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The importance of validating intracranial bleeding diagnoses in The Health Improvement Network, United Kingdom: misclassification of onset and its impact on the risk associated with low-dose aspirin therapy

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Running title: Validation of intracranial bleeding onset in THIN

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Take-home messages/key points

- Low-dose aspirin is an effective preventive therapy for ischemic stroke, but is associated with a small excess risk of bleeding.
- As hemorrhagic stroke cannot be reliably distinguished from ischemic stroke based on signs and symptoms alone, antithrombotic treatment is generally withheld pending results of urgent brain imaging – except if transient ischemic attack is suspected.
- Among 1635 initial incident cases of ICB in THIN, review of medical records including free text comments, showed that the first recorded sign/symptom was a mean of 26 days (inter-quartile range 6–30) before the date of the recorded diagnosis.
- Estimates of ICB risk with low-dose aspirin use can be notably affected if the true date of onset is misclassified, particularly among patients recently starting on low-dose aspirin.
- Identifying the true date of onset of ICB events in THIN is important to obtain accurate measures of association with low-dose aspirin, and review of free text comments is necessary to achieve this.

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This study has not been presented or posted anywhere previously although some parts of the original study (methods and certain results) were presented at the American Heart Association Congress in New Orleans, November 2016.

ABSTRACT

Purpose: To evaluate misclassification of intracranial bleeding (ICB) onset in The Health Improvement Network (THIN) and assess its impact on risk associated with low-dose aspirin preventive therapy.

Methods: 199,049 new users of low-dose aspirin and 1:1 matched non-users were followed to identify incident ICB cases with validation involving manual review of patient records and linked hospital data. Index date was the date of the recorded diagnosis (initial cases). After a second manual review including free text comments, the index date was backdated to the first symptom date; prevalent cases were excluded. Two nested case–control analyses were undertaken: using initial cases and using final cases (with backdated index date). Current, recent and past low-dose aspirin use was defined as 0–7, 8–90 and 91–365 days before index date, respectively.

Results: Among 1635 initial and 1611 final ICB cases, there were, respectively, 37% vs. 38% current users of low-dose aspirin, 10% vs. 8% recent users and 7% vs. 7% past users. Current users with duration <3 months accounted for 6% of initial cases and 4% of final cases. Compared with never use, odds ratios (95% confidence intervals) using

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initial and final cases respectively, were: current use 0.97 (0.84–1.12) vs. 0.97 (0.84–1.12); <3 months current use, 1.65 (1.28–2.13).vs. 1.13 (0.85–1.50); recent use 1.52 (1.24–1.88) vs. 1.10 (0.88–1.37); and past use 1.30 (1.03–1.64) vs. 1.17 (0.92–1.48).

Conclusions: Misclassifying ICB onset in THIN marginally impacts the categorization of low-dose aspirin use yet notably effects estimates of associated risk.

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INTRODUCTION

Ischemic and hemorrhagic stroke, as well as other cerebrovascular disorders are major contributors to the overall burden of neurological disorders worldwide in terms of disability-adjusted life-years and deaths.[1] Approximately 15% of all strokes are hemorrhagic caused by a bleed in the brain parenchyma (intracerebral hemorrhage [ICH]) or the subarachnoid space (subarachnoid hemorrhage [SAH]).[2] Along with subdural hematoma (SDH, an extracerebral event), ICH and SAH are the most common forms of intracranial bleeds (ICBs). Subarachnoid hemorrhage onset is typically preceded by a thunder clap headache, and usually there are no focal signs (e.g., hemiplegia, dysphasia). Intracerebral hemorrhage, on the other hand, typically presents with acute onset focal signs, but cannot be distinguished with clinical certainty from ischemic stroke based only on signs and symptoms. Subdural hematoma has been coined the great imitator due to its numerous clinical presentations, and may have an

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acute (hours to days) or a more subacute/chronic (weeks to months) onset.[3, 4] Correct diagnosis of different ICB types has been greatly enhanced through the advent and increased accessibility of brain imaging studies. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain can, in most instances, rapidly provide the diagnosis and help ensure timely treatment. These scans are also important in differentiating hemorrhagic and ischemic stroke, thereby ensuring the correct treatment is administered. While thrombolysis, antiplatelet or anticoagulant therapies are appropriate treatments for an ischemic stroke, these should be avoided in the acute phase of hemorrhagic stroke.

Computerized healthcare databases are powerful sources of information from which population-based studies on the effects of drugs can be carried out. They are logistically attractive, holding previously recorded, prospectively collected data, and cover populations that are relatively unselected. A clear understanding of the clinical event of interest and the way it is recorded in these databases is crucial to avoid misclassification of both status and time of onset. This is key to accurately define clinical outcome data in order to obtain valid measures of association between exposures of interest and clinical outcomes. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance maintains that for database studies, validation of clinical outcomes (as well as drug exposure and covariates) is crucial.[5] Such methodological rigor helps minimize bias and increase confidence in the use of observational data for healthcare decision making.

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We have previously validated recorded diagnoses of ICB in a population-based primary care database in the UK – The Health Improvement Network (THIN) – through manual review of patient records, including free text comments, and linkage to hospitalization data.[6, 7] Also in THIN, we have previously investigated the completeness of low-dose aspirin prescription data, by evaluating the extent that over-the-counter obtained preventative aspirin is unrecorded, and have found this to be minimal (~2%).[8] The aim of this current study was to assess the importance of validating diagnoses ICB in THIN. The specific objective was to evaluate the extent of misclassification of ICB onset when using dates of recorded ICB diagnoses, and its impact on the association between ICB and low-dose aspirin therapy.

METHODS

Data source

The Health Improvement Network has been described in detail elsewhere.[6] Briefly, the database contains the anonymized electronic medical records (EMRs) of patients registered with participating general practices in the UK; the data recorded are therefore those entered as part of routine patient care. Diagnoses are entered using the Read coding system.[9] Symptoms and other clinical details are also entered using Read codes, although the free text section enables healthcare practitioners to add additional notes and specific details related to the medical event/encounter. Approximately 6% of the UK population is covered by THIN, and the database is representative of the UK

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demographic in terms of age, sex and geography.[10, 11] For approximately 20% of practices contributing to THIN, patient-level linkage to hospitalization data (hospital episode statistics [HES]) is possible.[12]

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Study design

This study was based on a previous pharmacoepidemiological study – a cohort study of 199,079 new users of low-dose aspirin and 1:1 matched non-users of low-dose aspirin with nested case–control analyses, among individuals aged 40–84 years in THIN (2000–2012) at study entry, which evaluated the association between use of low-dose aspirin and risk of ICB.[7] Details of the methods used, including identification and follow-up of the study cohorts, case identification and validation, selection of controls (individuals without ICB during follow-up) using incidence density sampling, frequency matching of controls to cases, classification of low-dose aspirin exposure in the nested case–control analyses, and statistical methods, have all been described previously.[7] In the previous study we defined ICB onset as the date of first symptom of the bleed. In the present analysis, we explored the influence of using an alternative ICB onset definition, i.e., corresponding to the original computer-detected date of ICB, and assessed the influence of this choice on estimates of association between low-dose aspirin and ICB risk.

Case validation

As a brief description of the case validation process, individuals with a computer-detected diagnosis of ICB in their EMRs (potential ICB cases; N=2092) had their diagnosis either confirmed or not confirmed through a three-step process. Firstly, potential cases were cross-linked with patients with a confirmed ICB diagnosis in

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previous research projects using THIN.[13, 14] Secondly, we searched for ICB discharge diagnoses in HES data (for individuals in linked practices). Thirdly, we manually reviewed patients' EMRs, including free text comments, while masked to information on all prescribed medications. Following these steps, there were a total of 1635 confirmed incident ICB cases (initial cases); the index date was the date of the computer-detected ICB diagnosis.

Backdating the index date

To more accurately determine the date of onset of the intracranial bleed among the 1635 initial ICB cases, the first symptom(s) that led to the ICB diagnosis was identified during a second manual review of these patients' EMRs in THIN, again while masked to information on drug exposure. In doing so, the index date was backdated to the date of first symptom or other entry relating to the event; for example, if hemiparesis of sudden onset was recorded in the free text before the date of the ICH diagnosis, then the index date was moved back to the date this hemiparesis was recorded.

Among the initial 1635 cases of ICB, the first recorded sign/symptom was a mean of 26 days (interquartile range 6–30) before the date of the recorded diagnosis. Following the second manual review (to more accurately identify the date of onset of the bleed), 1611 confirmed ICB cases remained – 24 patients (14 ICH, 7 SDH and 3 SAH) were no longer retained as incident cases of ICB. Of these 24 cases, 20 were excluded because after backdating the date of ICB onset (index date) to the date of the first recorded

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symptom that led to the ICB diagnosis, the event no longer occurred within the study period but occurred on or before the start of follow-up. In the other 4 patients (all with a diagnosis of ICH), the event was revealed to be an episode of hemorrhagic transformation of an ischemic stroke. **Supplementary Figure 1** shows the medical record entries of one patient whose first symptom of ICB (new index date) was recorded on the first date of follow-up and so was consequently not retained as an incident case of ICB. **Supplementary Figure 2** shows a patient whose index date was backdated by approximately 1 month owing to the final ICB diagnosis being recorded this length of time after the first entry relating to the event.

Low-dose aspirin exposure

Low-dose aspirin exposure (and other medication exposure) was based on recorded prescriptions any time before the index date and was classed into five categories: *current use*, when supply of the most recent prescription lasted until the index date or ended 0–7 days before the index date; *recent use*, when supply of the most recent prescription ended 8–90 days before the index date; *past use*, when supply of the most recent prescription ended 91–365 days before the index date; *distant use*, when supply of the most recent prescription ended >365 days before the index date; *never use*, when there was no recorded use at any time before the index date.

Analysis

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Results of our nested case–control analysis using the final set of 1611 incident cases of ICB and 10,000 frequency-matched controls have been published previously.[7] To determine the impact of not backdating the index date to the date of first ICB symptom on low-dose aspirin exposure status and the risk of ICB, we performed the same nested case–control analysis, calculating adjusted odds ratios (ORs) with 95% confidence intervals (CIs), but among the initial set of 1635 ICB cases where the index date was the date of the computer-detected ICB diagnosis.

RESULTS

Re-classification of low-dose aspirin exposure

Table 1 shows the classification of low-dose aspirin exposure among the final 1611 incident ICB cases before and after the second manual review; 68/1611 had their low-dose aspirin exposure status changed from the initial assigned status. After backdating the computer-detected index date there were 614 current users of low-dose aspirin (use on the index date or in the previous 7 days); of these, 568 had initially been classed as current users, while 46 cases had previously been classed as either a recent user (44 cases; use 8–90 days before the index date) or a past user (2 cases; use 91–365 days before the index date). Of 168/1611 ICB cases originally classed as recent users, 44 were reclassified as current users after backdating the computer-detected index date; A graphical illustration of one such case is shown in **Supplementary Figure 3**.

<<Table 1 to be placed approximately here>>

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Impact of misclassifying date of ICB onset on estimates of risk with low-dose aspirin exposure

The association between low-dose aspirin and risk of ICB is shown in **Table 2**. Compared to the 36.6% of ICB cases who were initially classed as current users of low-dose aspirin, 38.1% were classed as current users after backdating their index date. The corresponding percentages of cases who were recent or past users of low-dose ASA were 10.3% and 7.4% before backdating the index date, compared with 7.8% and 7.0% afterwards. The most noticeable change was among ICB cases initially classed as current users and who had recently started low-dose aspirin (first 3 months of therapy): 6.1% of initial ICB cases were current users, compared with 4.4% of final ICB cases.

The risk of ICB associated with current use of low-dose aspirin was identical among both sets of cases: OR 0.97 (95% CI; 0.84–1.12). However, for recent use of low-dose aspirin, the OR decreased from 1.52 (95% CI: 1.24–1.88) in the analysis of 1635 initial ICB cases to 1.10 (95% CI: 0.88–1.37) when using the final set of 1611 ICB cases. When we evaluated ICB risk in relation to duration of current low-dose aspirin, we observed an increased risk with initiation of low-dose aspirin (first 3 months; OR 1.65 (95% CI: 1.28–2.13) using the initial set of ICB cases but no association when using the final set of ICB cases (OR 1.13, 95% CI: 0.85–1.50). Also, using the initial 1635 ICB cases, we saw a trend of increased ICB risk among recent aspirin users with increasing

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duration of use (up to 5 years' duration), yet when using the final set of ICB cases there was no such trend.

<<Table 2 to be place approximately here>>

DISCUSSION

This study has demonstrated the importance of ascertaining the true date of onset of ICB events when evaluating risks associated with low-dose aspirin in THIN and the importance of validating ICB diagnoses in pharmacoepidemiological research. Associations observed between current use of recently initiated low-dose aspirin and ICB when using the date of recorded ICB diagnoses as the clinical event date differed from those observed when using the date of first symptom as the event date. Also, the increased risk of ICB associated with discontinuation of low-dose aspirin before assigning the correct date of ICB onset was no longer seen. This is a good example of how misclassification of outcome onset can translate into misclassification of a drug exposure leading to biased associations.

As the three most common types of ICB – ICH, SAH and SDH – differ in regards to both onset and presenting signs and symptoms, obtaining all available clinical details from first symptoms to diagnostic work-up and final diagnosis helps not only determine the date of bleeding onset but also the specific type of bleed. In this study, four patients originally classed as cases of ICH based on the computer-detected recorded diagnosis

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were instead found to have hemorrhagic transformations of an ischemic stroke following review of preceding medical entries and associated free text comments. Erroneous inclusion of such individuals as cases of ICB could frequently result in misclassification of low-dose aspirin exposure because aspirin is a treatment for ischemic stroke.

The importance of reviewing free text comments from EMRs for validating recorded diagnoses in THIN and for gaining additional details about the clinical event has been shown in previous studies.[13, 15, 16] and is strongly supported by our research. While manual review of EMRs is a labour intensive process, free text entries frequently contain information regarding symptoms, referrals, suspected or uncertain diagnoses, and diagnostic tests that are not always entered using the computer software coding systems, and which therefore are missed when using automatic computer searches of coded entries alone. Studies using THIN, or similar data sources, require a good understanding of the way data are recorded for the particular clinical event under investigation, in addition to knowledge of the presenting symptoms, management, differential diagnoses and treatment pathways of both the event and those of differential diagnoses. For pharmacoepidemiological research in general, and especially where establishing correct timing of events is crucial, such as in studies of ICBs, the value of using THIN, and other similar databases, is dependent on this premise and the application of thorough validation processes to confirm the recorded diagnoses and identify the true date of onset.

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Conflicts of Interest/Disclosure

This work was sponsored by Bayer AG. Lucía Cea Soriano and Luis A. García Rodriguez work for CEIFE, which received funding from Bayer AG. Dr García Rodríguez has also served as a consultant and advisory board member for Bayer AG. Dr Gaist reported receiving honoraria from AstraZeneca (Sweden) for participation as a coinvestigator on a research investigation. Montse Soriano-Gabarró is an employee of Bayer AG. The sponsor had no role in the the collection, analysis and interpretation of data, nor in the writing of the report nor the decision to submit the report for publication, but contributed to the study design.

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Table 1. Classification low-dose aspirin use before and after manual review of ICB onset date.

Initial low-dose aspirin exposure category*	Low-dose aspirin exposure (final ICB cases; N=1611)†					
	Never	**Current**	**Recent**	**Past**	**Distant**	**Total**
Never	462	0	0	0	0	462
Current	7	**568**	0	0	1	**576**
Recent	5	44	118	1	0	168
Past	0	2	8	111	0	121
Distant	0	0	0	0	284	284
Total	474	**614**	126	112	285	1611

*Date of onset based on date of recorded diagnosis code. Originally, there were 1635 individuals with a computer-detected diagnostic code for an ICB; of these, 24 were not retained following the second manual review process (20 were excluded because their 'new' backdated index date occurred on or before the start of follow-up, and 4 were excluded because their diagnosis of ICH was revealed to actually be hemorrhagic transformation of an ischemic stroke).

†Date of onset determined after evaluation of free text comments in THIN.

ICB, intracranial bleed; ICH, intracranial hemorrhage

Note: patients' electronic medical records were manually reviewed while masked to information on low-dose aspirin exposure.

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Table 2. Influence of re-classification of date of onset of ICB on measures of frequency of low-dose ASA aspirin use and associated risk of ICB.

Medication use	**Initial ICB cases*** **N=1635**	**Final ICB cases†** **N=1611**	**Controls** **N=10,000**	**Initial ICB cases** **(N=1635)**	**Final ICB cases** **N=1611)**
	n (%)	**n (%)**	**n (%)**	**OR (95% CI)‡**	**OR (95% CI)‡**
Low-dose ASA					
Never use	462 (28.3)	474 (29.4)	3344 (33.4)	1 (–)	1 (–)
Current use (0–7 days)	599 (36.6)	614 (38.1)	3852 (38.5)	0.97 (0.84–1.12)	0.97 (0.84–1.12)
Recent use (8–90 days)	169 (10.3)	126 (7.8)	656 (6.6)	1.52 (1.24-1.88)	1.10 (0.88–1.37)
Past use (91–365)	121 (7.4)	112 (7.0)	492 (4.9)	1.30 (1.03–1.64)	1.17 (0.92–1.48)
Distant use (>365 days)	284 (17.4)	285 (17.7)	1656 (16.6)	0.91 (0.77–1.08)	0.89 (0.75–1.06)
Duration of low-dose ASA among current users					

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Medication use	**Initial ICB cases*** **N=1635**	**Final ICB cases†** **N=1611**	**Controls** **N=10,000**	**Initial ICB cases** **(N=1635)**	**Final ICB cases** **N=1611)**
<3 months	100 (6.1)	71 (4.4)	362 (3.6)	1.65 (1.28–2.13)	1.13 (0.85–1.50)
3 to <6 months	46 (2.8)	52 (3.2)	253 (2.5)	1.07 (0.76–1.50)	1.19 (0.86–1.65)
6 months to <1 year	73 (4.5)	81 (5.0)	432 (4.3)	0.94 (0.71–1.25)	1.04 (0.80–1.37)
1 to <5 years	259 (15.8)	281 (17.4)	1949 (19.5)	0.82 (0.69–0.98)	0.88 (0.74–1.05)
≥5 years	121 (7.4)	129 (8.0)	856 (8.6)	0.91 (0.72–1.15)	0.97 (0.77–1.21)
Duration of low-dose ASA among recent users					
<3 months	33 (2.0)	28 (1.7)	143 (1.4)	1.34 (0.89–2.01)	1.13 (0.85–1.50)
3 to <6 months	20 (1.2)	15 (0.9)	94 (0.9)	1.37 (0.83–2.28)	1.19 (0.86–1.65)
6 months to <1 year	27 (1.7)	19 (1.2)	98 (1.0)	1.50 (0.95–2.38)	1.04 (0.80–1.37)

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Medication use	Initial ICB cases* N=1635	Final ICB cases† N=1611	Controls N=10,000	Initial ICB cases (N=1635)	Final ICB cases N=1611)
1 to <5 years	72 (4.4)	55 (3.4)	229 (2.3)	1.90 (1.41–2.56)	0.88 (0.74–1.05)
≥5 years	17 (1.0)	9 (0.6)	90 (0.9)	1.06 (0.62–1.83)	0.97 (0.77–1.21)
Dose of low-dose ASA among current users					
75 mg	560 (34.3)	575 (35.7)	3660 (36.6)	0.95 (0.82–1.10)	0.96 (0.83–1.11)
150 mg	29 (1.8)	31 (1.9)	164 (1.6)	1.02 (0.67–1.56)	1.10 (0.73–1.67)
300 mg	10 (0.6)	8 (0.5)	28 (0.3)	1.76 (0.82–3.79)	1.37 (0.60–3.16)

*Date of onset based on date of recorded diagnosis code.

†Date of onset determined after evaluation of free text comments in THIN.

‡Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

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BMI, body mass index; CI, confidence interval; ICB, intracranial bleed; OR, odds ratio; PCP, primary care practitioner; THIN, The Health Improvement Network; TIA, transient ischemic attack.

Note: patients' electronic medical records were manually reviewed while masked to information on low-dose aspirin exposure.

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