Original Investigation

New Oral Anticoagulants and the Risk of Intracranial Hemorrhage

Traditional and Bayesian Meta-analysis and Mixed Treatment Comparison of Randomized Trials of New Oral Anticoagulants in Atrial Fibrillation

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IMPORTANCE Randomized studies have shown a decreased risk of intracranial hemorrhage (ICH) with use of novel oral anticoagulants (NOACs). However, it is unclear whether the magnitude of benefit is similar for all NOACs currently available.

OBJECTIVE To perform a systematic review and meta-analysis to quantitatively assess the rates of ICH within the framework of both conventional and Bayesian statistics.

DATA SOURCES The MEDLINE, CENTRAL, CINAHL, and EBSCO databases, supplemented with conference abstracts, were searched up to December 1, 2012, with no language restriction.

STUDY SELECTION Randomized trials comparing NOACs vs a comparator and reporting on ICH events.

DATA EXTRACTION AND SYNTHESIS The NOACs were pooled to perform a comparison with all comparators and among themselves in both traditional frequentist and Bayesian random-effects models using vague priors and Markov chain Monte Carlo simulation with Gibbs sampling, calculating pooled odds ratios and associated 95% confidence intervals as well as numbers needed to treat and 95% credible intervals for the Bayesian analysis.

MAIN OUTCOMES AND MEASURES Intracranial hemorrhage events associated with NOACs in comparison with comparators, expressed as odds ratios.

RESULTS Six studies (1 administering dabigatran etexilate mesylate, 2 administering rivaroxaban, and 3 administering apixaban) enrolling a total of 57 491 patients were included for analysis. The NOACs significantly reduced the risk of ICH against all comparators (odds ratio = 0.49; 95% CI, 0.36-0.65). Each of the 3 drugs reduced the risk of ICH, with Bayesian indirect comparison analysis not revealing a significant credible difference between the specific medications.

CONCLUSIONS AND RELEVANCE Novel oral anticoagulants are uniformly associated with an overall reduced risk of ICH when used for stroke prevention in atrial fibrillation. Any of the currently available NOACs can be considered first line for patients at high risk for ICH.

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JAMA Neurol. 2013;70(12):1486-1490. doi:10.1001/jamaneurol.2013.4021
Published online October 28, 2013.

Intracranial hemorrhage (ICH) is arguably the most devastating complication of anticoagulation therapy with warfarin sodium in patients with atrial fibrillation (AF).[1,2] It translates into high mortality rates and is responsible for severe disability and long-term morbidity.[1,2] Individual trials with novel oral anticoagulants (NOACs) have shown lower rates of ICH with NOACs.[3-8] Three NOACs are currently approved for stroke prevention in AF: dabigatran etexilate mesylate, rivaroxaban, and apixaban. The absolute and relative effectiveness of these 3 NOACs in the prevention of ICH is unknown. We performed conventional and Bayesian analyses to evaluate the approved NOACs in patients with AF for the risk of ICH.

Methods

Data Sources and Searches

The following search algorithm was used for MEDLINE:

1. "randomized controlled trial".pt.
2. (random$ or placebo$ or single blind$ or double-blind$ or triple blind$).ti,ab.
3. (retraction of publication or retracted publication).pt.
4. or/1-3
5. (animals not humans).sh.
6. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
7. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
8. ((oral or direct) adj3 thrombin inhibitor$).ti,ab.
9. ((factor$ or antifactor$) adj3 (Xa inhibitor$ or drug$)).ti,ab.
10. (apixaban or eliquis).ti,ab.
11. BMS-562247-01.mp.
12. (dabigatran or pradaxa or pradax or prazaxa).ti,ab.
13. EC3-4-21-5.mp.
14. (rivaroxaban or xarelto).ti,ab.
15. BAY59-7939.mp.)

It was modified and adapted for search of the CENTRAL, CINAHL, and EBSCO databases and supplemented with searches in conference abstract books and on http://www.clinicaltrials.gov. The searches were performed up to December 1, 2012, with no language restriction. Reference lists of appropriate review articles and of the original retrieved studies were searched to identify studies potentially missed by the database searches (eFigure 1 in Supplement).

Study Selection

Two of us (S.C. and P.S.) performed independent article review and study quality assessment per Cochrane criteria.[9] We included randomized trials that compared NOACs with conventional anticoagulants, aspirin, or placebo for stroke prevention in patients with AF. Both double-blind and open-label trial designs were eligible for inclusion (as our intent was to assess for ICH rates with use of NOACs—a safety end point reported in the individual trials). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for reporting of systematic reviews and meta-analyses of randomized clinical trials was followed for the protocol of our meta-analysis.[10] Events on intracranial bleeding were collected for the NOACs and the comparators for the individual trials.

Data Extraction and Quality Assessment

Two physician-reviewers (S.C. and P.S.) independently extracted data from relevant published articles after determining the eligibility for inclusion. Disagreements regarding data incorporation were resolved by consensus among all of us. Methods specified in the *Cochrane Handbook for Systematic Reviews of Interventions*[9] were followed for objective assessment of the included trials. We extracted data from published sources regarding total number of treated patients, duration of follow-up, and drugs for the intervention and control groups. The occurrence of the following end point(s) was abstracted according to the intention-to-treat population for individual trials and separately for the study drug and control drug(s): ICH and/or hemorrhagic stroke. The definition for each end point was as per the individual trial(s) as referenced. Risk of bias for individual trials was assessed as per Cochrane metrics.[9]

In a further attempt to delineate the exact sites and types of ICH, we further stratified ICH events into intracerebral, intraparenchymal, or intraventricular hemorrhages (to identify the bleeds into the brain) and epidural, subdural, or subarachnoid hemorrhages (to identify bleeds occurring outside the brain parenchyma).

Data Synthesis and Analysis

The NOACs were pooled to perform a comparison with all comparators and among themselves in both a traditional frequentist framework and Bayesian random-effects models (as appropriate for conservative assessment of varied clinical moieties using data from published sources) using vague priors (to account for a wide variation among the baseline variables in the study subjects) and Markov chain Monte Carlo simulation and Gibbs sampling with RevMan version 5.1 software (Cochrane IMS) and WinBUGS version 1.4.3 software (MRC Biostatistics Unit), respectively, while calculating pooled odds ratios and associated 95% confidence intervals as well as numbers needed to treat and 95% credible intervals for the Bayesian analysis. The Cochrane metrics for performing a meta-analysis and the PRISMA statement[10] were followed. The Cochran Q test and the Higgins I^2 test were used for heterogeneity testing.[6] A Cochran Q $P < .10$ and $I^2 > 50\%$ were considered indicative of significant heterogeneity. We also created funnel plots graphically showing the logarithm of the standard error and the effect size to evaluate publication bias. Sensitivity analyses were planned to identify the source of heterogeneity by exclusion of 1 trial at a time to assess the effect on the pooled odds. We also performed a traditional pairwise meta-analysis of the subgroups of ICH events with bleeds into the brain parenchyma and outside the brain parenchyma, where reported, in an attempt to note any deviation from the results of the overall outcomes.

For the Bayesian random-effects analysis, vague or noninformative priors were used to yield results that are not too

Table 1. Baseline Characteristics

Source	Study Drug		Control Drug		Time in Therapeutic Range, %	Duration of Therapy	Male, %		Mean Age, y	
	Drug	Dosage	Drug	Dosage			Study Drug	Control Drug	Study Drug	Control Drug
Connolly et al,[3] 2009	Dabigatran etexilate mesylate (n = 12 091)	110 or 150 mg twice daily	Warfarin (n = 6022)	INR 2.0-3.0[a]	64[b]	2.0 y[c]	63.7	63.3	71.4	71.6
Patel et al,[4] 2011	Rivaroxaban (n = 7081)	20 mg once daily	Warfarin (n = 7090)	INR 2.0-3.0[a]	55[b]	590 d[c]	60.3	60.3	73[c]	73[c]
Granger et al,[5] 2011	Apixaban (n = 9120)	5 mg twice daily	Warfarin (n = 9081)	INR 2.0-3.0[a]	62.2[b]	1.8 y[c]	64.5	65	70[c]	70[c]
Hori et al,[6] 2012	Rivaroxaban (n = 640)	15 mg once daily	Warfarin (n = 640)	INR 2.0-3.0[a]	65	71 and 69 wk	82.9	78.2	71	71.2
Ogawa et al,[7] 2011	Apixaban (n = 48)	2.5 or 5 mg twice daily	Warfarin (n = 74)	INR 2.0-3.0[a]	60	12 wk	83.7	81.1	69.6	71.7
Connolly et al,[8] 2011	Apixaban (n = 2808)	5 mg twice daily	Aspirin (n = 2791)	81-324 mg/d	NA	1.1 y[b]	59	58	70	70

Abbreviations: INR, international normalized ratio; NA, not applicable.

[a] In trials comparing novel oral anticoagulants against warfarin sodium, the dosage of the warfarin was adjusted to maintain an INR as recorded here.

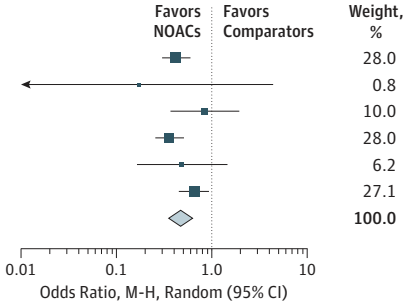
[b] Mean value.

[c] Median value.

Figure. Odds Ratios of Intracranial Hemorrhage With Use of Novel Oral Anticoagulants

Source	NOACs, No. Events	NOACs, No. Total	Comparator, No. Events	Comparator, No. Total	Odds Ratio, M-H, Random (95% CI)	Weight, %
Granger et al,[5] 2011	52	9088	122	9052	0.42 (0.30-0.58)	28.0
Ogawa et al,[7] 2011	0	143	1	75	0.17 (0.01-4.30)	0.8
Connolly et al,[8] 2011	11	2808	13	2791	0.84 (0.38-1.88)	10.0
Connolly et al,[3] 2009	63	12091	87	6022	0.36 (0.26-0.49)	28.0
Hori et al,[6] 2012	5	639	10	639	0.50 (0.17-1.46)	6.2
Patel et al,[4] 2011	55	7061	84	7082	0.65 (0.46-0.92)	27.1
Total (95% CI)	**186**	**31830**	**317**	**25661**	**0.49 (0.36-0.65)**	**100.0**

Heterogeneity: $\tau^2 = 0.05$; $\chi^2_5 = 9.13$ ($P = .10$); $I^2 = 45\%$
Test for overall effect: $Z = 4.87$, $P < .001$



M-H indicates Mantel-Haenszel; NOACs, novel oral anticoagulants.

different from conventional statistical analysis. We checked and confirmed convergence and lack of autocorrelation after a 10 000-simulation burn-in phase. Finally, we based direct probability statements on an additional 500 000-simulation phase to identify the best and most representative data, assuming comparable interstudy variances for all treatment effects for the same outcomes. We used deviance and the deviance information criterion to appraise model fit. Multiarm trials (eg, the study by Connolly et al[3]) were explicitly accounted for in the model by taking into account the correlation among the effect estimates for the pairs of arms. Zero total event trials were accounted for in the model by applying the standard continuity correction of 0.5 in both arms.

Results

We retrieved 6 studies (1 administering dabigatran,[3] 2 administering rivaroxaban,[4,6] and 3 administering apixaban[5,7,8]) with NOACs being compared against 2 comparators (warfarin and aspirin), enrolling a total of 57 491 patients with certain differences in baseline variables and bias risk (**Table 1**, and eFigure 2 and eTable in Supplement). The mean time in the therapeutic range was 61.2% for warfarin overall for the pooled analysis, the minimum duration of follow-up was 12 weeks, and the maximum follow-up was 2 years. The NOACs significantly reduced the risk of ICH against all comparators (odds ratio = 0.49; 95% CI, 0.36-0.65) (**Figure**). No significant heterogeneity was identified with the frequentist analysis (I^2 = 45%). Most of the heterogeneity was attributable to inclusion of the ROCKET AF trial[4] (residual I^2 = 4% on exclusion of the ROCKET AF trial). Each of the 3 NOACs significantly reduced the risk of ICH, with Bayesian analysis not revealing a statistically significant difference between the specific medications. (Absolute risk of ICH was 0.52% for dabigatran etexilate mesylate [for combined 110-mg and 150-mg doses], 0.78% for rivaroxaban, and 0.52% for apixaban vs 1.24% for warfarin). We also found that the lower dose of dabigatran (currently not approved in the United States for stroke prevention in AF) had a rate of bleeding numerically comparable to aspirin (81-324 mg) (0.45% vs 0.46%, respectively; median numbers needed to treat, 29.32 vs 39.60, respectively) when compared in a Bayesian framework (**Table 2**).

Table 2. Numbers Needed to Treat in Comparison With Warfarin Sodium for the Prevention of Intracranial Hemorrhage

Drug	NNT vs Warfarin Sodium		
	Median	2.5% CrI	97.5% CrI
Dabigatran etexilate mesylate, 110 mg	29.32	6.56	130.20
Dabigatran etexilate mesylate, 150 mg	34.53	7.57	156.80
Rivaroxaban	59.11	10.98	348.10
Apixaban	35.07	7.85	157.20
Aspirin	39.60	−188.60	376.30

Abbreviations: CrI, credible interval; NNT, number needed to treat.

In an exploratory subgroup analysis, we found that the rates of ICH events were reduced with the use of NOACs irrespective of the site of the bleed (intracerebral, intraparenchymal, or intraventricular: odds ratio = 0.42, 95% CI, 0.18-1.00; epidural, subdural, or subarachnoid: odds ratio = 0.54, 95% CI, 0.34-0.85), with the subgroup difference not being statistically significant (P = .64) (eFigure 3 in Supplement).

Discussion

In this systematic review of 6 randomized clinical trials, we found that compared with warfarin, all 3 NOACs significantly reduced the risk of ICH. Bayesian analyses did not reveal a statistically significant difference between the newer agents. We also found that the lower dose of dabigatran (currently not approved in the United States for stroke prevention in AF) had a rate of bleeding numerically comparable to aspirin. We also found a consistently reduced rate of ICH events with use of NOACs regardless of the site of the bleed into or outside the brain parenchyma.

The results from our frequentist and Bayesian analyses are well validated internally and externally. Acquiring data only from well-designed, randomized trials of NOACs for stroke prevention in AF identifies a patient population for which our results are most likely to be of significant relevance and provides external validity of our approach. For the traditional pairwise analysis, our data followed a formulated hypothesis and a detailed search strategy, and the studies combined did not exhibit significant statistical heterogeneity on pooled analysis. Use of random-effects models to account for anticipated differences in the individual trials and consistency and directionality of the outcomes noted in our sensitivity analyses corroborate internal validity of the approach. For the Bayesian indirect treatment analyses, aside from the earlier-stated reasons, multiple repeated simulations and assessment of convergence using deviance information criteria affirm the accuracy of the results. Similarly, congruence of the results from the Bayesian analysis with the frequentist outcomes affirms the validity.

The exact mechanism for the lower rate of intracranial bleeding with the NOACs compared with warfarin is unknown. Targeting a single site rather than multiple sites in the coagulation cascade with NOACs might be a probable explanation (as dabigatran is a direct thrombin inhibitor, while rivaroxaban and apixaban are factor Xa antagonists). Another factor that might contribute to this beneficial effect is that in contrast to warfarin, NOACs have no direct effect on factor VIIa. Modest time in the therapeutic range (mean 61.2% overall in these trials) is also a concern with warfarin use, although most of the "real-world" data indicate that this percentage is the most realistically achievable in regular clinical practice.

Our findings have implications for clinical decision making, and our analysis suggests that any of the currently available NOACs are reasonable choices when risk of ICH is a consideration. Previous meta-analyses have attempted to evaluate the combined effects of all NOACs against warfarin in the reduction of ICH risk in patients with AF and have reported a lower risk of ICH with NOACs compared with warfarin.[11] Indirect comparison analyses also attempted to evaluate the risk of ICH with data from only 3 trials.[12,13] However, effect of the individual NOACs in a Bayesian framework has not been reported with due importance to the relative estimates of the agents against a wider group of pharmacologically active comparators and accounting for the differences in the baseline variables of the different trials. The comparable rate of intracranial bleeding risk with low-dose dabigatran and aspirin is also a significant finding and may suggest a need for additional research with dabigatran etexilate mesylate, 110 mg, as an alternative to aspirin.

As in other meta-analyses, our analysis has potential limitations. There were differences in study population, protocol, intervention, and duration of follow-up across the included trials. These differences may have influenced the results despite our best efforts to adjust for these by using a wide range of noninformative priors and multiple simulations showing convergence of the results. Analysis of the different components of intracranial bleeding such as intracerebral, subarachnoid, and subdural hemorrhages could not be evaluated owing to a paucity of reported data. However, we attempted to overcome these limitations by including a large sample size and consequent increased power in the context of the traditional frequentist analysis, while the influence on the overall results of the baseline differences as noted earlier is likely to have been minimized with the large number of simulations in the Bayesian analysis.

Conclusions

Novel oral anticoagulants are associated with an overall reduced risk of ICH when used for stroke prevention in AF. They should be considered first line for patients at high risk for ICH without any credible differences among the individual agents.

ARTICLE INFORMATION

Accepted for Publication: June 24, 2013.

Published Online: October 28, 2013. doi:10.1001/jamaneurol.2013.4021.

Author Contributions: Dr Chatterjee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition of data: Chatterjee, Sardar, Biondi-Zoccai.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Biondi-Zoccai, Kumbhani.
Statistical analysis: Chatterjee, Sardar, Biondi-Zoccai.
Administrative, technical, or material support: Chatterjee.
Study supervision: Kumbhani.

Conflict of Interest Disclosures: None reported.

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