META-ANALYSIS

The association between non-vitamin K antagonist oral anticoagulants and gastrointestinal bleeding: a meta-analysis of observational studies

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Particular concerns have been raised regarding the association between non-vitamin K antagonist oral anticoagulants (NOACs) and the risk of gastrointestinal bleeding (GIB); however, current findings are still inconclusive. We conducted a systematic review with a meta-analysis to examine the association between NOACs and GIB in real-life settings. We performed a systematic search of PubMed, EMBASE and CINAHL Plus up to September 2015. Observational studies that evaluated exposure to NOACs reporting GIB outcomes were included. The inverse variance method using the random-effects model was used to calculate the pooled estimates. Eight cohort studies were included in the primary meta-analysis, enrolling 1442 GIB cases among 106 626 dabigatran users (49 486 patient-years), and 184 GIB cases among 10 713 rivaroxaban users (4046 patient-years). The pooled incidence rates of GIB were 4.50 [95% confidence interval (CI) 3.17, 5.84] and 7.18 (95% CI 2.42, 12.0) per 100 patient-years among dabigatran and rivaroxaban users, respectively. The summary risk ratio (RR) was 1.21 (95% CI 1.05, 1.39) for dabigatran compared with warfarin, and 1.09 (95% CI 0.92, 1.30) for rivaroxaban. Subgroup analyses showed a dose-related effect of dabigatran, with a significantly higher risk of GIB for 150 mg b.i.d. (RR = 1.51, 95% CI 1.34, 1.70) but not for 75 mg b.i.d. or 110 mg b.i.d.. In addition, the use of proton pump inhibitors (PPIs)/histamine H₂-receptor antagonists (H₂RAs) influenced the association in dabigatran users, whereas this effect was modest among rivaroxaban users. In conclusion, our meta-analysis suggested a slightly higher risk of GIB with dabigatran use compared with warfarin, whereas no significant difference was found between rivaroxaban and warfarin for GIB risk.

Introduction

As alternatives to traditional standard anticoagulant warfarin, a new generation of oral anticoagulants has been approved for stroke prevention in atrial fibrillation (AF) and the prevention and/or treatment of venous thromboembolism (VTE) [1]. Unlike the vitamin K antagonist (VKA) warfarin, non-vitamin K

antagonist oral anticoagulants (NOACs) directly target individual clotting proteins, including the direct thrombin inhibitor dabigatran [2] and direct factor Xa inhibitors (rivaroxaban [3], apixaban [4] and edoxaban [5]). Compared with warfarin, NOACs have a rapid onset of action, no food interactions and fewer drug interactions, and do not require bridging with subcutaneous administration of shorter-acting VKA low-

molecular-weight heparins (LMWH). Large randomized controlled trials (RCTs) show superior or non-inferior [2–5] efficacy of NOACs compared with warfarin in stroke prevention in AF and the prevention/treatment of VTE [6–8], with a lower or non-inferior risk of major bleeding.

Although NOACs are recommended by several guidelines from the USA [9], Canada [10] and Europe [11], gastrointestinal bleeding (GIB) remains a major concern of NOAC use. NOAC-associated GIB is potentially severe and even fatal [12–14]. The possible non-adherence of NOACs due to GIB may increase the risk of stroke and VTE [15]. However, existing findings from meta-analyses of RCTs are heterogeneous. A meta-analysis of 43 pivotal trials by Holster *et al.* [16] first reported a 1.6- and 1.5-fold increased GIB risk among dabigatran and rivaroxaban users, respectively, compared with standard care. Subsequent meta-analyses have reported varying association between NOACs and GIB, indicating no increase in risk [17–19] or a significant but marginal increased risk [20–22].

In 2012, the US Food and Drug Administration (FDA) reported a 1.6–2.2-fold higher GIB risk for warfarin than dabigatran based on a postmarketing Mini Sentinel Modular Program analysis [23, 24], which contradicted RCT findings [16]. However, in May 2014, the FDA gave an updated dabigatran safety announcement which reported a higher GIB risk [hazard ratio (HR) = 1.28; 95% confidence interval (CI) 1.14, 1.44] compared with warfarin [25, 26]. Recently, postmarketing pharmacovigilance studies using available public databases of spontaneous adverse drug reactions (ADRs) from Japan [27], Australia, Canada and the USA [24, 28–30] also reported signals of GIB risk among NOAC users. Moreover, increasing observational studies [26, 31–45] have been continuously conducted to investigate the association of GIB risk with NOAC use in real-world clinical practice, with conflicting results. Clarification about this association is therefore needed, especially to compare the results from the real-life setting vs. those from pivotal RCTs.

To resolve this issue, we conducted a systematic review with a meta-analysis of published observational studies to clarify the association between NOAC use and GIB, and also to investigate the effects of various factors that may affect GIB risk.

Materials and methods

The present systematic review was conducted following guidance provided by the Cochrane Handbook [46] and is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [47] for the flowchart of study inclusion and exclusion; and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement [48] for overall reporting.

Study definitions

The exposure of interest was defined as exposure to NOAC or warfarin in the clinical setting. The different doses of NOACs studied in the present meta-analysis were indication-specific daily doses based on recommendations by the FDA or the European Medicines Agency (EMA) [16], and the outcome was the risk of GIB. In observational studies, GIB was defined

as any bleeding in the gastrointestinal tract that was identified through medical records or by International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) codes, as described in the original literature. The classification of the severity of GIB was based on the description in the original studies [26, 38]. Major GIB was defined as a fatal GI haemorrhagic event, or a severe GIB event resulting in hospitalization or even requiring transfusion [26, 38], and the remaining were defined as nonmajor GIB.

Data sources and search strategy

A systematic literature search was conducted using PubMed, EMBASE and CINAHL Plus with the search strategy: (gastrointestinal ulcer OR peptic ulcer OR gastric ulcer OR duodenal ulcer OR gastrojejunal ulcer OR stomach ulcer OR peptic ulcer disease OR gastrointestinal bleeding OR gastrointestinal hemorrhage OR peptic ulcer hemorrhage OR GI hemorrhage OR GI bleeding OR GI bleed) AND (dabigatran OR rivaroxaban OR apixaban OR edoxaban OR pradaxa OR xarelto OR eliquis OR lixiana OR new oral anticoagulant OR novel oral anticoagulant OR direct oral anticoagulant OR oral anticoagulant OR TSOAC). Key words, MeSH and Emtree terms were used where appropriate. All databases were searched up to 28 September 2015. English titles and abstracts were screened and full texts of relevant articles were retrieved for further review to identify relevant studies. The bibliographies of review articles were also searched to identify any pertinent studies.

Study selection

Studies included in this meta-analysis were comparative observational studies that investigated the association between NOAC use and the risk of GIB. Studies were included if they: (i) clearly defined exposure to NOACs and other comparative exposure groups; (ii) clearly defined the outcome of GIB; (iii) reported HRs, relative risks (RRs) or odds ratios (ORs), or provided data for the calculation of HRs, RRs or ORs. There were no restrictions on study size. Conference proceedings were excluded as we were unable to assess the quality of these studies and some might have been preliminary results. Single-arm observational studies without comparisons, including case series, case reports and medical chart review studies, were excluded. Studies were also excluded if there were insufficient data for determining the HRs, RRs or ORs with 95% CIs.

Quality assessment

The methodological quality of the included cohort and cross-sectional studies was assessed using the Newcastle–Ottawa scale [49], as recommended by the Cochrane Collaboration. This scale provides specific criteria to assess the study selection (four items), comparability (two items) and ascertainment of exposure/outcome (three items). The ‘high’-quality items were scored with an asterisk and the maximum score was nine; this scale has been used in many published meta-analyses [50–52]. A final score ≥ 7 was considered to represent high quality. Two researchers (YH and SA) reviewed and scored each of the studies independently. Any discrepancies were addressed by re-evaluation to reach consensus.

Data abstraction

YH and XL performed the initial searches, and screened abstracts and full texts for eligibility. Study characteristics and measures of effect were extracted using a standardized data collection form by YH, XL and SA independently. For each study, the risk estimates that were adjusted for the largest number of confounding variables were extracted for analysis. The incidence rates of GIB among specific NOAC users were also extracted. For studies that did not report an adjusted result [53, 54], the unadjusted result was extracted for analysis. If the unadjusted estimates were not directly reported, patient and event number, patient-years or other available data were used to compute the HRs, RRs or ORs manually. For the Danish studies that only reported dose-specific estimates of dabigatran (110 mg b.i.d. and 150 mg b.i.d. separately) [34, 43], the HR of high-dose dabigatran was used. This is because all other cohort studies were from the USA, where 150 mg b.i.d. dabigatran was the most commonly used dose, and 110 mg b.i.d. was not available. The dose-specific association between dabigatran and risk of GIB was examined in the subgroup analysis.

Statistical methods

Using data available from original studies, unreported incidence rate and crude incidence rate ratio were calculated manually, based on Rothman–Greenland's formula [55] or computed using Review Manager 5.3 [56]. Meta-analyses with forest plots of comparative groups were generated using Review Manager 5.3 [56]. The inverse variance method with random-effects model was used to compute the pooled estimates and 95% CIs. Heterogeneity was assessed using Cochran's Q statistical test and $P < 0.10$ was considered significant. The I^2 statistic was also calculated to estimate the proportion of total variation among studies, where a value of 25%, 50% and 75% was regarded as low, moderate and high heterogeneity, respectively [57]. The point estimate of the pooled incident rates (IRs) of GIB among dabigatran and rivaroxaban users were analysed separately with the random-effects model, using an established and validated module published by Neyeloff *et al.* [58]. Forest plots of point estimate meta-analysis were generated using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). P -values (two-tailed) < 0.05 were regarded as statistically significant, except in the heterogeneity test. The publication bias test was not performed as funnel plots are more informative in cases where ten or more studies are included in the meta-analysis [59], and also the power of the test is considered too low to distinguish between chance and real asymmetry.

The primary analysis focused on assessing the risk of GIB among NOAC users in cohort studies. In the observational studies, HRs, RRs or ORs with their 95% CIs were extracted and log-transformed for the meta-analysis. The pooled estimates were reported as RRs. Analyses were performed on both crude and adjusted estimates from the studies.

Owing to the heterogeneity of study design and the study quality, three cross-sectional studies [31, 42, 60] which also investigated the GIB outcome of NOAC users were included in the secondary meta-analyses. The cross-sectional studies did not adjust for confounding factors nor include a follow-up, and therefore provided a lower quality of evidence.

Post hoc sensitivity analyses were performed to assess the robustness of the main results. Of the included studies, Larsen *et al.* [32, 34] and Staerk *et al.* [43] used the Danish registry database, whereas Graham *et al.* [26] and Hernandez *et al.* [40] used the US Medicare database, with an overlapping study period. To rule out the influence of possible repeated subjects, studies with a better representative population, better study design, and longer follow-up time or with the most recent publication date were included in the primary analysis. We performed a sensitivity analysis by substituting the results of Larsen *et al.* [34] and Graham *et al.* [26] with those of Staerk *et al.* [43]/Larsen *et al.* [32] and Hernandez *et al.* [40], respectively, to test the robustness of these inclusion criteria. Moreover, another sensitivity analysis was performed by removing the study by Abraham *et al.* [37], which had obvious heterogeneous results, to examine the influence of this study on the pooled estimate. Lastly, a sensitivity analysis was carried out by removing the study by Chan *et al.* [38], to investigate the effect of including this study specifically on patients with renal dysfunction.

Predefined subgroup analyses, stratified according to study characteristics, were also carried out to investigate the source of heterogeneity, which included different comparison groups of NOAC type, study location (USA and Denmark), indication of NOAC use, dabigatran doses (75 mg b.i.d., 110 mg b.i.d. and 150 mg b.i.d.), patient age group (≥ 18 years, 18–64 years and ≥ 65 years), GIB severity (major vs. nonmajor). Studies were further stratified based on whether there was adjustment for a history of warfarin use, or use of drugs that are associated with GIB, including nonsteroidal anti-inflammatory drugs (NSAIDs); aspirin or antiplatelet agents; steroids; selective serotonin reuptake inhibitors (SSRIs); and gastroprotective agents, including proton pump inhibitors (PPIs) and histamine H₂-receptor antagonists (H₂RAs).

Results

Search results

A total of 1634 records were retrieved from the literature search, and 51 records were identified through bibliographies and other sources. After removal of duplicates, 1427 titles and abstracts were screened and full texts of 81 articles were further reviewed. Sixteen studies met the criteria for the present systematic review (Figure 1), including 11 cohort studies and five cross-sectional studies. Among them, eight cohort studies [26, 33, 34, 36–39, 41] investigating the GIB risk of NOAC compared with warfarin were included in the primary meta-analysis and the remaining three [32, 40, 43] were included for sensitivity analysis to test the influence of possible repeated subjects. Three cross-sectional studies [31, 42, 60] were included in the secondary meta-analysis and the remaining two [35, 45] were reviewed narratively.

Characteristics and quality of included studies

As shown in Table S1, the quality scores of the cohort studies ranged from 6 to 9, which are of modest to high quality (Newcastle–Ottawa score ≥ 7). The cross-sectional studies were of lower quality, with scores from 2 to 7. The study characteristics and results from individual studies are

Figure 1

Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart summarizing study identification and selection. GIB, gastrointestinal bleeding; NOAC, non-vitamin K antagonist oral anticoagulant

summarized in Table 1 and Table S2. The cohort studies were conducted in the USA ($n = 8$) and Denmark ($n = 3$). Five studies used propensity score analysis [26, 33, 37, 39, 41] either by matching the propensity scores or adjusting them in the statistical model to minimize the influence of confounding factors and heterogeneity of patient characteristics between comparison groups. Studies were matched for demographic variables, and several also accounted for other potential confounders, including the use of drugs that are associated with GIB (NSAIDs, aspirin, steroids and SSRIs), gastroprotective agents (PPIs and H2RAs), as well as comorbidities (cardiovascular and cerebrovascular diseases, diabetes and GIB history).

Risk of gastrointestinal bleeding

Primary analysis: cohort studies. Eight cohort studies were included in the primary analysis, enrolling 106 626 patients on dabigatran and 10 713 on rivaroxaban. Abraham *et al.* [37], Chan *et al.* [38] and Chang *et al.* [39] compared both dabigatran and rivaroxaban with warfarin, and the subgroups by different NOACs were also stratified in the primary result. The crude analysis showed a trend of increased GIB risk in both the dabigatran and rivaroxaban groups compared with warfarin use, albeit not significant (Figure 2). The adjusted estimate showed that dabigatran was associated with a 21% increase in GIB risk compared with warfarin, with an RR of 1.21 (1.05–1.39) and a moderate-to-high heterogeneity

($I^2 = 69\%$, $P_{\text{heterogeneity}} = 0.004$; Figure 2B), whereas rivaroxaban showed no higher risk of GIB than warfarin (RR = 1.09, 95% CI 0.92, 1.30), with no substantial heterogeneity ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.42$; Figure 2B).

Secondary analysis: cross-sectional studies. Of the five cross-sectional studies with comparison arms of NOAC users, three studies [31, 42, 60] compared the use of dabigatran vs. warfarin, whereas Nagao *et al.* [45] specifically compared the GIB outcome in apixaban vs. warfarin. Sherid *et al.* [35] firstly conducted a direct head-to-head analysis of rivaroxaban vs. dabigatran in GIB risk. Meta-analysis showed a trend of increased GIB risk among dabigatran compared with warfarin users, albeit not significant (RR = 1.47, 95% CI 0.45, 4.85), with a high heterogeneity ($I^2 = 88\%$, $P_{\text{heterogeneity}} < 0.001$; Figure S1). In Nagal *et al.* [45], there was one GIB event among 105 apixaban users but none in 105 warfarin users, which led to a wide CI. Sherid *et al.* [35] reported seven GIB events (4.8%) among 147 rivaroxaban users compared with 12 GIB events (5.3%) among 227 dabigatran users, for which the crude analysis showed no significant difference between rivaroxaban and dabigatran (RR = 0.90, 95% CI 0.36, 2.24, data not shown) (Table S2).

Incidence rate of GIB. In total, our meta-analysis of eight cohort studies enrolled 1442 GIB cases among 106 626 dabigatran users (49 486 patient-years), and 184 GIB cases

Table 1

Characteristics of included observational studies

Study	Study design	Study period	Region	Data ascertainment	Inclusion criteria	Exclusion criteria	Outcome ascertainment
Abraham <i>et al.</i> [37]	R, C	November 2010 – September 2013	USA	Medical and pharmacy administrative claims from Optum Labs Data Warehouse	≥18 years, received dabigatran, rivaroxaban or warfarin on the index date	Patients had Rx for targeted treatment ≤12 months before index date; did not have continuous enrolment; with mechanical heart valve or mitral stenosis, chronic haemodialysis or peritoneal dialysis and kidney transplant; residing in skilled nursing facility or nursing home	ICD-9 codes
Chan <i>et al.</i> [38]	P, C	October 2010 – October 2014	USA	Fresenius Medical Care North America (FMCNA) ESRD database	Chronic haemodialysis patients with AF who started <i>de novo</i> OAC	Patients with a previous diagnosis of warfarin skin necrosis, protein S deficiency, protein C deficiency or calciphylaxis	Medical records
Chang <i>et al.</i> [39]	R, C	October 2010 – March 2012	USA	IMS Health LifeLink Health Plan Claims Database	≥18 years; continuous enrolment in 6 months before the entry date; received no NOAC at baseline; without a history of bleeding	Not reported	ICD-9 codes
Graham <i>et al.</i> [26]	R, C	October 2010 – December 2012	USA	Claim files from Medicare beneficiaries enrolled for Medicare program	Patient aged ≥65 years with AF or atrial flutter who newly received ≥1 Rx for dabigatran or warfarin; having ≥6 months of enrolment in Medicare before index date	In a skilled nursing facility or hospice at index, hospitalization that extended beyond the index dispensing date; undergoing dialysis/kidney transplant; with mitral valve disease, heart valve repair or replacement, VTE, or joint replacement surgery in the preceding 6 months	ICD-9 codes
Hernandez <i>et al.</i> [40]	R, C	October 2010 – October 2011	USA	Pharmacy and medical claims of Medicare beneficiaries	Newly diagnosed with AF, filled an outpatient Rx for dabigatran or warfarin within 2 months of the first diagnosis	Filled prescriptions for dabigatran and warfarin during the first 2 months after diagnosis	ICD-9 codes
Larsen <i>et al.</i> [34]	P, C	Dabigatran: August 2011 – May 2013; warfarin: August 2009 – May 2013	Denmark	Danish National Prescription Registry	Naïve dabigatran users/any warfarin users during the study period, with a prior diagnosis of AF	With a diagnoses of mitral stenosis, VTE or valvular surgery; with a previous purchase of phenprocoumon	ICD-10 codes
Staerk <i>et al.</i> [43]	R, C	August 2011 – December 2012	Denmark	The Danish Civil Registration system; Danish National Patient Registry; Danish National Prescription Registry	An OAC-naïve AF patient initiated first-time OAC, or a warfarin-experienced AF patient initiated dabigatran	Aged <30 years or >100 years; with valvular disease, total hip or knee replacement surgery ≤8 weeks or VTE ≤6 months before baseline; with GIB, gastroesophageal reflux, gastritis, gastric/duodenal ulcer, gastroscopy, and PPI use 180 days before baseline	ICD-10 codes

(Continues)

Table 1

(Continued)

Study	Study design	Study period	Region	Data ascertainment	Inclusion criteria	Exclusion criteria	Outcome ascertainment
Larsen et al. [32]	P, C	August 2009 – December 2012	Denmark	The Danish Civil Registration system; Danish National Patient Registry; Danish National Prescription Registry	AF patients who were previously untreated (both warfarin and dabigatran)	Not reported	ICD-10 codes
Lauffenburger et al. [41]	R, C	2009–2012	USA	Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement database	AF patients ≥ 18 years and continuously enrolled for ≥ 12 months before index date, filling ≥ 1 Rx for warfarin or dabigatran	Anticoagulant Rx filled in the 12 months prior to the index date, with valvular or transient AF in the baseline period	Validated ICD-9 coding algorithms
Vaughan Sarrazin et al. [36]	R, C	June 2010 – June 2011	USA	National Veterans Affairs administrative encounter and pharmacy data	AF patients who received warfarin for ≥ 180 days within study period, with the most recent fill date ≤ 90 days before June 2011	Without a diagnosis of AF during the 12 months before June 2011; with a GFR < 30 ml min ⁻¹ 1.73 m ⁻² during the prior 12 months or with a prosthetic heart valve	Validated ICD-9 codes
Laliberte et al. [33]	R, C	May 2011 – July 2012	USA	Symphony Health Solutions' (SHS) Patient Transactional Datasets	AF patients ≥ 18 years newly initiated on rivaroxaban or warfarin after November 2011; CHADS ₂ score ≥ 1 during the 180-day baseline period, ≥ 6 months of clinical activity	Patients diagnosed at baseline with valvular, pregnancy, malignant cancers and transient causes of AF	ICD-9 codes
Bell et al. [31]	P, CS	July 2011 – June 2012	New Zealand	Medical records from ACH Emergency Department in Auckland, City Hospital	Patients admitted with upper GIB and concurrent warfarin or dabigatran therapy	Not reported	Hospital admission records
Choi et al. [60]	P, CS	September 2011 – November 2011	USA	The National Health and Wellness Survey, Lightspeed Research Internet panel, telephone databases of AF patients	Patients ≥ 18 years with self-reported AF diagnosed by healthcare provider, had used warfarin or dabigatran as stroke prophylaxis	Less technologically able patients	Self-reported
Sherid et al. [42]	R, CS	October 2010 – October 2012	USA	Medical records from CGH Medical Center in Sterling, IL & Saint Francis Hospital in Evanston, IL	Patients aged ≥ 18 years taking either dabigatran for ≥ 3 days or rivaroxaban for ≥ 4 days	An unknown duration of rivaroxaban and dabigatran, lack of follow-up, with pregnancy, mechanical valve replacement and advanced kidney disease (GFR < 15 ml min ⁻¹ 1.73 m ⁻²) or end-stage renal disease on dialysis	Medical records

(Continues)

Table 1

(Continued)

Study	Study design	Study period	Region	Data ascertainment	Inclusion criteria	Exclusion criteria	Outcome ascertainment
Nagao <i>et al.</i> [45]	R, CS	April 2013 – March 2014	Japan	Medical records from Nagoya University Hospital,	Patients who received warfarin or apixaban, and underwent radiofrequency catheter ablation for AF	Not reported	Medical records
Sherid <i>et al.</i> [35]	R, CS	October 2010 – April 2013	USA	Medical records from CGH Medical Center in Sterling, IL & Saint Francis Hospital in Evanston, IL	Patients aged ≥ 18 years taking either dabigatran for ≥ 3 days or rivaroxaban for ≥ 4 days	An unknown duration of rivaroxaban and dabigatran, lack of follow-up, pregnancy, mechanical valve replacement and advanced kidney disease (GFR $< 15 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ or end-stage renal disease on dialysis)	Medical records

ACH, Auckland City Hospital; AF, atrial fibrillation; C, cohort; CHADS₂, congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus, prior stroke or transient ischaemic attack or thromboembolism; CS, cross-sectional; ESRD, end-stage renal disease; FDA, Food and Drug Administration; GFR, glomerular filtration rate; GI, gastrointestinal; GIB, gastrointestinal bleeding; ICD-9 (-10), International Classification of Diseases, Ninth (Tenth) Revision; IMS, Intercontinental Marketing Services; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation; P, prospective; PPI, proton pump inhibitor; R, retrospective; Rx, prescription; VTE, venous thromboembolism.

among 10 713 rivaroxaban users (4046 patient-years) (Table S2). The pooled incidence rate of GIB was 4.50 (95% CI 3.17, 5.84) and 7.18 (95% CI 2.42, 12.0) per 100 patient-years for dabigatran and rivaroxaban, respectively (Figure 3).

Sensitivity analyses. We performed four sensitivity analyses (Table 2). First, sensitivity analysis by substituting the results of Larsen *et al.* [34] with those of Staerk *et al.* [43], and the results of Graham *et al.* [26] with those of Hernandez *et al.* [40] yielded similar results to those of the primary analysis (Figure 2), with an RR of 1.30 (95% CI 1.01, 1.66) for dabigatran compared with warfarin. Substituting the Larsen *et al.* [34] results with Larsen *et al.* [32] results yielded a similar but nonsignificant result (RR 1.24, 95% CI 0.98, 1.59). Moreover, The I^2 reduced from 69% to 48% with omission of the Abraham *et al.* study [37], which led to a similar RR of 1.27 (95% CI 1.13, 1.41) compared with the main result of 1.21 (95% CI 1.05, 1.39). The fourth sensitivity analysis, conducted by removing the Chan *et al.* study [38], also showed similar results to the main analysis. The results of our sensitivity analyses supported the robustness of the main results.

Subgroup analyses. A series of subgroup analyses were performed on the eight cohort studies included in the primary analysis, to examine how the different factors might have affected the risk of developing GIB in NOAC users (Table 2; Figures S2–S10). The results of dabigatran and

rivaroxaban groups were stratified accordingly. Subgroup analyses based on dabigatran dose showed that dabigatran 150 mg b.i.d. was associated with a significantly higher risk of GIB, with an RR of 1.51 (95% CI 1.34, 1.70). However, this association was marginal for 75 mg b.i.d. (RR = 1.01, 95% CI 0.78, 1.31) and was not reflected for the 110 mg b.i.d. dose (RR = 0.53, 95% CI 0.29, 0.98). However, it is important to note that the data for 75 mg b.i.d. and 110 mg b.i.d. were from separate single studies (Figure 4). Subgroup analysis by different indications for dabigatran or rivaroxaban use yielded similar results between subgroups (Table 2; Figure S2).

By stratifying major and nonmajor GIB, dabigatran was shown to be associated with a significantly increased risk of major GIB (RR = 1.30, 95% CI 1.17, 1.46); however, no significant association was observed with nonmajor GIB (RR = 0.85, 95% CI 0.40, 1.79) (Table 2; Figure S3).

In the cohort studies, the majority (60–97%) of patients were aged 65 years or above (Table S2). Specifically, subjects from the study by Graham *et al.* [26] were all aged 65 years or above. Stratified analysis of the older NOAC users (≥ 65 years) showed a higher GIB risk when on dabigatran or rivaroxaban compared with that of adult patients in general (Table 2; Figure S4), although it was not statistically significant.

Subgroup analysis also showed that dabigatran was associated with a trend of nonsignificantly higher GIB risk among warfarin-experienced patients than warfarin-naïve patients (Table 2; Figure S5). When considering the adjustment

A. Crude estimate

B. Adjusted estimate

Figure 2

Primary analysis of cohort studies: summarized estimates (crude and adjusted) of gastrointestinal bleeding risk among users of non-vitamin K antagonist oral anticoagulants vs. warfarin. CI; confidence interval; IV, intravenous; NOAC, non-vitamin K antagonist oral anticoagulant; SE, standard error

for different confounders, this showed a high impact of concomitant PPI or H2 use ($I^2 = 83.8\%$, $P_{\text{heterogeneity}} = 0.01$) on dabigatran-associated GIB, whereas the effect on rivaroxaban-associated GIB was relatively modest ($I^2 = 46.7\%$, $P_{\text{heterogeneity}} = 0.17$). A 1.3-fold increase in GIB risk with

dabigatran use was only observed in studies that did not adjust for the use of antiplatelet agents, steroids or SSRIs; however, the difference between subgroups was not significant. There were no significant differences between subgroups that had adjusted or not adjusted for NSAID use (Table 2; Figures S6–S10).

Figure 3

Summarized estimates of incidence rate of GIB in NOAC users. CI, confidence interval; GIB, gastrointestinal bleeding; IR, incidence rate per 100 patient-years; LCL, 95% lower confidence limit; UCL, 95% upper confidence limit

Discussion

To our knowledge, this was the first meta-analysis of observational studies investigating the association of NOAC use and the risk of GIB in the real-world setting. We undertook a rigorous systematic review and meta-analysis with data extraction and statistical analysis by independent reviewers. Based on our results, a slightly higher risk of GIB in dabigatran use compared with warfarin was observed, with an RR of 1.21 (95% CI 1.05, 1.39). No significant difference was found between rivaroxaban and warfarin for GIB risk (RR = 1.09, 95% CI 0.92, 1.30).

Heterogeneity

Notably, there was substantial heterogeneity between studies on dabigatran both for meta-analyses on cohort studies ($I^2 = 69\%$, $P_{\text{heterogeneity}} = 0.004$) and for cross-sectional studies

($I^2 = 88\%$, $P_{\text{heterogeneity}} < 0.001$). However, there seemed low or no substantial heterogeneity between included studies for rivaroxaban.

Our sensitivity analysis showed that this substantial heterogeneity was mainly attributed to the study by Abraham *et al.* [37]. However, this did not significantly change the pooled result, with an even slightly higher RR (1.27 vs. 1.21 in primary analysis) with overlapping confidence intervals. This finding suggests no substantial influence of heterogeneity, and that a possible association between dabigatran use and an increased risk of GIB cannot be ruled out.

Of the cross-sectional studies, Choi *et al.* [60] was survey based and the other two studies were based on hospital medical records. Additionally, the sample size in Sherid *et al.* [42] and Choi *et al.* [60] were limited, which may have affected the robustness of the result. Therefore, findings from

Table 2

Subgroup and sensitivity analyses of the GIB risk among users of NOAC vs. warfarin

Sensitivity analyses	Comparison groups		No. of studies	Adjusted estimate (95% CI)	Heterogeneity between studies
Sensitivity analysis 1*	Dabigatran vs. warfarin		7	1.30 (1.01, 1.66)	$P < 0.00001$, $I^2 = 91\%$
Sensitivity analysis 2†	Dabigatran vs. warfarin		7	1.24 (0.98, 1.59)	$P < 0.00001$, $I^2 = 91\%$
Sensitivity analysis 3‡	Dabigatran vs. warfarin		6	1.27 (1.13, 1.41)	$P = 0.09$, $I^2 = 48\%$
Sensitivity analysis 4§	Dabigatran vs. warfarin		6	1.18 (1.02, 1.36)	$P = 0.004$, $I^2 = 71\%$
	Rivaroxaban vs. warfarin		4	1.10 (0.87, 1.38)	$P = 0.28$, $I^2 = 22\%$
Subgroup analyses			No. of studies	Adjusted estimate (95% CI)	Heterogeneity between groups
Variable	Subgroups				
Indication	Dabigatran	AF	6	1.21 (1.03, 1.42)	$P = 0.99$, $I^2 = 0\%$
		Non-AF	1	1.14 (0.54, 2.39)	
		Unspecified	1	1.21 (0.96, 1.53)	
	Rivaroxaban	AF	3	1.08 (0.87, 1.35)	$P = 0.70$, $I^2 = 0\%$
		Non-AF	1	0.89 (0.60, 1.32)	
		Unspecified	1	0.98 (0.36, 2.69)	
GIB severity	Dabigatran	Major	2	1.30 (1.17, 1.46)	$P = 0.33$, $I^2 = 10.3\%$
		Nonmajor	1	0.85 (0.40, 1.79)	
		Any	5	1.15 (0.95, 1.40)	
	Rivaroxaban	Major	1	0.96 (0.58, 1.59)	$P = 0.78$, $I^2 = 0\%$
		Nonmajor	1	0.82 (0.30, 2.22)	
		Any	3	1.10 (0.87, 1.38)	
Patient age	Dabigatran	18–64 years	1	1.34 (0.98, 1.83)	$P = 0.63$, $I^2 = 0\%$
		≥65 years	3	1.46 (0.99, 2.13)	
		All adults ≥18 years	6	1.21 (1.00, 1.45)	
	Rivaroxaban	18–64 years	1	1.03 (0.33, 3.18)	$P = 0.92$, $I^2 = 0\%$
		≥65 years	2	1.49 (0.33, 6.68)	
		All adults ≥18 years	4	1.09 (0.92, 1.30)	
Prior use of warfarin	Dabigatran	Yes	2	1.40 (1.01, 1.96)	$P = 0.31$, $I^2 = 3.0\%$
		No	6	1.16 (1.01, 1.34)	
NSAID	Dabigatran	Yes	5	1.20 (0.98, 1.47)	$P = 0.87$, $I^2 = 0\%$
		No	2	1.24 (0.94, 1.63)	
	Rivaroxaban	Yes	3	1.10 (0.87, 1.38)	$P = 0.63$, $I^2 = 0\%$
		No	1	0.96 (0.58, 1.59)	
PPI/H2	Dabigatran	Yes	4	1.11 (0.95, 1.30)	$P = 0.01$, $I^2 = 83.8\%$
		No	3	1.50 (1.25, 1.80)	
	Rivaroxaban	Yes	2	0.93 (0.70, 1.24)	$P = 0.17$, $I^2 = 46.7\%$
		No	2	1.20 (0.96, 1.50)	
Antiplatelet agents	Dabigatran	Yes	5	1.17 (0.99, 1.40)	$P = 0.43$, $I^2 = 0\%$
		No	2	1.31 (1.07, 1.59)	

(Continues)

Table 2

(Continued)

Sensitivity analyses	Comparison groups		No. of studies	Adjusted estimate (95% CI)	Heterogeneity between studies
	Rivaroxaban	Yes	2	1.10 (0.81, 1.49)	$P = 0.64, I^2 = 0\%$
		No	2	0.96 (0.61, 1.51)	
	Dabigatran	Yes	3	1.09 (0.83, 1.43)	$P = 0.26, I^2 = 20.9\%$
		No	4	1.33 (1.07, 1.64)	
Steroid	Rivaroxaban	Yes	2	0.93 (0.70, 1.24)	$P = 0.17, I^2 = 46.7\%$
		No	2	1.20 (0.96, 1.50)	
	Dabigatran	Yes	2	1.02 (0.64, 1.64)	$P = 0.37, I^2 = 0\%$
		No	5	1.28 (1.10, 1.50)	
SSRI	Rivaroxaban	Yes	1	0.93 (0.69, 1.25)	$P = 0.19, I^2 = 42.4\%$
		No	3	1.19 (0.96, 1.48)	

CI, confidence interval; GIB, gastrointestinal bleeding; H2RA, histamine H2-receptor antagonists; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor. ^aSubstitution of the result of Larsen *et al.* [34] with that of Staerk *et al.* [43], and the result of Graham *et al.* [26] with that of Hernandez *et al.* [40]. [†]Substitution of the result of Larsen *et al.* [34] with that of Larsen *et al.* [32], and the result of Graham *et al.* [26] with that of Hernandez *et al.* [40]. [‡]Exclusion of the result of Abraham *et al.* [37].

[§]Exclusion of the result of Chan *et al.* [38].

this secondary analysis should be interpreted cautiously owing to the intrinsic heterogeneity of the included studies and limited number of available studies.

Risk of GIB: comparison of our meta-analysis with findings from RCTs

Four landmark phase III RCTs, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial for dabigatran [2], the Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial for rivaroxaban [3], the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial for apixaban [4], the Effective aNticoagulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF-TIMI 48) for edoxaban [5] were conducted which supported the approval of each of the NOACs. Various meta-analyses of RCTs have been published to investigate the association of NOACs and GIB. A meta-analysis by Holster *et al.* [16] reported that NOACs were associated with a significantly higher risk of GIB, with a pooled OR of 1.45 (95% CI 1.07, 1.97), compared with standard care (defined as the use of any of the following: a LMWH, a VKA, an antiplatelet agent, placebo or no additional therapy). The GIB risk varied among different NOACs, with ORs of 1.58 (95% CI 1.29, 1.93) for dabigatran and 1.48 (95% CI 1.21, 1.82) for rivaroxaban [16]. Subsequently, two meta-analyses, including trials that were more up to date, reported a significant but modest association between all NOACs and GIB, with RRs of 1.25 (95% CI 1.01, 1.55) (from Ruff *et al.* [20]) and 1.23 (95% CI 1.03, 1.46) (from Loffredo *et al.* [21]). However, these two studies did not report the results of specific NOACs separately. By contrast, findings

from four recent meta-analyses [17–19, 61] did not support an association between NOACs and GIB, and did not report separate risks for specific NOACs. Additionally, a recent meta-analysis by Caldeira *et al.* [62], which included the most recent RCTs, reported that NOACs were not associated with a risk of major GIB.

Our meta-analysis found a modest association between dabigatran use and risk of GIB and a nonsignificant association for rivaroxaban use, compared with the use of warfarin; however, both associations were slightly weaker than those found in RCTs [16]. This suggests that in real-life practice, dabigatran and rivaroxaban do not cause more harm or raise unexpected safety concerns compared with findings from RCTs.

The lower risk of GIB found in the present meta-analysis of observational studies might have been due to patient selection. In RCTs, only patients at high risk of stroke were recruited, resulting in an older group of patients than in real-life practice. In the RE-LY trial, the mean age was 71.4 [standard deviation (SD) 8.6] years and 71.5 (SD 8.8) years for dabigatran 110 mg b.i.d. and 150 mg b.i.d. users, respectively [2]. However, NOAC users in five studies included in the present meta-analysis had a mean age below 70 years (Table S2) [36–39, 41]. Moreover, we cannot exclude the possibility of a 'healthy subject effect'. Over 40% of subjects from some included observational studies had a low CHADS₂ (congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism) score of 0 to 1 [33, 37]. However, only approximately a third of the RE-LY cohort and none of the ROCKET-AF cohort had a CHADS₂ score of 0 to 1. With better awareness of the potential GIB-inducing safety issue with NOACs, clinicians may tend to prescribe these agents to lower-risk patients, preventing exposure of NOACs to many high-risk patients. However, most of the

Figure 4

Subgroup analysis: summarized estimates of GIB risk by different dabigatran doses. CI, confidence interval; IV, intravenous; SE, standard error

studies we analysed had already controlled for various factors using propensity score adjustment [26, 33, 37, 39, 41], so the 'healthy subject effect' is unlikely to have been a significant issue in the present analysis.

Notably, among the included studies, the outcome was specifically defined as major GIB in Graham *et al.* [26], while Chan *et al.* [38] stratified the outcomes and reported the results of minor and major GIB separately. It was reported in the meta-analysis of RCTs that dabigatran and rivaroxaban were associated with an approximately 50% increase in overall GIB risk compared with warfarin [16]; however, they were not associated with the risk of major GIB [62]. Thus, the lower risk of GIB observed in the present meta-analysis may also be partially attributed to the effect of combining overall GIB and major GIB in the outcome. Interestingly, in contrast to the results reported by Caldeira *et al.* [62], our subgroup analysis found that dabigatran use was mainly associated with major GIB rather than nonmajor GIB (RR 1.30, 95% CI 1.17, 1.46). However, because of the limited number of studies ($n = 2$), we cannot draw firm conclusions (Figure S2).

It is important to note that, although the results from our meta-analysis showed a significant association for dabigatran but a nonsignificant one for rivaroxaban, indirect comparison of the risk of GIB associated with dabigatran and with rivaroxaban should be evaluated with caution. Rivaroxaban is a newer agent than dabigatran, with fewer

available real-life studies and shorter follow-up duration. Further, in included studies, patients receiving rivaroxaban were younger compared with those on dabigatran. This might be another possible explanation for the lower risk of GIB found. Moreover, subgroup analysis showed that among patients aged ≥ 65 years, a 50% nonsignificant increased risk of GIB was observed both in dabigatran and rivaroxaban use compared with warfarin (Table 2; Figure S3). Therefore, an increased risk of GIB in rivaroxaban users cannot be ruled out.

Risk factors of GIB

Subgroup analyses show that there was a dose-related effect with respect to the safety of dabigatran, with a higher risk of GIB in the dabigatran 150 mg b.i.d. group compared with the low-dose groups, which is consistent with findings from the RE-LY trial. However, there was only one study available for both the 75 mg b.i.d. and 110 mg b.i.d. dabigatran subgroups, respectively. Data for different doses of dabigatran are still needed from further studies to confirm this finding. Furthermore, the subgroup analysis by different indications (AF and non-AF) showed similar results, probably because of the limited data available [only one study (Abraham *et al.* [37])] reported data from non-AF patients]. Notably, the patient's age would be a main risk factor for an increased GIB risk among NOAC users, so specific caution is needed for prescribing NOAC to elderly patients. In the RE-LY trial,

the increased risk of GIB was only observed in patients aged ≥ 75 years for both 110 mg b.i.d. (RR = 1.39, 95% CI 1.03, 1.98) and 150 mg b.i.d. (RR = 1.79, 95% CI 1.35, 2.37) dabigatran groups, but not in patients aged < 75 years [63]. However, for rivaroxaban, a secondary analysis of the ROCKET-AF trial comparing outcomes in patients aged ≥ 75 and < 75 years showed no significant difference between older and younger patients [64]. This suggests that rivaroxaban may be an alternative for older patients. Our meta-analysis investigated the age group ≥ 65 years and showed a nonsignificant trend of a higher risk of GIB among these elderly patients, possibly due to the scanty number of studies with available data.

In addition, normal renal function is crucial in the elimination of dabigatran [65]. A population pharmacokinetic analysis of the AF patients from the RE-LY trial suggested that patients with renal dysfunction need a dabigatran dose adjustment, which highlights the importance of renal function monitoring in patients already on, or being considered for, dabigatran [66]. In our meta-analysis, only Chan *et al.* [38] focused specifically on AF patients with end-stage renal disease who were on haemodialysis, which may partially explain the higher incidence of GIB found among NOAC users in that study. However, in our sensitivity analysis, removal of the Chan *et al.* [38] study produced similar results to those of the main analysis (Table 2), supporting the robustness of the main analysis. Further studies are needed to investigate the efficacy and safety of NOACs in patients with renal dysfunction.

A prior history of warfarin use has also been noted to be a factor that may influence the risk of GIB in NOAC users. Ezekowitz *et al.* [67] conducted a secondary analysis of the RE-LY trial and reported a similarly higher rate of GIB with dabigatran 150 mg b.i.d. both in VKA-naïve and -experienced cohorts, whereas similar nonsignificant findings were observed for dabigatran 110 mg b.i.d. in both cohorts. Of the studies in our meta-analysis, Larsen *et al.* [34] specifically investigated both VKA-naïve and -experienced cohorts and reported similar GIB risk in both groups. Our subgroup analysis by the history of warfarin use suggested that previous warfarin exposure did not influence the GIB risk of dabigatran compared with warfarin, which is consistent with the RE-LY study findings.

Discrepancies between the findings from subgroups of adjustment for the use of gastroprotective agents (PPIs or H2RAs), antiplatelet agents, steroid and SSRI implied that concomitant use with these agents would affect the safety profile of NOACs. Further studies to investigate the potential protective role of gastroprotective agents (PPIs or H2RAs) would be of great clinical impact [68] as there is currently no well-developed specific antidote for NOACs for the management of their adverse drug reactions. In addition, we were unable to investigate the drug–drug interaction directly as this was not evaluated or reported in the original studies.

Strengths and limitations

Our study was the first meta-analysis to include all relevant observational studies and provide a thorough summarized analysis and systematic review of NOAC safety in respect to GIB risk in the real-world setting. The eight cohort studies

included in the primary analysis were of high quality in study design, as indicated by the Newcastle–Ottawa scale quality assessment. Sensitivity analysis showed that there was no significant difference between various studies using the same data source, which supports the robustness of the main result.

However, the present review had several limitations. Firstly, studies not in the English language were excluded in the meta-analysis and potential language bias cannot be ruled out. However, this effect may have been minimal, and diminished owing to the shift in the publication tendency towards journals publishing in English in recent decades [69]. Secondly, our meta-analysis attempted to investigate the influence of different doses of dabigatran, patient age and GIB severity. However, the studies reporting corresponding outcomes were scant and therefore the conclusions of the present study should be interpreted with caution. Further studies may be helpful to strengthen the evidence. Thirdly, the present meta-analysis compiled results from available nonrandomized epidemiological studies. The risk of our results being influenced by bias and confounding factors therefore would have been higher than in meta-analyses of RCTs. In an attempt to overcome some of the confounder issues, we performed subgroup and sensitivity analyses to evaluate confounding factors, including patient characteristics, concomitant diseases and medications, although some of the above-mentioned factors were not analysed owing to the lack of availability of data. Some heterogeneity can be partially overcome through subgroup analysis by confounder adjustments. Sensitivity analyses by omitting certain specific studies significantly reduce the level of heterogeneity, and similar pooled results support the robustness of the primary analysis. Fourthly, to date, Sherid *et al.* [35] has been the only study available to report a direct head-to-head comparison of rivaroxaban vs. dabigatran. Owing to the small sample size and relatively low power of their study, it is difficult to draw any firm conclusion from it. Likewise, apixaban and edoxaban are also relatively new [27, 45], so few studies have used them and sample sizes are small. Long-term monitoring is required to assess their association with GIB.

Conclusion

In conclusion, our meta-analysis suggests a slightly higher risk of GIB with dabigatran use compared with warfarin, whereas no significant difference was found between rivaroxaban and warfarin for GIB risk. Dabigatran and rivaroxaban do not raise unexpected safety concerns in terms of GIB compared with findings from RCTs.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: EWC has received financial support from Janssen, a division of Johnson and Johnson, Bristol Myers Squibb, Pfizer and

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Contributors

YH, ICKW and EWC had the original idea for this study and contributed to the development of the idea and the study design. YH and XL independently conducted a systematic review and reviewed the literature for relevance. YH, SA and XL undertook the analysis. YH, ICKW, SA, XL, WKL, CWS and EWC contributed to the interpretation of the analysis. YH wrote the first draft of the paper. EWC, WKL, CWS and ICKW critically reviewed the results and the manuscript. ICKW and EWC provided oversight over all aspects of this project. YH and EWC are the guarantors. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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Table S1 Newcastle–Ottawa scale for assessment of the quality of the included comparative observational studies

Table S2 Summary of the main characteristics and results of included comparative studies*

Figure S1 Secondary analysis of cross-sectional studies: summarized estimates of gastrointestinal bleeding risk in non-vitamin K antagonist oral anticoagulant users

Figure S2 Summarized estimates of subgroup analysis by indication

Figure S3 Summarized estimates of subgroup analysis by gastrointestinal bleeding severity

Figure S4 Summarized estimates of subgroup analysis by different age groups

Figure S5 Summarized estimates of subgroup analysis by prior use of warfarin: gastrointestinal bleeding risk among dabigatran users

Figure S6 Summarized estimates of subgroup analysis by use of nonsteroidal anti-inflammatory drugs

Figure S7 Summarized estimates of subgroup analysis by use of gastroprotective agents (proton pump inhibitors or histamine H₂-receptor antagonists)

Figure S8 Summarized estimates of subgroup analysis by use of antiplatelet agents

Figure S9 Summarized estimates of subgroup analysis by use of steroids

Figure S10 Summarized estimates of subgroup analysis by use of serotonin reuptake inhibitors