Neuroimaging and clinical outcomes of oral anticoagulant associated ICH

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Abstract

Objective: Whether intracerebral haemorrhage (ICH) associated with non-vitamin K antagonist oral anticoagulants (NOAC-ICH) has a better outcome compared to ICH associated with vitamin-K antagonists (VKA-ICH) is uncertain.

Methods: We performed a systematic review and individual patient data meta-analysis of cohort studies comparing clinical and radiological outcomes between NOAC-ICH and VKA-ICH patients. The primary outcome measure was 30-day all-cause mortality. All outcomes were assessed in multivariable regression analyses adjusted for age, sex, ICH location and intraventricular haemorrhage extension.

Results: We included 7 eligible studies comprising 219 NOAC-ICH and 831 VKA-ICH patients (mean age:77 years,52.5% females). The 30-day mortality was similar between NOAC-ICH and VKA-ICH (24.3% vs. 26.5%; HR=0.94, 95%CI: 0.67 to 1.31). However, in multivariable analyses adjusting for potential confounders, NOAC-ICH was associated with: lower admission National Institutes of Health Stroke Scale (NIHSS) score (linear regression coefficient=-2.83, 95%CI:-5.28 to -0.38); lower likelihood of severe stroke (NIHSS>10 points) on admission (OR=0.50, 95%CI: 0.30 to 0.84); and smaller baseline haematoma volume (linear regression coefficient=-0.24,95%CI:-0.47 to -0.16). The two groups did not differ in the likelihood of: baseline haematoma volume less than $30cm^3$ (OR=1.14, 95%CI: 0.81 to 1.62); haematoma expansion (OR=0.97, 95%CI: 0.63 to 1.48); in-hospital mortality (OR=0.73,95%CI: 0.49 to 1.11); functional status at discharge (common OR=0.78, 95%CI: 0.57 to 1.07); or functional status at three months (common OR=1.03, 95%CI: 0.75 to 1.43).

Interpretation: Although functional outcome at discharge, one month or three months were comparable after NOAC-ICH and VKA-ICH, patients with NOAC-ICH had smaller baseline haematoma volumes and less severe acute stroke syndromes.

Text

Introduction

Intracerebral haemorrhage (ICH) is the most feared complication of oral anticoagulation with mortality approaching 50%.[1] Despite advances in primary prevention and especially the treatment of hypertension, the global incidence of ICH has remained stable,[2] in part due to the increase of anticoagulant-related ICH in the elderly.[3]

Use of oral anticoagulation with vitamin K antagonists (VKA) is known to double the ICH risk even under optimal treatment conditions [international normalized ratio (INR) between 2 and 3]; the annual risk of ICH is estimated to range from 0.3% to 0.6% per year.[4,5] Apart from the increased incidence, VKA associated ICH (VKA-ICH) is associated with larger haematoma volumes, increased case fatality and poor functional outcome.[6,7] Non-vitamin K antagonist oral anticoagulants (NOAC) have similar efficacy in ischaemic stroke prevention in patients with non-valvular atrial fibrillation (NVAF), with half the incidence of ICH compared to warfarin.[8] Even though the pharmacodynamics, short half-life and discriminate anticoagulant action of NOACs have been associated with the lower risk of incident ICH, findings are conflicting regarding the outcome of patients with NOAC associated ICH (NOAC-ICH) compared to VKA-ICH.[9,10]

We therefore performed a systematic review and individual patient data meta-analysis (IPDM), including data from available cohort studies comparing clinical and radiological outcomes between NOAC-ICH and VKA-ICH patients.

Methods

Literature search and trial identification

This meta-analysis is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data (PRISMA-IPD) guidelines[11] and was written according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal.[12] We followed a pre-specified study protocol that has been

published in the International Register PROSPERO (International Prospective Register of Ongoing Systematic Reviews).[13]

Eligible study protocols reporting clinical and radiological characteristics of NOAC-ICH in comparison to VKA-ICH were identified by searching MEDLINE and SCOPUS. The combination of search strings that was used in all database searches included the terms: "intracerebral haemorrhage", "intracranial haemorrhage", "intracranial bleeding", "cerebral haemorrhage", "cerebral haematoma", "vitamin K antagonists" (including also the names of all pharmaceutical substances), "novel oral anticoagulants", "direct oral anticoagulants", "non-vitamin K antagonist oral anticoagulants" (including also the names of all pharmaceutical substances). No language or other restrictions were imposed. Last literature search was conducted on August 25th, 2017. Reference lists of all articles that met our inclusion criteria and of relevant review articles were examined to identify studies that may have been missed by the initial database search. Literature searches were performed by two independent teams of reviewers (GT & AHK, DW & DJW), while emerging disagreements were resolved with consensus.

Data transfer and verification

Anonymised data were transferred from participating centres to the Coordinating and Data Management Centre (National Hospital for Neurology and Neurosurgery, Queen Square University College Hospitals, NHS Foundation Trust). The data obtained from each participating study were checked with respect to range, internal consistency, consistency with published reports and missing items.[14] Inconsistencies or missing data were discussed with the individual principal investigators and emerging problems were resolved with consensus. Finally, data supplied were either recoded or transformed to reflect common definitions and common units of measurement across the generated individual patient database, while computer-generated detailed summary tabulations based on the converted data were returned to each collaborator for review and verification.

Inclusion criteria, exclusion criteria and outcomes of interest

To be eligible for inclusion in the IPDM individual studies, registries or databases (reported variously as prospective or retrospective observational cohort studies or trials) were asked to include data available for compulsory baseline characteristics of interest [age, sex, oral anticoagulant agent, ICH location (lobar vs non-lobar), intraventricular haemorrhage (IVH) extension in baseline neuroimaging] and survival data (number of days from index event to death). The list of non-compulsory variables that were requested is available in the Supplementary Table 1.

Haematoma volume was calculated with the same method for NOAC-ICH and VKA-ICH using either the ABC/2 method or planimetric measurement with adjustments made for multilobar haemorrhage and scans with non-uniform slice thickness.[15] Haematoma expansion at follow-up neuroimaging was defined as an absolute increase of more than 12.5 cm^3 or a relative increase of more than 33% in haematoma volume at the follow-up scan compared to the admission neuroimaging.[16] In patients with sufficient data we additionally calculated the corresponding CHA_2DS_2-VASc scores,[17] in case not provided in the original databases.

In the present IPDM we included patients older than 18 years of age with diagnosis of acute primary ICH, who were confirmed to be receiving VKA (with INR>1.5 on admission)[18] or NOAC (definite evidence of intake within 24h before the ICH onset). We excluded patients with ICH secondary to trauma (i.e. major head trauma thought to be sufficient to have caused the ICH in the previous 24h), vascular malformation, tumour, cavernoma, aneurysm, or haemorrhagic transformation of ischaemic stroke. We additionally excluded patients with primary subarachnoid haemorrhage (with or without an ICH component), isolated intraventricular bleeding, and VKA-ICH patients with INR≤1.5 on admission.[13]

The primary outcome was 30-day all-cause mortality between NOAC-ICH and VKA-ICH. Secondary outcomes were admission stroke severity [assessed with the National Institutes of Health Stroke Scale score (NIHSS)]; severe stroke (NIHSS >10) on admission,[19] level of consciousness (quantified by Glasgow Coma Scale score) on admission, haematoma volume on admission; small haematoma volume (<30cm^3) rates on admission,[20] haematoma expansion rate on follow-up neuroimaging, in-hospital mortality, functional status at

discharge and at three months, quantified by the distribution of modified Rankin Scale (mRS) scores.

Quality assessment in included studies

We used the Newcastle-Ottawa Scale to assess the quality of each observational study that met our inclusion criteria.[21] According to this scale, a maximum of one star can be awarded for each item within the selection and exposure/outcome categories and a maximum of two stars for the comparability category; studies can earn a maximum of 9 star-points. Quality control and bias identification were performed by two independent reviewers (DW & GA) and all disagreements were resolved with consensus.[21]

Statistical analysis

We summarised normally distributed continuous variables as means with corresponding standard deviations (SDs), while non-normally distributed variables were reported as medians with their corresponding interquartile ranges (IQRs). All categorical variables were presented as absolute numbers with corresponding percentages.

Univariate Kaplan Meier survival probabilities were estimated for each anticoagulant group; the log rank test was used to compare groups. For the primary pre-specified outcome analysis, we fitted a Cox proportional hazards model with a frailty term for study. In this observational study, the exposure (NOAC vs VKA) precedes acute ICH and thus the exposure itself might affect some of the markers of ICH severity (ICH volume and GCS). For multivariable models of the outcome variables (mortality, functional outcomes) we therefore only included covariates which should not be affected by anticoagulant choice (age, sex, ICH location and IVH extension); we added a shared frailty term to allow for possible site related factors (e.g. general ICH management, resources, ethnicity). The assumption of proportional hazards was assessed using Schoenfeld residuals.

For the secondary outcomes of interest we performed mixed effects multivariable logistic or ordinal regression analyses, as indicated. Anticoagulant (NOAC vs. VKA), age, sex, IVH extension and ICH location were treated as fixed effects and registry as a random

effect in each analysis exploring clinical severity or functional outcome/mortality, whilst anticoagulant (NOAC vs. VKA), age, sex and ICH location were treated as fixed effects and registry as a random effect in the analysis exploring ICH volume and ICH expansion. Associations in all logistic and ordinal regression analyses are presented using odds ratios (OR) and common ORs (cOR) respectively with their corresponding 95% confidence intervals (CI).[13] In the final multivariable analyses statistical significance was achieved if two-sided $p<0.05$, calculated using the likelihood ratio test. In multivariable models, we excluded patients with missing data from the analysis; we did not impute missing data.

Where applicable, the adjusted individual study results were displayed using a forest plot and a two stage meta-analysis was performed to calculate I^2, a measure of heterogeneity across studies, and τ^2, a measure of variance of the true effect sizes.[22] The pooled estimate was suppressed in these plots since their sole purpose here is to display the results from each individual study.

Finally we performed pre-specified subgroup analyses on the primary outcome according to the NOAC drug used (apixaban, dabigatran, rivaroxaban), reporting the relevant p-value for interaction for each one.

Results

Study selection and study characteristics

Systematic search of MEDLINE and SCOPUS databases yielded 600 and 684 results respectively. After removing duplicates, the titles and abstracts from the remaining 974 studies were screened and 12 potentially eligible studies for the meta-analysis were retained. After retrieving the full-text version of the aforementioned 12 studies, 3 studies were excluded because they included patients with traumatic brain injury[23-25] and 1 study due to the lack of VKA-ICH comparator group (Supplementary Table 2).[26] In the final presentation of the literature search results, there was no conflict or disagreement between the reviewers and the corresponding authors from the 8 studies that met the protocol's inclusion criteria were contacted by e-mail. Individual patient data were obtained from all study protocols, except for

one,[27] and the 7 eligible studies were finally included in the qualitative and quantitative synthesis (Figure 1).[28-34]

Prior to applying our own inclusion and exclusion criteria, we received 100% of expected patient numbers from each study (Supplementary Table 3). No important issues with IPD integrity were identified after checks according to PRISMA checklist recommendations. Quality assessment of included studies highlighted one study[32] that reported enrolment of some VKA patients before the start of enrolment of their first NOAC patient (Supplementary Table 4).

After excluding 74 patients on a VKA with an inital INR value ≤1.5 we were left with a total of 1050 patients (219 on NOACs and 831 on a VKA) from 7 individual studies. Baseline characteristics and outcomes of the total 1050 eligible ICH patients (NOAC-ICH: 219, VKA-ICH: 831, mean age: 77 years, 52.5% women) are summarized in Supplementary Table 5. The use of any reversal strategy was approximately three times more common ($p<0.001$) in VKA-ICH patients (n=621, 89%) compared to NOAC-ICH patients (n=58, 31%). More specifically, use of vitamin K was reported in 25% and 75% of NOAC-ICH and VKA-ICH patients, respectively. Protein complex concentrate was used in 21% and 79% of NOAC-ICH and VKA-ICH patients, while fresh frozen plasma was used in 22% and 78% of NOAC-ICH and VKA-ICH patients, respectively. Use of a specific reversal agent (idarucizumab) was reported in only one patient with NOAC-ICH.[33]

Primary analysis

Two studies had follow up times which were too short to allow inclusion into our primary outcome of 30 day mortality. Therefore our primary analysis was comprised 909 patients from five studies. In survival analysis, adjusting for age, sex, ICH location and IVH extension as well as clustering by centre, NOAC-ICH and VKA-ICH patients did not differ in the risk of 30-day mortality (24.3% vs. 26.5%; adjusted HR= 0.94, 95%CI: 0.67 to 1.31, p=0.702; Figure 2 & Table 1). The proportional hazard assumption was not violated (global

test p=0.247). Unadjusted Kaplan-Meier plots for each included study on the primary outcome of 30-day mortality are available in the Figure 3.

In a post-hoc sensitivity analysis, including the 74 VKA-ICH patients with INR values ≤1.5 and the patients from the 2 centres with short follow-up times (after imputation of missing baseline values) we documented similar results for the risk of 30-day mortality between NOAC- and VKA-ICH patients (HR=0.90, 95% CI 0.66 to 1.21, p=0.476; Table 1).

Secondary outcomes

Results of adjusted analyses on secondary outcomes of interest are presented in Table 1 and in the Supplemental Table 6 - Supplemental Table 15. An overview of unadjusted analyses on the primary and secondary outcomes of interest is provided in the Supplemental Table 16 & Figure 4. Four studies comprising of 398 patients had information available on NIHSS. NOAC-ICH was associated with lower admission NIHSS scores (adjusted linear regression coefficient= -2.83, 95%CI: -5.28 to -0.38) and a lower likelihood of severe stroke (NIHSS>10 points) on admission (adjusted OR= 0.50, 95%CI: 0.30 to 0.84).

Four studies comprising 845 patients had data available on GCS. In adjusted analysis the two groups did not differ in GCS-score on hospital admission (adjusted linear regression coefficient= -0.01, 95%CI: -0.57 to 0.55).

Seven studies comprising 1006 patients had data available on ICH volume. NOAC-ICH was associated with smaller baseline haematoma volumes on admission (adjusted linear regression coefficient= -0.24, 95%CI: -0.47 to -0.16). However, the odds of admission haematoma volume being less than $30cm^3$ did not differ between the groups (adjusted OR= 1.14, 95%CI: 0.81 to 1.62)

Seven studies comprising of 617 patients had data available on ICH expansion on follow up neuroimaging, which did not differ between the two groups (adjusted OR= 0.97, 95%CI: 0.63 to 1.48)

Seven studies comprising of 902 patients had data on in-hospital mortality and mRS at discharge. However, one of the studies did not collect data on IVH extension, thus could

not be included in multivariable analysis. In adjusted analysis comprising of 824 patients from 6 studies no significant differences between the two groups were found regarding in-hospital mortality (adjusted OR= 0.73, 95%CI: 0.49 to 1.11) and functional status at hospital discharge (adjusted cOR per 1-point increase in mRS-score= 0.78, 95%CI: 0.57 to 1.07).

Three studies comprising of 748 patients had data available on 90 day mRS which again shows no statistical difference between the groups (adjusted cOR= 1.03, 95%CI: 0.75 to 1.43).

Analysis of individual NOAC drug type (Table 2) revealed no significant differences in their 30-day mortality risk compared with VKA (apixaban: adjusted HR=0.56, 95%CI: 0.20 to 1.51, dabigatran: adjusted HR=0.69, 95%CI: 0.34 to 1.40, rivaroxaban adjusted HR=1.11, 95%CI: 0.78 to 1.68; overall p=0.267; Figure 5).

Discussion

Our IPDM showed comparable 30-day mortality rates after NOAC-ICH and VKA-ICH, with no statistically significant differences in risk for different NOAC agents. However, NOAC-ICH was independently associated with less severe acute ICH as measured by baseline haematoma volume and stroke severity (NIHSS) on admission. VKA-ICH and NOAC-ICH had similar functional outcome at discharge and at three-month follow-up.

Our findings highlighting similar outcomes in NOAC-ICH and VKA-ICH patients differ from those reported from a recent retrospective analysis from the Get With The Guidelines–Stroke (GWTG-Stroke) registry, including 141,311 total ICH patients admitted in 1662 US hospitals, suggesting that NOAC-ICH patients have lower risk of in-hospital mortality and functional disability at discharge compared to VKA-ICH patients.[35] This disparity could be attributed to the more stringent definition of oral anticoagulant related ICH in patients from our cohort compared to that used in the cohort from the GWTG-Stroke registry (any use of oral anticoagulant within 7 days prior to hospital arrival), and the lack of adjustment for baseline stroke severity in the multivariable models of in-hospital mortality and functional outcome in both GWTG-Stroke registry and our protocol.[35] Our study provides

an invaluable insight in the anticoagulant-related ICH neuroimaging outcomes, which are known to be significant predictors of clinical outcomes but in turn are less affected by demographic characteristics compared to clinical outcomes. Taking into account that demographic characteristics have been inadequately assessed in our study protocol and in the study by Inohara et al,[35] the importance of findings on neuroimaging outcomes is further highlighted. We also consider that the results from the current IPDM, incorporating data from international multicenter cohorts, are likely to be more easily generalizable to every clinical setting. Finally, it should be noted that findings from a very recent meta-analysis of available randomized clinical trials on the use of NOACs for the prevention of thromboembolism in patients with NVAF, suggesting similar case fatality rates in NOAC-related and VKA-related ICH,[36] corroborate further our results on the similar 30-day mortality risk between NOAC- and VKA-related ICH patients and contradict further the finding of lower in-hospital mortality risk for NOAC-ICH patients reported in the study by Inohara et al.[35]

Our results are also in accordance with a previously published systematic review and pairwise meta-analysis of aggregate level data from 12 observational studies (393 NOAC-ICH and 3482 VKA-ICH), suggesting no significant differences in haematoma expansion, mortality and functional outcome between NOAC-ICH and VKA-ICH patients.[36] A non-significant association for lower baseline ICH volume in NOAC-ICH compared to VKA-ICH was also reported in this meta-analysis (standardized mean difference: -0.24; 95% CI -0.52 to 0.04, p=0.093), while the association of NOAC-related ICH with 30-day mortality was not evaluated in this meta-analysis.[37]

The finding of lower baseline haematoma volumes in NOAC-ICH compared to VKA-ICH could be attributed to the more favourable pharmacological properties of NOACs, including shorter plasma half-life and selective inhibition of the extrinsic coagulation pathway, compared to VKAs.[38] The one-to-one direct stoichiometric inhibition of thrombin or factor Xa by NOACs favours the physiological cerebrovascular haemostatic response after an ICH, in contrast to the impaired haemostasis due to thrombin substrates deficiency induced by VKAs.[39] However, although haematoma volume on admission is associated with stroke

severity,[40] and long-term outcome after an ICH,[41] we detected no significant differences between NOAC-ICH and VKA-ICH patients in 30-day mortality risk, the rate of haematoma expansion, in-hospital mortality, or functional outcome at discharge and 3-month follow-up. Since the trajectory of recovery of ICH might be slower than that after ischaemic stroke,[42] it is possible that with longer follow-up the apparent benefits of NOACs on acute ICH volume and stroke severity might translate into better functional outcome. Longer term studies of outcome after VKA- and NOAC-ICH will be needed to investigate this possibility.

Our study has strengths. We included a large sample of individual participant data allowing us to perform adjusted analyses for both clinical and radiological outcomes between NOAC-ICH and VKA-ICH. We included high quality observational studies, using pre-specified inclusion criteria at both study and individual patient level. However, there are also several limitations that should be taken into consideration. First, individual participant data from one study including 27 participants was not available,[27] but we consider the potential impact of this to be negligible. Second, although we collected detailed baseline data, we were not able to assess and further adjust the potential impact of some clinical (e.g. the degree of blood pressure reduction),[43] laboratory (e.g. cholesterol levels on admission)[44] and neuroimaging (e.g. presence of cerebral microbleeds or cortical superficial siderosis)[45-48] parameters on the outcomes of interest. It should also be noted that there was no central adjudication in image analysis for both baseline and follow-up neuroimaging scans. Moreover, since patients in the two groups were not randomized to NOAC or VKA administration, imbalances in both baseline characteristics and other potential confounders, including onset-to-neuroimaging time,[49] could be present. Despite adjustment for baseline factors, there is also a risk of residual confounding by indication, which is not completely addressed in current IPDM or in the previous report from the GWTG-Stroke registry.[35] Moreover, it should also be noted that we were unable to assess for the temporal and geographical differences in ICH care or practice patterns, including the choice and administration timing of reversal agents, which are known to influence ICH outcomes. Due to complexity of reasons for clinician selection of an anticoagulant regimen for particular

patients and the presence of significant disparities in ICH management we consider that only randomised controlled trial data will be able to firmly account for these potential biases.

The availability of reversal strategies for oral anticoagulants and the timing of their administration after ICH onset could also account for potential difference in outcomes between NOAC- and VKA-ICH patients in the present IPDM. The use of any reversal strategy was approximately three times more common in VKA-ICH than in NOAC-ICH cases. Given that NOAC-specific reversal agents may be associated with a lower case fatality rate in NOAC-related ICH,[36] the more widespread future use of these agents might result in a substantial decrease of NOAC-ICH mortality.

Due to the lack of significant differences in clinical outcomes between NOAC-ICH and VKA-ICH, despite the disparities in neuroimaging findings, we performed a post-hoc power calculation to investigate for the possibility of a ceiling effect and underpowering; this indicated that our IPDM had 80% power to detect a 10% absolute difference (and a corresponding HR of 0.56) for the primary outcome of interest (30-day mortality) between NOAC- and VKA-ICH patients. Thus, our IPDM was not powered to detect smaller differences in the 1-month mortality rates between NOAC-ICH and VKA-ICH patients. We note that the adjusted absolute risk difference in the in-hospital mortality that was detected in the GWTG-Stroke registry was 6%.[35] The missing functional evaluations in 20% and 30% of our study population at discharge and at three months may have diluted the potential beneficial effect of NOACs on functional outcomes in ICH patients, but these were secondary outcomes. Since pre-morbid mRS scores were not available in the included study protocols, the lack of significant differences on clinical outcomes could also be attributed to the inability for adjustment for the presence of disability prior to index event. Finally, as in the primary analysis, we consider the subgroup analysis according to NOAC regimen underpowered and the risk of residual confounding in the NOAC-ICH subgroup possible.

In conclusion, our IPDM provides preliminary evidence that although 30-day clinical outcomes appear to be comparable between NOAC-ICH and VKA-ICH patients, NOAC-ICH may be related to lower baseline haematoma volumes and lower admission stroke severity

scores. This observation requires independent confirmation in larger prospective cohort studies adjusting for all potential confounders, including neuroimaging parameters and pre-ICH functional status. Longer term follow-up studies should determine whether outcomes beyond 30 days differ between VKA- and NOAC-ICH.

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Potential Conflicts of Interest:

Nothing to report

References

1. Bamford J, Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 1990; 53:16-22.

2. van Asch CJ, Luitse MJ, Rinkel GJ, et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 2010; 9:167-76.

3. Flaherty ML, Kissela B, Woo D, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology 2007; 68:116-21.

4. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. Stroke 2005; 36:1588-93

5. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. Ann Intern Med 1999; 131: 492–501.

6. Flaherty ML, Tao H, Haverbusch M, et al. Warfarin use leads to larger intracerebral hematomas. Neurology 2008; 71:1084-9.

7. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007; 120:700-5.

8. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383:955-62.

9. Purrucker JC, Haas K, Rizos T, et al. Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants. JAMA Neurol 2016; 73:169-77.

10. Wilson D, Charidimou A, Shakeshaft C, et al. Volume and functional outcome of intracerebral hemorrhage according to oral anticoagulant type. Neurology 2016; 86:360-6.

11. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;

313:1657-1665.

12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008-12.

13. Tsivgoulis G, Wilson D, Katsanos AH, Werring D. Clinical and radiological characteristics of non-vitamin K antagonist oral anticoagulants-associated ICH (NOAC-ICH) in comparison to vitamin K antagonist (VKA)-associated ICH (VKA-ICH): international collaborative individual patient data meta-analysis. PROSPERO 2017; CRD42017075757 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017075757

14. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010; 340:c221.

15. Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke 1996; 27:1304-5.

16. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013; 368:2355-65.

17. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864-70.

18. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA 2015;313:824–836.

19. Cheung RT, Zou LY. Use of the original, modified, or new intracerebral hemorrhage score to predict mortality and morbidity after intracerebral hemorrhage. Stroke 2003;34:1717-22.

20. Broderick JP, Brott TG, Duldner JE, et al. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke 1993;24:987-93.

21. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for

assessing the quality if nonrandomized studies in meta-analyses. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

22. Deeks JJ, Higgins JP, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions website.http://handbook.cochrane.org/chapter_9/9_analysing_data_and_undertaking_meta_analyses.htm. Updated March 2011. Accessed October 4th, 2017.

23. Becattini C, Franco L, Beyer-Westendorf J, et al. Major bleeding with vitamin K antagonists or direct oral anticoagulants in real-life. Int J Cardiol 2017;227:261-266.

24. Singer AJ, Quinn A, Dasgupta N, Thode HC Jr. Management and Outcomes of Bleeding Events in Patients in the Emergency Department Taking Warfarin or a Non-Vitamin K Antagonist Oral Anticoagulant. J Emerg Med 2017;52:1-7.

25. Saji N, Kimura K, Aoki J, et al. Intracranial Hemorrhage Caused by Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)- Multicenter Retrospective Cohort Study in Japan. Circ J 2015;79:1018-23.

26. Akiyama H, Uchino K, Hasegawa Y. Characteristics of Symptomatic Intracranial Hemorrhage in Patients Receiving Non-Vitamin K Antagonist Oral Anticoagulant Therapy. PLoS One 2015;10:e0132900.

27. Melmed KR, Lyden P, Gellada N, Moheet A. Intracerebral Hemorrhagic Expansion Occurs in Patients Using Non-Vitamin K Antagonist Oral Anticoagulants Comparable with Patients Using Warfarin. J Stroke Cerebrovasc Dis 2017; 26:1874-1882.

28. Adachi T, Hoshino H, Takagi M, Fujioka S; Saiseikai Stroke Research Group. Volume and Characteristics of Intracerebral Hemorrhage with Direct Oral Anticoagulants in Comparison with Warfarin. Cerebrovasc Dis Extra 2017; 7:62-71.

29. Hagii J, Tomita H, Metoki N, et al. Characteristics of intracerebral hemorrhage during rivaroxaban treatment: comparison with those during warfarin. Stroke 2014; 45:2805-7.

30. Marques-Matos C, Alves JN, Marto JP, et al. POST-NOAC: Portuguese observational study of intracranial hemorrhage on non-vitamin K antagonist oral anticoagulants. Int J

Stroke 2017; 12:623-627.

31. von der Brelie C, Doukas A, Naumann R, et al. Clinical and radiological course of intracerebral haemorrhage associated with the new non-vitamin K anticoagulants. Acta Neurochir (Wien) 2017; 159:101-109.

32. Takahashi H, Jimbo Y, Takano H, et al. Intracerebral Hematoma Occurring During Warfarin Versus Non-Vitamin K Antagonist Oral Anticoagulant Therapy. Am J Cardiol 2016; 118:222-5.

33. Tsivgoulis G, Lioutas VA, Varelas P, et al. Direct oral anticoagulant- vs vitamin K antagonist-related nontraumatic intracerebral hemorrhage. Neurology 2017; 89:1142-1151.

34. Wilson D, Seiffge DJ, Traenka C, et al. Outcome of intracerebral hemorrhage associated with different oral anticoagulants. Neurology 2017; 88:1693-1700.

35. Inohara T, Xian Y, Liang L, et al. Association of intracerebral hemorrhage among patients taking non–Vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality. JAMA 2018;319:463-473.

36. Katsanos AH, Schellinger PD, Köhrmann M, et al. Fatal oral anticoagulant-related intracranial hemorrhage: a systematic review and meta-analysis. Eur J Neurol. 2018 Jun 28. doi: 10.1111/ene.13742. [Epub ahead of print]

37. Boulouis G, Morotti A, Pasi M, et al. Outcome of intracerebral haemorrhage related to non-vitamin K antagonists oral anticoagulants versus vitamin K antagonists: a comprehensive systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2018;89:263-270.

38. Kubitza D, Becka M, Mueck W, Zuehlsdorf M. Safety, tolerability, pharmacodynamics, and pharmacokinetics of rivaroxaban–an oral, direct factor Xa inhibitor–are not affected by aspirin. J Clin Pharmacol 2006; 46:981–990.

39. Hart RG, Pogue J, Eikelboom JW. Direct-acting oral anticoagulants: the brain gets a break. JAMA Neurol 2013; 70:1483-4.

40. Vespa P, McArthur D, Miller C, et al. Frameless stereotactic aspiration and thrombolysis of deep intracerebral hemorrhage is associated with reduction of hemorrhage volume and neurological improvement. Neurocrit Care 2005; 2:274-81.

41. LoPresti MA, Bruce SS, Camacho E, et al. Hematoma volume as the major determinant of outcomes after intracerebral hemorrhage. J Neurol Sci 2014; 345:3-7.

42. Schepers VP, Ketelaar M, Visser-Meily AJ, et al. Functional recovery differs between ischaemic and haemorrhagic stroke patients. J Rehabil Med 2008;40:487-9.

43. Tsivgoulis G, Katsanos AH, Butcher KS, et al. Intensive blood pressure reduction in acute intracerebral hemorrhage: a meta-analysis. Neurology 2014; 83:1523-9

44. Chang JJ, Katsanos AH, Khorchid Y, et al. Higher low-density lipoprotein cholesterol levels are associated with decreased mortality in patients with intracerebral hemorrhage. Atherosclerosis 2017; 269:14-20.

45. Lee SH, Ryu WS, Roh JK. Cerebral microbleeds are a risk factor for warfarin-related intracerebral hemorrhage. Neurology 2009; 72:171–176.

46. Orken DN, Uysal E, Timer E, et al H. New cerebral microbleeds in ischemic stroke patients on warfarin treatment: two-year follow-up. Clin Neurol Neurosurg 2013; 115:1682–1685.

47. Saito T, Kawamura Y, Sato N, et al. Non-vitamin k antagonist oral anticoagulants do not increase cerebral microbleeds. J Stroke Cerebrovasc Dis 2015; 24:1373-7.

48. Boulouis G, van Etten ES, Charidimou A, et al. Association of Key Magnetic Resonance Imaging Markers of Cerebral Small Vessel Disease With Hematoma Volume and Expansion in Patients With Lobar and Deep Intracerebral Hemorrhage. JAMA Neurol 2016; 73:1440-1447.

49. Cucchiara B, Messe S, Sansing L, et al. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. Stroke 2008; 39:2993-6.

Table 1. Overview of primary and secondary adjusted analyses

Outcome	Number of studies	Number of patients	Effect size for NOAC (95% confidence interval)	p-value
Primary outcome				
30-day mortality	5	909	HR= 0.94 (0.67 to 1.31)	0.702
30-day mortality (sensitivity analysis)*	7	1098	HR=0.90 (0.66 to 1.21)	0.476
Secondary outcomes				
Admission NIHSS	4	398	LRC= -2.83 (-5.28 to -0.38)	0.024
Admission NIHSS more than 10	4	398	OR= 0.50 (0.30 to 0.84)	0.009
Baseline GCS	4	845	LRC= -0.01 (-0.57 to 0.55)	0.979
Baseline ICH volume**	7	1006	LRC= -0.24 (-0.47 to -0.16)	0.036
Baseline haematoma volume less than 30 cm^3**	7	1006	OR= 1.14 (0.81 to 1.62)	0.447
Haematoma expansion**	7	617	OR= 0.97 (0.63 to 1.48)	0.883
In-hospital mortality	6	824	OR= 0.73 (0.49 to 1.11)	0.140
mRS at hospital discharge	6	824	cOR= 0.78 (0.57 to 1.07)	0.127
mRS at 90 days	3	748	cOR= 1.03 (0.75 to 1.43)	0.842

*including the 74 VKA-ICH patients with INR values INR <1.5 and after imputation of the patients from 2 centres with short follow-up times

** Adjusted for age, sex and ICH location. The remainder adjusted for age, sex IVH extension and ICH location.

HR: hazard ratio, OR: odds ratio, NIHSS: National Institutes of Health Stroke Scale, GCS: Glasgow Coma Scale, ICH: intracerebral haemorrhage, mRS: modified Rankin Scale; cOR: common odds ratio; LRC: linear regression coefficient, IVH: intraventricular haemorrhage extension

Table 2. Adjusted subgroup analysis on the primary outcome of 30-day mortality according to the type of non-vitamin K oral anticoagulant based upon 5 studies and 909 patients

	HR	**95% CI**	**p value**
VKA	Baseline		
Rivaroxaban	1.11	0.78 to 1.68	0.494
Dabigatran	0.69	0.34 to 1.40	0.300
Apixaban	0.56	0.20 to 1.51	0.249
Age (per year increase)	1.02	1.01 to 1.04	0.006
Sex (female/ male)	1.13	0.87 to 1.46	0.370
IVH (yes/no)	3.16	2.39 to 4.16	<0.001
ICH location (lobar/ non-lobar)	1.19	0.91 to 1.55	0.211

HR: hazard ratio, 95%CI: 95% confidence interval, VKA: vitamin k oral anticoagulant, IVH: intraventricular haemorrhage extension, ICH: intracerebral haemorrhage

FIGURES

Figure 1. Flow chart presenting the selection of eligible studies.

Figure 2. Adjusted for each included study cox regression analyses on the primary outcome of 30-day mortality between patients receiving pretreatment with non-Vitamin K antagonist oral anticoagulants and patient receiving treatment with Vitamin K antagonist oral anticoagulants

Figure 3. Unadjusted Kaplan-Meier plots for each included study on the primary outcome of 30-day mortality.

Figure 4. Unadjusted Kaplan Meier curves on the probability of 30-day survival between patients with intracerebral haemorrhage related to non-vitamin k antagonist oral anticoagulants and patients with intracerebral haemorrhage related to vitamin k antagonist oral anticoagulants.

Figure 5. Subgroup analysis on the risk of 30-day mortality in patients with intracerebral haemorrhage related to the use of different non-vitamin k antagonist oral anticoagulants.