1C antiarrhythmic drugs, calcium-channel blockers, and amiodarone), non-steroidal anti-inflammatory drugs, antidepressants, or proton pump inhibitors dispensed are defined as concomitant medication.

Statistics

All statistical analyses are performed with SPSS 21.0, MySQL (Oracle), or R version 3.1 (R Foundation for Statistical Computing). The statistical significance level is defined as P≤0.05 with no adjustments for multiple comparisons. For each patient exposure periods for antithrombotic medications will be calculated according to the World Health Organization’s recommendation for drug utilization studies using the ATC classification system and the DDD as a measuring unit. Exposure is defined as having occurred when patients have drug available and discontinuation as when they have no more drug(s) available. For many patients, treatment regimens are expected to change during the study period, so we treat use of antithrombotic medications in the analyses as time varying exposures. Consequently, patients can change exposure group according to dispensed prescriptions during the entire span of the study period. We consider patients to be at risk only when exposed to the drug(s) (during active treatment). We calculate risk time (person years) only for the active treatment period. Patients are followed until death, emigration or end of study period. Drug exposure and registration of comorbidity are discontinued (censored) at the time of the first event after 2008 (ICH). Due to strict Norwegian data privacy regulations the exact dates for prescription dispensing, ICH, and death are not made available to the study authors, and all time measurements are from a reference date known only to NPR and NorPD. The calendar year for ICH is available. The month and calendar year for death is available. Incidence rates will be calculated for overall risk of intracranial hemorrhage and for the subgroups non-traumatic intracerebral hemorrhage, acute or chronic subdural hematoma, and subarachnoid hemorrhage. We will estimate hazard ratios with 95% confidence intervals for ICH using Cox regression models with adjustments for age, sex, comitant drugs, and comorbidity. The time variable in the Cox model is patient age. We will investigate case fatality rates at three-month and one-year timepoints in addition to an analysis of overall survival following ICH. Differences in time to event (death) will also be presented in survival curves. We will investigate the proportions of patients with ICH undergoing neurosurgical procedures for different antithrombotic drug exposures. We will analyze continuous variables using an unpaired two-tailed t test for normally distributed data and continuous data with skewed distribution using the Mann-Whitney U test. The Chi-square test is used to examine the associations between categorical variables. For all outcome measures the statistician (ÖS) will be blinded to drug exposure. All tables and figures are determined before any statistical procedure is undertaken, all tables will be filled in with results before the code for actual drug exposure is broken, and no information will be deleted when results are known.

Ethical approval

The study protocol has been approved by the Regional Committee for Medical Research in Central Norway (2014/9538).

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### Table 2. Oral antithrombotics and concomitant medication included in this study.

<table>
<thead>
<tr>
<th>ATC#</th>
<th>Concomitant medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>B01AC06</td>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>B01AC07</td>
<td>Dipyridamol</td>
</tr>
<tr>
<td>B01AC04</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>B01AC30</td>
<td>Dipyridamole-acetylsalicylic acid</td>
</tr>
<tr>
<td>B01AC22</td>
<td>Prasugrel</td>
</tr>
<tr>
<td>B01AC24</td>
<td>Ticagrelor</td>
</tr>
<tr>
<td>B01AC05</td>
<td>Tirofiban</td>
</tr>
<tr>
<td>B01A03</td>
<td>Warfarin</td>
</tr>
<tr>
<td>B01A07</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>B01F02</td>
<td>Apiksaban</td>
</tr>
<tr>
<td>B01F01</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>B01A01</td>
<td>Dukumarol</td>
</tr>
<tr>
<td>B01A02</td>
<td>Fenylindandion</td>
</tr>
<tr>
<td>C01AA05</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td>C01AA04</td>
<td>Antiplatelet agents</td>
</tr>
<tr>
<td>C00</td>
<td>Antiplatelet agents</td>
</tr>
<tr>
<td>C03C</td>
<td>Loop diuretic</td>
</tr>
<tr>
<td>C03A</td>
<td>Thiazide</td>
</tr>
<tr>
<td>C01BC</td>
<td>Antiarrhythmic drug</td>
</tr>
<tr>
<td>C07, C08, C01AA05, C01AA04, C01BD01, C07AA07, C01BC</td>
<td>Antiarrhythmic drug</td>
</tr>
<tr>
<td>C02BC</td>
<td>Proton-pump inhibitor</td>
</tr>
<tr>
<td>A10</td>
<td>Oral glucose-lowering drug</td>
</tr>
<tr>
<td>N06A</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>H02AB</td>
<td>Glucocorticoid</td>
</tr>
</tbody>
</table>

ATC = Anatomical Therapeutic Chemical classification system
User involvement
No patients are involved in setting the research question or the outcome measures; nor are they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Access to data
There will be no additional data available.

Dissemination policy
The study will give rise to a scholarly publication that will be published in an international, peer-reviewed journal.

Discussion
In this article, we present a protocol for a nationwide study designed to investigate incidence rates of intracranial hemorrhage requiring hospitalization in users of different oral antithrombotic drugs. Treatment and outcome data are obtained from the Norwegian patient registry and the Norwegian prescription database. Secondary end-points are case-fatality rates at 3 months and 1 year after ICH, overall survival after ICH, and proportion of patients undergoing neurosurgical procedures in users and non-users of various antithrombotic drugs. In addition we will provide incidence rates for the different antithrombotic drugs in subgroups of ICH as they are defined in this study.

Study strengths and limitations
The major strength of this study is the large nationwide sample size collecting real world data for antithrombotic medication and its relation to ICH. Further, the study is performed in a well-defined region, Norway, where patients have equal access to a public health care system and medications. This will assure results with high external validity. Another strength is the inclusion of subdural hematomas, which are often omitted from studies evaluating the incidence of ICH in patients on antithrombotic treatment (except when associated with high energy or penetrating trauma mechanism). We will also like to stress that all tables will be set in advance before any statistical procedure is undertaken, the statistical procedures will be performed by a statistician blinded to the actual antithrombotic treatment, all results will be filled in the tables before the codes for actual treatment are broken, and no information will be deleted when the results are known. By performing the study by these strict methodological measures we will as far as possible avoid presenting biased results.

The main limitation of our study is its observational design and lack of randomization. There is a lack of information about important clinical parameters including body mass index, blood pressure, tobacco use, lipid levels, and coagulation profile; hence the effect of unmeasured confounders cannot be excluded. Since data are partly based on diagnoses codes set in clinical practice, the results may be affected by the quality of coding practice.

There are tools available to estimate the risk of major bleeding for patients on anticoagulation treatment to help determine risk-benefit. Unfortunately, we have no data on the necessary variables in our patient population. Antithrombotic drugs are prescribed to patients with perceived higher risks of thrombosis. Some risk factors associated with thrombosis are also risk factors for ICH. Making causal inference from observed incidence rates of ICH in various categories of users and non-users of antithrombotic medications is difficult.

In large registry- and population-based pharmacoepidemiological studies some assumptions concerning drug exposure must be made. The ATC/DDD system has been in use for more than four decades in drug utilization studies. It has been found suitable for comparisons of drug utilization between different population groups and to monitor trends in drug use. Further, the ATC/DDD system is useful for providing denominator data for drug safety assessments. In everyday clinical practice individual patient characteristics and pharmacokinetic considerations must be accounted for. Consequently, the prescribed daily dose may differ from the DDD. Other researchers have estimated a daily drug exposure for the individual patient after comparing the accumulated drug dose and the elapsed time from consecutive prescriptions. Information about the prescribed daily dose is unfortunately not available in NorPD. However, the prescribed daily dose does not necessarily reflect actual drug doses consumed. All time measurements are from a reference date known only to NPR and NorPD. Prescriptions dispensed in the last few months of 2014 might extend beyond our study period. Some patients might therefore have had an undetected ICH in early 2015 with ongoing exposure. Moreover, only patients with ICH admitted to hospital are included in the present study. Together, these factors contribute to a more conservative risk estimate of ICH in users of antithrombotic medications. Further, there is likely to be some missing drug exposure in the first few months of the study period in 2008 as prescriptions were dispensed in 2007. This might increase the incidence rate of ICH in the control group without antithrombotic drug exposure.

Due to data privacy regulations all patient data are de-identified and we are not allowed to access patients electronic hospital records or diagnostic imaging to validate diagnoses and drug exposure. Validation of diagnoses and drug exposure, at least in a representative subgroup of patients, would probably strengthen our results.

Conclusion
In this article, we present a protocol for a nationwide study designed to investigate incidence rates of ICH requiring hospitalization in users of different oral antithrombotic drugs. Treatment and outcome data are obtained from the Norwegian patient registry and the Norwegian prescription database. We want to perform this study by strict methodological measures and have discussed some of the methodological issues pertinent to the successful execution of this large-scale pharmacoepidemiological study.

List of abbreviations
ATC = Anatomical Therapeutic Chemical
DDD = Defined Daily Dose
ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICH = Intracranial hemorrhage
ICPC-2 = version 2 of the International Classification of Primary Care
Author contributions

All authors read and approved the final manuscript. SG is the guarantor and gave the original concept of the study. SG and HJ were involved in the study design, collection of the data, statistics and writing of the manuscript. OS, SMC, LRØ, AMG, CG and ASJ took part in the study design and writing. OS contributed in the study design, writing of the manuscript and statistics.

Competing interests

The authors declare that they have no competing interests.

Grant information

This study is funded by a grant from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology. The funders have no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

I confirm that the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

The authors would like to thank the Norwegian patient registry, the Norwegian prescription database, and Ingrid I. Riphagen at the Unit for Applied Clinical Research, NTNU.

References


NorPD = Norwegian prescription database
NPR = Norwegian patient registry
RCT = Randomized controlled trials
STROBE = strengthening the reporting of observational studies in epidemiology
The present study outline by Gulati et al. aims to evaluate the incidence and relative risk of ICH after parenteral anti-thrombotic drug use. The aim is meritorious since very little data of these are known. Mostly the question of prolongation of anti-thrombotic therapy after ICH have been discussed. The presentation and discussion of the strengths and limitations of the proposed study is adequate and well organised. The only alternative to the present design would be a prospective trial but, given the limitations, the proposed retrospective study will be able to make a reasonable estimate of incidence and relative risks.

References

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
This is a well-written and ambitious study proposal. Many patients are prescribed antiplatelet and anticoagulant therapies, and intracranial hemorrhage (ICH) is a particularly feared complication as it is associated with severe morbidity and mortality. These therapies are most frequently used in elderly people, and the extent of their use and adverse effects will be increasingly relevant, as the population is progressively getting older. This study aims to assess the risk of ICH in patients on different anti-thrombotic therapies in Norway. We agree with the authors that the reported incidence rates of ICH in such patients are probably lower than what is seen in regular clinical practice. Thus, it is of considerable interest to evaluate this in a real-world and heterogeneous population where these drugs are in use, and especially within a homogenous and transparent health system such as in Norway.

The study is generally well designed and methodologically sound. The described analyses will involve large groups of patients from the Norwegian Patient Registry and the Norwegian Prescription Database. However, we find the inclusion and exclusion criteria somewhat unclear and not in concordance with other sections of the manuscript. The first inclusion criterion is “hospitalization due to ICH”; this will enable the analysis of incidence rates of antithrombotic use in ICH patients. The most interesting incidence rates are those of ICH among all patients on these therapies, which will require inclusion of all Norwegian citizens on these drugs. These analyses are however described repeatedly throughout other sections of the protocol, and will give sound estimates of ICH incidence rates and a foundation for comparative analyses between different drugs and patient groups.

We also find the exclusion criteria slightly confusing. With the collected information, which specifically does not include detailed information from hospital journals, it will not be possible to exclude patients with “traumatic (high energy) intracranial injury” or “parenteral antithrombotic treatment”. On the other hand, it would be very interesting to evaluate the in-hospital incidence (and outcomes) of ICH in patients undergoing such treatments for stroke and myocardial infarction, but this is beyond the scope of this study.

The authors also want to assess the frequency of neurosurgical procedures in users and non-users of antithrombotic drugs. It is not clear which types of procedures this analysis will involve, but we suppose that craniotomies with hematoma evacuation, burr hole evacuation, ventricular drainage and intracranial pressure measurement are relevant procedures. The NOMESCO Classification of Surgical Procedures (NCSP) codes should be clearly described.

We believe that it will be difficult to differentiate between chronic and acute subdural hematomas (no specific ICD code for chronic or acute), as well as traumatic and non-traumatic hematomas (divergent practices using traumatic ICD code S06.5 and non-traumatic ICD code I62.0). One could deduce if the hematoma was chronic or acute through linkage analysis with the conducted neurosurgical procedures. However, it will be impossible to assess if it was chronic or acute in non-operated patients, or traumatic or non-traumatic, without detailed review of patient journals.

Taken together, this study protocol outlines a comprehensive and interesting study that can provide clinically relevant estimates of ICH risk in patients on antithrombotic drugs. In our opinion, the authors only need to provide minor clarifications to the study protocol.
Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.