Risk of Major Gastrointestinal Bleeding With New vs Conventional Oral Anticoagulants: A Systematic Review and Meta-analysis

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BACKGROUND & AIMS: **There is controversy over whether use of non-vitamin K antagonist oral anticoagulants (NOACs) associates with increased risk of major gastrointestinal bleeding (GIB) compared with conventional therapies (such as vitamin K antagonists or anti-platelet agents). We performed a systematic review and meta-analysis of data from randomized controlled trials and high-quality real-world studies.**

METHODS: **We performed a systematic search of the MEDLINE, EMBASE, Cochrane Library, and ClinicalTrials.gov Website databases (through Oct 12, 2018) for randomized controlled trials and high-quality real-world studies that reported major GIB events in patients given NOACs or conventional therapy. Relative risks (RRs) for randomized controlled trials and adjusted hazard ratios (aHRs) for real-world studies were calculated separately using random-effects models.**

RESULTS: **We analyzed data from 43 randomized controlled trials (183,752 patients) and 41 real-world studies (1,879,428 patients). The pooled major rates of GIB for patients on NOACs (1.19%) vs conventional treatment (0.92%) did not differ significantly (RR from randomized controlled trials, 1.09; 95% CI, 0.91–1.31 and aHR from real-world studies, 1.02; 95% CI, 0.94–1.10; $P_{interaction}$ = .52). Rivaroxaban, but not other NOACs, was associated with an increased risk for major GIB (RR from randomized controlled trials, 1.39; 95% CI, 1.17–1.65 and aHR from real-world studies, 1.14; 95% CI, 1.04–1.23; $P_{interaction}$ = .06). Analyses of subgroups, such as patients with different indications, dosage, or follow-up time, did not significantly affect results. Meta-regression analysis failed to detect any potential confounding to impact the primacy outcome.**

CONCLUSIONS: **In a systematic review and meta-analysis of data from randomized controlled trials and real-world studies, we confirmed that there is no significant difference in risk of major GIB between patients receiving NOACs vs conventional treatment. Rivaroxaban users had a 39% increase in risk for major GIB.**

Keywords: Stroke Prevention; Clotting; Venous Thromboembolism; Dabigatran.

Millions of patients worldwide are treated with oral anticoagulation therapy, primarily for the prevention of stroke in atrial fibrillation (AF) and the prophylaxis or treatment of venous thromboembolism (VTE).[1] Non–vitamin K antagonist oral anticoagulants (NOACs) (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban), because of their favorable efficacy profile, represent an alternative to conventional treatment (such as vitamin K antagonists [VKAs] and antiplatelet agents).[1,2] Meanwhile, the need for frequent monitoring,

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Abbreviations used in this paper: AF, atrial fibrillation; aHR, adjusted hazard ratio; CI, confidence interval; GIB, gastrointestinal bleeding; LMWH, low-molecular-weight heparin; NOAC, non–vitamin K antagonist oral anticoagulant; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; RWS, real-world study; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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narrow therapeutic range, dietary restrictions, and multiple drug interactions related to VKAs have contributed to increasing uptake of NOACs worldwide.[2] However, the extensive clinical application of NOACs has raised concerns on bleeding risk. Gastrointestinal bleeding (GIB) as a serious medical condition has always been the focus of attention owing to its being the most frequent cause of major bleeding (30%–40%), its considerable mortality (5%–15%), and its enormous burden on global health care utilization.[3] Pivotal efficacy randomized controlled trials (RCTs) have documented an increased risk of GIB for NOACs compared with warfarin.[4] During the past few years, no specially ad hoc designed RCTs have been conducted to assess the GIB risk for NOACs, and several high-quality meta-analyses have yielded conflicting results and were limited by inclusion of only RCTs, use of placebo as control, concomitant antiplatelet agents in acute coronary syndrome patients, and of a composite outcome of major and minor GIB, possibly introducing bias and leading to underestimation or overestimation of GIB risk.[4–6]

Publication of many more contemporary RCTs (APLX, PIONEER AF-PCI, RE-DUAL PCI, COMPASS, EINSTEIN CHOICE, ENSURE-AF, Hokusai VTE Cancer, SELECT-D, RE-CIRCUIT, and EMANATE) fueled systematic reassessment of risk for major GIB associated with NOACs. Moreover, real-world studies (RWSs) by integrating data from electronic health records, claims databases, and disease registries could extend findings of RCTs to large patient populations in real-world practice. Therefore, in the present study we summarized all available evidences from RCTs and high-quality RWSs for a comprehensive and rigorous meta-analysis on the GIB risk for NOACs.

What You Need to Know

Background

Non–vitamin K antagonist oral anticoagulants (NOACs) have been used increasingly as alternatives to conventional anticoagulants for stroke prevention and venous thromboembolism prophylaxis or treatment. The extensive use of NOACs has raised concerns about risk of gastrointestinal bleeding (GIB). Previous high-quality meta-analyses have produced conflicting results, so it is important to reassess risk.

Findings

We analyzed pooled results from 43 randomized controlled trials and 41 real-world studies and found similar risk for major GIB between patients given NOACs and patients receiving conventional therapy. We conclude that there is no association between NOACs and increased risk of major GIB. As for individual NOACs, rivaroxaban, but not dabigatran or apixaban, increased risk for major GIB by 39%.

Implications for patient care

The risk of major GIB does not differ significantly between patients receiving NOACs compared with conventional treatment. Rivaroxaban, but not dabigatran and apixaban, increased risk of major GIB. These results might be used to select oral anticoagulant therapy.

Methods

Literature Search and Study Selection

We followed a pre-specified protocol (PROSPERO: CRD42018105151) and standards in Cochrane Collaboration and PRISMA Statement for reporting systematic reviews.[7,8] We searched MEDLINE, EMBASE, and Cochrane Library databases from inception to October 12, 2018, with the language restriction of English, for RCTs and RWSs of NOAC treatment with major GIB as an outcome. Full details of search terms are presented in Supplementary File. We also identified potential studies from ClinicalTrials.gov platform (www.clinicaltrials.gov) and bibliographies of pertinent articles identified by search strategy. RCTs or RWSs that compared NOACs with conventional therapy (ie, VKAs or antiplatelet agents) and reported data on major GIB were eligible for inclusion. Studies that compared NOACs with placebo were excluded because of inevitable overestimation of major GIB risk associated with NOACs. Details of study selection are shown in Supplementary File.

Study Outcomes, Data Extraction, and Quality Evaluation

The primary outcome was major GIB, and the secondary outcomes were upper and lower major GIB, according to International Society on Thrombosis and Hemostasis criteria.[9] We extracted data by using an a priori designed form, which included study and clinical characteristics, patient demographics, bleeding history and concomitant drugs, and data on major GIB (occurrence number and total number for RCTs; adjusted hazard ratio [aHR] for RWSs). Because use of data from VKAs-switchers may lead to overestimation of major GIB risk of NOACs, we extracted data from NOACs-naive patients and VKAs-switchers separately, if available. The methodological quality of RCTs was evaluated according to the Cochrane Collaboration Risk of Bias Tool.[10] Because RWSs have a higher risk for bias relative to RCTs, we considered important factors in RWS design and methods used to mitigate bias when comparing outcomes between NOAC and comparator.[11] Details of study outcomes and quality assessment are presented in Supplementary File.

Data Analysis

In brief, we performed data analyses for RCTs and RWSs separately and then used interaction analysis to

assess the comparability between RCTs and RWSs. For RCTs, we used forest plots to measure the primary and secondary outcomes, and relative risks (RRs) and associated 95% confidence intervals (95% CIs) were calculated by using random-effects models. For RWSs, we pooled aHR and their 95% CI by using random-effects models. Statistics were performed using STATA software (version 13; StataCorp, College Station, TX), and $P < .05$ indicated a statistically significant difference. Details of statistical process are outlined in Supplementary File.

Results

Search Results and Study Evaluation

Our initial search identified 21,867 records from databases and 956 records from ClinicalTrials.gov platform; 17,957 records were excluded by screening titles and abstracts. We reviewed the remaining 265 full-text articles and excluded 181 articles for reasons listed in Figure 1, Supplementary File. Finally, 84 studies fulfilled inclusion criteria; 43 were RCTs (10 for dabigatran, 16 for rivaroxaban, 8 for apixaban, 8 for edoxaban, and 1 for betrixaban), and 41 were RWSs (25 for dabigatran, 7 for rivaroxaban, 4 for apixaban, and 5 for NOACs). The indication was AF in 14 RCTs and 32 RWSs, VTE prophylaxis or treatment in 21 RCTs and 4 RWSs, and special clinical scenarios in 8 RCTs and 2 RWSs. A total of 183,752 patients (102,122 patients treated with NOACs and 81,630 patients with conventional treatment) in RCTs and 1,879,428 patients (852,780 patients treated with NOACs and 1,026,648 patients with conventional treatment) in RWSs were included. Details of study evaluation are summarized in Supplementary File.

Major Gastrointestinal Bleeding in Randomized Controlled Trials

The overall major GIB rate was 1.07% (1973/183,752) after summing 43 RCTs data: 1.19% (1220/102,122) in NOACs group and 0.92% (753/81,630) in conventional treatment group. Three trials (PETRO, Weitz 2010, Raskob 2010) had no events in both groups and hence were excluded from the pooled analyses. Major GIB risk was similar between NOACs and conventional treatment (RR, 1.09; 95% CI, 0.91–1.31; $I^2 = 38.9\%$). Also, major upper (RR, 1.17; 95% CI, 0.71–1.93; $I^2 = 32\%$) and lower GIB risk (RR, 0.87; 95% CI, 0.67–1.13; $I^2 = 0\%$) did not differ between NOACs and conventional treatment. Subgroup analyses were conducted according to indications (AF, VTE, and other special clinical scenarios). For the population of AF, 14 RCTs involving 84,567 patients were identified, and the incidence of major GIB was 2.07% (1029/49,794) in NOACs group compared with 1.78% (618/34773) in conventional treatment group, indicating that NOACs were not associated with significantly increased risk for major GIB (RR, 1.01; 95% CI, 0.80–1.26; $I^2 = 57.5\%$). For the population of VTE, 66,147 patients from 21 RCTs were included, among them 0.21% (74/35,100) of NOAC users and 0.23% (71/31,047) of conventional anticoagulant users experienced major GIB, with similar risk between NOACs and conventional treatment (RR, 0.95; 95% CI, 0.67–1.34; $I^2 = 0\%$). Consistent results were also found in other key subgroups (VKAs as control: RR, 1.01; 95% CI, 0.83–1.24; $I^2 = 46.4\%$; low-molecular-weight heparin [LMWH] as control: RR, 1.17; 95% CI, 0.52–2.64; $I^2 = 0\%$; standard-dose NOAC: RR, 1.11; 95% CI, 0.91–1.34; $I^2 = 38.2\%$; reduced-dose NOAC: RR, 0.85; 95% CI, 0.63–1.17; $I^2 = 22.4\%$), with the exception of increased major GIB risk in cancer patients (RR, 2.77;

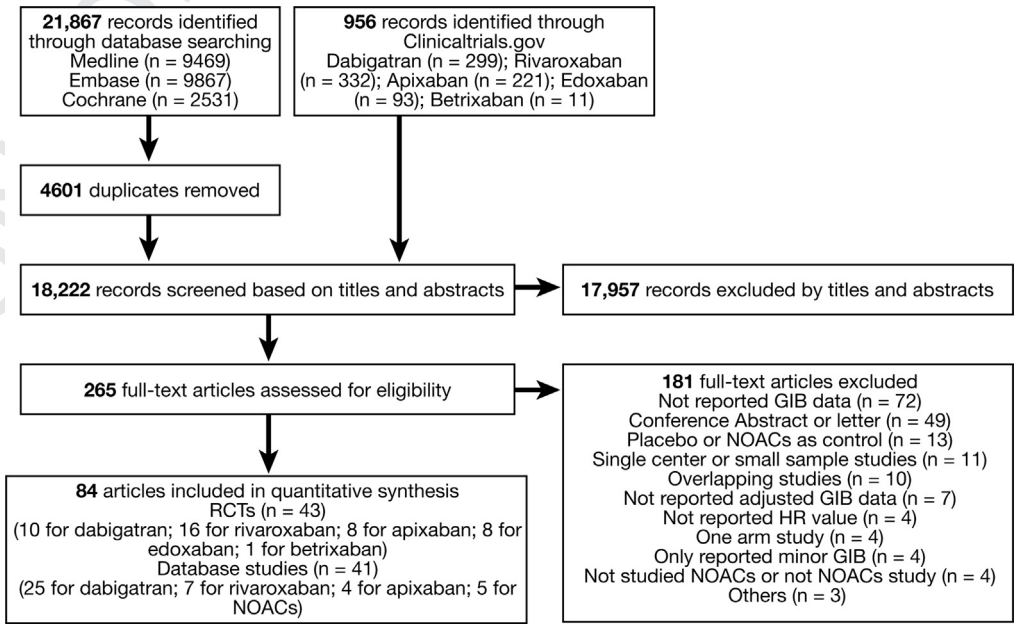

Figure 1. Flow diagram for selection of eligible studies. GIB, gastrointestinal bleeding; HR, hazard ratio; NOACs, non–vitamin K antagonist oral anticoagulants; RCTs, randomized controlled trials.

95% CI, 1.35–5.68; I^2 = 0%) and acutely ill medical patients (RR, 2.44; 95% CI, 1.31–4.57; I^2 = 0%) (Figure 2*A*, Supplementary File). As for individual NOACs, rivaroxaban (RR, 1.39; 95% CI, 1.17–1.65; I^2 = 0%) and its standard dose (RR, 1.48; 95% CI, 1.22–1.80; I^2 = 0%) were associated with a higher major GIB risk compared with conventional treatment, whereas other NOACs were not (Figure 3, Supplementary File). Sensitivity analyses failed to identify any individual trial as having influenced the primacy outcome (Supplementary File). Also, no potential confounding of clinical characteristics was detected to lead to bias on primacy outcome (Supplementary File).

Major Gastrointestinal Bleeding in Real-World Studies

Overall, 37 RWSs reported 72 aHR data on major GIB, with 6 NOACs-naive data in 4 studies.[12–15] No significant difference was observed between NOACs and conventional treatment in terms of major GIB risk (aHR, 1.02; 95% CI, 0.94–1.10; I^2 = 90%) as well as major upper (aHR, 0.94; 95% CI, 0.76–1.11; I^2 = 63.7%) and lower GIB risk (aHR, 1.25; 95% CI, 0.97–1.53; I^2 = 2.8%). In line with pooled RCTs result, cancer patients with NOACs appeared at increased risk for major GIB (aHR, 1.93; 95% CI, 1.07–3.19), whereas AF patients (aHR, 1.03; 95% CI, 0.94–1.12; I^2 = 91.1%) and VTE patients (aHR, 0.84; 95% CI, 0.67–1.01; I^2 = 51.2%) were not. In addition, women and elderly patients receiving NOACs also appeared at increased risk for major GIB (aHR in women, 1.31; 95% CI, 1.14–1.48; I^2 = 55%; aHR in elderly, 1.27; 95% CI, 1.05–1.48; I^2 = 89.6%; aHR in patients older than 75 years, 1.38; 95% CI, 1.20–1.55; I^2 = 66.6%), whereas patients younger than 75 were at decreased risk (aHR, 0.89; 95% CI, 0.78–0.99; I^2 = 8.3%). Because patients who switched VKAs to NOACs may experience a bleeding event and have a relatively high bleeding susceptibility, these patients therefore showed the higher risk for major GIB (aHR, 1.47; 95% CI, 1.17–1.78; I^2 = 53.7%). Furthermore, Taiwan population, but not American or other populations, had a 40% decrease in risk of major GIB (aHR, 0.60; 95% CI, 0.42–0.79; I^2 = 72.1%). Other key subgroup analyses (VKAs as control: aHR, 1.02; 95% CI, 0.94–1.10; I^2 = 89.8%; standard-dose NOAC: aHR, 0.97; 95% CI, 0.79–1.15; I^2 = 86.5%; reduced-dose NOAC: aHR, 0.92; 95% CI, 0.79–1.05; I^2 = 76.7%) were in accordance with the primacy result (Figure 2*B*, Supplementary File). Regarding individual NOACs, rivaroxaban, but not dabigatran, significantly increased the risk for major GIB (aHR, 1.14; 95% CI, 1.04–1.23; I^2 = 75.3%). By contrast, apixaban decreased the risk for major GIB (aHR, 0.65;

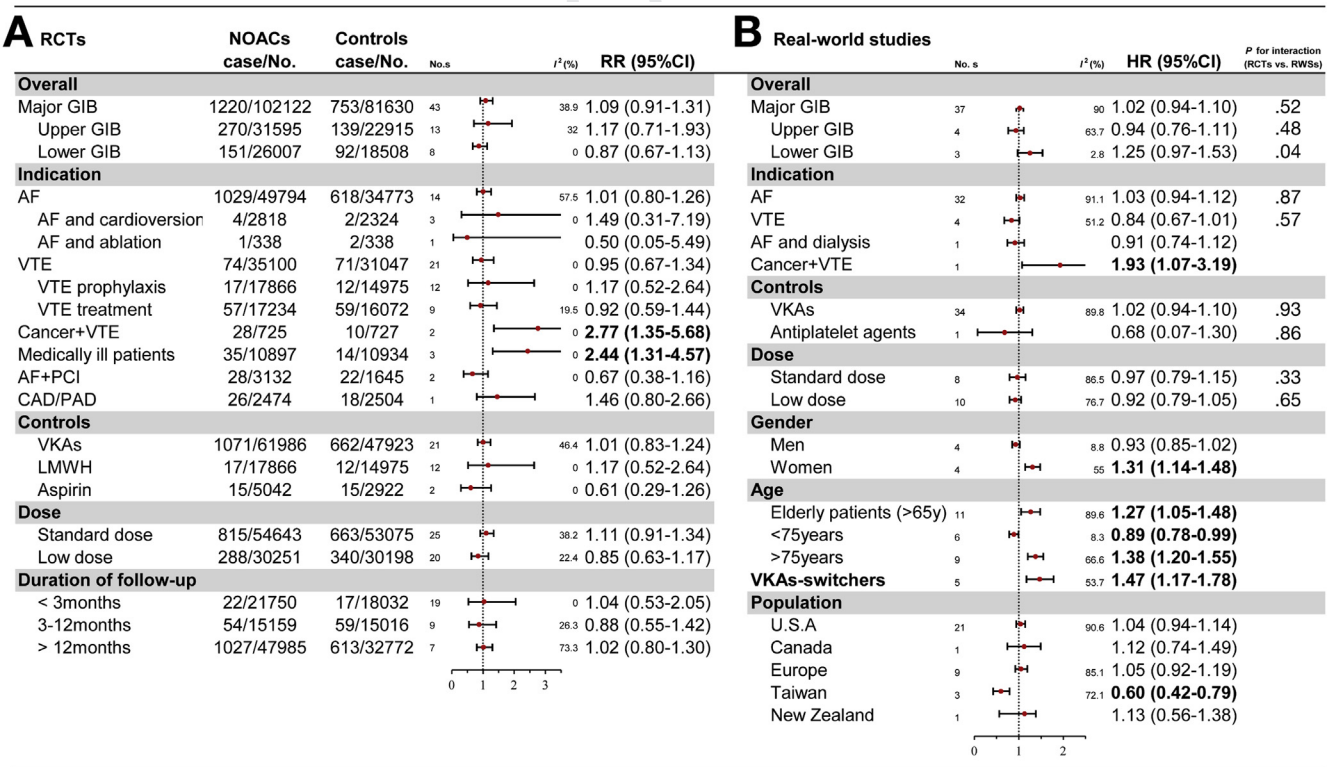

Figure 2. (*A*) Risk for major GIB in RCTs and (*B*) risk for major GIB in real-world studies. AF, atrial fibrillation; CAD, carotid artery disease; CI, confidence interval; GIB, gastrointestinal bleeding; HR, hazard ratio; LMWH, low-molecular-weight heparin; NOACs, non–vitamin K antagonist oral anticoagulants; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials; RR, relative risk; RWSs, real-world studies; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

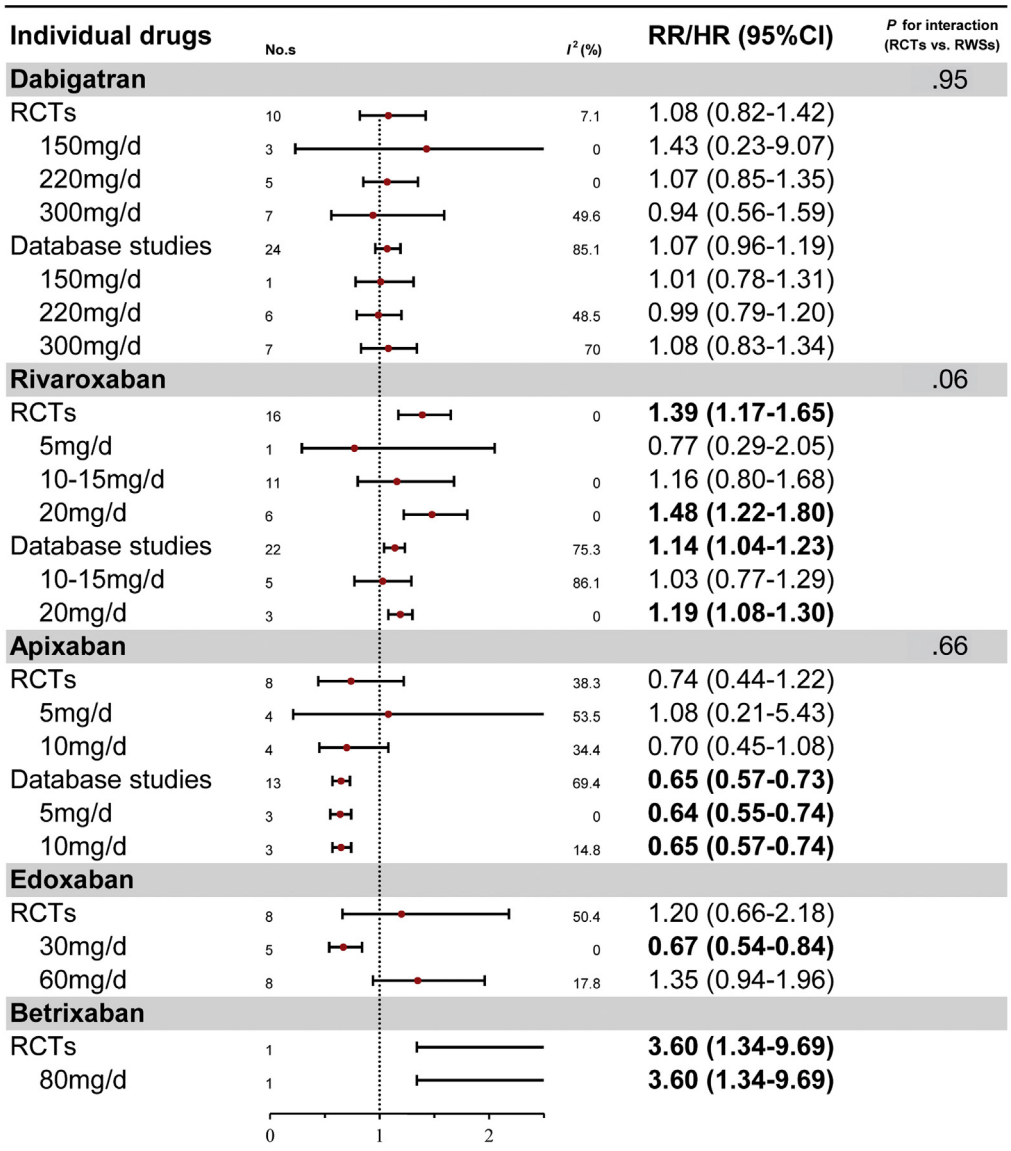

Figure 3. Risk for major GIB by individual NOACs. CI, confidence interval; HR, hazard ratio; RCTs, randomized controlled trials; RR, relative risk; RWSs, real-world studies.

95% CI, 0.57–0.73; I^2 = 69.4%) (Figure 3, Supplementary File). The results of sensitivity analyses were in line with the primacy outcome (Supplementary File). Also, meta-regression analysis failed to detect any potential confounding to impact the primacy outcome (Supplementary File). In addition, we conducted further analyses by excluding trials with antiplatelet agents as control or outside of the approved indications and therapeutic doses, and the results are consistent with primacy analyses (RCTs: RR, 1.08; 95% CI, 0.88–1.32; I^2 = 44.1%; RWSs: aHR, 1.03; 95% CI, 0.95–1.10; I^2 = 89.5%). The full detailed results of the latter analyses are presented in Supplementary File.

Comparison Between Randomized Controlled Trials and Real-World Studies

Interaction analyses were carried out to test the comparability between RCTs and RWSs. For major GIB risk, the results of RCTs and RWSs were consistent, with a $P_{interaction}$ of 0.52. Other results of interaction analyses were in line with the primacy analyses, regardless of indications, controls, dosage, and individual NOACs ($P_{interaction} > .05$ for each; Figure 2, Figure 3).

Discussion

This study simultaneously involves all available Q7 evidence from RCTs and high-quality RWSs for evaluating the association between NOACs and major GIB risk. Pooled results from 43 RCTs and 41 RWSs revealed a similar risk for major GIB between patients given NOACs and patients receiving conventional therapy, thereby validating the conclusion of no association between NOACs and increased risk of major GIB. Comparable major GIB risk between NOAC treatment and conventional therapy was also present in AF and VTE patients. However, rivaroxaban, but not

dabigatran and apixaban, did confer a higher risk for major GIB.

Up to now, several systematic reviews and meta-analyses have been conducted to assess the GIB risk of NOACs. The earliest meta-analysis, which pooled 19 RCTs of 75,081 patients, indicated an increased GIB risk of NOACs compared with standard care (odds ratio [OR], 1.45; 95% CI, 1.07–1.97).[4] Although this study was a standard and high-quality meta-analysis that included all available RCTs, it had 2 important limitations: use of the combination of major and minor GIB as primary outcome and inclusion of acute coronary syndrome studies in which placebo was used as controls and NOACs were administered on the basis of other antiplatelet agents, which inevitably may introduce certain bias and lead to the overestimation of major GIB risk. In addition, the investigators also reported a higher risk of GIB with dabigatran, which mainly derived from the inclusion of the acute coronary syndrome study RE-DEEM (OR, 3.79; 95% CI, 1.41–10.2; contributing weight, 17%).[16] In 2015, Caldeira and colleagues reported an opposite result to the previous meta-analysis.[4,6] This study used a precise definition of major GIB and pooled data by all indications. Two trials (AMPLIFY-EXT and RE-SONATE) comparing NOACs with placebo also were included. Moreover, the authors reported that none of the individual NOACs was associated with an increased risk for major GIB. Notably, the results for each individual NOAC were obtained according to different controls (VKAs, LMWH, aspirin, and placebo), which inevitably reduced statistical power because of limited sample size in each subgroup. Recently, an updated meta-analysis of 28 RCTs reported a similar risk between NOACs and conventional treatment.[5] Studies (EINSTEIN-continued treatment, RE-SONATE, AMPLIFY-EXT, ERIKA, Fuji et al) that compared NOACs with placebo were also included. Furthermore, the investigators emphasized that patients treated with dabigatran and rivaroxaban were at higher risk for major GIB. It should be noted that the results for dabigatran and rivaroxaban were inconsistent among effects models, with positive results in fixed-effects models (dabigatran: OR, 1.27, 95% CI, 1.04–1.55; rivaroxaban: OR, 1.40; 95% CI, 1.15–1.70) and negative results in random-effects models (dabigatran: OR, 1.17; 95% CI, 0.80–1.72; rivaroxaban: OR, 1.17; 95% CI, 0.63–2.18). Because of the latter limitations, our meta-analysis excluded studies that compared NOACs with placebo, restricted the definition of major GIB according to International Society on Thrombosis and Hemostasis criteria, used the random-effects model regardless of presence of heterogeneity, and included all indications and available types of NOACs to comprehensively estimate major GIB risk of NOACs.

It is well-known that the stringent inclusion and exclusion criteria of RCTs might lead to the enrollment of patients with a relatively low risk for GIB when on anticoagulants, which inevitably restricts generalizability of results. Conversely, RWSs entail a longer follow-up duration and more representative populations of patients than RCTs, which provide more valuable information to identify additional risk of novel agents. Certainly a comprehensive analysis of RCTs and RWSs data would provide more robust evidence on drug efficacy and safety. In our study, 41 high-quality RWSs were collected to evaluate the major GIB risk of NOACs, and all perceived sources of heterogeneity were addressed by pre-specified subgroup analyses and meta-regression analyses. Of particular importance, the results from RWSs (aHR, 1.02; 95% CI, 0.94–1.10) conformed to those from RCTs (RR, 1.09; 95% CI, 0.91–1.31), with a $P_{\text{interaction}}$ of .52, thereby validating and replicating the conclusion. Analyses of RWSs can provide more detailed information than RCTs. First, NOACs increased risk of major GIB in women but not in men (aHR, 1.31; 95% CI, 1.14–1.48). Because of their lean body, women have decreased creatinine clearance compared with men and hence may attain higher serum levels of NOACs that predispose them to bleeding.[17] Differences in sex hormones influence variability in vascular reactivity and hemostasis, which may also contribute to gender differences in bleeding susceptibility.[18] Second, elderly patients (aHR, 1.27; 95% CI, 1.05–1.48) carried a high risk for major GIB with NOACs treatment. Reduced renal function caused by advanced age and consequently increased plasma concentration of NOACs might explain the greater rate of bleeding events in the elderly.[13] Third, the merged data from Taiwan population (aHR, 0.60; 95% CI, 0.42–0.79), but not American or other populations, documented decreased risk for major GIB of NOACs, which might be explained by the prevalent use of low-dose NOACs and the poor international normalized ratio stability among Asians.[19]

At present, there is controversy over whether an individual NOAC is associated with increased GIB risk, especially when focusing on dabigatran and rivaroxaban. The above-mentioned limitations of previously published meta-analyses rendered it difficult to generate a definite answer for this topic.[4–6] In our study, 10 RCTs and 24 RWSs of dabigatran were collected, and a nonsignificant association between dabigatran use and increased major GIB risk was found in both RCTs and RWSs ($P_{\text{interaction}} = .95$). Although dabigatran has a direct anticoagulant effect on the esophageal and gastric mucosa, these may only predispose to minor GIB.[20] The pathophysiological mechanisms require further scientific verification. Conversely, the data from 16 RCTs and 22 RWSs supported that rivaroxaban and corresponding standard dose (20 mg daily) were associated with increased major GIB risk ($P_{\text{interaction}} = .06$). It should be stated that apixaban reduced the risk of major GIB by 35% in real-life practice. Taken together, the current evidence from RCTs and RWSs suggests variability across NOACs regarding major GIB risk, with a concern for rivaroxaban but not for dabigatran and apixaban.

To date, a number of published trials have extended the use of NOACs to special clinical settings, including VTE treatment for cancer patients, VTE prophylaxis for acutely ill medical patients, cardiovascular prevention for AF patients after percutaneous coronary intervention, and patients with stable carotid artery disease or peripheral artery disease. The major GIB risk of these populations was assessed in our study. Two RCTs comparing NOACs with long-term dalteparin have been conducted so far to evaluate the efficacy and safety among patients with cancer.[21,22] The results indicated that NOACs (edoxaban and rivaroxaban) lower the rate of recurrent VTE at the expense of more GIB, with cumulative rate of 3.9% for NOACs and 1.4% for dalteparin (RR, 2.77; 95% CI, 1.35–5.68), which also was seen in one RWS (aHR, 1.93; 95% CI, 1.07–3.19). Hence, limited data suggest cautious use of NOACs in cancer patients. In addition, an increased risk for major GIB was found in patients with acute medical illnesses (RR, 2.44; 95% CI, 1.31–4.57), whereas similar risk was not detected for patients with AF and percutaneous coronary intervention or with stable carotid artery disease/peripheral artery disease. Because of the limited number of studies, more RCTs and RWSs are warranted to validate the latter association.

The major strength of this study was to reassess the risk for major GIB of NOACs by comparing the results between RCTs and high-quality RWSs. Certainly there are inherent limitations in this meta-analysis. First, 72 studies were excluded from the pooled analyses because of unavailable data, which might reduce the statistical power. Second, all indications of NOAC were comprised in our study, and then the generalizability of findings was inevitably limited because of the difference in important characteristics among each indication. Also, the presence of residual confounding in RWSs might partly explain the considerable heterogeneity between RWSs. To account for these issues, we have conducted the subgroup analysis for indications and meta-regression for confounding. No significant increased risk for major GIB was found in both AF and VTE populations. Third, a limited number of studies with subgroup analyses on cancer patients and medically ill patients could not draw robust conclusions on this topic, and we did not obtain patient-level data to conduct better powered subgroup analyses. Fourth, all included trials reported major GIB events according to the International Society on Thrombosis and Hemostasis criteria; however, it is not possible to evaluate whether small variations may have an impact on results obtained. Finally, we did not have the resources to review non-English articles. However, we included studies identified in a comprehensive search of broad databases and are confident that this study covered the majority of high-quality studies.

In conclusion, the results from RCTs and RWSs confirm the similar risk for major GIB between patients receiving NOACs compared with conventional regimen. However, rivaroxaban, especially its standard dose, did confer a higher risk for major GIB. These results might be used to select oral anticoagulant treatment based on risk for major GIB.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.05.056.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

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Supplementary Methods

Study Selection

To focus on the highest-quality RWSs, we only included nationwide or health insurance database studies that reported adjusted or matched major GIB results by using authorized method to minimize confounding (propensity score adjustment, propensity score matching, inverse probability of treatment weighting, and covariate adjustment).[1] When several RWSs used the same data source from an overlapping period, such as the Danish health insurance data set from 2011 to 2014 (Danish Civil Registration system, National Patient Register, and National Prescription Registry), we only included the one that reported adjusted GIB data with the longest study period. Studies that reported only crude results or published only in conference abstract or letter form were excluded. Three reviewers (Z. G., A. W., C. Z.) independently assessed all study titles and abstracts for determining eligibility, and then full articles were retrieved and assessed according to inclusion criteria, with any disagreements being resolved by corresponding authors (J. P., H. L.).

Study Outcomes

The primary outcome was major GIB, defined as a decrease in hemoglobin level of 2 g/dL or greater within a 24-hour period, or leading to a transfusion of 2 or more units of packed red cells, or requiring an additional endoscopy intervention, according to the International Society on Thrombosis and Hemostasis criteria for RCTs and International Classification of Disease revision 9 or 10 codes of major GIB for RWSs.[2] The secondary outcomes were upper and lower major GIB, with the same definition as the primary outcome.[2]

Quality Evaluation of Real-World Studies

Low, moderate, or high risk of bias was assigned to each citation within the following items: (1) use of authorized adjustment method to deal with selection bias, (2) potential for residual confounding, (3) use of methods to handle time-varying covariates and information censoring, and (4) reporting baseline characteristics and outcome measures in detail.[3]

Data Analysis

In brief, we performed data analyses for RCTs and RWSs separately and then used interaction analysis to assess the comparability between RCTs and RWSs. Statistical heterogeneity was assessed with I^2 test, with a value >50% representing considerable heterogeneity.[4] For RCTs, we used forest plots to measure the primary and secondary outcomes, and RRs and associated 95% CIs were calculated by using random-effects models. We then conducted subgroup analyses according to indications (AF, VTE, and other special clinical scenarios), controls (VKAs, LMWH, and aspirin), dosage (standard dose and low dose), and follow-up duration (<3 months, 3–12 months, and >12 months). For RWSs, we pooled aHRs and their 95% CIs by using random-effects models and performed subsequent subgroup analyses according to indications (AF, VTE, and other special clinical scenarios), controls (VKAs and antiplatelet agents), dosage (standard dose and low dose), gender (men and women), age (elderly patients, <75 years, and >75 years), VKA switchers, and population (United States, Canada, Europe, Taiwan, and New Zealand). We also conducted further analysis by excluding trials with antiplatelet agents as control and trials that are outside of the approved indications and therapeutic doses, as well as based on individual NOACs (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) and their corresponding daily dose, for RCTs as well as for RWSs. To test the robustness of the primary results, we conducted a series of sensitivity analyses by sequential elimination of each study from the pool or excluding studies that involved special clinical scenarios (cancer, acutely ill medical patients, AF, and percutaneous coronary intervention for RCTs; cancer, AF, and dialysis for RWSs). Because potential effect modifiers (patient demographics, bleeding risk factors, concomitant drugs, among others) may lead to bias on primacy outcome, we performed a meta-regression analysis to explore the influence of these factors on risk for major GIB. Publication bias was evaluated by visual funnel plots as well as quantitative Begg's test and Egger's test.[5] Statistics were performed using STATA software (version 13; StataCorp, College Station, TX), and $P < .05$ indicated a statistically significant difference.

Study Evaluation

Follow-up duration in RCTs ranged from 30 days to 2.8 years, with shorter period for VTE prophylaxis studies (hip/knee operation and acutely ill medical patients) and AF cardioversion studies and a longer period for AF studies (Supplementary Table 3). The mean age of patients in RCTs ranged from 54.7 to 76.4 years, and the percent of women ranged widely from 17.8 to 72.0 (Supplementary Table 4). Forty-one RWSs were conducted in 10 countries or regions, with half of the studies in the United States (n = 21). All RWSs reported the adjustment method in detail; 20 studies used propensity score matching, 8 used inverse probability of treatment weighting, 7 applied propensity score adjustment, and 6 used covariate adjustment (Supplementary Table 5). The mean CHA_2DS_2-VASc score in RWSs ranged from 2.1 to 5.3 and HAS-BLED score from 1.6 to 3.7. Other patients and clinical characteristics are outlined in Supplementary Table 6. The information on bleeding

history and concomitant drugs used in RWSs is summarized in Supplementary Table 7. The included RCTs satisfied all bias tool items except for 14 trials (RE-LY, Weitz 2010, EINSTEIN-DVT, Chung 2011, EINSTEIN-PE, X-VeRT, J-EINSTEIN, PIONEER AF-PCI, RE-DUAL PCI, ENSURE-AF, Hokusai VTE Cancer, SELECT-D, RE-CIRCUIT, and EMANATE), which were not blinded (Supplementary Table 8). No high-risk bias tool items were detected in RWSs (Supplementary Table 9). Thus, the included studies were of modest to high quality. We did not observe potential publication bias by qualitative funnel plots as well as Begg's test and Egger's test (Supplementary Figures 1 and 2).

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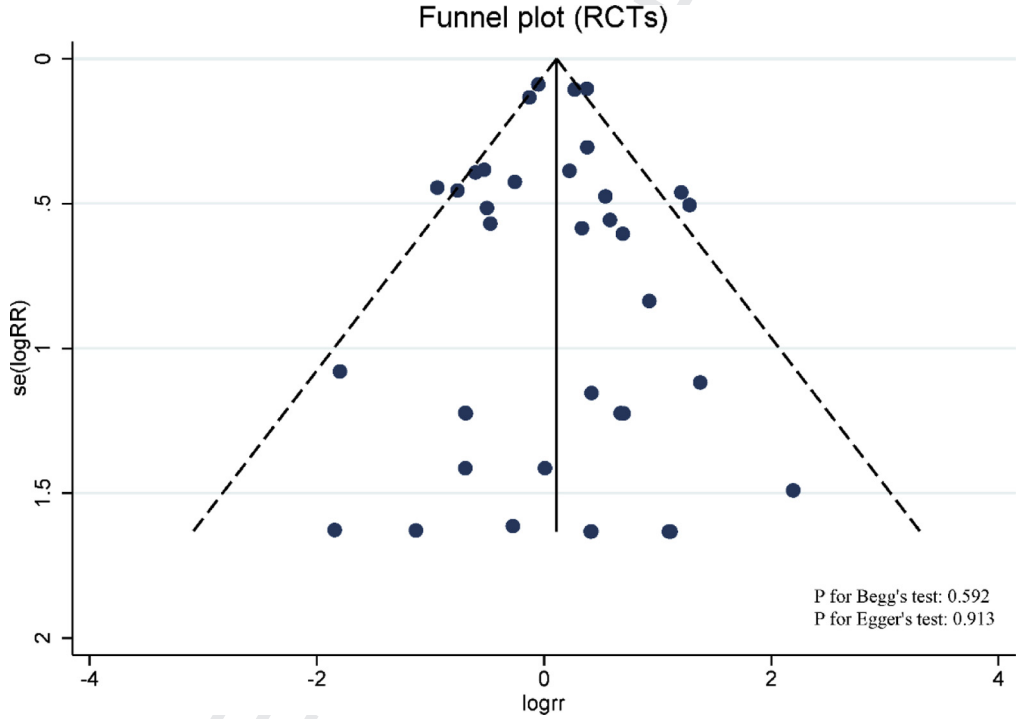

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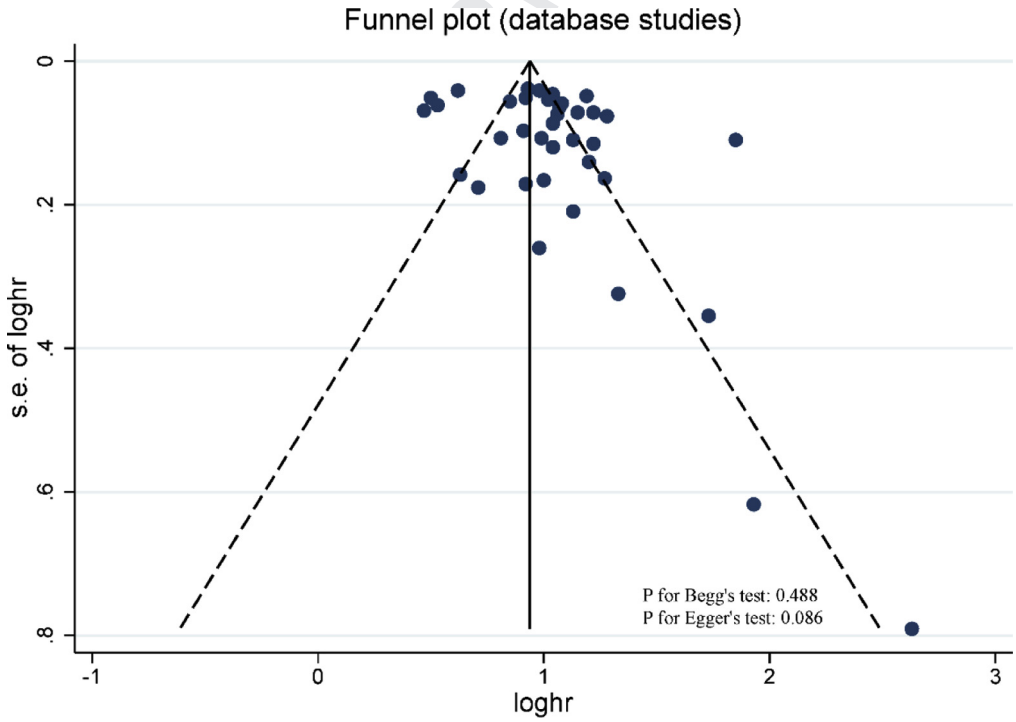
Supplementary Figure 1. Funnel plot of randomized controlled trials (RCTs).



Supplementary Figure 2. Funnel plot of real-world studies. loghr, ■■■.

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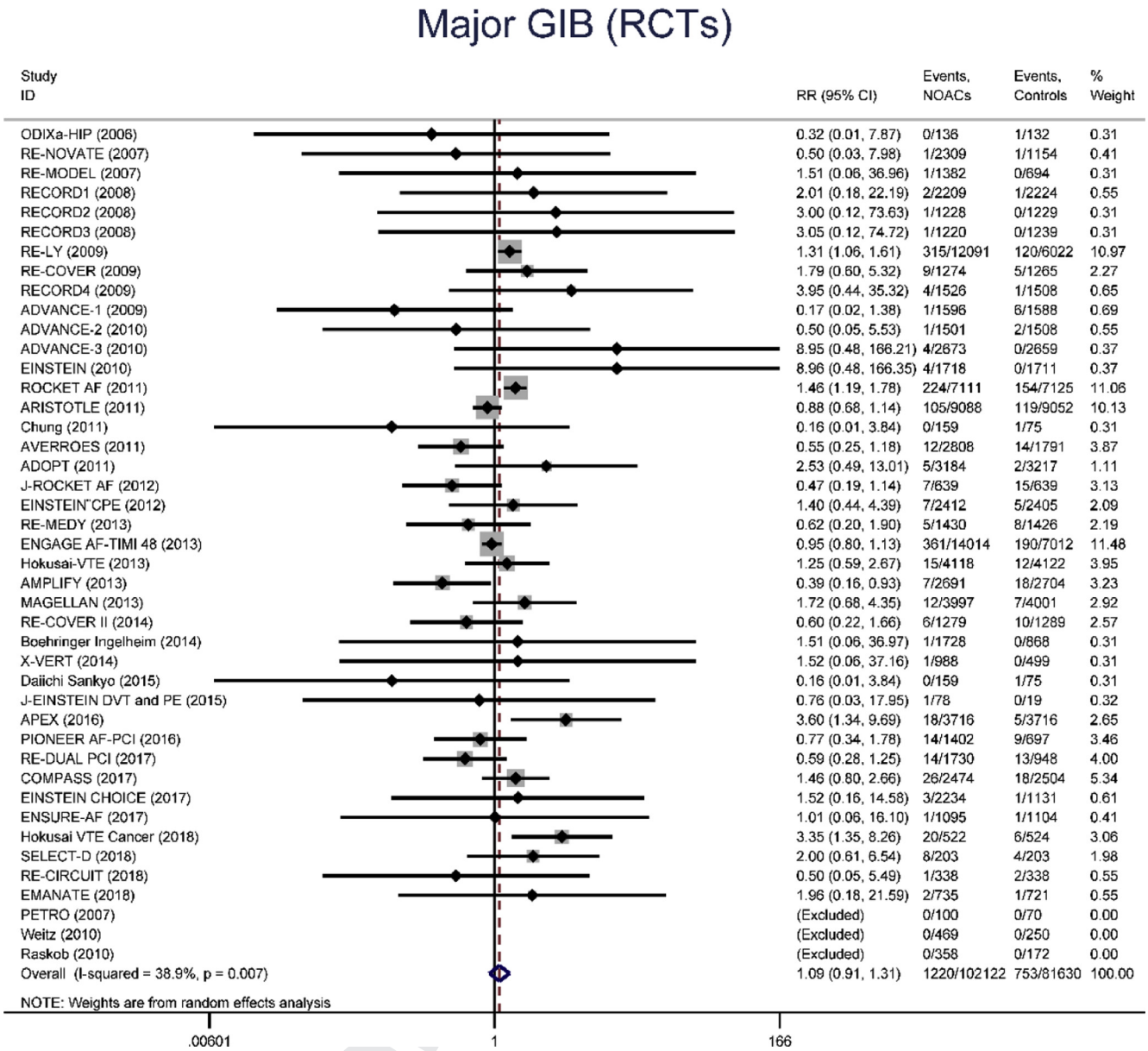
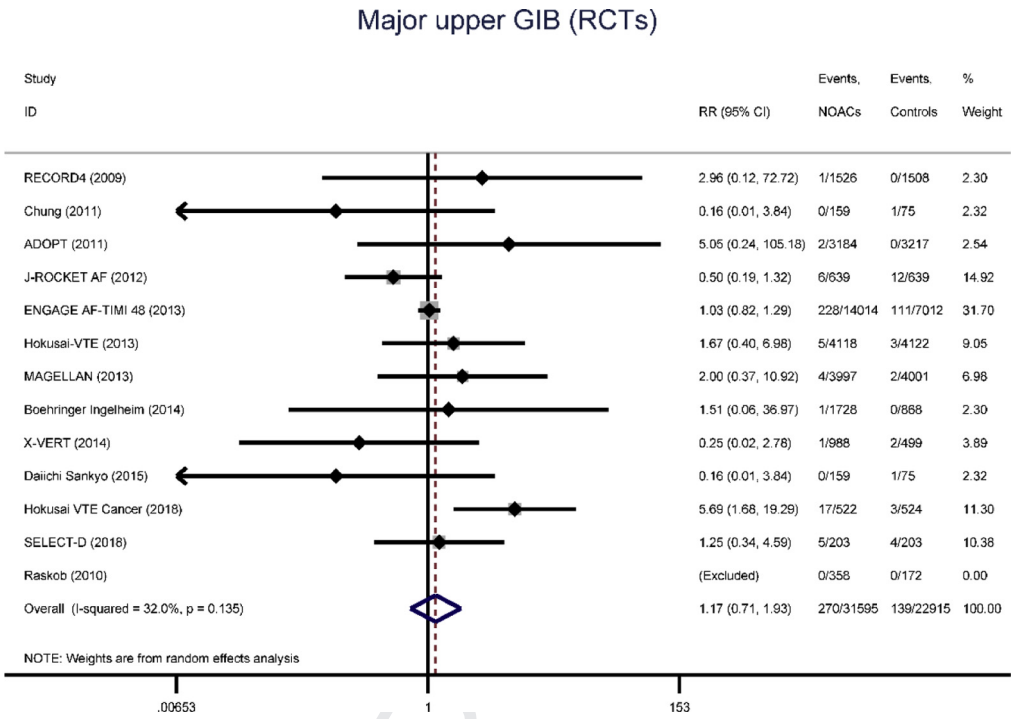
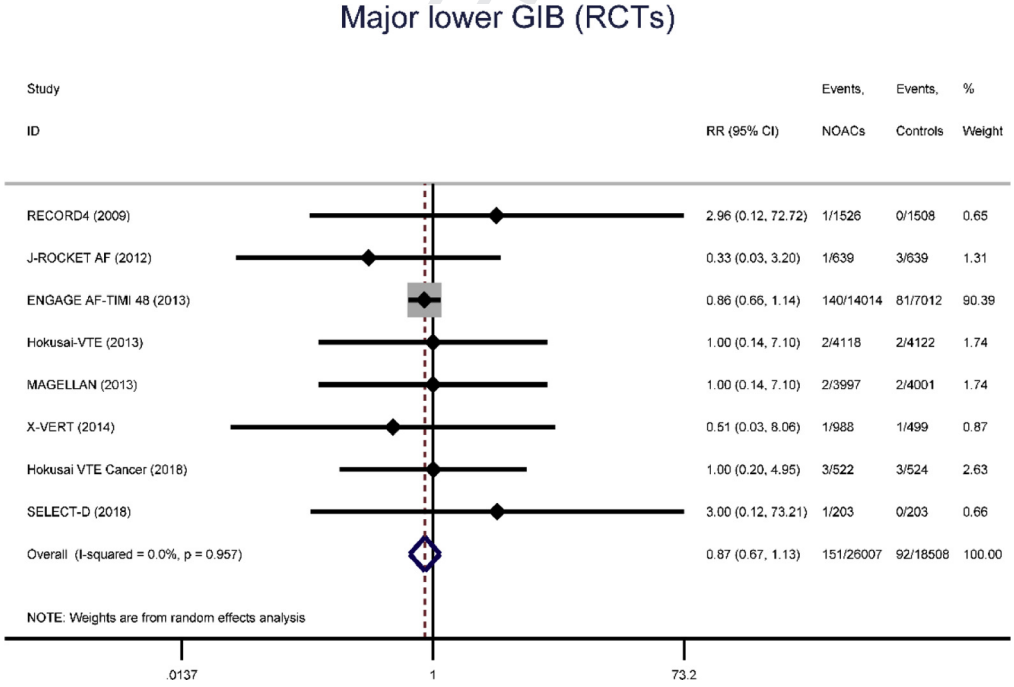


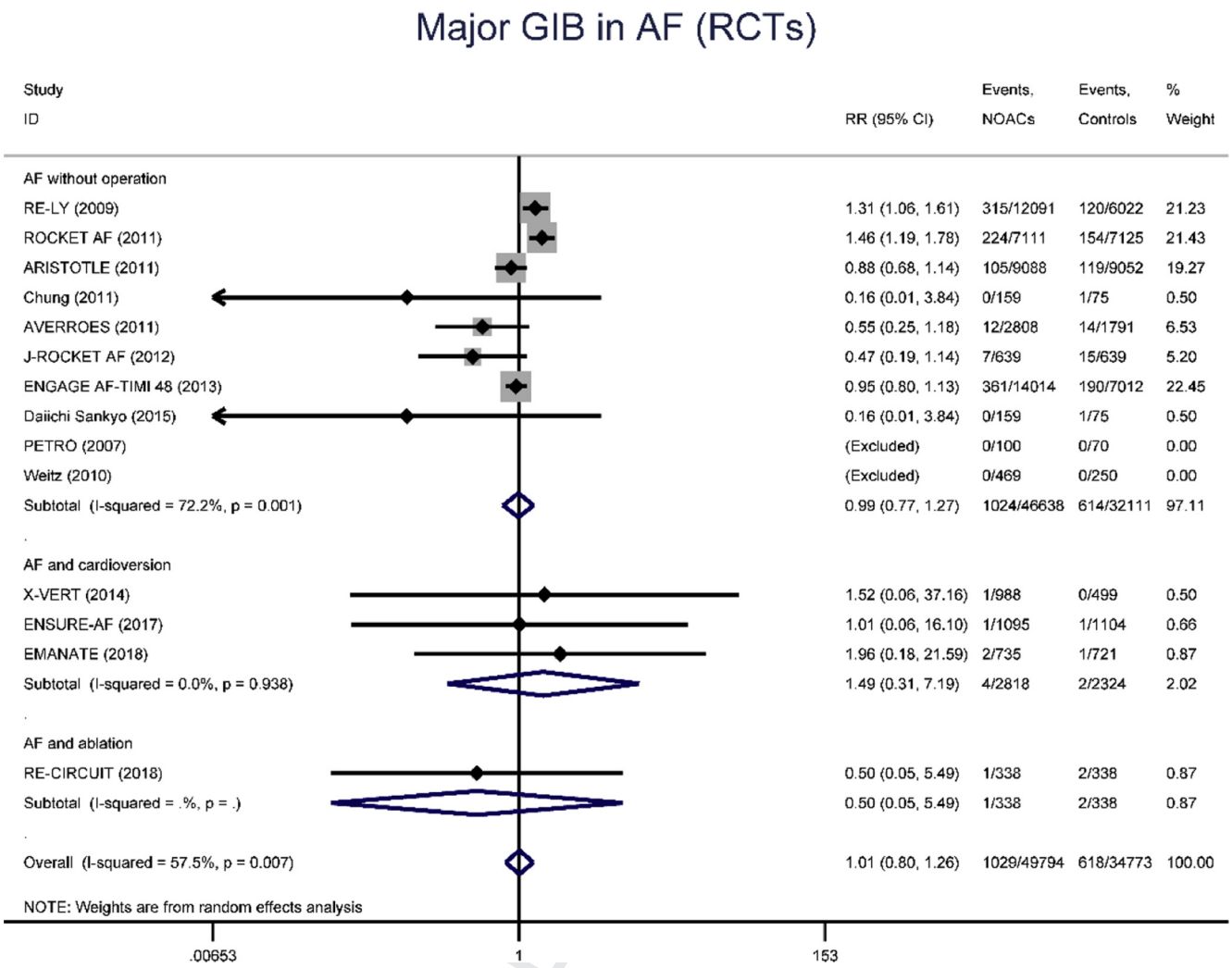
Supplementary Figure 3. Major GIB of RCTs. CI, confidence interval; GIB, gastrointestinal bleeding; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk.



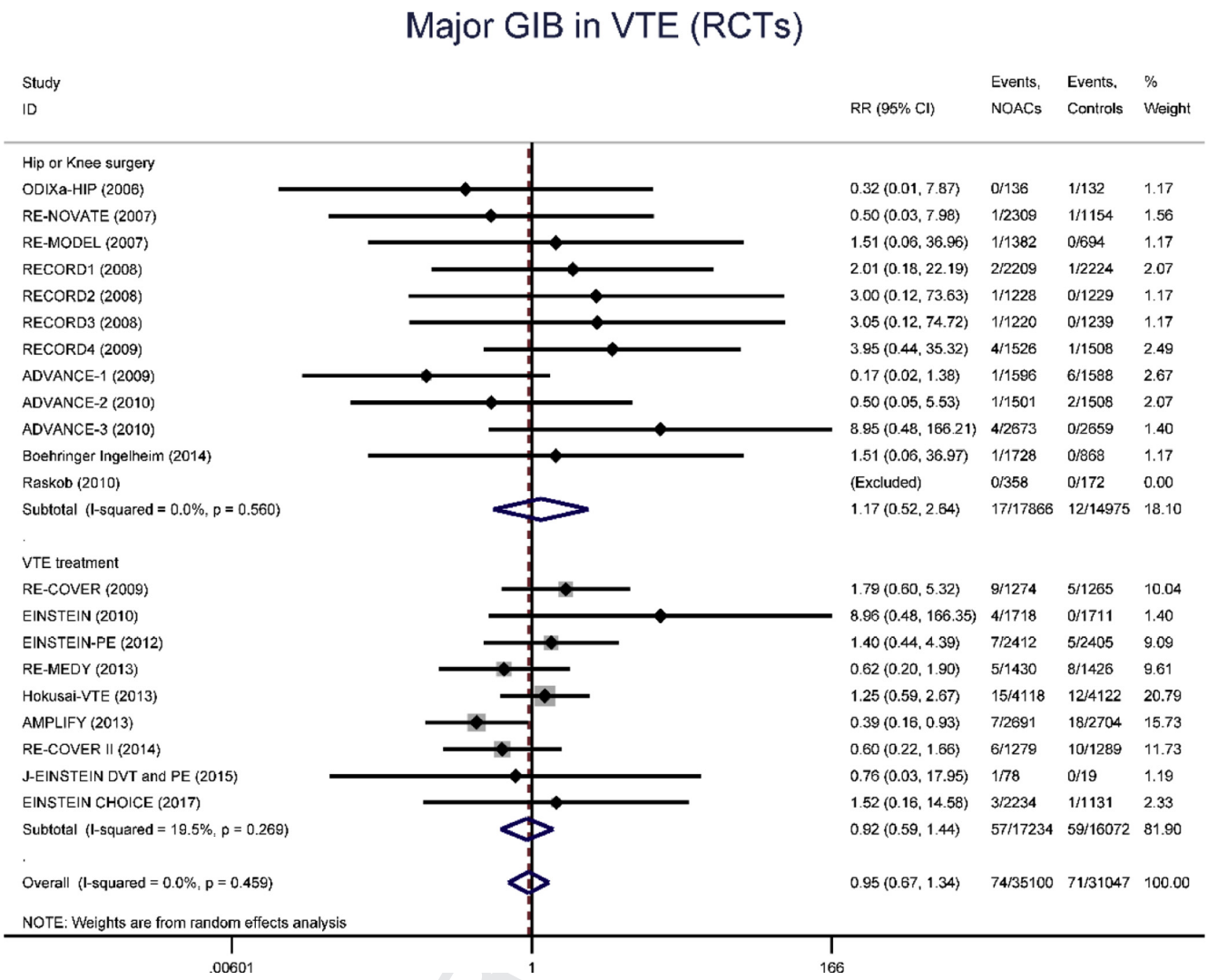
Supplementary Figure 4. Major upper GIB of RCTs. CI, confidence interval; GIB, gastrointestinal bleeding; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk.



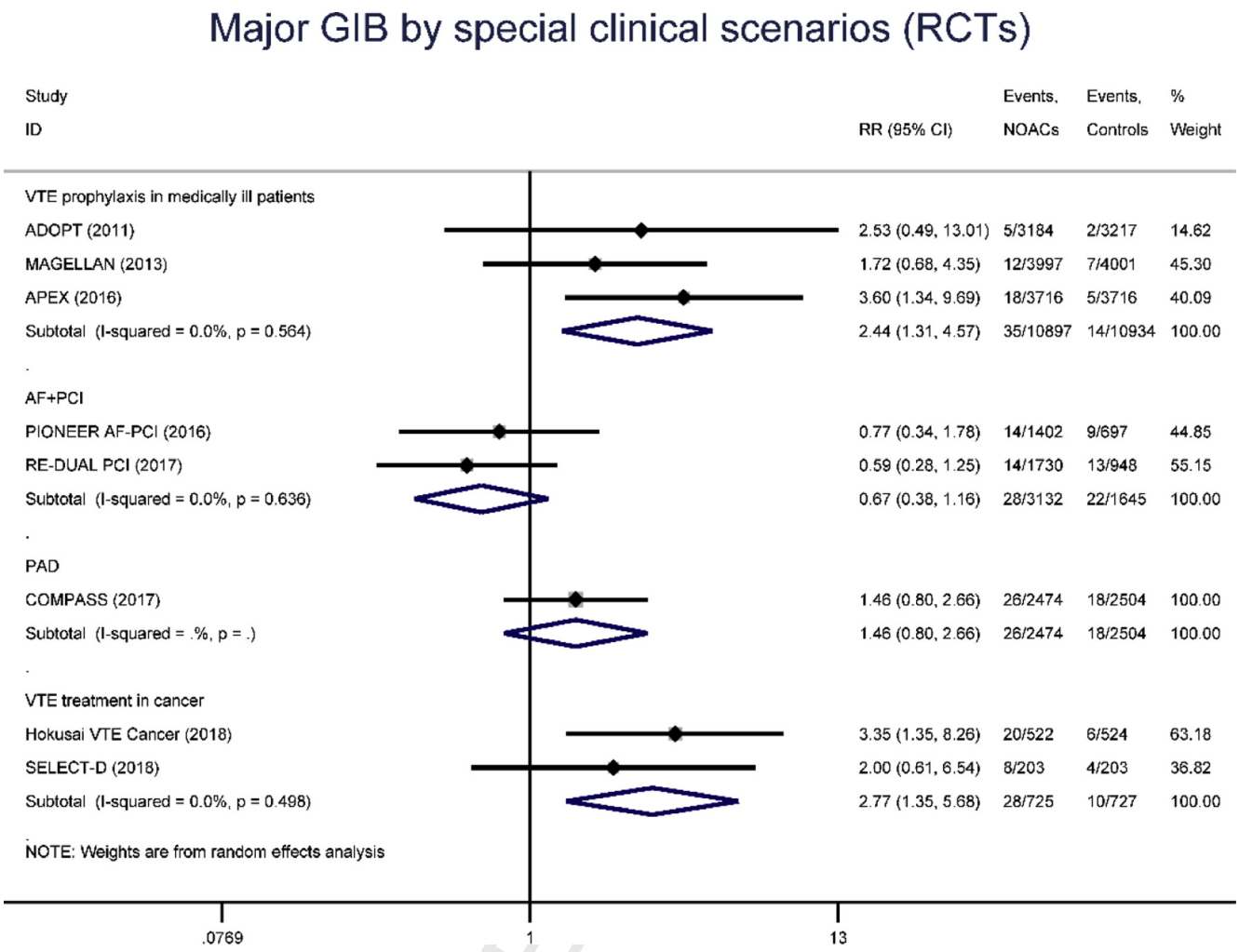
Supplementary Figure 5. Major lower GIB of RCTs. CI, confidence interval; GIB, gastrointestinal bleeding; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk.



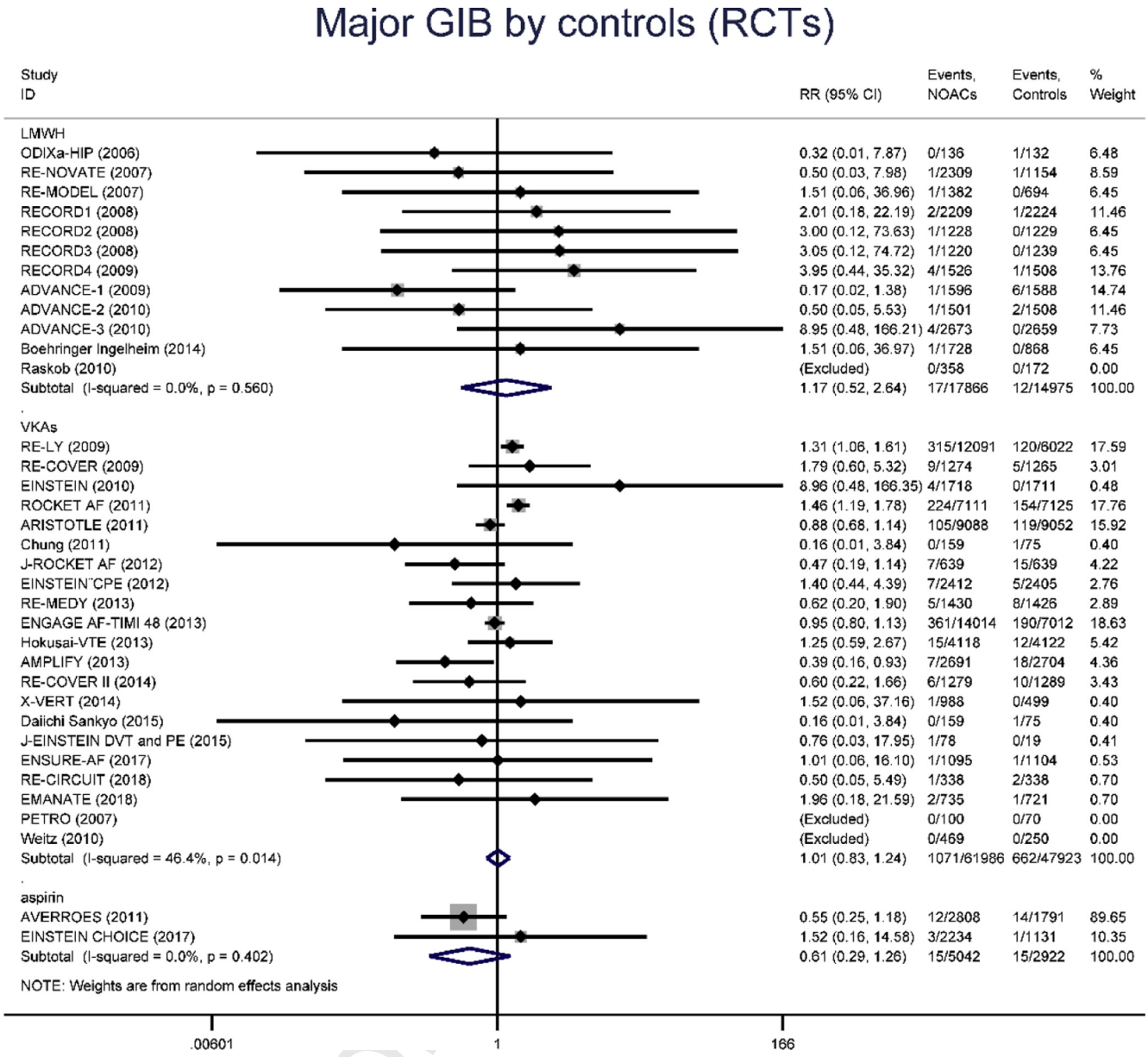
Supplementary Figure 6. Major GIB in AF (RCTs). AF, atrial fibrillation; CI, confidence interval; GIB, gastrointestinal bleeding; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk.



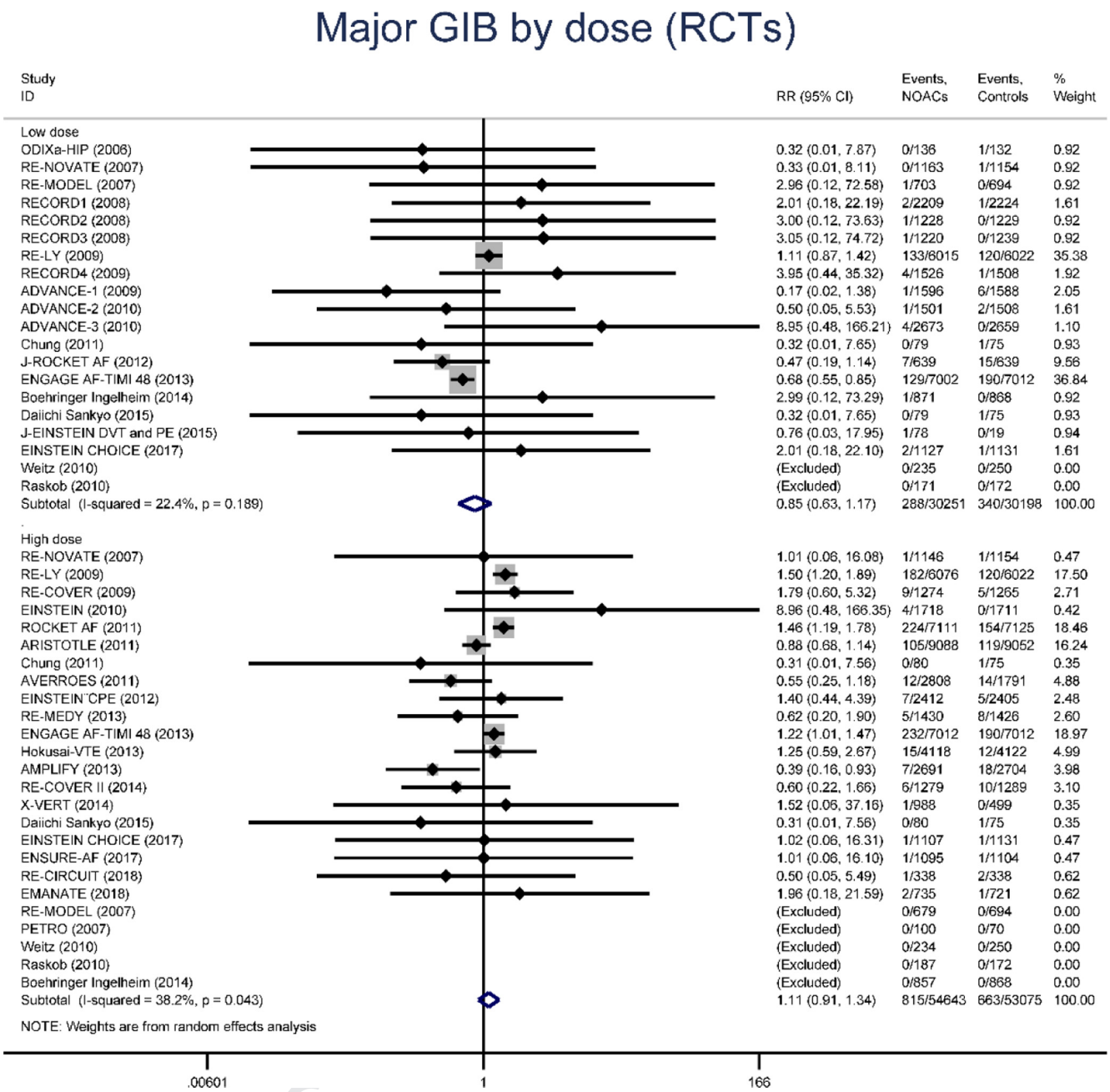
Supplementary Figure 7. Major GIB in VTE (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk; VTE, venous thromboembolism.



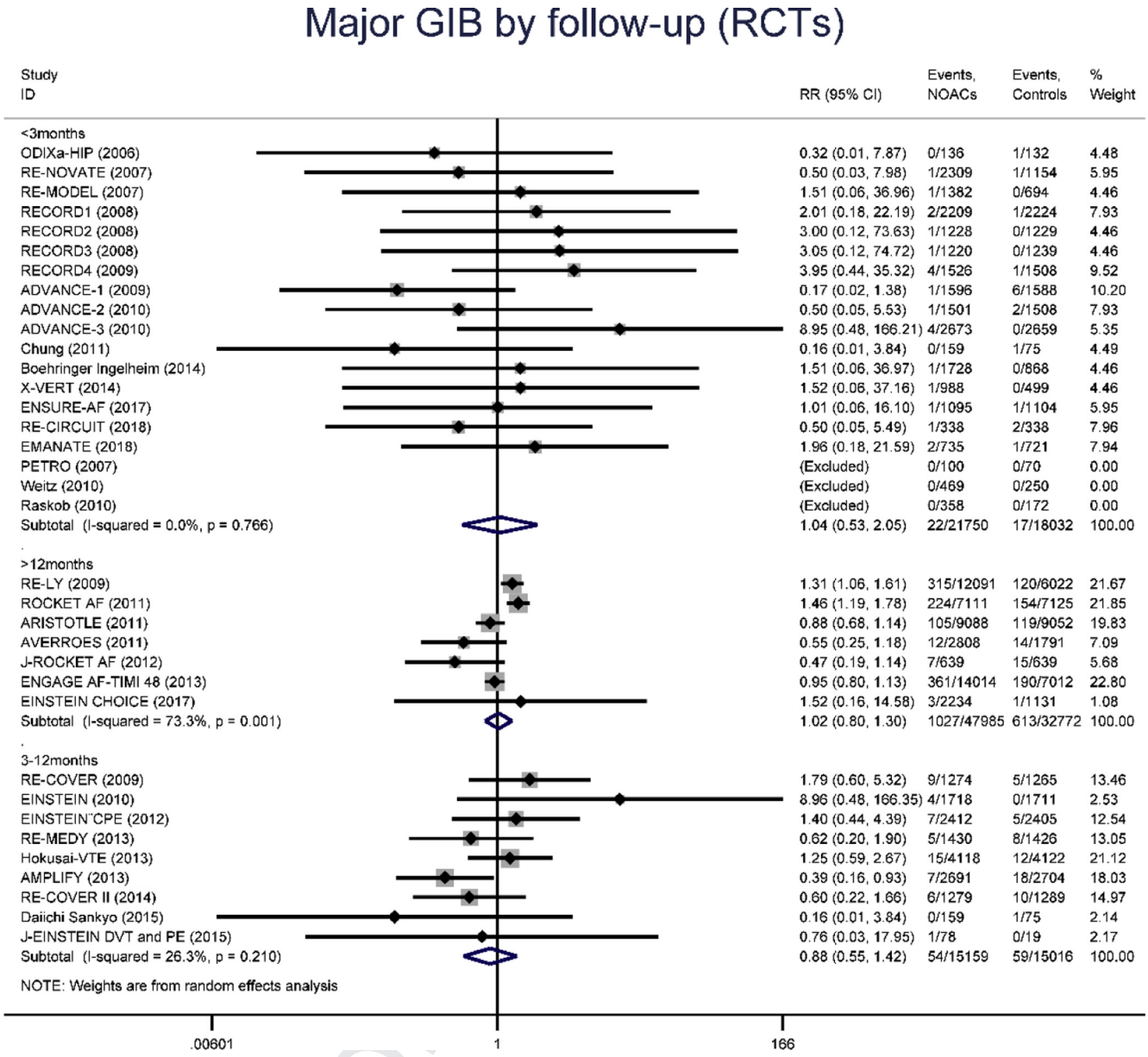
Supplementary Figure 8. Major GIB in special clinical scenarios (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk; VTE, venous thromboembolism.



Supplementary Figure 9. Major GIB by controls (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; LMWH, low-molecular-weight heparin; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk.



Supplementary Figure 10. Major GIB by dose (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk.



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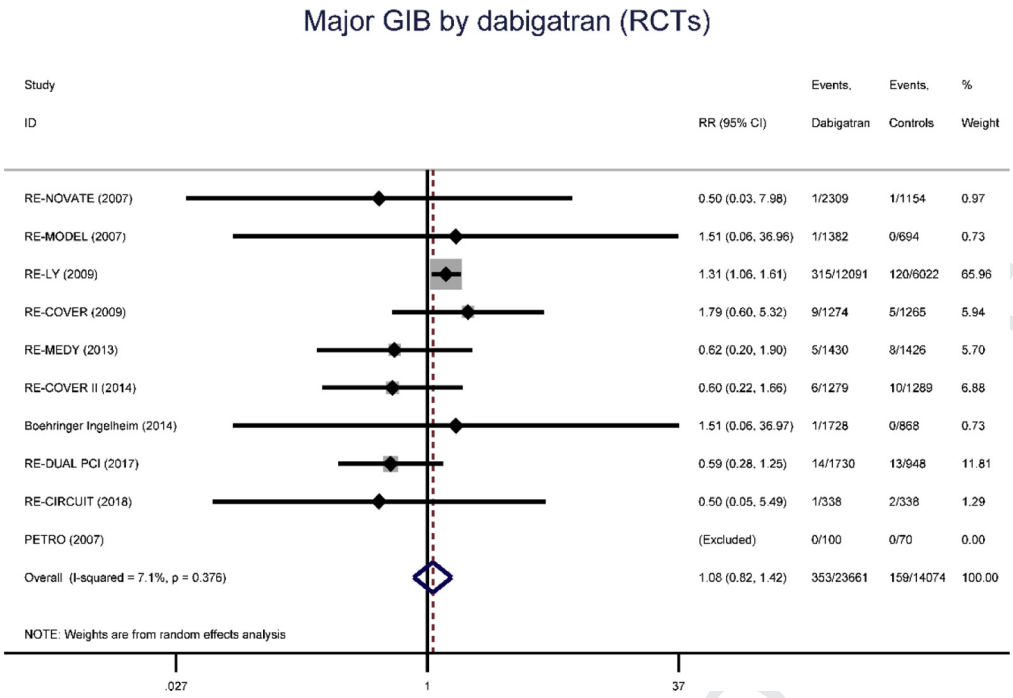
Supplementary Figure 11. Major GIB by follow-up (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk.



Supplementary Figure 12. Major GIB in dabigatran (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.

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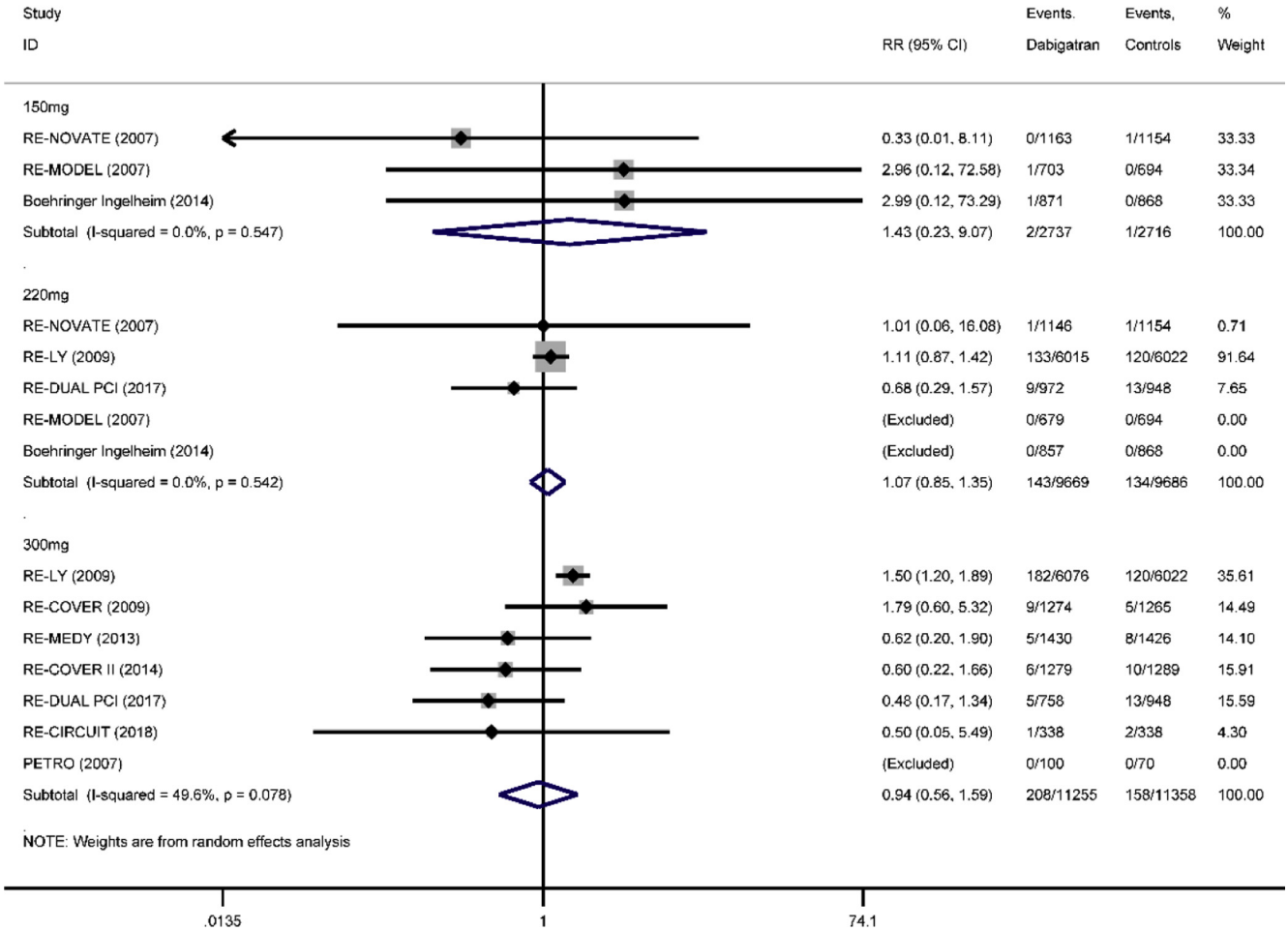

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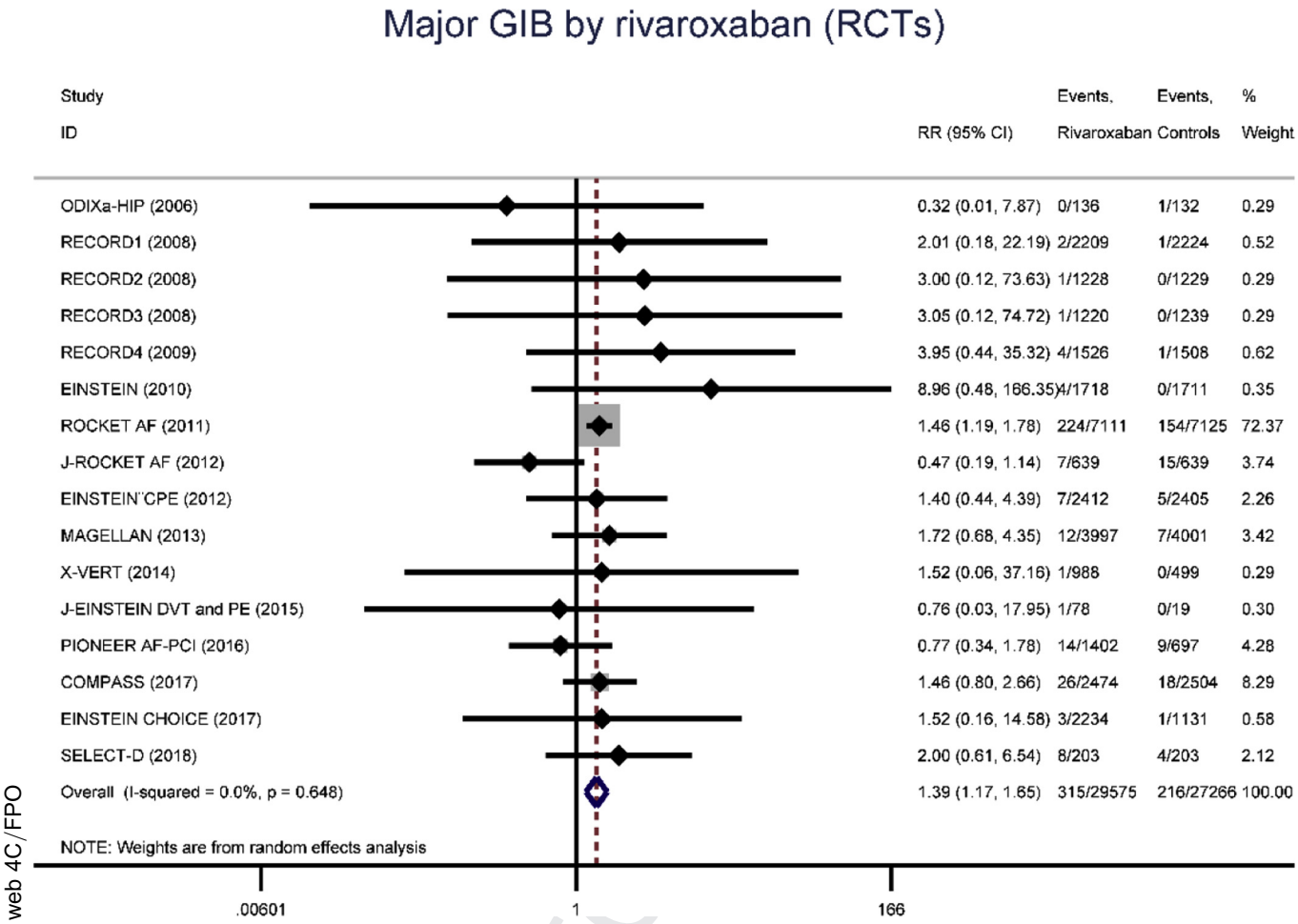
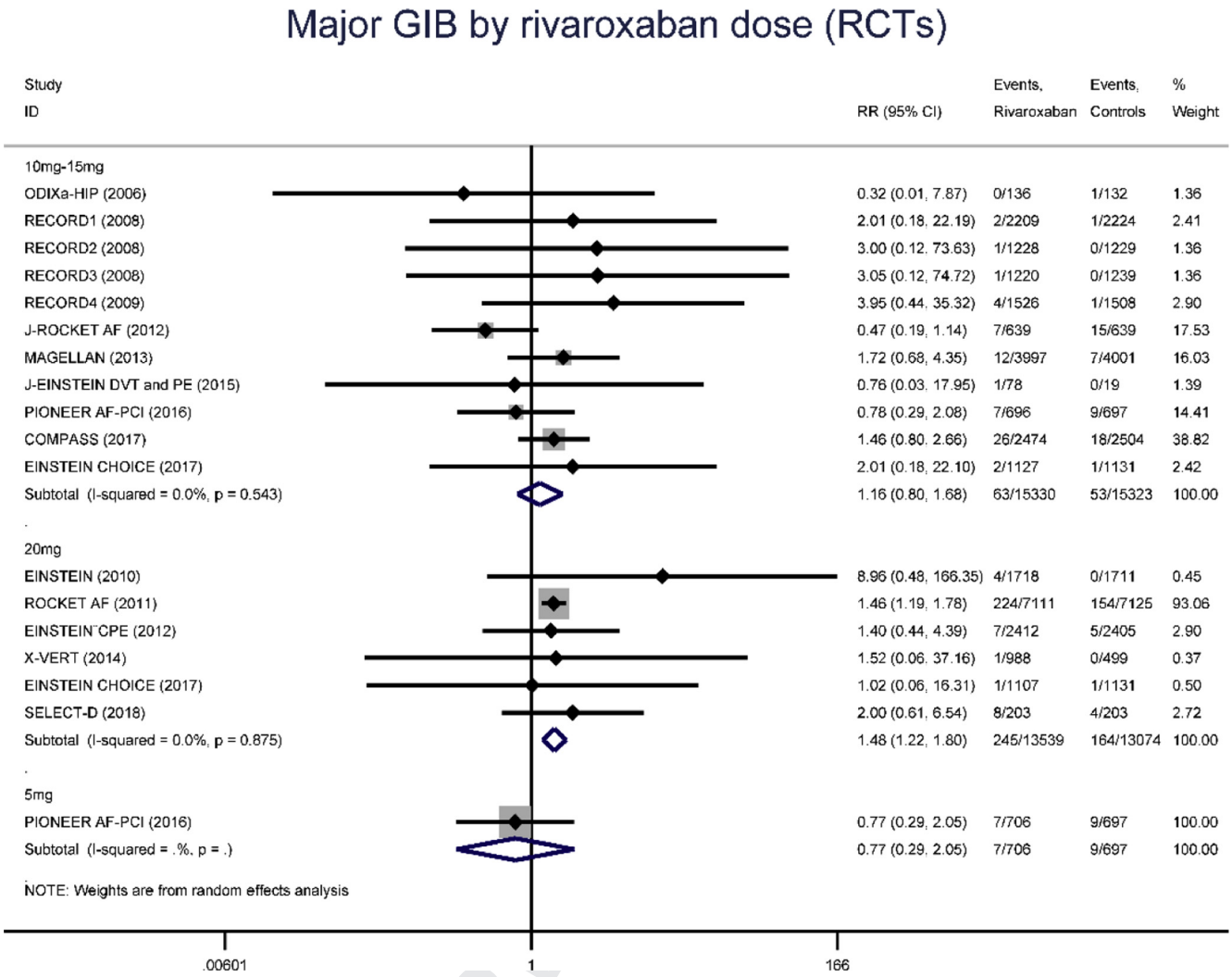
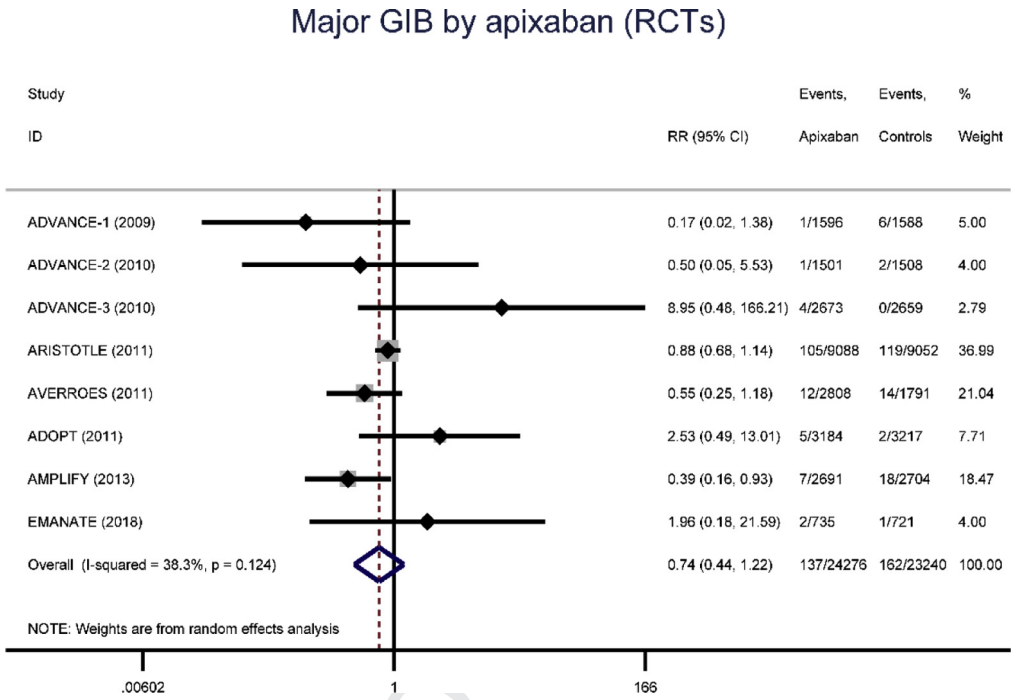
Supplementary Figure 13. Major GIB by dabigatran dose (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.



Supplementary Figure 14. Major GIB in rivaroxaban (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.



Supplementary Figure 15. Major GIB by rivaroxaban dose (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.



Supplementary Figure 16. Major GIB in apixaban (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.

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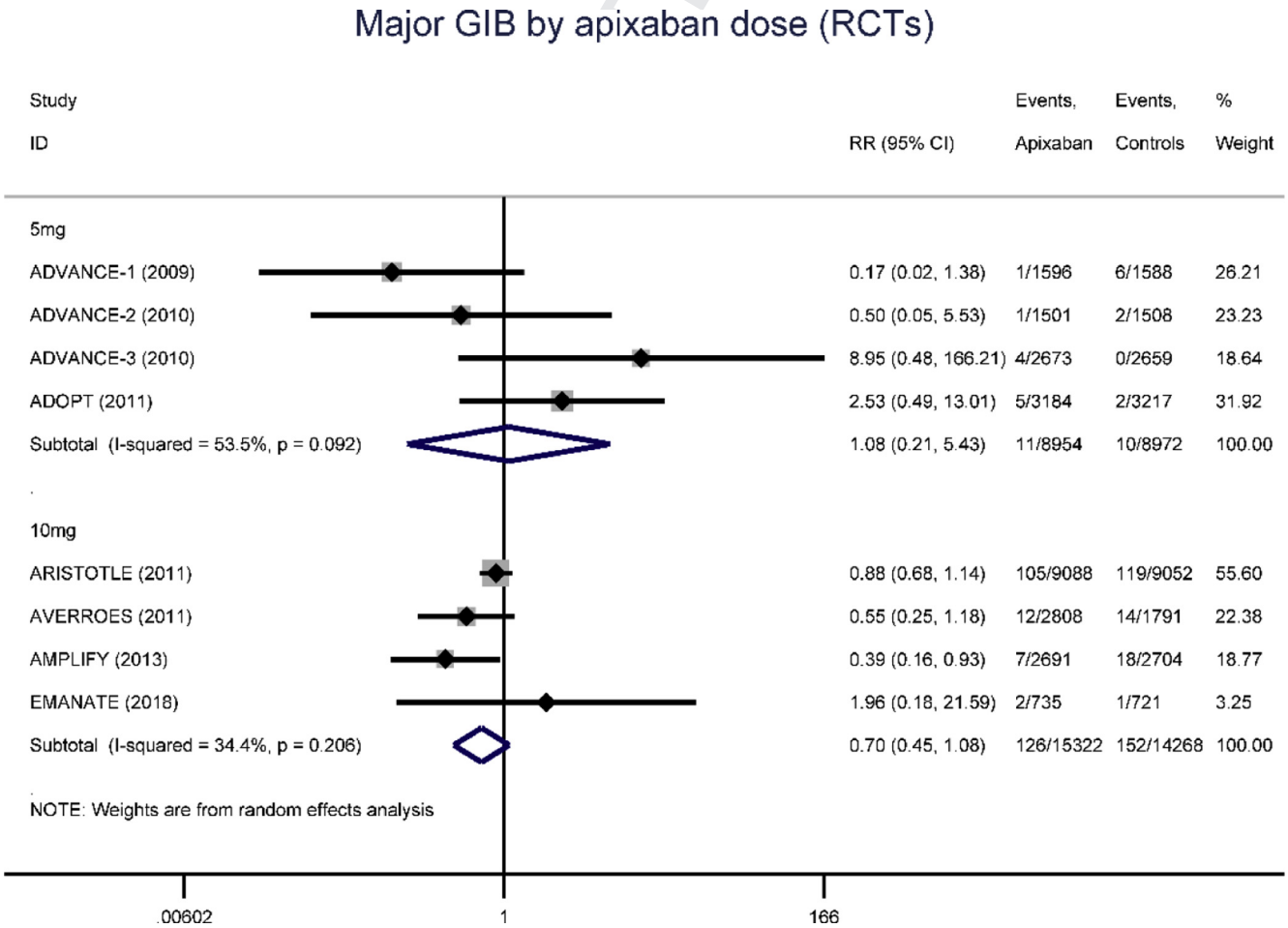

Supplementary Figure 17. Major GIB by apixaban dose (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.

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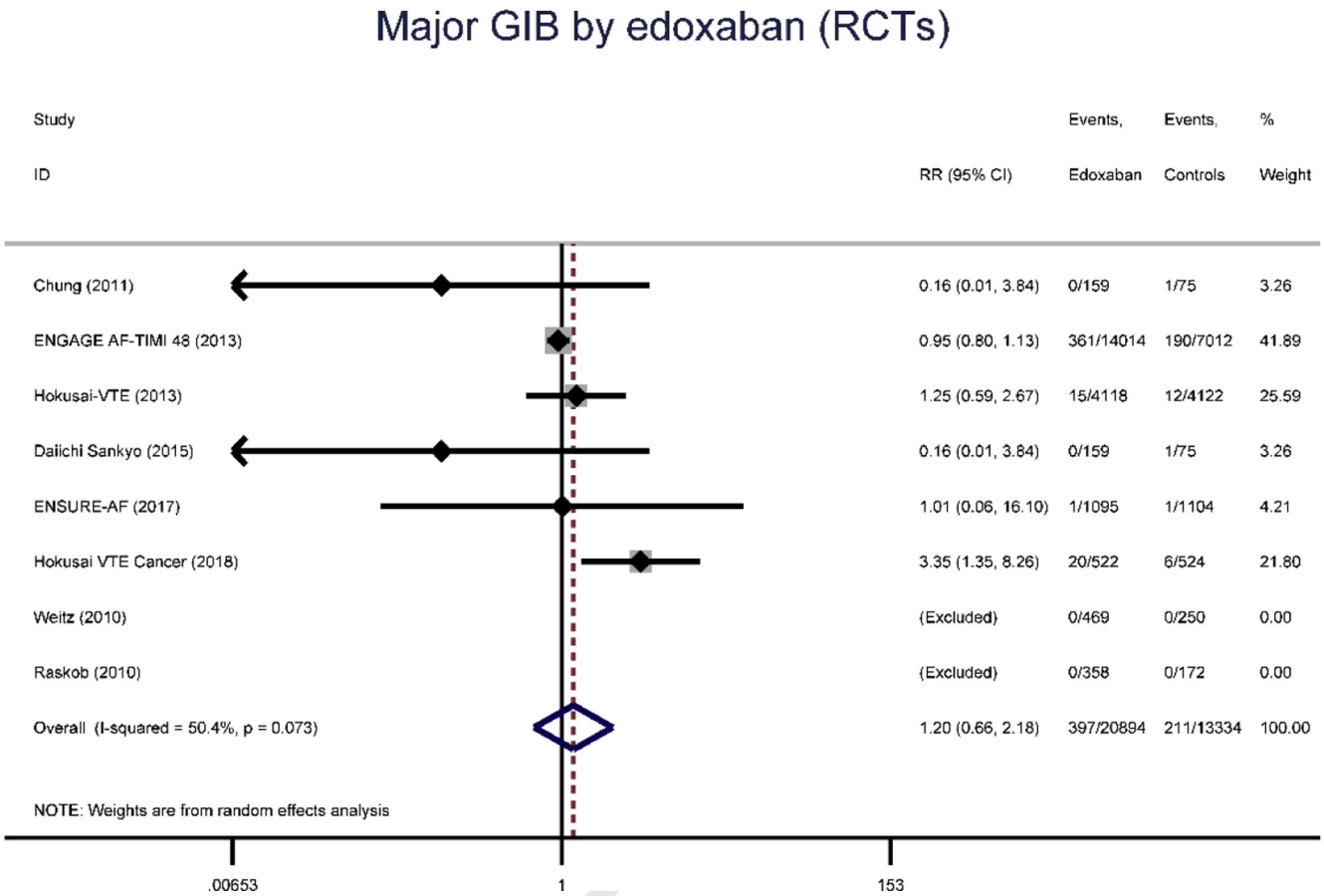
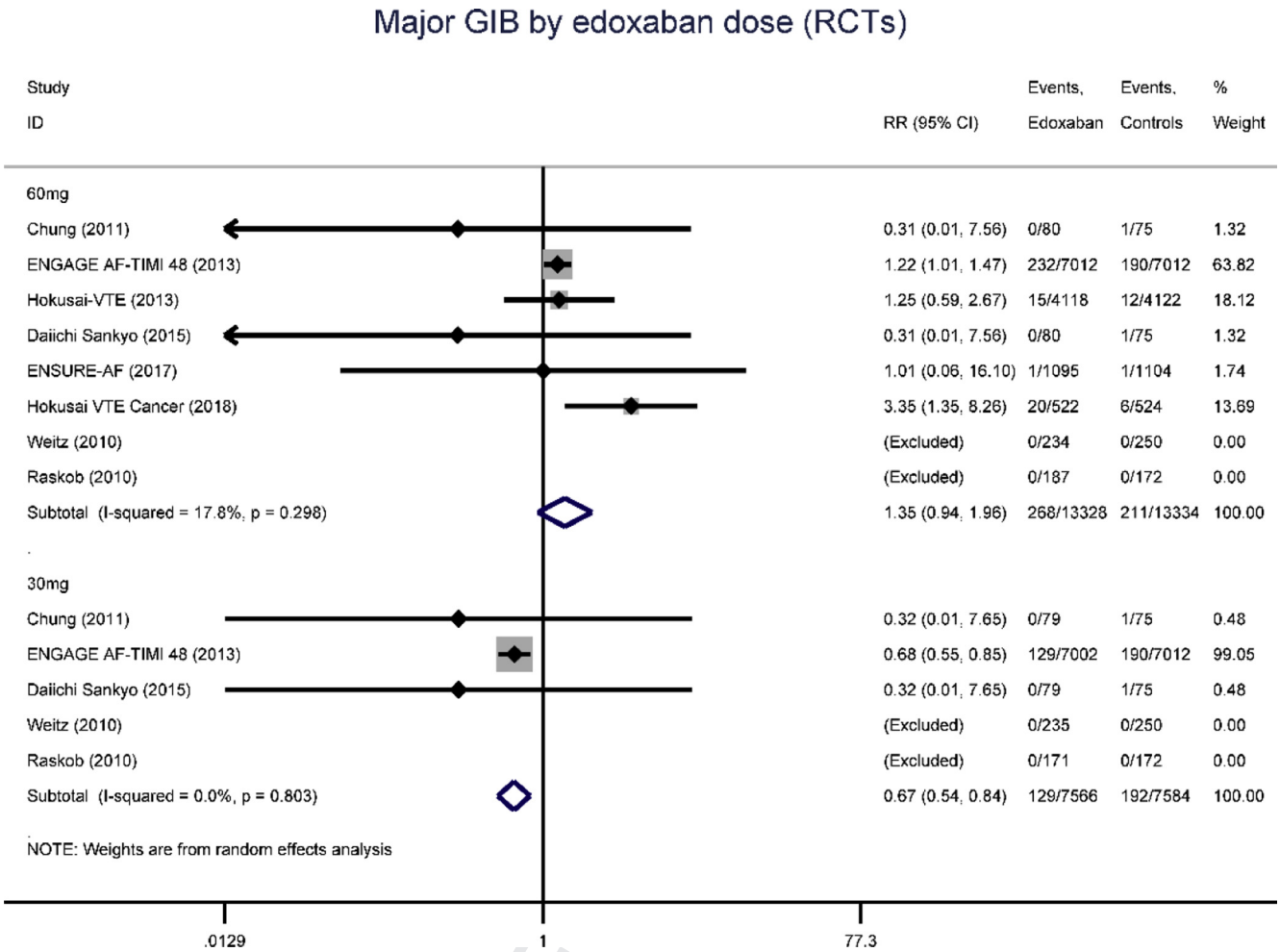
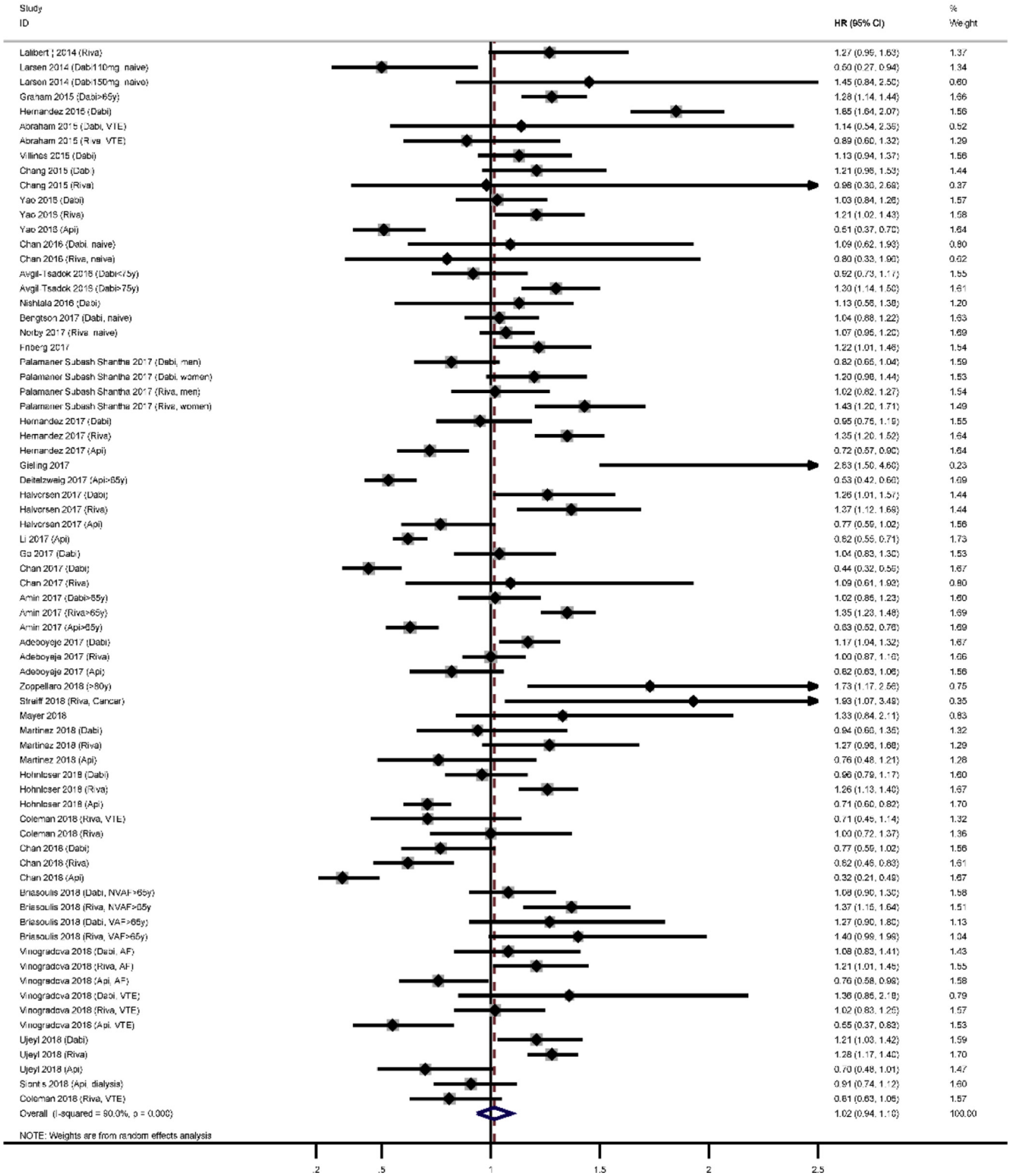


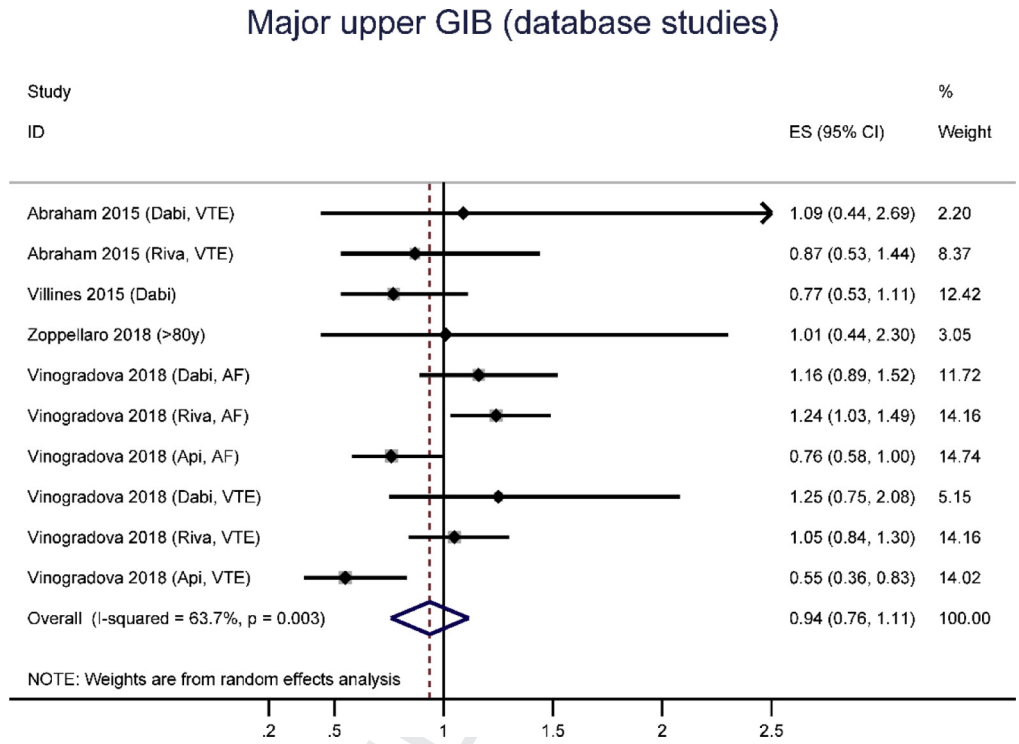
Supplementary Figure 18. Major GIB in edoxaban (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.



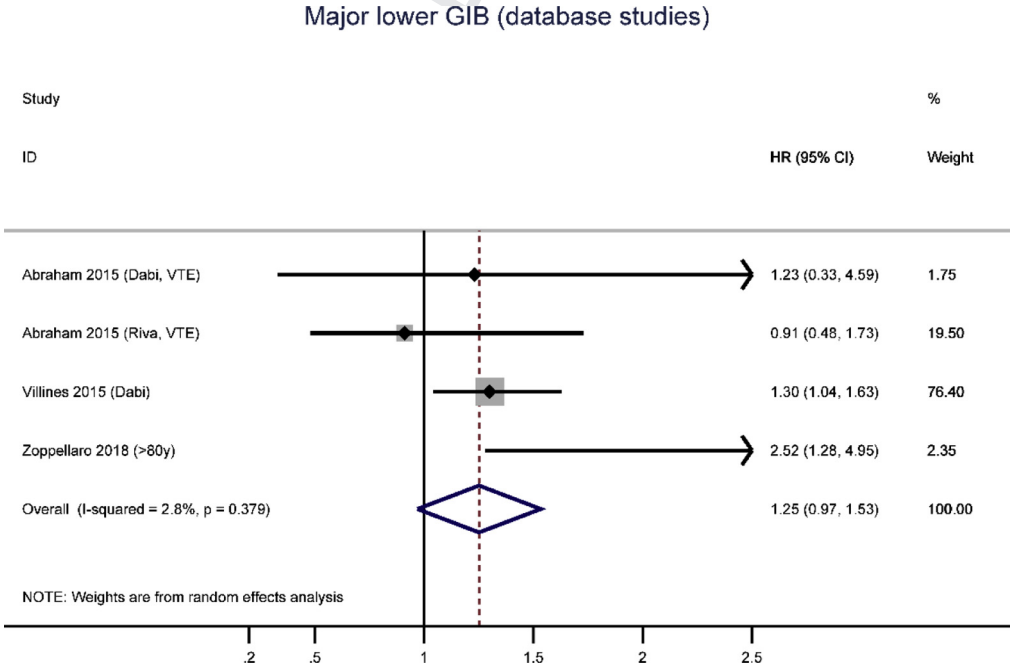
Supplementary Figure 19. Major GIB by edoxaban dose (RCTs). CI, confidence interval; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.



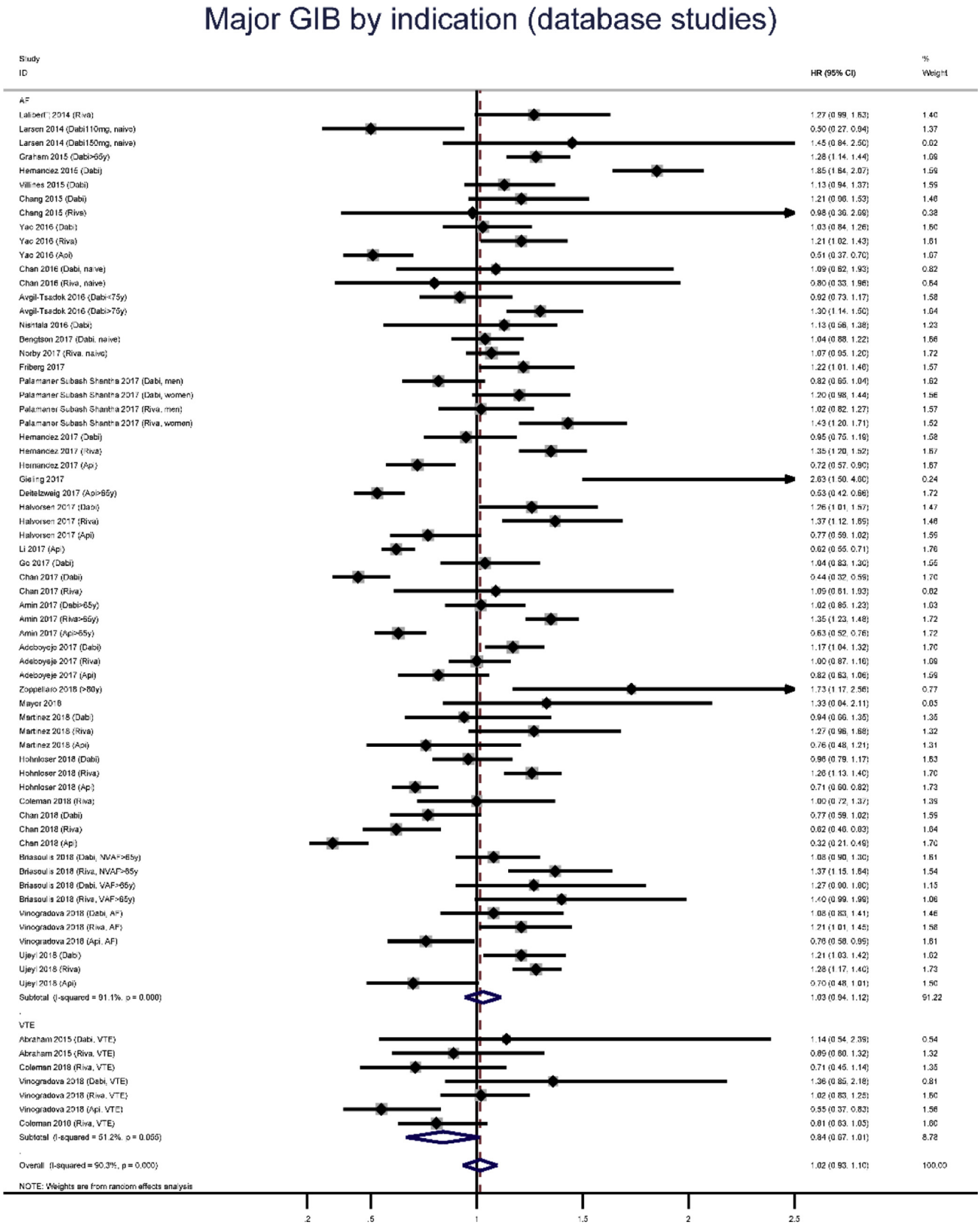
Supplementary Figure 20. Major GIB of real-world studies. Api, apixaban; CI, confidence interval; Dabi, dabigatran; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; Riva, rivaroxaban; RR, relative risk; VTE, venous thromboembolism.



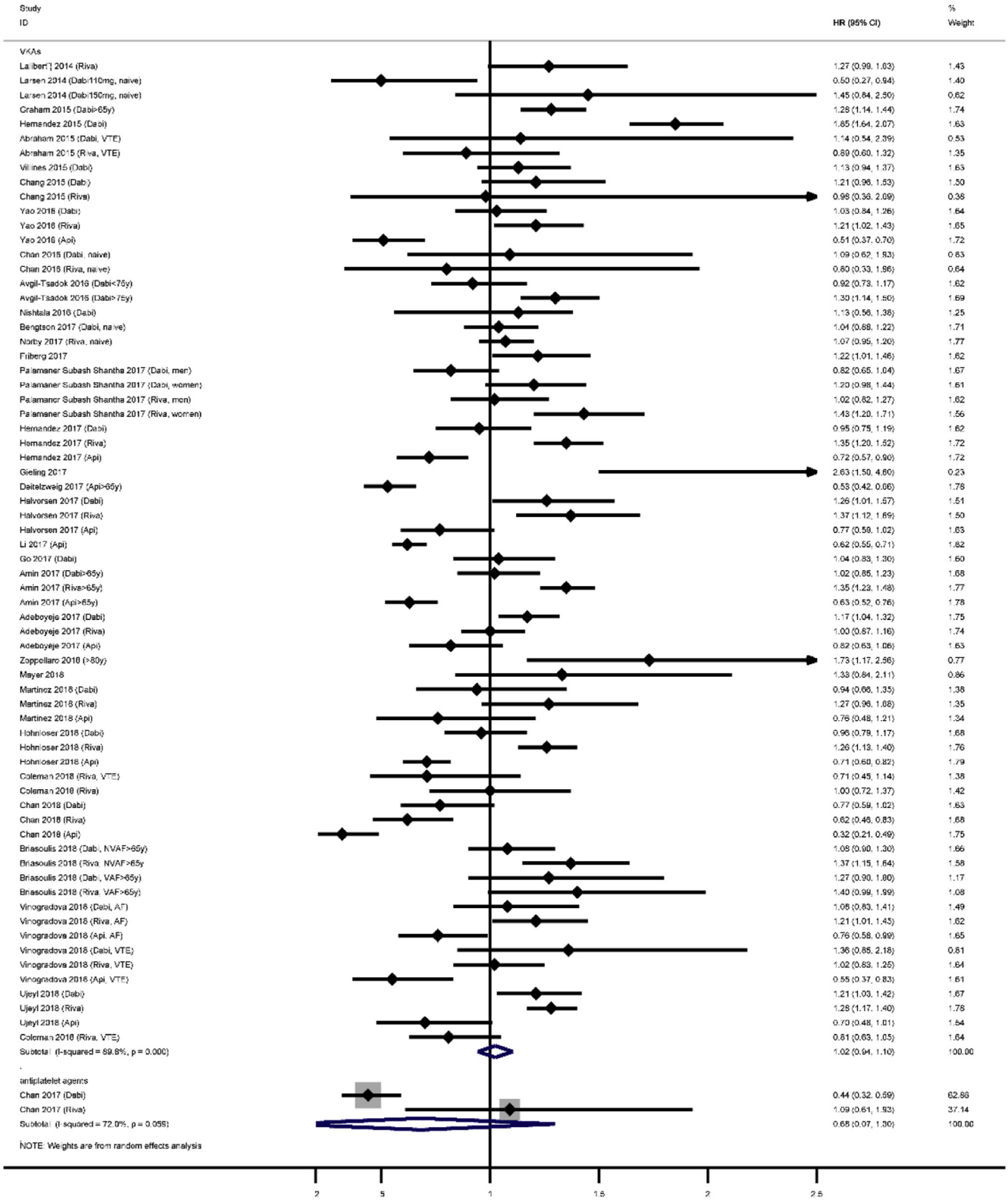
Supplementary Figure 21. Major upper GIB of real-world studies. AF, atrial fibrillation; Api, apixaban; CI, confidence interval; Dabi, dabigatran; ES, ■■■; GIB, gastrointestinal bleeding; RCT, randomized controlled trial; Riva, rivaroxaban; VTE, venous thromboembolism.



Supplementary Figure 22. Major lower GIB of real-world studies. CI, confidence interval; HR, hazard ratio; GIB, gastrointestinal bleeding; VTE, venous thromboembolism.



Supplementary Figure 23. Major GIB by indication (real-world studies). AF, atrial fibrillation; Api, apixaban; CI, confidence interval; Dabi, dabigatran; HR, hazard ratio; GIB, gastrointestinal bleeding; Riva, rivaroxaban; VTE, venous thromboembolism.



Supplementary Figure 24. Major GIB by controls (real-world studies). AF, atrial fibrillation; Api, apixaban; CI, confidence interval; Dabi, dabigatran; HR, hazard ratio; GIB, gastrointestinal bleeding; Riva, rivaroxaban; VTE, venous thromboembolism.

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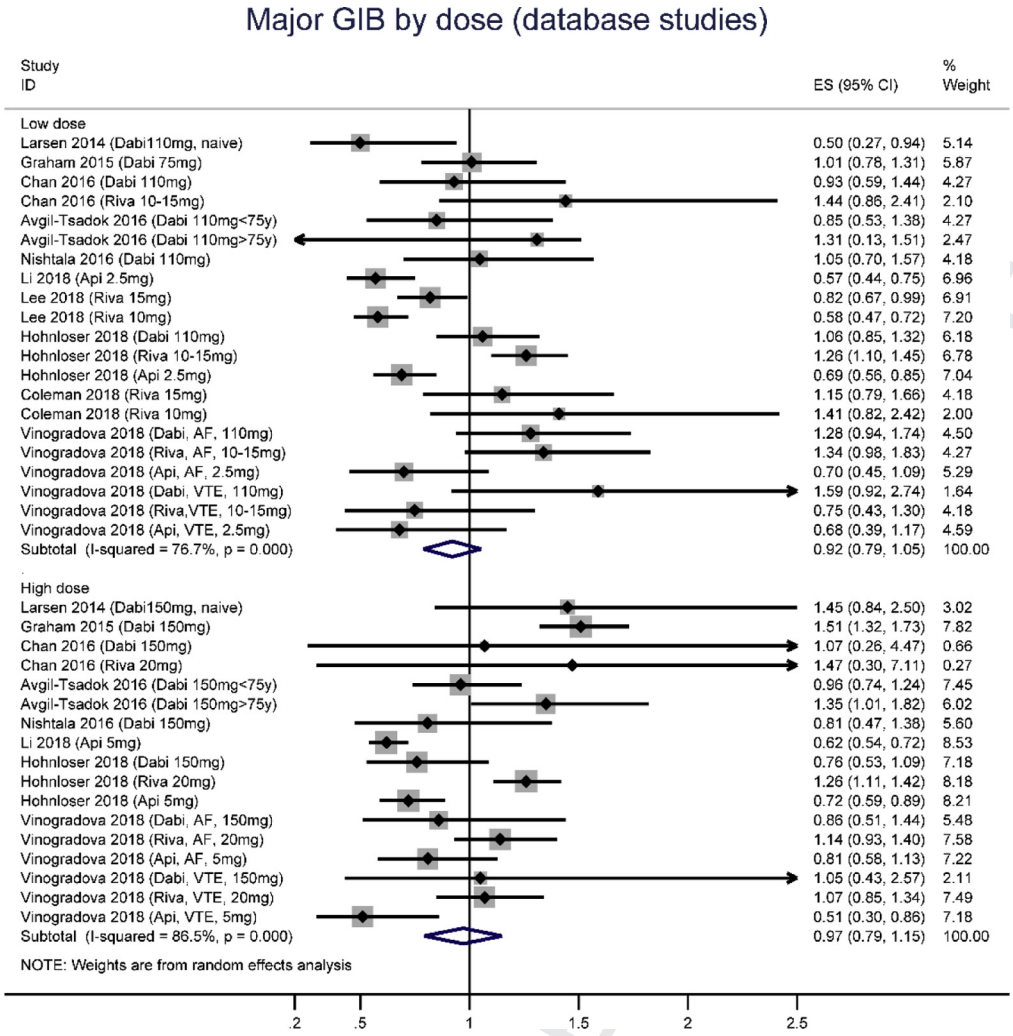
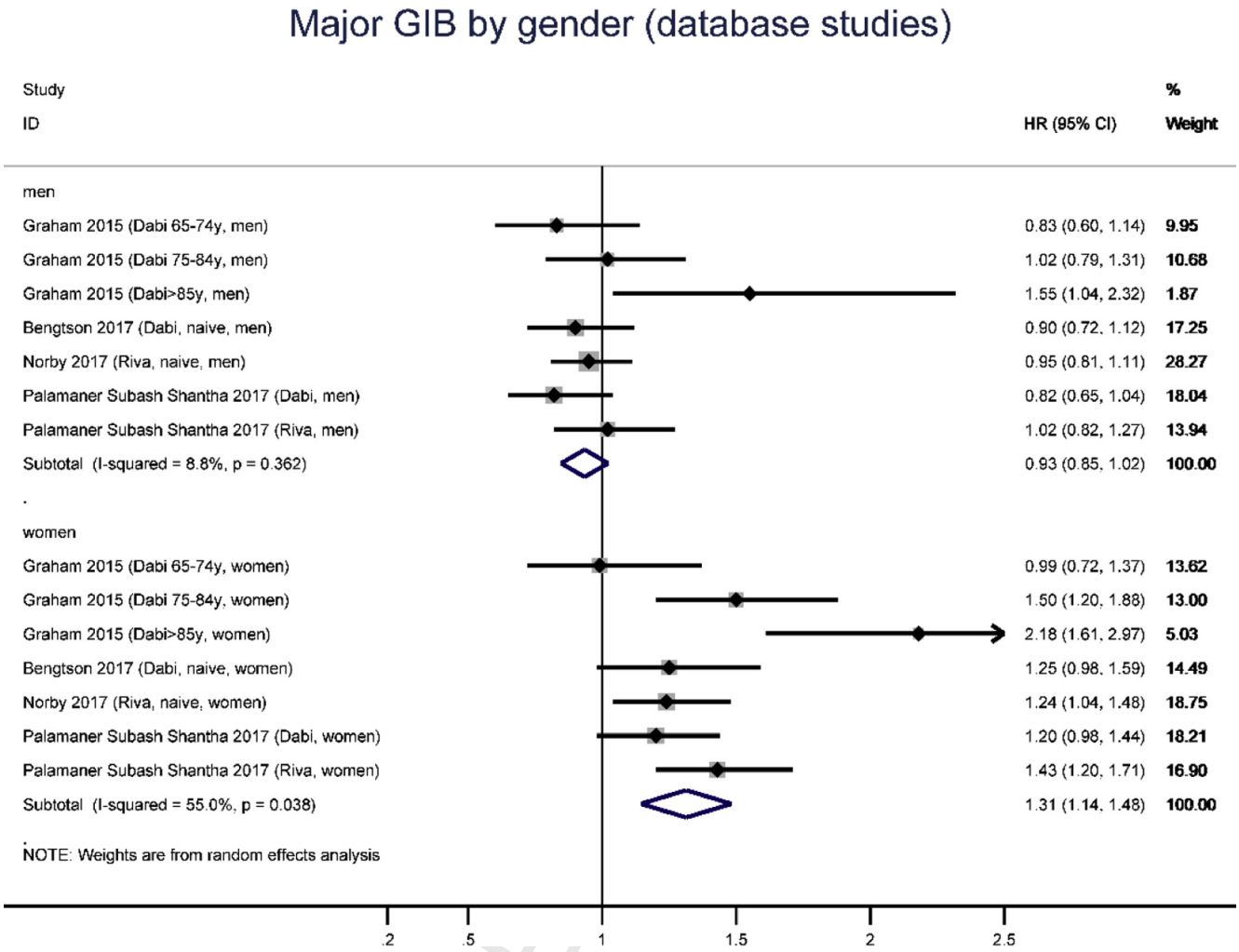
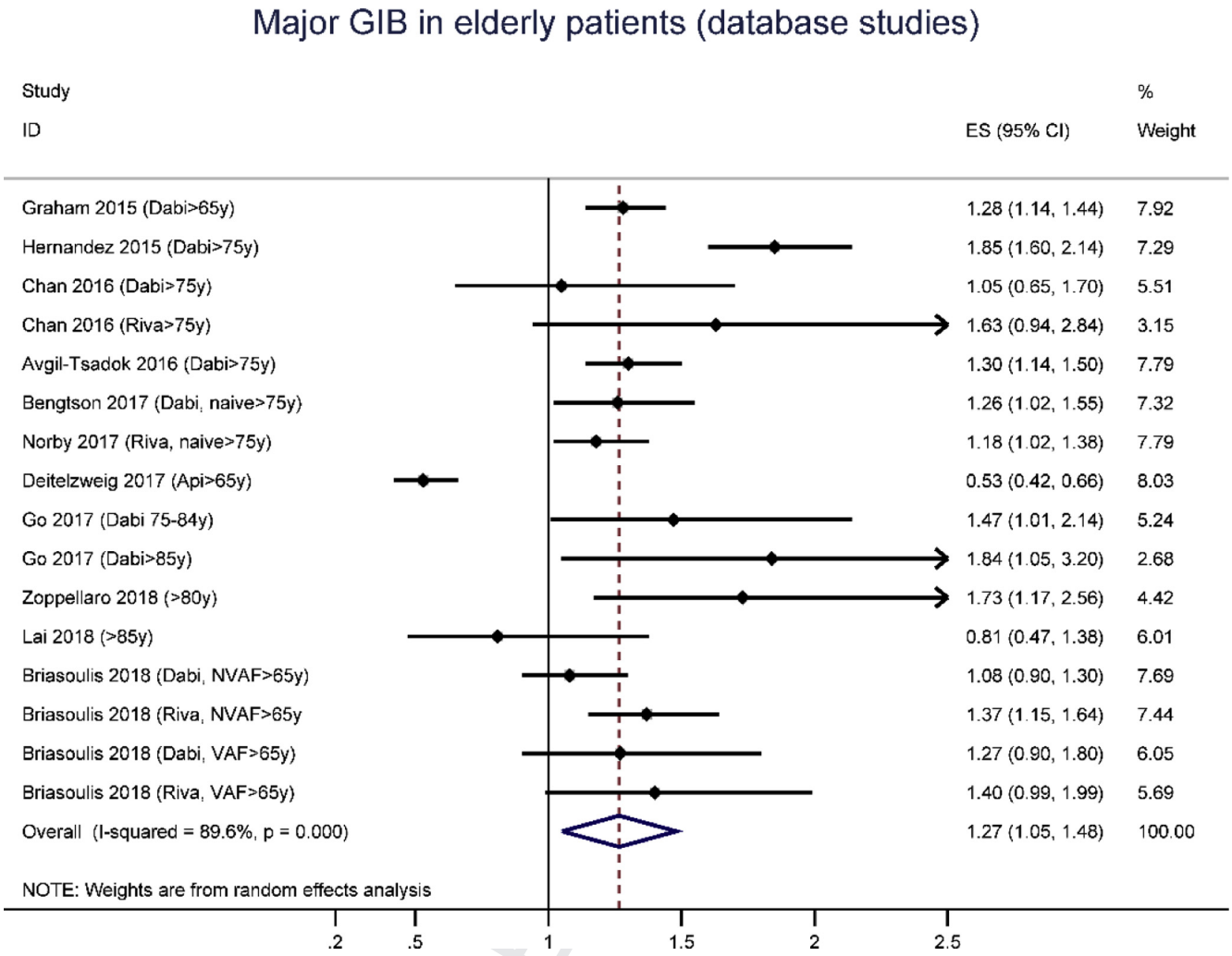


Supplementary Figure 25. Major GIB by dose (real-world studies). AF, atrial fibrillation; Api, apixaban; CI, confidence interval; Dabi, dabigatran; ES, ■■■; GIB, gastrointestinal bleeding; Riva, rivaroxaban; VTE, venous thromboembolism.

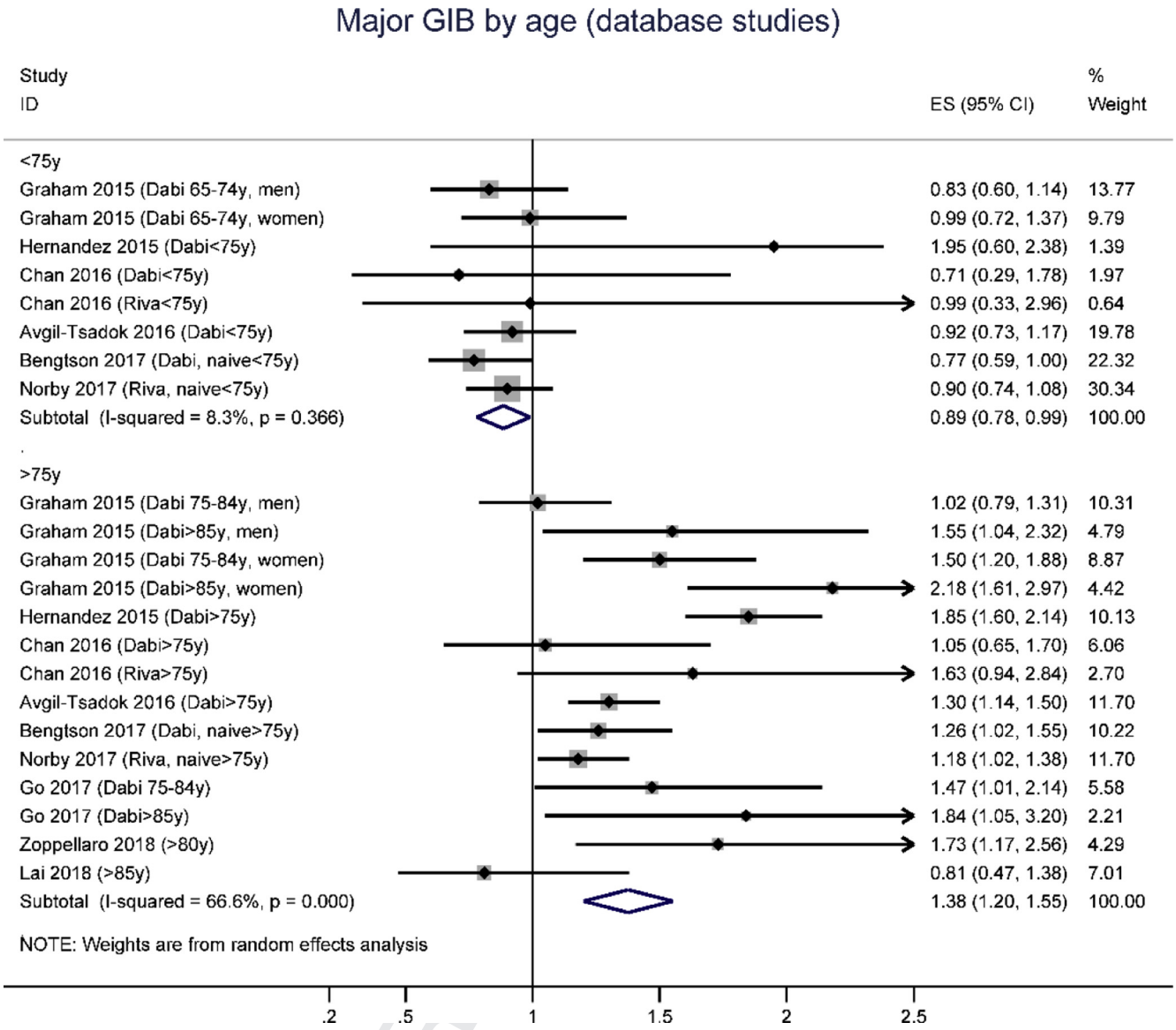
web 4C/FPO



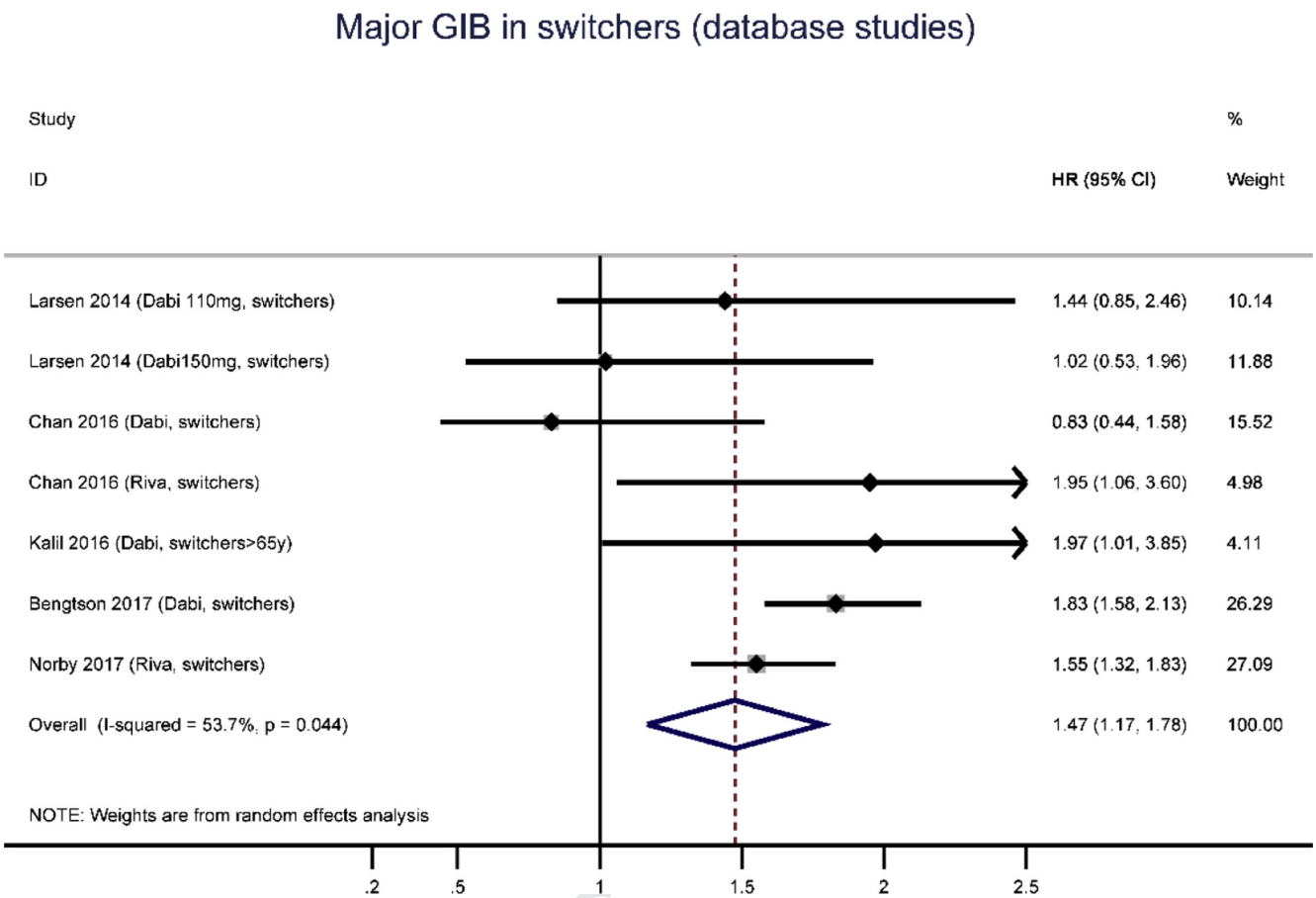
Supplementary Figure 26. Major GIB by gender (real-world studies). CI, confidence interval; Dabi, dabigatran; HR, hazard ratio; GIB, gastrointestinal bleeding; Riva, rivaroxaban.



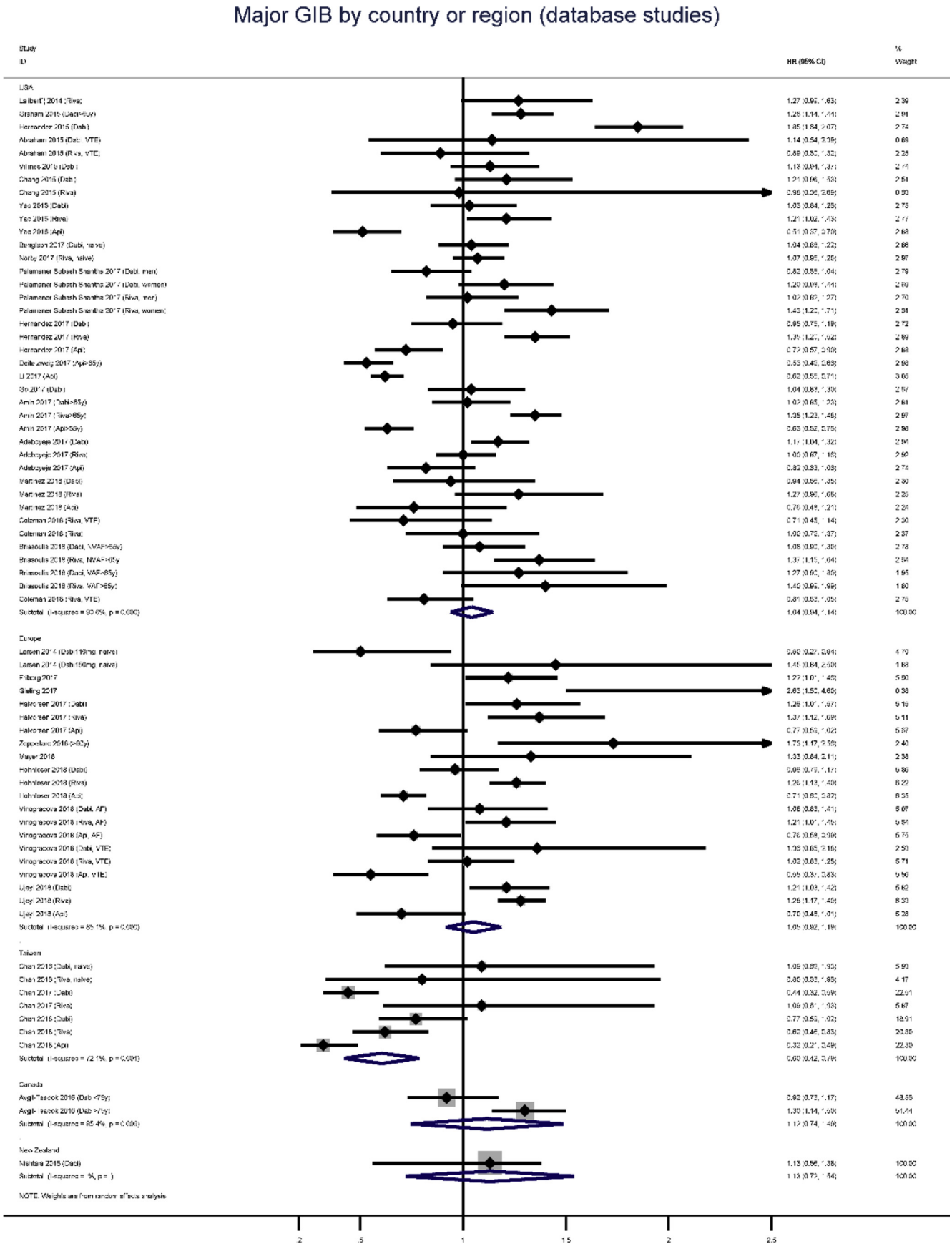
Supplementary Figure 27. Major GIB in elderly patients (real-world studies). CI, confidence interval; Dabi, dabigatran; ES, ■■■; GIB, gastrointestinal bleeding; Riva, rivaroxaban.



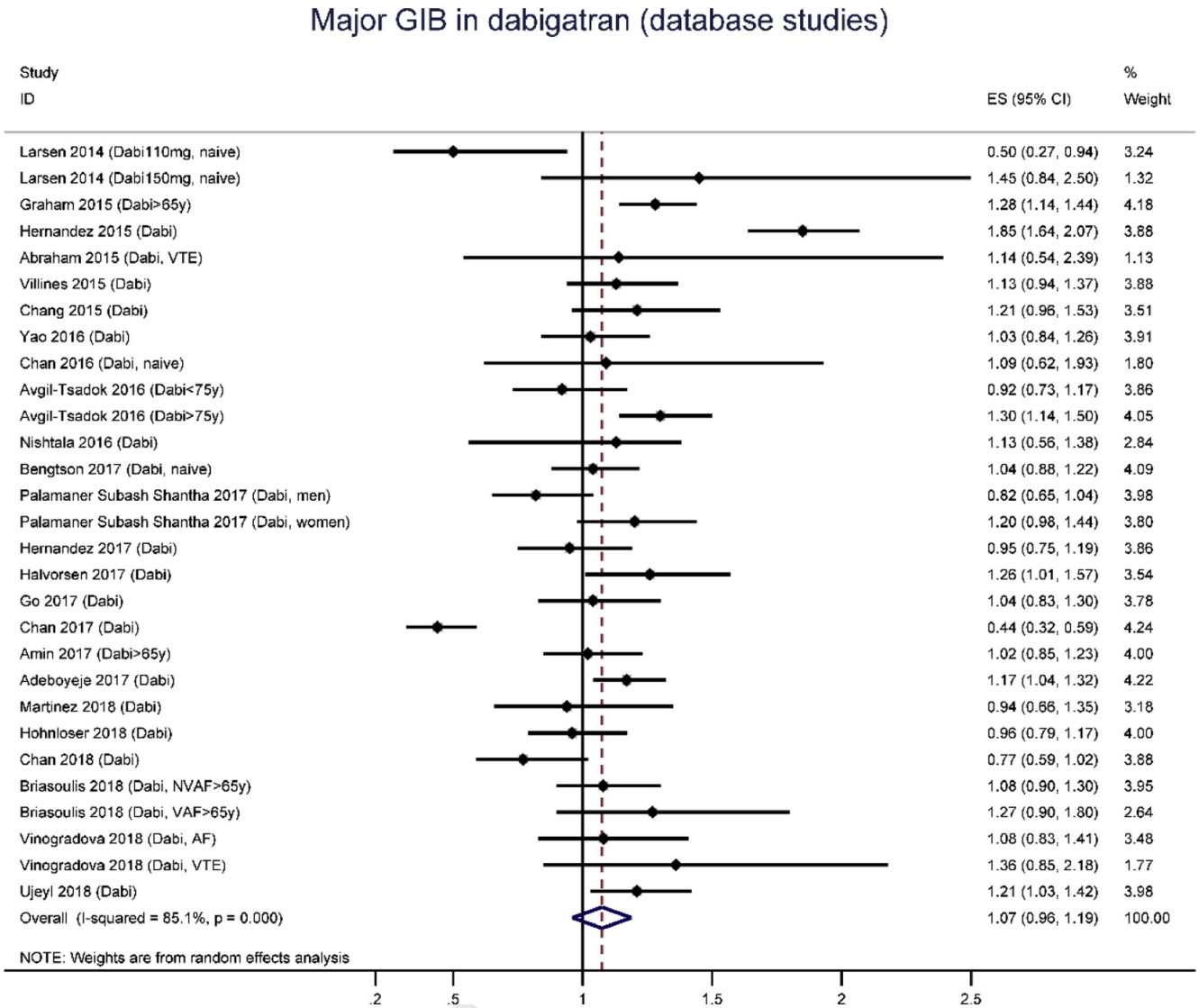
Supplementary Figure 28. Major GIB by age (real-world studies). CI, confidence interval; Dabi, dabigatran; ES, ■■■; GIB, gastrointestinal bleeding; Riva, rivaroxaban.



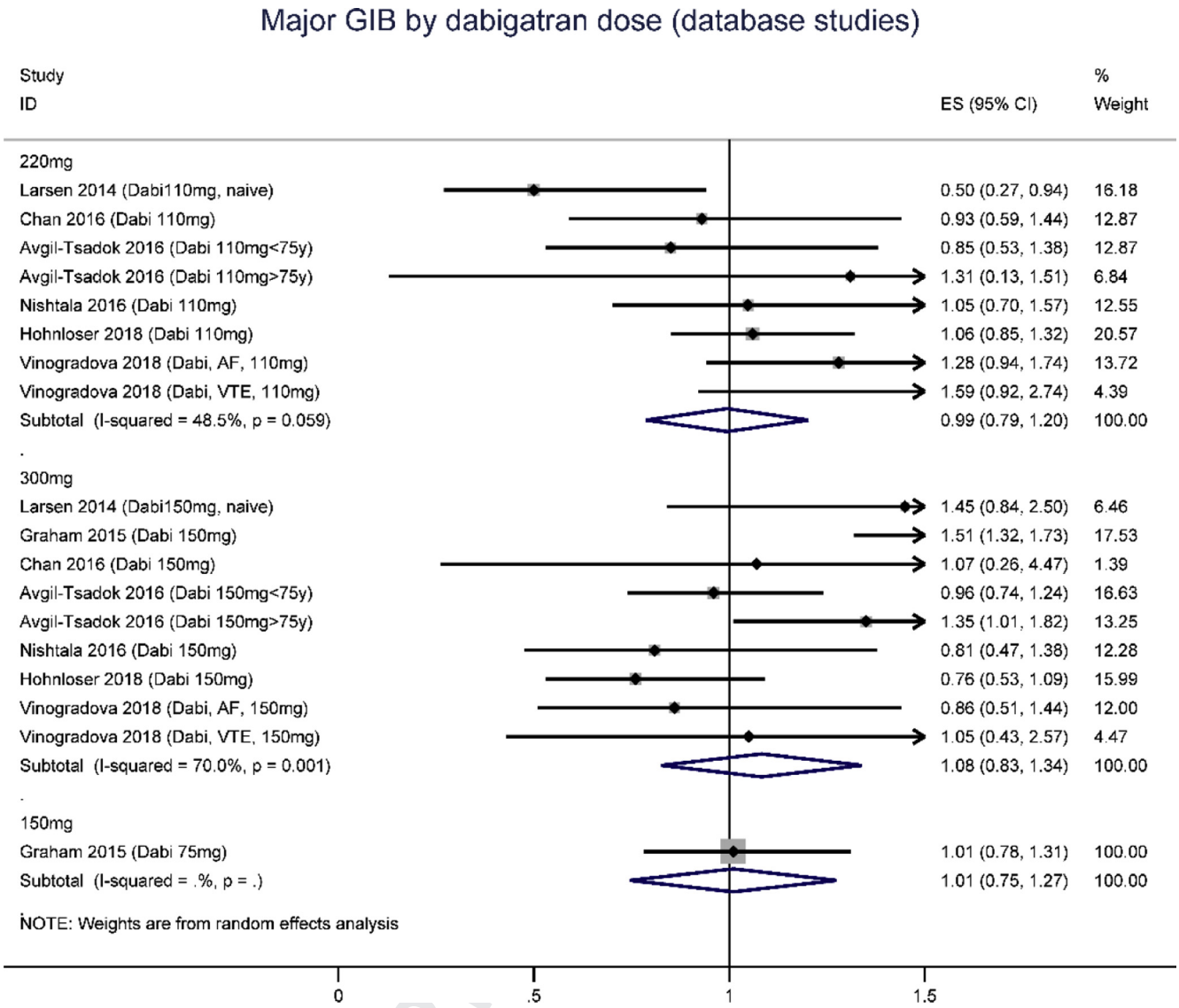
Supplementary Figure 29. Major GIB in switchers (real-world studies). CI, confidence interval; Dabi, dabigatran; GIB, gastrointestinal bleeding; HR, hazard ratio; Riva, rivaroxaban.



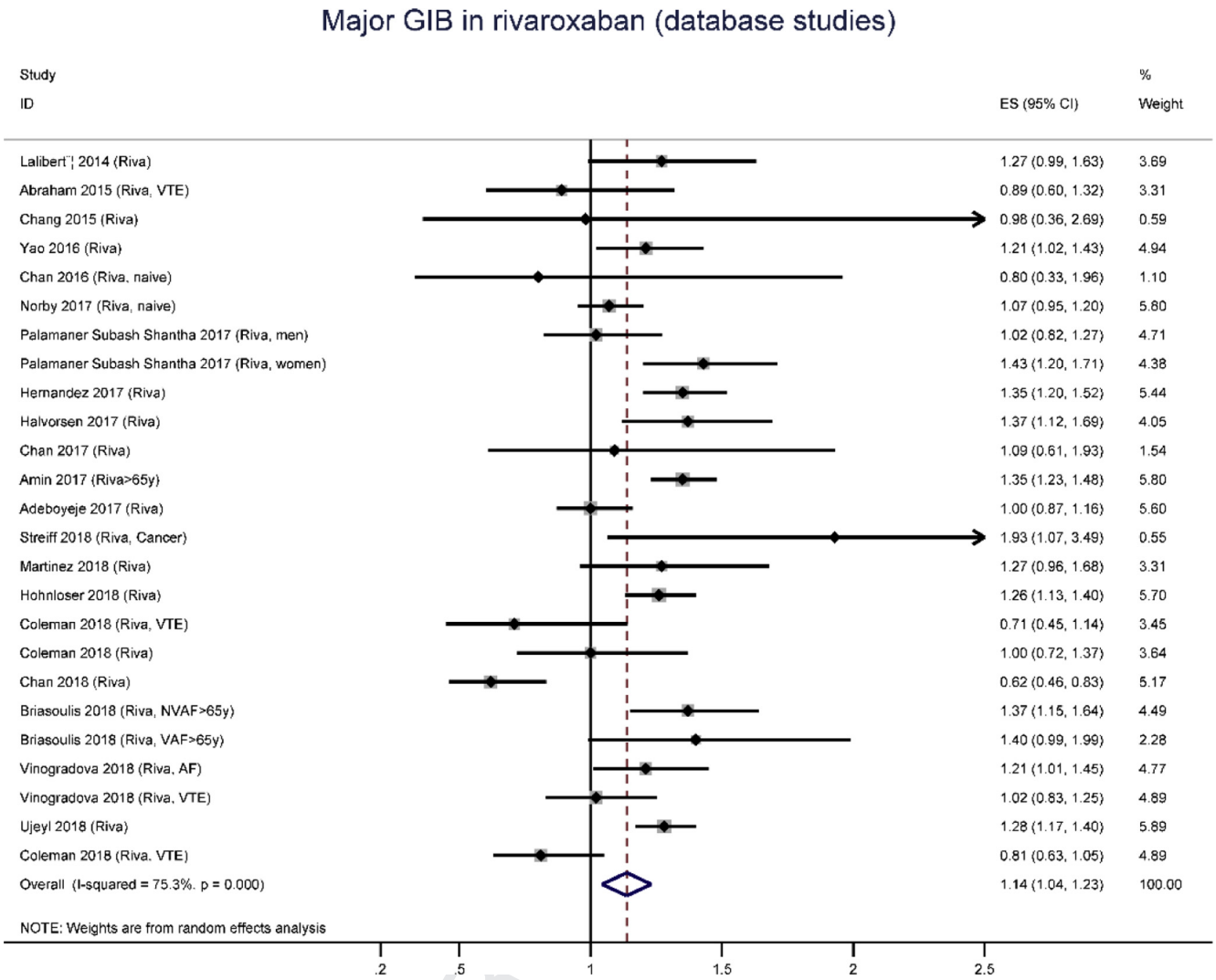
Supplementary Figure 30. Major GIB by country or region (real-world studies). AF, atrial fibrillation; Api, apixaban; CI, confidence interval; Dabi, dabigatran; GIB, gastrointestinal bleeding; HR, hazard ratio; Riva, rivaroxaban; VTE, venous thromboembolism.



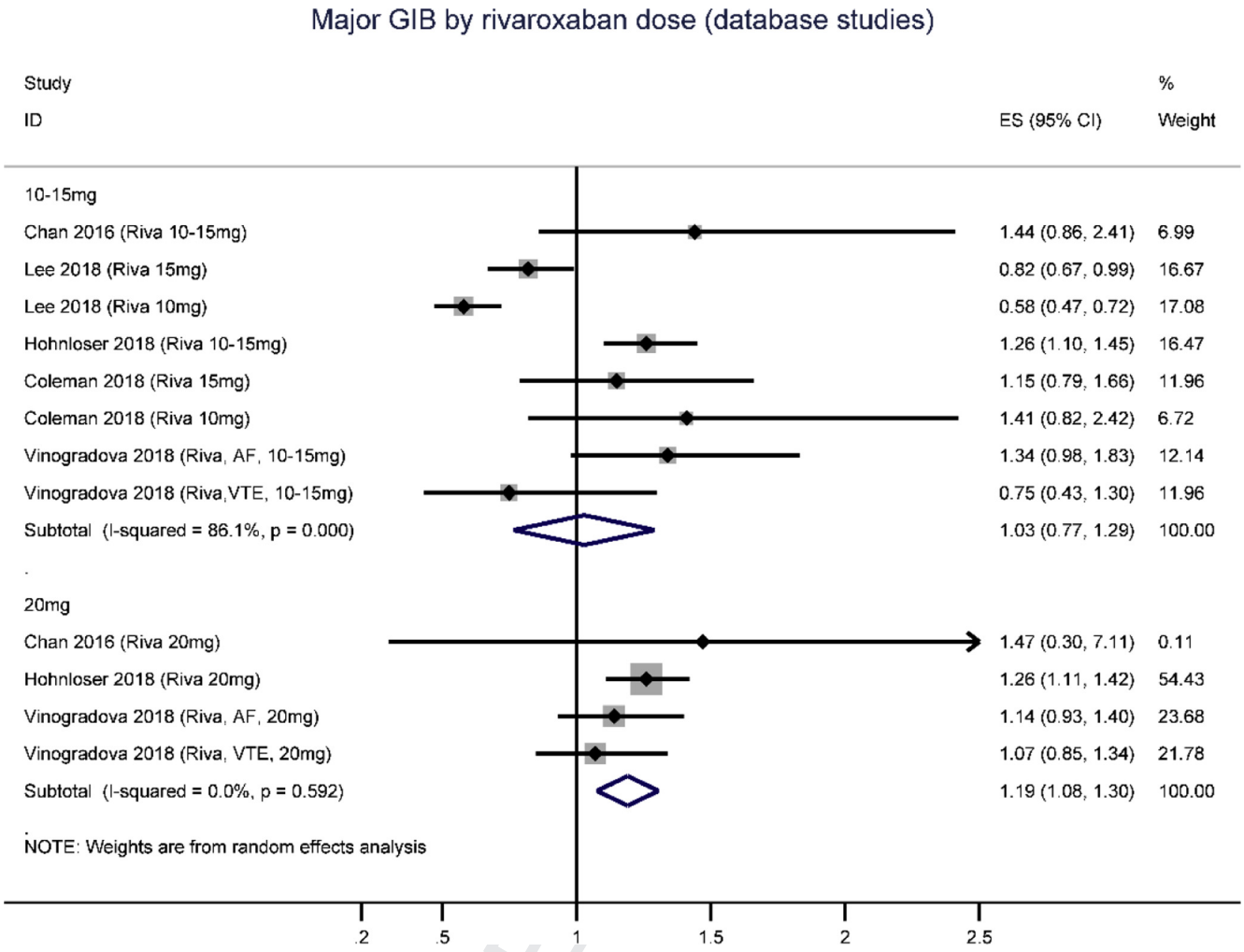
Supplementary Figure 31. Major GIB in dabigatran (real-world studies). AF, atrial fibrillation; CI, confidence interval; ES, ■■■; GIB, gastrointestinal bleeding; VTE, venous thromboembolism.



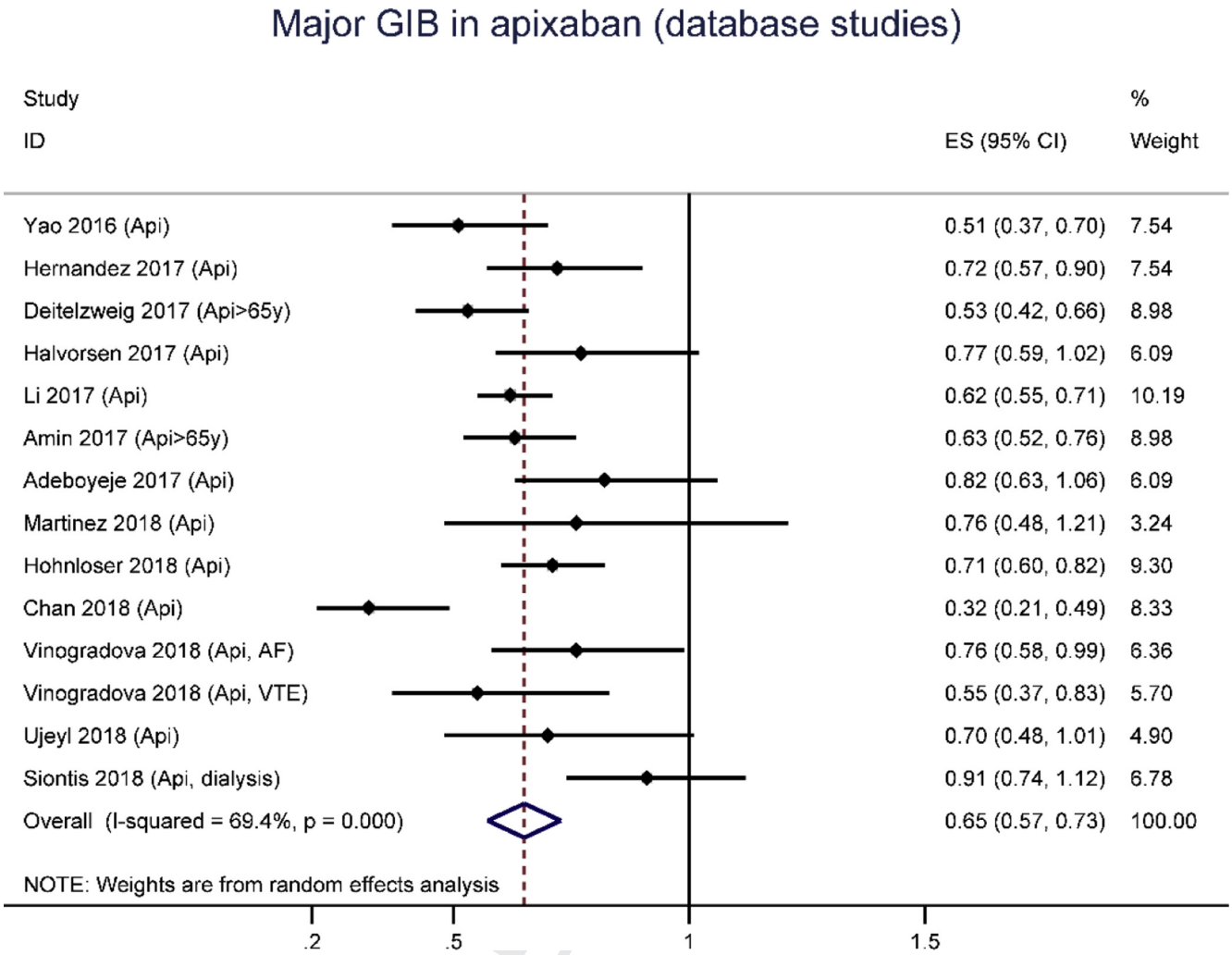
Supplementary Figure 32. Major GIB by dabigatran dose (real-world studies). AF, atrial fibrillation; CI, confidence interval; ES, ■■■; GIB, gastrointestinal bleeding; VTE, venous thromboembolism.



Supplementary Figure 33. Major GIB in rivaroxaban (real-world studies). AF, atrial fibrillation; CI, confidence interval; ES, ■■■; GIB, gastrointestinal bleeding; VTE, venous thromboembolism.



Supplementary Figure 34. Major GIB by rivaroxaban dose (real-world studies). AF, atrial fibrillation; CI, confidence interval; ES, ■■■; GIB, gastrointestinal bleeding; VTE, venous thromboembolism.



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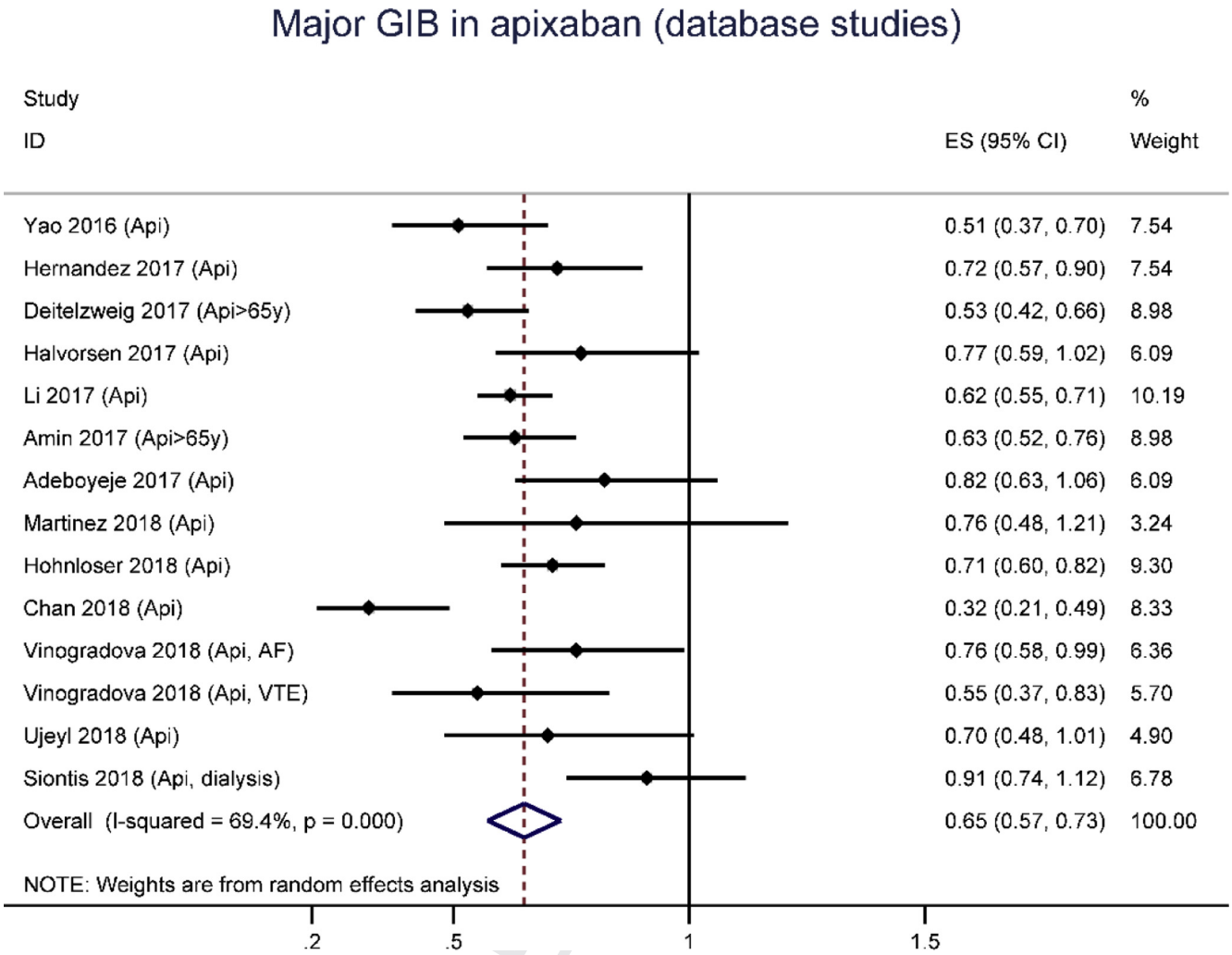
Supplementary Figure 35. Major GIB by rivaroxaban dose (real-world studies). AF, atrial fibrillation; CI, confidence interval; ES, ■■■; GIB, gastrointestinal bleeding; VTE, venous thromboembolism. Q13



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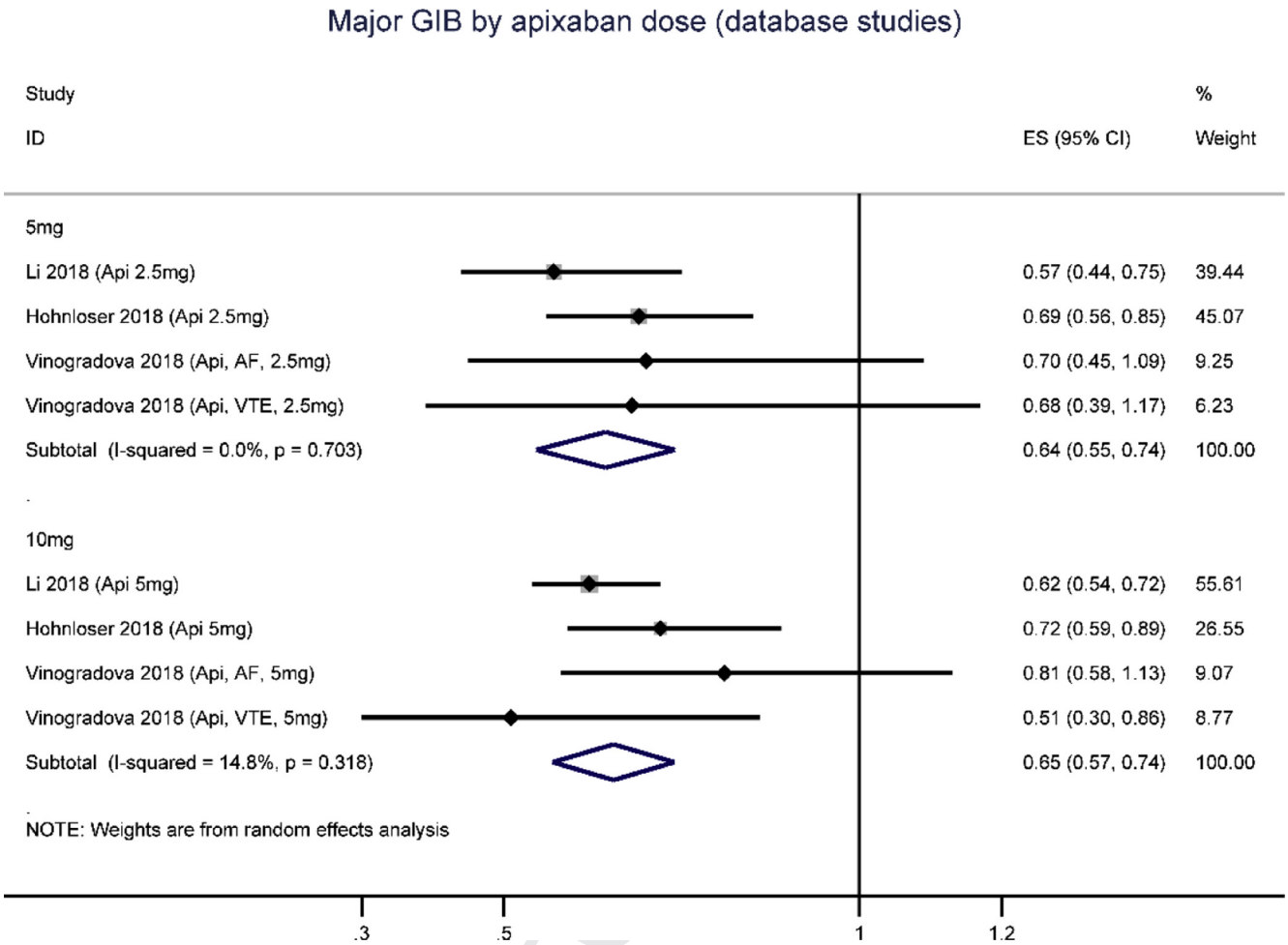
Supplementary Figure 36. Major GIB in apixaban (real-world studies). AF, atrial fibrillation; CI, confidence interval; ES, ■■■; GIB, gastrointestinal bleeding; VTE, venous thromboembolism.



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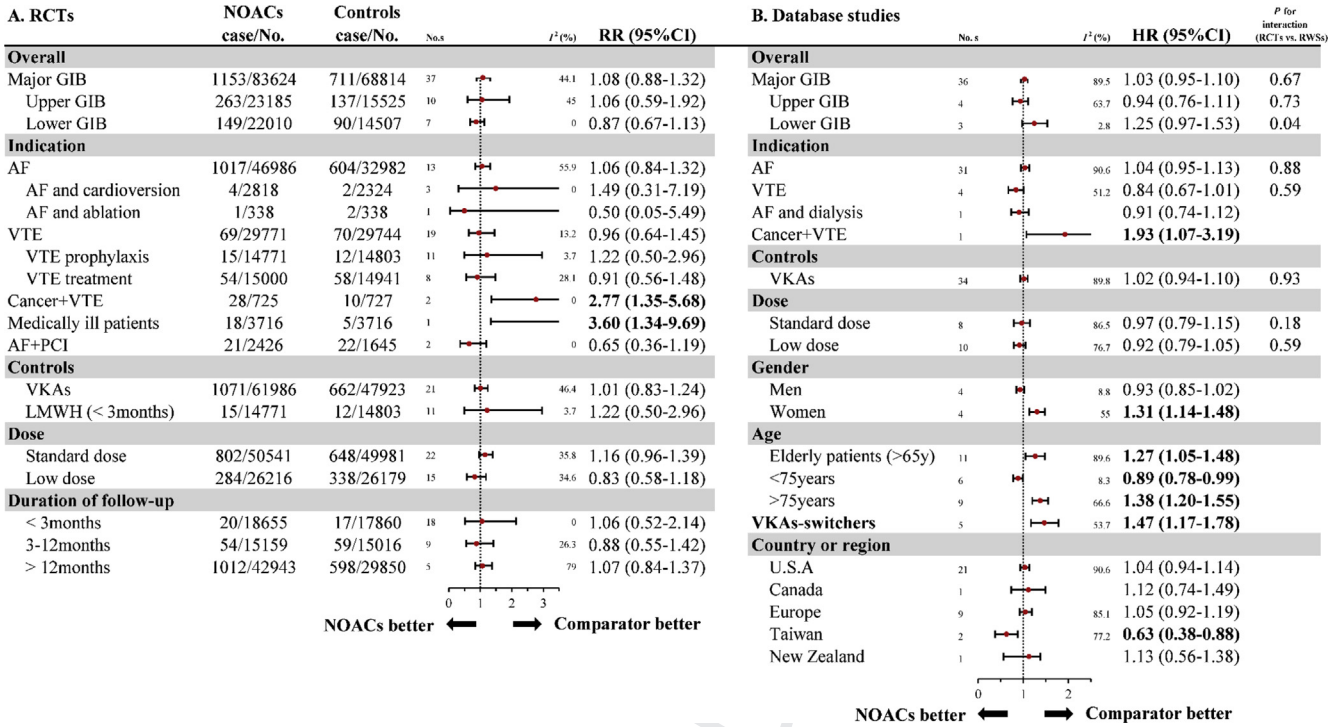
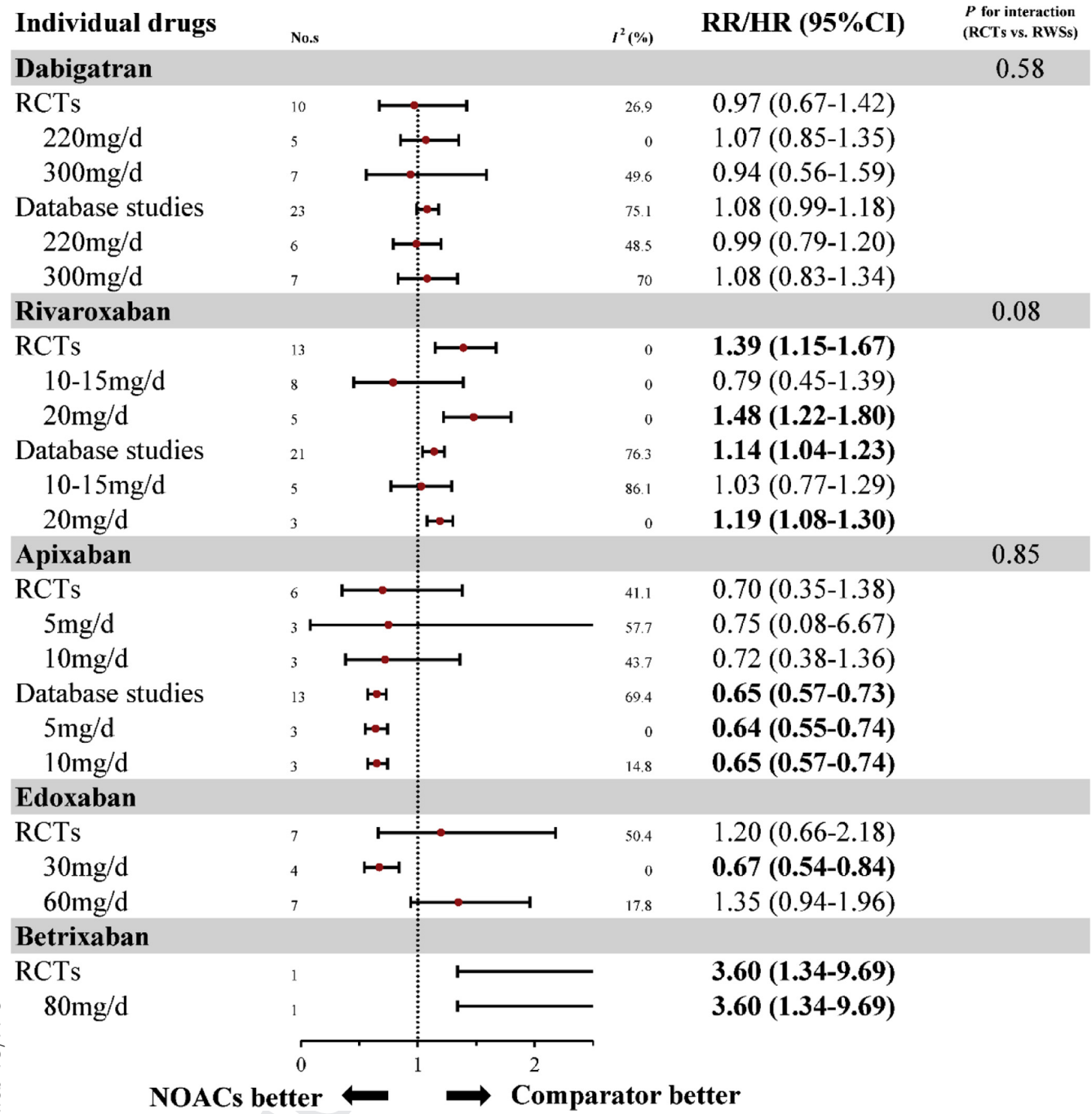
Supplementary Figure 37. Major GIB by apixaban dose (real-world studies). AF, atrial fibrillation; CI, confidence interval; ES, ■■■; GIB, gastrointestinal bleeding; VTE, venous thromboembolism.



Supplementary Figure 38. Further analyses by excluding trials with antiplatelet agents as control and trials that are outside of the approved indications and therapeutic doses. (*A*) Risk for major GIB in RCTs and (*B*) risk for major GIB in real-world studies. AF, atrial fibrillation; CI, confidence interval; GIB, gastrointestinal bleeding; HR, hazard ratio; LMWH, low-molecular-weight heparin; NOAC, non–vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; RWS, real-world study; VKA, vitamin K antagonist; VTE, venous thromboembolism.



Supplementary Figure 39. Further analyses by excluding trials with antiplatelet agents as control and trials that are outside of the approved indications and therapeutic doses. Risk for major GIB by individual NOACs. CI, confidence interval; GIB, gastrointestinal bleeding; HR, hazard ratio; NOAC, non–vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk; RWS, real-world study.

Supplementary Table 1. Search Strategy Used on October 12, 2018

Literature databases	Search items	Items found
PUBMED	"dabigatran"[MeSH Terms] OR "dabigatran"[Title/Abstract] OR "Pradaxa"[Title/Abstract] OR "rivaroxaban"[MeSH Terms] OR "rivaroxaban"[Title/Abstract] OR "Xarelto"[Title/Abstract] OR "apixaban" [MeSH Terms] OR "apixaban"[Title/Abstract] OR "Eliquis"[Title/Abstract] OR "edoxaban"[MeSH Terms] OR "edoxaban"[Title/Abstract] OR "Savaysa"[Title/Abstract]) OR "betrixaban"[MeSH Terms] OR "betrixaban"[Title/Abstract] OR "Bevyxxa"[Title/Abstract]) OR "Non-vitamin K antagonist oral anticoagulants"[Title/Abstract] OR "NOACs"[Title/Abstract]) OR "direct oral anticoagulants"[Title/Abstract]) OR "DOACs"[Title/Abstract]) OR "novel oral anticoagulants"[Title/Abstract]) OR "new oral anticoagulants"[Title/Abstract]) OR "factor Xa inhibitors"[Title/Abstract]) OR "factor IIa inhibitors"[Title/Abstract]	9469
EMBASE	'dabigatran'/exp OR 'dabigatran':ti,ab,kw OR 'Pradaxa': ti,ab,kw OR 'rivaroxaban'/exp OR 'rivaroxaban': ti,ab,kw OR 'Xarelto': ti,ab,kw OR 'apixaban'/exp OR 'apixaban': ti,ab,kw OR 'Eliquis': ti,ab,kw OR edoxaban'/exp OR 'edoxaban': ti,ab,kw OR 'Savaysa': ti,ab,kw OR 'betrixaban'/exp OR 'betrixaban': ti,ab,kw OR 'Bevyxxa': ti,ab,kw OR 'Non-vitamin K antagonist oral anticoagulants': ti,ab,kw OR 'NOACs': ti,ab,kw OR 'direct oral anticoagulants': ti,ab,kw OR 'DOACs': ti,ab,kw OR 'novel oral anticoagulants': ti,ab,kw OR 'new oral anticoagulants': ti,ab,kw OR 'factor Xa inhibitors': ti,ab,kw OR 'factor IIa inhibitors': ti,ab,kw	9867
COCHRANE	MeSH descriptor: [dabigatran] OR dabigatran: ti,ab,kw OR Pradaxa: ti,ab,kw OR MeSH descriptor: [rivaroxaban] OR rivaroxaban: ti,ab,kw OR Xarelto: ti,ab,kw OR MeSH descriptor: [apixaban] OR apixaban: ti,ab,kw OR Eliquis: ti,ab,kw OR MeSH descriptor: [edoxaban] OR edoxaban: ti,ab,kw OR Savaysa: ti,ab,kw OR MeSH descriptor: [betrixaban] OR betrixaban: ti,ab,kw OR Bevyxxa: ti,ab,kw OR Non-vitamin K antagonist oral anticoagulants: ti,ab,kw OR NOACs: ti,ab,kw OR direct oral anticoagulants: ti,ab,kw OR DOACs: ti,ab,kw OR novel oral anticoagulants: ti,ab,kw OR new oral anticoagulants: ti,ab,kw OR factor Xa inhibitors: ti,ab,kw OR factor IIa inhibitors: ti,ab,kw	2531
Overall		21,867
Duplication		17,266

Supplementary Table 2. Excluded Studies With Reasons

Study	Drugs	Reason for exclusion
Yoshimura 2018[6]	NOACs	Not reported adjusted GIB data
Yoshida 2018[7]	NOACs	Single center study
Yavuz 2016[8]	Dabigatran	Not reported adjusted GIB data
Yap 2016[9]	Dabigatran	Single center study
Yamashita 2012[10]	Edoxaban	Not reported GIB data
Wurnig 2015[11]	Dabigatran	One-arm study
Weir 2017[12]	Rivaroxaban	Not reported GIB data
Vranckx 2013[13]	Dabigatran	Not reported GIB data
Vaughan Sarrazin 2014[14]	Dabigatran	Not reported adjusted GIB data
Turpie 2005[15]	Rivaroxaban	Not reported GIB data
Turpie 2009[16]	Betrixaban	Not reported GIB data
Stolk 2017[17]	NOACs	Not reported GIB data
Steinberg 2018[18]	NOACs	Not reported GIB data
Staerk 2015[19]	Antithrombotic agents	Not NOACs study
Staerk 2015[20]	Dabigatran	Overlapping period with Larsen 2014[21]
Staerk 2017[22]	NOACs	Not reported HR value
Staerk 2017[23]	NOACs	Not reported GIB data
Staerk 2018[24]	Oral anticoagulation	Not reported GIB data
Sorensen 2013[25]	Dabigatran	Not reported GIB data
Song 2017[26]	Dabigatran	Not reported GIB data
Sjogren 2017[27]	NOACs	Overlapping period with Friberg 2017[28]
Sindet-Pedersen 2018[29]	Rivaroxaban and apixaban	Not reported HR value
Sindet-Pedersen 2017[30]	Rivaroxaban	Not reported HR value
Simmons 2018[31]	Rivaroxaban	Small sample study
Shimokawa 2018[32]	Rivaroxaban	One-arm study
Shah 2018[33]	NOACs	Not reported GIB data
Seeger 2015[34]	Dabigatran	Overlapping period with Bengtson 2017[35]

Supplementary Table 2. Continued

Study	Drugs	Reason for exclusion
Schafer 2018[36]	Apixaban	Single center study
Piazza 2016[37]	Edoxaban	Not reported GIB data
Palamaner Subash Shantha 2017[38]	Dabigatran and rivaroxaban	Not reported GIB data
Oldgren 2011[39]	Dabigatran	Placebo as control
Okumura 2016[40]	Rivaroxaban	Not reported GIB data
Ohman 2017[41]	Rivaroxaban	Not reported GIB data
Ogawa 2011[42]	Apixaban	Only reported minor GIB
Ogawa 2013[43]	Apixaban	Placebo as control
Oakland 2017[44]	NOACs	Patients with a history of GIB
Nielsen 2017[45]	NOACs	Not reported GIB data
Nielen 2016[46]	NOACs	Not reported GIB data
Nakamura 2015[47]	Apixaban	Not reported GIB data
Nagata 2017[48]	NOACs	Endoscopy study
Moustafa 2018[49]	NOACs	Not reported GIB data
Moll 2018[50]	Edoxaban	Not reported GIB data
Mega 2012[51]	Rivaroxaban	Placebo as control
Mega 2009[52]	Rivaroxaban	Placebo as control
Maura 2015[53]	Dabigatran and rivaroxaban	Not reported GIB data
Loo 2018[54]	NOACs	Overlapping period with Vinogradova 2018[55]
Lip 2017[56]	NOACs	Not reported GIB data
Lip 2016[57]	NOACs	Not reported GIB data
Lip 2016[58]	NOACs	Not reported GIB data
Lindquist 2018[59]	Rivaroxaban	Single center study
Lin 2017[60]	NOACs	Not reported GIB data
Li 2017[61]	Dabigatran and rivaroxaban	Single center study
Levine 2012[62]	Apixaban	Placebo as control
Leschke 2017[63]	Rivaroxaban	One-arm study
Lauffenburger 2015[64]	Dabigatran	Overlapping period with Bengtson 2017[35]
Lau 2017[65]	Dabigatran	Not reported HR value
Lassen 2007[66]	Apixaban	Not reported GIB data
Larsen 2016[67]	Apixaban	Not reported GIB data
Larsen 2013[68]	Dabigatran	Overlapping period with Larsen2014[21]
Larsen 2014[69]	Dabigatran	Not reported GIB data
Larsen 2014[70]	Dabigatran	Not reported GIB data
Lamsam 2018[71]	NOACs	Not reported GIB data
Lamberts 2017[72]	NOACs	Not reported GIB data
Lai 2017[73]	Dabigatran and rivaroxaban	NOACs as control
Kwong 2017[74]	Rivaroxaban	One-arm study
Korenstra 2016[75]	Dabigatran	Single center study
Kohsaka 2018[76]	Apixaban	Not reported GIB data
Jun 2017[77]	NOACs	Not reported GIB data
Inohara 2018[78]	NOACs	Not reported GIB data
Hsu 2018[79]	Dabigatran and rivaroxaban	Small sample study
Hong 2017[80]	Rivaroxaban	Not reported GIB data
Hohnloser 2017[81]	NOACs	Overlapping period with Hohnloser 2018[82]
Ho 2015[83]	Dabigatran	Single center study
Hernandez 2018[84]	NOACs	Overlapping period with Amin 2017[85]
Hernandez 2017[86]	Dabigatran	Not reported GIB data
Hernandez 2017[87]	Dabigatran and rivaroxaban	Not reported GIB data
Harel 2016[88]	NOACs	Not reported GIB data
Gorst-Rasmussen 2016[89]	Dabigatran and rivaroxaban	Not reported GIB data
Ginsberg 2009[90]	Dabigatran	Not reported GIB data
Fuji 2014[91]	Edoxaban	Only reported minor GIB
Fuji 2014[92]	Edoxaban	Not reported GIB data
Fuji 2010[93]	Edoxaban	Not reported GIB data
Fuji 2014[94]	Edoxaban	Only reported minor GIB
Fuji 2015[95]	Edoxaban	Only reported minor GIB
Fuji 2010[96]	Dabigatran	Placebo as control
Frederiksen 2017[97]	NOACs	Two centers study
Eriksson 2010[98]	Darexaban	Not studied NOACs
Eriksson 2007[99]	Darexaban	Not studied NOACs
Eriksson 2011[100]	Dabigatran	Not reported GIB data
Eriksson 2005[101]	Dabigatran	Not reported GIB data

Supplementary Table 2. Continued

Study	Drugs	Reason for exclusion
Eriksson 2004[102]	Dabigatran	Not reported GIB data
Eriksson 2006[103]	Rivaroxaban	Not reported GIB data
Eriksson 2007[104]	Rivaroxaban	Not reported GIB data
Ellis2016[105]	Dabigatran and rivaroxaban	Not reported GIB data
Eikelboom 2013[106]	Dabigatran	Not reported GIB data
Devereaux 2018[107]	Dabigatran	Placebo as control
Denas 2017[108]	NOACs	Not reported GIB data
Connolly 2013[109]	Betrixaban	Not reported GIB data
Coleman 2018[110]	Rivaroxaban	Overlapping with Coleman 2018[111]
Coleman 2018[112]	Rivaroxaban	Small sample study
Coleman 2017[113]	NOACs	Not reported GIB data
Coleman 2018[114]	Apixaban	Not reported GIB data
Coleman 2016[115]	Rivaroxaban and apixaban	Not reported GIB data
Chao 2018[116]	NOACs	Not reported GIB data
Chan 2016[117]	Dabigatran	Overlapping period with Chan 2016[118]
Chan 2015[119]	Dabigatran and rivaroxaban	Not reported adjusted GIB data
Cha 2017[120]	NOACs	Not reported GIB data
Cappato 2015[121]	Rivaroxaban	Not reported GIB data
Cangemi 2017[122]	NOACs	Not reported GIB data
Camporese 2015[123]	Rivaroxaban	Not reported GIB data
Buller 2008[124]	Rivaroxaban	Not reported GIB data
Botticelli 2008[125]	Apixaban	Not reported GIB data
Bouillon 2015[126]	Dabigatran	Not reported GIB data
Becattini 2017[127]	NOACs	Not database study
Avgil Tsadok 2015[128]	Dabigatran	Not reported GIB data
Bouillon 2015[126]	Dabigatran	Not reported GIB data
Avgil Tsadok 2015[128]	Dabigatran	Not reported GIB data
Arihiro 2016[129]	NOACs	Not reported adjusted GIB data
Andersson 2018[130]	NOACs	NOACs as control
Anderson 2018[131]	Rivaroxaban	Not reported GIB data
Amin 2018[132]	NOACs	Not reported GIB data
Alonso 2014[133]	Dabigatran	Not reported GIB data
Alexander 2011[134]	Apixaban	Placebo as control
Alexander 2009[135]	Apixaban	Placebo as control
Agnelli 2007[136]	Rivaroxaban	Not reported GIB data
Agnelli 2013[137]	Apixaban	Placebo as control
Ageno 2016[138]	Rivaroxaban	Not reported adjusted GIB data
Agaba 2017[139]	Rivaroxaban and apixaban	Not reported GIB data
Abraham 2017[140]	NOACs	NOACs as control
Abraham 2013[141]	Antithrombotic treatment	Not NOACs study
Abe 2015[142]	Dabigatran	Not reported adjusted GIB data
Yamashita 2017[143]	NOACs	Not reported GIB data

GIB, gastrointestinal bleeding; HR, hazard ratio; NOAC, non–vitamin K antagonist oral anticoagulant.

Supplementary Table 3. Characteristics of Randomized Controlled Trials

Study	Indication	NCT	Interventions	N	Controls	N	Follow-up
ODIXa-HIP 2006[144]	Hip replacement	NCT00398905	Rivaroxaban 5 mg twice	136	Enoxaparin 40 mg once	132	30–60 days
RE-NOVATE 2007[145]	Hip replacement	NCT00168818	Dabigatran 220 or 150 mg once	2309	Enoxaparin40 mg once	1154	94 days
RE-MODEL 2007[146]	Knee replacement	NCT00168805	Dabigatran 220 or 150 mg once	1382	Enoxaparin 40 mg once	694	90 days
PETRO 2007[147]	AF	NCT01227629	Dabigatran 150 mg twice	100	Warfarin	70	14 days
RECORD1 2008[148]	Hip arthroplasty	NCT00329628	Rivaroxaban 10 mg once	2209	Enoxaparin 40 mg once	2224	30–35 days
RECORD2 2008[149]	Hip arthroplasty	NCT00332020	Rivaroxaban 10 mg once	1228	Enoxaparin 40 mg once	1229	30–35 days
RECORD3 2008[150]	Knee arthroplasty	NCT00361894	Rivaroxaban 10 mg once	1220	Enoxaparin 40 mg once	1239	30–35 days
RE-LY 2009[151]	AF	NCT00262600	Dabigatran 110 mg or 150 mg twice	12091	Warfarin	6022	2 y
RE-COVER 2009[152]	VTE	NCT00291330	Dabigatran 150 mg twice	1274	Warfarin	1265	180 days
RECORD4 2009[153]	Knee arthroplasty	NCT00362232	Rivaroxaban 10 mg once	1526	Enoxaparin 30 mg twice	1508	30–35 days
ADVANCE-1 2009[154]	Knee replacement	NCT00371683	Apixaban 2.5 mg twice	1596	Enoxaparin 30 mg twice	1588	60 days
ADVANCE-2 2010[155]	Knee replacement	NCT00452530	Apixaban 2.5 mg twice	1501	Enoxaparin 40 mg once	1508	60 days
ADVANCE-3 2010[156]	Hip replacement	NCT00423319	Apixaban 2.5 mg twice	2673	Enoxaparin 40 mg once	2659	60 days
Weitz 2010[157]	AF	NCT00504556	Edoxaban 30 mg or 60 mg once	469	Warfarin	250	12 weeks
EINSTEIN 2010[158]	VTE	NCT00440193	Rivaroxaban 15 mg twice and then 20 mg once	1718	Enoxaparin 1.0 mg per kg +VKA	1711	365 days
Raskob 2010[159]	Hip replacement	NCT00398216	Edoxaban 30 mg or 60 mg once	358	Dalteparin 2500 IU and then 5000 IU	172	30–60 days
ROCKET AF 2011[160]	AF	NCT00403767	Rivaroxaban 20 mg once	7111	Warfarin	7125	2.5 y
ARISTOTLE 2011[161]	AF	NCT00412984	Apixaban 5 mg twice	9088	Warfarin	9052	1.8 y
Chung 2011[162]	AF	NR	Edoxaban 30 mg or 60 mg once	159	Warfarin	75	90 days
AVERROES 2011[163]	AF	NCT00496769	Apixaban 5 mg twice	2808	Aspirin 81–324 mg once	1791	1.1 y
ADOPT 2011[164]	Acutely ill medical patients	NCT00457002	Apixaban 2.5 mg twice	3184	Enoxaparin 40 mg once	3217	30 days
J-ROCKET AF 2012[165]	AF	NCT00494871	Rivaroxaban 15 mg once	639	Warfarin	639	30 mo
EINSTEIN–PE 2012[166]	PE	NCT00439777	Rivaroxaban 15 mg twice and then 20 mg once	2412	Enoxaparin 1.0 mg per kg and VKA	2405	365 days
RE-MEDY 2013[167]	VTE	NCT00329238	Dabigatran 150 mg twice	1430	Warfarin	1426	6 mo
ENGAGE AF-TIMI 48 2013[168]	AF	NCT00781391	Edoxaban 30 mg or 60 mg once	14014	Warfarin	7012	2.8 y
Hokusai-VTE 2013[169]	VTE	NCT00986154	Edoxaban 60 mg once	4118	Warfarin	4122	365 days
AMPLIFY 2013[170]	VTE	NCT00643201	Apixaban 10 mg twice and then 5 mg twice	2691	Enoxaparin 1.0 mg per kg and warfarin	2704	6 mo
MAGELLAN 2013[171]	Acutely ill medical patients	NCT00571649	Rivaroxaban 10 mg once	3997	Enoxaparin 40 mg once	4001	35 days
RE-COVER II 2014[172]	VTE	NCT00680186	Dabigatran 150 mg twice	1279	Warfarin	1289	180 days
Boehringer Ingelheim 2014[173]	Knee replacement	NCT00152971	Dabigatran 220 mg or 150 mg once	1728	Enoxaparin 30 mg twice	868	12–15 days
X-VeRT 2014[174]	AF and cardioversion	NCT01674647	Rivaroxaban 20 mg once	988	VKA	499	30 days
Daiichi Sankyo 2015[175]	AF	NCT00806624	Edoxaban 30 mg or 60 mg once	159	Warfarin	75	180 days
J-EINSTEIN DVT and PE 2015[176]	VTE	NCT01516840 and NCT01516814	Rivaroxaban 15 mg once	78	UFH and then warfarin	19	365 days

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APEX 2016[177]	Acutely ill medical patients	NCT01583218	Betrixaban 80 mg once	3716	Enoxaparin 40 mg once	3716	30 days
PIONEER AF-PCI 2016[178]	PCI and AF	NCT01830543	Rivaroxaban 15 mg once and $P2Y_{12}$; rivaroxaban 2.5 mg twice and aspirin and $P2Y_{12}$	1402	VKA and aspirin and $P2Y_{12}$	697	12 mo
RE-DUAL PCI 2017[179]	PCI and AF	NCT02164864	Dabigatran 110 mg or 150 mg twice, and $P2Y_{12}$	1730	Warfarin and aspirin and $P2Y_{12}$	948	14 mo
COMPASS 2017[180]	SPAD or SCAD	NCT01776424	Rivaroxaban 5 mg twice	2474	Aspirin 100 mg once	2504	9 mo
EINSTEIN CHOICE 2017[181]	VTE	NCT02064439	Rivaroxaban 10 mg or 20 mg once	2234	Aspirin 100 mg once	1131	390 days
ENSURE-AF 2017[182]	AF and cardioversion	NCT02072434	Edoxaban 60 mg once	1095	Enoxaparin and warfarin	1104	58 days
Hokusai VTE Cancer 2018[183]	Cancer and VTE	NCT02073682	Edoxaban 60 mg once	522	Dalteparin 200 IU per kg	524	1 y
SELECT-D 2018[184]	Cancer and VTE	NCT02583191	Rivaroxaban 15 mg twice and then 20 mg once	203	Dalteparin 200 IU per kg	203	6 mo
RE-CIRCUIT 2018[185]	AF and ablation	NCT02348723	Dabigatran 150 mg twice	338	Warfarin	338	56 days
EMANATE 2018[186]	AF and cardioversion	NCT02100228	Apixaban 5 mg twice	735	Heparin and VKA	721	30 days

AF, atrial fibrillation; NCT, national clinical trial; NR, not reported; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SCAD, stable carotid artery disease; SPAD, stable peripheral artery disease; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Supplementary Table 4. Patient Demographics and Clinical Characteristics of Randomized Controlled Trials

Study	N	Mean age (*y*)	Female (%)	Weight (*kg*)	BMI (kg/m^2)	HF (%)	HBP (%)	DM (%)	Stroke/ TIA (%)	MI (%)	Cancer (%)	Ccr (*mL/min*)	Ccr >80 mL/min (%)	Antiplatelet drugs
ODIXa-HIP 2006	268	64	56	78	28	NR	NR	NR	NR	NR	NR	NR	NR	NR
RE-NOVATE 2007	3463	64	57	79	NR	NR	NR	NR	NR	NR	NR	89	NR	NR
RE-MODEL 2007	2076	68	66	83	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PETRO 2007	170	70	17.8	NR	NR	32.8	71	24.2	18	NR	NR	NR	NR	NR
RECORD1 2008	4433	63.2	55.5	78.2	27.9	NR	NR	NR	NR	NR	NR	NR	NR	NR
RECORD2 2008	2457	61.5	53.6	74.8	27	NR	NR	NR	NR	NR	NR	NR	NR	NR
RECORD3 2008	2459	67.6	68.3	80.7	29.7	NR	NR	NR	NR	NR	NR	NR	NR	NR
RE-LY 2009	18,113	71.5	36.43	NR	NR	32	78.9	23.3	20	16.6	NR	NR	NR	40.1
RE-COVER 2009	2539	56	41.6	84	28.7	NR	NR	NR	NR	NR	4.8	105.1	NR	NR
RECORD4 2009	3034	64.5	65	84.6	30.8	NR	NR	NR	NR	NR	NR	NR	NR	NR
ADVANCE-1 2009	3184	65.8	37.9	86.7	31.1	NR	NR	NR	NR	NR	NR	NR	NR	NR
ADVANCE-2 2010	3009	67	72	78	29.2	NR	NR	NR	NR	NR	NR	NR	83	NR
ADVANCE-3 2010	5332	60.8	53.3	79.7	28.2	NR	NR	NR	NR	NR	NR	NR	NR	NR
Weitz 2010	719	65.3	37.9	88.3	30.3	NR	NR	NR	NR	NR	NR	86.7	NR	52.4
EINSTEIN 2010	3429	56.2	56.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	68.5	NR
Raskob 2010	530	57.7	35	NR	27.9	NR	NR	NR	NR	NR	NR	NR	NR	NR
ROCKET AF 2011	14,236	73	39.7	NR	28.2	62.4	90.6	40	54.7	17.3	NR	67	NR	36.7
ARISTOTLE 2011	18,140	70	35.3	82	NR	35.5	87.4	25	19.4	14.2	NR	NR	NR	NR
Chung 2011	234	65.1	49	70	NR	28.7	71.3	29.4	24.4	NR	NR	NR	NR	39.7
AVERROES 2011	4599	70	41	NR	28	39	86	19	14	NR	NR	NR	NR	NR
ADOPT 2011	6401	66.7	50.9	NR	NR	NR	NR	NR	NR	NR	9.7	NR	NR	NR
J-ROCKET AF 2012	1278	71.1	19.4	NR	NR	40.8	79.5	38	63.6	7.7	NR	NR	26.4	36.4
EINSTEIN–PE 2012	4817	57.7	42.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	66.1	NR
RE-MEDY 2013	2856	54.7	39	86	NR	NR	NR	NR	NR	NR	4.2	105.4	NR	NR
ENGAGE AF-TIMI 48 2013	21,026	72	38.1	NR	NR	57.4	93.6	36.1	28.3	NR	NR	NR	19.3	29.3
Hokusai-VTE 2013	8240	55.8	42.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
AMPLIFY 2013	5395	56.9	41.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	64.5	NR
MAGELLAN 2013	7998	71	45.9	77.4	28.2	32.3	NR	NR	17.3	NR	7.3	NR	38.5	NR
RE-COVER II 2014	2568	54.9	39.4	80.5	28.4	NR	NR	NR	NR	NR	3.9	107.6	NR	9.4
Boehringer Ingelheim 2014	2596	66.1	57.7	NR	31.5	NR	NR	NR	NR	NR	NR	NR	NR	NR
X-VeRT 2014	1487	64.8	27.2	NR	30.14	18.1	65.8	20.3	6.3	8.2	NR	NR	60.2	27.1
Daiichi Sankyo 2015	234	65.1	34.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
J-EINSTEIN DVT and PE 2015	97	65.7	47.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	42.3	NR
APEX 2016	7432	76.4	54.4	80.3	29.4	44.6	NR	NR	11.2	NR	12.1	NR	18.5	NR
PIONEER AF-PCI 2016	2099	70.1	25.5	NR	NR	NR	NR	NR	NR	NR	NR	78.8	NR	NR
RE-DUAL PCI 2017	2678	71	24	NR	NR	NR	NR	36.4	8.2	25.6	NR	78	NR	NR

COMPASS 2017	4978	67.8	28	NR	28.4	NR	79.5	44	6.7	NR	NR	NR	NR	NR
EINSTEIN CHOICE 2017	3365	58.5	44.6	NR	NR	NR	NR	NR	NR	NR	2.7	NR	69.9	NR
ENSURE-AF 2017	2199	64.2	35	91.1	30.7	44	18	19	6	NR	NR	94.1	58	NR
Hokusai VTE Cancer 2018	1046	64	47.7	79	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
SELECT-D 2018	406	67	47	NR	26.7	NR	NR	NR	NR	NR	NR	NR	NR	NR
RE-CIRCUIT 2018	676	59.2	20.2	28.7	NR	10.7	54.1	10.1	3	NR	NR	NR	NR	NR
EMANATE 2018	1456	64.6	33.2	NR	NR	NR	65.2	19.6	NR	NR	NR	NR	NR	NR

BMI, body mass index; Ccr, creatinine clearance rate; DM, diabetes; HF, heart failure; HBP, hypertension; MI, myocardial infarction; NR, not reported; TIA, transient ischemic attack.

Supplementary Table 5. Characteristics of Real-World Studies

Study (indication)	Country or region/data source/inclusion period	Interventions/N	Controls/N	Adjusted method	Follow-up	Outcome ascertainment
Laliberté 2014 (AF)[187]	USA/Symphony Health Solutions' Patient Transactional Datasets/2011.5-2012.7	Rivaroxaban/3654	Warfarin/14,616	PSM	At least 6 mo	ICD-9
Larsen 2014 (AF)[21]	Denmark/Danish Civil Registration system; National Patient Register; National Prescription Registry/ 2011.8.1-2013.5.30	Dabigatran/7063	Warfarin/14,126	CA	13.2 mo	ICD-10
Graham 2015 (AF)[188]	USA/Beneficiary Base and Chronic Conditions segments/ 2010.10.19-2012.12.31	Dabigatran/67,207	Warfarin/67,207	PSM	At least 6 mo	ICD-9
Hernandez 2015 (AF)[189]	USA/the Centers for Medicare and Medicaid Services/ 2010.10.1-2011.10.31	Dabigatran/1302	Warfarin/8102	IPTW	177 days	ICD-9
Abraham 2015 (VTE)[190]	USA/Optum Labs Data Warehouse/2010.11.1-2013.9.30	Dabigatran; rivaroxaban/ 11,535	Warfarin/11,535	PSM	NR	ICD-9
Villines 2015 (AF)[191]	USA/Department of Defense/2009.10.1-2013.7.31	Dabigatran/12,793	Warfarin/12,793	PSM	217–297days	ICD-9
Chang 2015 (NR)[192]	USA/IMS Health Life Link Health Plan Claims Database/ 2010.10.1-2012.3.31	Dabigatran; rivaroxaban/ 6556	Warfarin/39,607	PSA	At least 6 mo	ICD-9
Yao 2016 (AF)[193]	USA/Optum Labs Data Warehouse/2010.10.1-2015.6.30	Dabigatran; rivaroxaban; apixaban/38,177	Warfarin/38,177	PSM	0.7 y	ICD-9
Chan 2016 (AF)[118]	Taiwan/Taiwan National Health Insurance Research Database/1996.1.1-2013.12.31	Dabigatran; rivaroxaban/ 9837	Warfarin/5251	IPTW	NR	ICD-9
Avgil-Tsadok 2016 (AF)[194]	Canada/the provincial hospital discharge database and the provincial physician and prescription claims database/1999.1.1-2013.3.31	Dabigatran/15,918	Warfarin/47,192	PSA	NR	ICD-9 and -10
Nishtala 2016 (AF)[195]	New Zealand/the National Minimum Dataset/2011.7.1-2012.12.31	Dabigatran/4385	Warfarin/4385	PSM	NR	ICD-10
Kalil 2016 (AF)[196]	USA/VA National Patient Care inpatient and outpatient claims and VA Decision Support System/2011.6.1-2012.12.31	Dabigatran/864	Warfarin/1710	PSM	NR	ICD-9
Bengtson 2017 (AF)[35]	USA/MarketScan/2009.1.1-2012.12.31	Dabigatran/18,981	Warfarin/37,707	PSA	15 mo	ICD-9
Norby 2017 (AF)[197]	USA/MarketScan/2010.1.1-2014.12.31	Rivaroxaban/32,495	Warfarin/45,496	PSA	NR	ICD-9
Friberg 2017 (AF)[28]	Sweden/National Swedish Patient Register, Dispensed Drug Register, Cause of Death Register and the socioeconomic longitudinal integration database/ 2011.12.1-2014.12.31	Dabigatran; rivaroxaban; apixaban/18,638	Warfarin/49,418	PSA	NR	ICD-10
Palamaner Subash Shantha 2017 (AF)[198]	USA/Beneficiary Base and Chronic Conditions segments/ 2011-2013	Dabigatran; rivaroxaban/ 37,298	Warfarin/37,298	PSM	NR	ICD-9
Hernandez 2017 (AF)[199]	USA/Medical and pharmacy claims/2013.1.1-2014.12.31	Dabigatran; rivaroxaban; apixaban/8912	Warfarin/12,353	CA	185–274 days	ICD-9
Gieling 2017 (AF)[200]	UK/Clinical Practice Research Datalink/2008.3.18-2014.10.1	Dabigatran; rivaroxaban/ 1306	VKA/13,643	CA	1–2.7 y	ICD-9
Deitelzweig 2017 (AF)[201]	USA/Humana/2013.1.1-2015.9.30	Apixaban/7107	Warfarin/7107	PSM	NR	ICD-9
Halvorsen 2017 (AF)[202]	Norway/Norwegian Patient Registry and the Norwegian Prescription Database/2013.1-2015.6	Dabigatran; rivaroxaban; apixaban/21,248	Warfarin/11,427	CA	143–209 days	ICD-10

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Li 2017 (AF)[203]	USA/MarketScan and Optum and PharMetrics and Humana/2012.1.1-2015.9.30	Apixaban/38,470	Warfarin/38,470	PSM	158–166 days	ICD-9
Go 2017 (AF)[204]	USA/National U.S. Food and Drug Administration Sentinel network/2010.11.1-2014.5.31	Dabigatran/25,289	Warfarin/25,289	PSM	123 days	ICD-9
Chan 2017 (AF)[205]	Taiwan/Taiwan National Health Insurance Database/ 1996.1-2013.12	Dabigatran; rivaroxaban/ 9767	Aspirin + $P2Y_{12}$/12,854	IPTW	NR	ICD-9
Amin 2017 (AF)[85]	USA/the Centers for Medicare and Medicaid Services/ 2013.1.1-2014.12.31	Dabigatran; rivaroxaban; apixaban/90,010	Warfarin/90,010	PSM	NR	ICD-9
Adeboyeje 2017 (AF)[206]	USA/HealthCore Integrated Research Environment/ 2009.11.1-2016.1.31	Dabigatran; rivaroxaban; apixaban/20,626	Warfarin/23,431	IPTW	NR	ICD-9
Zoppellaro 2018 (AF)[207]	Italy/linked claims data in the Veneto Region using the drug prescriptions archive, the regional inpatients register, the database of residents registered in the regional health system and the archive of co-payment exemptions/2013.7-2015.12	Dabigatran; rivaroxaban; apixaban/2882	VKA/12,254	PSA	At least 3 mo	ICD-9
Streiff 2018 (Cancer and VTE[208]	USA/Humana/2007.1-2015.6	Rivaroxaban/685	LWMH/682	IPTW	NR	ICD-9
Mayer 2018 (AF)[209]	Italy/the Lazio Region healthcare assistance file/2013.7.1-2015.12.31	NOACs/5371	VKA/5371	PSM	NR	ICD-9
Martinez 2018 (AF)[210]	USA/MarketScan/2011.11-2016.12	Dabigatran; rivaroxaban; apixaban/5377	Warfarin/5377	PSM	0.9–1.4 y	ICD-9 and -10
Li 2018 (AF)[211]	USA/MarketScan and Optum and PharMetrics and Humana/2013.1.1-2015.9.30	Apixaban/38,427	Warfarin/38,427	PSM	NR	ICD-9
Lee 2018 (AF)[212]	Taiwan/Taiwan National Health Insurance Database/ 2010.1.1-2016.12.31	Rivaroxaban/26,000	Warfarin/16,000	PSA	1–1.4 y	ICD-9 and -10
Hohnloser 2018 (AF)[82]	Germany/the Health Risk Institute database/2013.1.1-2015.12.31	Dabigatran; rivaroxaban; apixaban/37,382	Phenprocoumon/ 23,823	CA and PSM	306–340 days	ICD-10
Coleman 2018 (VTE)[111]	USA/MarketScan/2012.1-2016.12	Rivaroxaban/1365	Warfarin/5504	IPTW	NR	ICD-9 and -10
Coleman 2018 (AF)[213]	USA/MarketScan/2011.11.1-2016.12.31	Rivaroxaban/5517	Warfarin/5517	PSM	NR	ICD-9 and -10
Lai 2018 (AF)[214]	Taiwan/Taiwan National Health Insurance Database/ 2012.6.1-2015.5.31	Dabigatran; rivaroxaban/ 2387	Warfarin/2387	PSM	6.6 mo	ICD-9 and -10
Chan 2018 (AF)[215]	Taiwan/Taiwan National Health Insurance Database/ 2010.1.1-2016.12.31	Dabigatran; rivaroxaban; apixaban /53,699	Warfarin/19,375	IPTW	0.76–1.55 y	ICD-9 and -10
Briasoulis 2018 (AF)[216]	USA/Beneficiary Base and Chronic Conditions segments/ 2010.1.1-2013.12.31	Dabigatran; rivaroxaban/ 30,728	Warfarin/30,728	PSM	211–248 days	ICD-9
Vinogradova 2018 (AF and VTE)[55]	UK/UK primary care databases Qresearch and Clinical Practice Research Datalink/2011.1-2016.10	Dabigatran; rivaroxaban; apixaban/32,685	Warfarin/70,585	CA	NR	ICD-10
Ujeyl 2018 (AF)[217]	Germany/health insurance fund AOK/2012.1.1-2013.12.31	Dabigatran; rivaroxaban; apixaban/87,997	Phenprocoumon/ 87,997	PSM	249–305 days	ICD-10
Siontis 2018 (AF)[218]	USA/Renal Data System Coordinating Center/2010.10-2015.12	Apixaban/2351	Warfarin/7053	PSM	NR	ICD-9 and -10
Coleman 2018 (VTE)[219]	USA/MarketScan/2012.1-2016.12	Rivaroxaban/10,489	Warfarin/26,364	IPTW	6 mo	ICD-9 and -10

AF, atrial fibrillation; CA, covariate adjustment; ICD, International Classification of Diseases; IPTW, inverse probability of treatment weighting; LWMH, low-molecular-weight heparin; NOACs, non–vitamin K antagonist oral anticoagulants; NR, not reported; PSA, propensity score adjustment; PSM, propensity score matching; UK, United Kingdom; USA, United States of America; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Supplementary Table 6. Patient Demographics and Clinical Characteristics of Real-World Studies

Study	N	Mean age (*y*)	Female (%)	Obesity (%)	HF (%)	HBP (%)	DM (%)	Stroke/ TIA (%)	MI (%)	Renal disease (%)	Liver disease (%)	Anemia (%)	Cancer (%)	CHADS2 (mean)	CHADS2-VASc (mean)	HAS-BLED (mean)	HAS-BLED >3 (%)
Laliberté 2014 (AF)	18,270	73.6	51.4	NR	NR	71.6	26.0	9.8	NR	12.7	NR	11.2	NR	2.0	3.4	1.9	18.5
Larsen 2014 (AF-Dabi 110 mg)	17,171	82.0	55.1	NR	NR	34.8	13.6	26.5	NR	3.1	0.5	NR	NR	1.9	3.7	2.3	NR
Larsen 2014 (AF-Dabi 150 mg)	18,144	67.0	36.6	NR	NR	33.0	11.2	16.3	NR	1.3	0.1	NR	NR	0.9	2.1	1.7	NR
Graham 2015 (AF)	134,414	NR	51.0	11.0	18.0	87.0	33.0	10.0	2.0	18.0	NR	NR	NR	NR	NR	NR	41.0
Hernandez 2015 (AF)	9404	75.1	57.9	NR	51.1	87.6	43.9	22.5	8.6	32.9	NR	NR	NR	NR	NR	NR	NR
Abraham 2015 (VTE-Dabi)	1464	64.6	37.2	NR	19.3	NR	28.6	NR	9.4	6.7	NR	NR	NR	NR	NR	NR	22.9
Abraham 2015 (VTE-Riva)	21,606	60.4	56.1	NR	4.1	NR	19.7	NR	2.1	4.3	NR	NR	NR	NR	NR	NR	20.3
Villines 2015 (AF)	25,586	73.8	41.2	NR	12.9	96.5	14.9	5.4	NR	11.7	NR	NR	NR	NR	3.9	3.4	76.8
Chang 2015 (Dabi)	44,514	62.0	30.9	NR	NR	NR	NR	NR	NR	4.2	NR	NR	NR	NR	NR	NR	NR
Chang 2015 (Riva)	41,256	57.6	51.5	NR	NR	NR	NR	NR	NR	2.1	NR	NR	NR	NR	NR	NR	NR
Yao 2016 (AF-Dabi)	28,614	70.0	40.0	17.6	27.2	85.2	34.0	13.8	NR	5.6	3.5	NR	NR	NR	3.0	2.0	33.7
Yao 2016 (AF-Riva)	32,350	72.0	43.5	18.3	28.9	85.7	34.6	14.0	NR	7.4	3.7	NR	NR	NR	4.0	2.0	38.6
Yao 2016 (AF-Api)	15,390	73.0	46.8	19.6	31.4	87.5	35.0	15.1	NR	10.1	4.0	NR	NR	NR	4.0	2.0	41.5
Chan 2016 (AF-Dabi)	11,172	75.0	42.0	NR	16.0	86.0	41.0	37.0	3.0	22.0	28.0	NR	NR	NR	4.1	3.1	NR
Chan 2016 (AF-Riva)	9167	76.0	54.0	NR	16.0	87.0	41.0	34.0	4.0	22.0	27.0	NR	NR	NR	4.1	3.1	NR
Avgil-Tsadok 2016 (AF-Dabi <75 y)	20,632	NR	36.5	NR	26.3	69.0	29.6	9.0	15.9	12.6	6.1	NR	8.3	NR	2.1	2.1	31.9
Avgil-Tsadok 2016 (AF-Dabi >75 y)	42,478	NR	54.9	NR	29.7	77.5	24.7	11.6	17.7	23.1	4.5	NR	11.0	NR	3.6	2.5	46.0

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Nishtala 2016 (AF)	8770	77.3	46.9	NR	22.4	NR	15.6	NR	13.0	7.6	0.2	NR	3.5	NR	NR	NR	NR
Kalil 2016 (AF)	2574	73.7	1.3	26.6	33.8	83.5	46.2	3.4	6	11.6	1.7	NR	NR	NR	3.67	2.88	NR
Bengtson 2017 (AF)	56,688	68.5	36.2	NR	24.3	75.2	28.6	20.6	7.6	7.6	4.8	NR	1.6	2.0	NR	NR	NR
Norby 2017 (AF)	77,991	69.3	38.7	NR	23.1	66.0	25.7	15.5	7.1	7.6	3.6	NR	1.6	NR	3.0	NR	NR
Friberg 2017	68,056	73.4	45.6	NR	19.5	61.1	16.1	19.5	10.8	2.5	1.4	8.8	8.6	NR	3.2	NR	NR
Palamaner Subash Shantha 2017 (AF-Dabi, men)	15,236	75.9	0.0	NR	24.9	82.5	34.5	11.1	NR	10.5	4.3	NR	NR	2.3	3.8	1.7	NR
Palamaner Subash Shantha 2017 (AF-Dabi, women)	22,062	76.8	100.0	NR	24.2	85.6	31.3	13.1	NR	8.1	4.0	NR	NR	2.4	4.8	1.6	NR
Palamaner Subash Shantha 2017 (AF-Riva, men)	15,236	75.1	0.0	NR	24.7	82.5	34.4	11.1	NR	10.9	3.8	NR	NR	2.3	3.8	1.7	NR
Palamaner Subash Shantha 2017 (AF-Riva, women)	22,062	76.8	100.0	NR	23.8	85.6	30.9	12.8	NR	7.9	4.1	NR	NR	2.4	4.8	1.6	NR
Hernandez 2017 (AF-Dabi)	13,768	74.9	53.0	NR	41.9	88.9	42.2	17.5	5.6	25.4	NR	NR	NR	NR	4.3	3.5	NR
Hernandez 2017 (AF-Riva)	17,492	76.4	56.3	NR	44.6	91.8	42.3	21.5	7.2	30.4	NR	NR	NR	NR	4.6	3.7	NR
Hernandez 2017 (AF-Api)	14,711	77.4	57.5	NR	45.9	93.6	44.7	21.0	7.4	34.1	NR	NR	NR	NR	4.7	3.7	NR
Gieling 2017 (AF)	14,949	72.6	45.1	NR	7.5	54.6	NR	NR	NR	1.0	NR	NR	1.2	NR	2.6	NR	NR
Deitelzweig 2017 (AF)	14,214	78.2	47.4	NR	NR	NR	NR	11.9	NR	NR	NR	NR	NR	2.7	4.6	3.0	63.3
Halvorsen 2017 (AF-Dabi)	19,352	70.8	38.0	NR	15.8	59.0	10.4	9.4	NR	NR	NR	2.0	7.4	NR	2.5	NR	37.0
Halvorsen 2017 (AF-Riva)	18,244	74.7	45.6	NR	20.4	66.0	11.7	16.1	NR	NR	NR	3.0	9.2	NR	2.9	NR	47.0
Halvorsen 2017 (AF-Api)	17,933	74.5	45.0	NR	20.6	65.4	12.3	13.9	NR	NR	NR	3.1	8.6	NR	2.9	NR	46.6
Li 2017 (AF)	76,940	70.9	40.4	NR	24.2	82.5	32.5	16.4	8.9	19.8	4.4	18.6	NR	2.1	3.2	2.6	50.5
Go 2017 (AF)	50,578	68.5	36.1	NR	38.6	81.6	30.1	8.1	4.9	11.6	0.3	5.9	1.2	NR	NR	NR	NR
Chan 2017 (AF-Dabi)	14,838	75.0	42.0	NR	15.0	86.0	40.0	40.0	2.0	22.0	27.0	NR	8.0	NR	4.1	3.1	NR

Supplementary Table 6. Continued

Study	N	Mean age (*y*)	Female (%)	Obesity (%)	HF (%)	HBP (%)	DM (%)	Stroke/ TIA (%)	MI (%)	Renal disease (%)	Liver disease (%)	Anemia (%)	Cancer (%)	CHADS2 (mean)	CHADS2-VASc (mean)	HAS-BLED (mean)	HAS-BLED >3 (%)
Chan 2017 (AF-Riva)	7783	76.0	47.0	NR	15.0	86.0	39.0	34.0	3.0	21.0	27.0	NR	8.0	NR	4.1	3.1	NR
Amin 2017 (AF-Dabi)	33,462	77.2	49.4	NR	28.6	88.1	37.1	19.2	10.8	19.1	NR	NR	NR	2.6	4.4	3.1	65.4
Amin 2017 (AF-Riva)	104,952	77.7	51.7	NR	29.0	88.7	36.2	19.9	12.2	21.1	NR	NR	NR	2.7	4.5	3.2	69.5
Amin 2017 (AF-Api)	41,606	78.4	52.3	NR	30.7	90.3	35.3	21.4	12.8	23.9	NR	NR	NR	2.8	4.6	3.3	71.3
Adeboyeje 2017 (AF-Dabi)	31,970	70.0	40.9	NR	27.8	59.8	28.4	NR	NR	10.1	4.7	NR	NR	NR	NR	2.1	NR
Adeboyeje 2017 (AF-Riva)	31,829	70.0	40.9	NR	27.8	59.8	28.4	NR	NR	10.1	4.7	NR	NR	NR	NR	2.1	NR
Adeboyeje 2017 (AF-Api)	27,120	70.0	40.9	NR	27.8	59.8	28.4	NR	NR	10.1	4.7	NR	NR	NR	NR	2.1	NR
Zoppellaro 2018 (AF)	15,136		37.4	NR	15.0	81.0	17.2	26.7	2.7	4.0	1.1	NR	9.8	NR	4.3	2.7	NR
Streiff 2018 (cancer and VTE)	1367	72.7	51.6	12.2	15.0	72.2	33.1	4.8	NR	16.1	17.4	NR	100.0	NR	NR	NR	NR
Mayer 2018 (AF)	10,742	NR	50.2	2.9	23.7	39.7	12.6	9.3	5.5	8.3	1.3	4.3	4.6	NR	NR	NR	42.5
Martinez 2018 (AF-Dabi)	2700	85.0	63.7	5.1	47.9	83.8	27.3	15.2	8.4	47.4	2.6	21.5	0.9	3.0	4.0	2.0	NR
Martinez 2018 (AF-Riva)	5270	86.0	64.8	7.1	49.1	86.0	27.5	15.0	9.5	57.2	3.1	25.1	2.0	3.0	4.0	2.0	NR
Martinez 2018 (AF-Api)	2784	86.0	63.3	7.3	48.2	88.4	29.5	18.2	12.1	69.7	3.5	26.4	1.9	3.0	4.0	2.0	NR
Li 2018 (AF-Api 2.5 mg)	13,200	82.5	58.2	NR	37.1	88.8	33.9	25.4	11.9	38.4	4.3	NR	NR	2.9	4.5	3.3	72.5
Li 2018 (AF-Api 5 mg)	63,654	68.6	37.1	NR	21.5	81.4	32.2	14.5	8.3	15.8	4.5	NR	NR	1.9	3	2.5	46
Lee 2018 (AF-Riva 15 mg)	30,971	78	48	NR	14	86	39	22	NR	28	16	NR	10	NR	4	3	NR
Lee 2018 (AF-Riva 10 mg)	27,029	78	48	NR	14	86	39	22	NR	29	16	NR	10	NR	4	3	NR
Hohnloser 2018 (AF-Dabi)	28,945	71.7	44.9	22.4	30.7	84.4	30.2	21.7	5.5	12.3	0.2	NR	17.5	NR	3.7	2.6	NR
Hohnloser 2018 (AF-Riva)	45,966	72.1	45.3	24.3	32.5	83.8	32.2	11.2	4.8	15.9	0.4	NR	18.2	NR	3.5	2.5	NR
Hohnloser 2018 (AF-Api)	33,940	74.5	48.6	22.9	35.5	87.0	33.4	20.1	5.7	21.0	0.6	NR	19.8	NR	4.0	2.8	NR

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Coleman 2018 (VTE-Riva)	6869	81.8	65.6	9.1	19.8	79.5	28.0	16.4	NR	32.9	3.5	21.5	3.0	NR	NR	NR	NR
Coleman 2018 (AF)	11,034	70.0	63.4	22.4	24.7	85.6	NR	7.4	8.0	34.0	4.7	17.9	1.8	2.0	3.0	2.0	33.1
Lai 2018 (AF)	4774	88.6	52	NR	27.8	51.3	15.9	14.5	1.4	NR	NR	1.1	NR	2.2	3.8	NR	NR
Chan 2018 (AF-Dabi)	39,454	76.0	45.0	NR	12.0	87.0	41.0	23.0	NR	28.0	16.0	NR	9.0	NR	3.9	3.0	NR
Chan 2018 (AF-Riva)	47,152	76.0	45.0	NR	13.0	86.0	41.0	23.0	NR	28.0	16.0	NR	9.0	NR	3.9	3.0	NR
Chan 2018 (AF-Api)	25,218	76.0	45.0	NR	13.0	87.0	41.0	23.0	NR	29.0	16.0	NR	10.0	NR	3.9	3.0	NR
Briasoulis 2018 (NVAF-Dabi)	26,814	75.5	47.0	NR	19.0	84.0	33.0	NR	7.0	8.0	4.0	NR	NR	NR	4.1	1.6	NR
Briasoulis 2018 (NVAF-Riva)	26,814	75.4	50.0	NR	19.0	84.0	34.0	NR	7.0	7.0	4.0	NR	NR	NR	4.1	1.6	NR
Briasoulis 2018 (VAF-Dabi)	3914	77.0	62.0	NR	47.0	90.0	33.0	NR	15.0	12.0	4.0	NR	NR	NR	5.0	1.8	NR
Briasoulis 2018 (VAF-Riva)	3914	77.0	60.0	NR	44.0	89.0	33.0	NR	16.0	12.0	6.0	NR	NR	NR	5.0	1.8	NR
Vinogradova 2018 (AF-Dabi)	76,122	74.7	42.0	NR	11.1	60.6	17.3	22.0	NR	1.0	1.4	NR	12.5	NR	NR	NR	NR
Vinogradova 2018 (AF-Riva)	87,132	75.8	45.6	NR	11.4	59.2	17.9	16.8	NR	1.6	1.4	NR	13.3	NR	NR	NR	NR
Vinogradova 2018 (AF-Api)	81,186	76.5	48.2	NR	12.8	59.9	19.3	22.7	NR	2.1	1.3	NR	13.1	NR	NR	NR	NR
Vinogradova 2018 (VTE-Dabi)	63,853	71.6	46.9	NR	6.6	51.3	17.0	20.6	NR	1.0	1.1	NR	10.8	NR	NR	NR	NR
Vinogradova 2018 (VTE-Riva)	82,962	68.2	51.2	NR	5.0	40.0	15.1	10.5	NR	1.3	1.2	NR	13.1	NR	NR	NR	NR
Vinogradova 2018 (VTE-Api)	69,268	73.9	48.3	NR	8.8	52.1	20.0	22.9	NR	2.2	1.4	NR	13.3	NR	NR	NR	NR
Ujeyl 2018 (AF-Dabi)	47,308	75.5	54.0	NR	30.2	82.3	37.3	15.0	4.0	17.2	0.3	7.6	14.8	NR	NR	NR	5.0
Ujeyl 2018 (AF-Riva)	118,898	75.5	54.0	NR	30.2	82.3	37.3	15.0	4.0	17.2	0.3	7.6	14.8	NR	NR	NR	5.0
Ujeyl 2018 (AF-Api)	9788	75.5	54.0	NR	30.2	82.3	37.3	15.0	4.0	17.2	0.3	7.6	14.8	NR	NR	NR	5.0
Siontis 2018 (AF)	9404	68.9	45.6	25.1	79.5	99.6	75.4	NR	26.9	100.0	9.4	99.3	14.0	NR	5.3	NR	NR
Coleman 2018 (VTE)	36,853	56.0	46.1	NR	1.8	46.2	20.2	2.1	NR	3.5	NR	NR	NR	NR	NR	NR	NR

AF, atrial fibrillation; Api, apixaban; Dabi, dabigatran; DM, diabetes; HF, heart failure; HBP, hypertension; MI, myocardial infarction; NR, not reported; Riva, rivaroxaban; TIA, transient ischemic attack; VTE, venous thromboembolism.

Supplementary Table 7. Patient Bleeding History and Concomitant Drugs of Real-World Studies

Study	Prior bleeding	Prior GI bleeding	ACEI/ ARB	Beta-blocker	Dil	Vera	CCB	Amio	Dron	Digoxin	Antia-drugs	Statin	Antip-drugs	Asp	Clo	NSAIDS	PPI	H2	SSRI	Glu	Estr
Laliberté 2014 (AF)	18,270	7.9	2.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	12.1	NR	NR	NR	NR
Larsen 2014 (AF-Dabi 110 mg)	17,171	18.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	49.2	41.1	8.1	5.9	NR	NR	NR	NR
Larsen 2014 (AF-Dabi 150 mg)	18,144	11.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	37.9	32.9	5.0	6.0	NR	NR	NR	NR
Graham 2015 (AF)	134,414	4.0	NR	59.0	70.0		2.0	42.0	10.0	5.0	17.0	25.0	57.0	17.0	NR	NR	15.0	26.0	5.0	13.0	NR
Hernandez 2015 (AF)	9404	11.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	8.0	NR	NR	8.6	NR	NR	NR	NR
Abraham 2015 (VTE-Dabi)	1464	NR	0.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	17.5	NR	NR	22.1	22.5		16.1	17.8
Abraham 2015 (VTE-Riva)	21,606	NR	0.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4.4	NR	NR	50.0	22.2		22.5	23.6
Villines 2015 (AF)	25,586	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	22.2	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chang 2015 (Dabi)	44,514	NR	9.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	15.6	18.7	NR	NR	NR
Chang 2015 (Riva)	41,256	NR	3.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	43.7	19.2	NR	NR	NR
Yao 2016 (AF-Dabi)	28,614	29.4	NR	45.4	44.6	17.5	1.9	13.3	8.4	3.7	13.6	12.8	41.5	10.3	NR	NR	NR	18.4	NR	14.5	NR
Yao 2016 (AF-Riva)	32,350	30.7	NR	45.5	45.6	17.5	1.7	14.9	8.3	2.4	10.8	11.0	43.0	11.6	NR	NR	NR	20.3	NR	15.3	NR
Yao 2016 (AF-Api)	15,390	31.4	NR	47.1	47.5	16.9	1.3	16.6	9.6	2.8	8.9	11.1	45.6	12.1	NR	NR	NR	21.9	NR	16.2	NR
Chan 2016 (AF-Dabi)	11,172	2.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	45.0	NR	NR	25.0	5.0	NR	NR	NR
Chan 2016 (AF-Riva)	9167	2.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	41.0	NR	NR	23.0	7.0	NR	NR	NR
Avgil-Tsadok 2016 (AF-Dabi <75 y)	20,632	6.3	NR	19.5	37.7	10.8	1.5	NR	9.5	NR	13.7	4.0	22.6	22.3	19.9	2.4	1.0	NR	NR	NR	NR
Avgil-Tsadok 2016 (AF-Dabi >75 y)	42,478	9.3	NR	19.3	40.2	12.1	1.5	NR	7.0	NR	16.9	2.1	21.2	19.3	17.1	2.2	0.5	NR	NR	NR	NR
Nishtala 2016 (AF)	8770	NR	NR	NR	NR	NR	2.7	NR	8.6	NR	23.9	NR	66.4	79.5	71.5	8.0	NR	49.6	4.0	NR	NR
Kalil 2016 (AF)	2574	NR	23.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bengtson 2017 (AF)	56,688	11.2	7.6	59.5	71.1	NR	NR	41.7	NR	NR	14.9	29.4	54.3	16.1	2.1	14.0	NR	NR	NR	NR	NR
Norby 2017 (AF)	77,991	6.8	4.4	50.2	63.9	NR	NR	36.0	NR	NR	11.4	20.2	46.6	11.3	1.8	9.5	NR	NR	NR	NR	NR
Friberg 2017	68,056	10.2	3.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Palamaner Subash Shantha 2017 (AF-Dabi, men)	15,236	NR	23.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	46.9	5.5	NR	NR	11.1	18.4	NR	NR	NR
Palamaner Subash Shantha 2017 (AF-Dabi, women)	22,062	NR	27.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	42.7	4.5	NR	NR	15.4	22.1	NR	NR	NR
Palamaner Subash Shantha 2017 (AF-Riva, men)	15,236	NR	23.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	46.6	5.6	NR	NR	10.8	17.9	NR	NR	NR
Palamaner Subash Shantha 2017 (AF-Riva, women)	22,062	NR	28.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	42.0	4.4	NR	NR	14.7	22.3	NR	NR	NR
Hernandez 2017 (AF-Dabi)	13,768	13.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10.7	NR	NR	11.8	NR	NR	NR	NR
Hernandez 2017 (AF-Riva)	17,492	15.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	12.5	NR	NR	12.7	NR	NR	NR	NR

Hernandez 2017 (AF-Api)	14,711	15.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	13.4	NR	NR	11.6	NR	NR	NR	NR
Gieling 2017 (AF)	14,949	NR	3.2	NR	NR	NR	NR	NR	NR	NR	NR	6.2	30.2	0.7	NR	NR	11.0	27.6	2.5	7.0	9.7
Deitelzweig 2017 (AF)	14,214	18.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Halvorsen 2017 (AF-Dabi)	19,352	11.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	48.8	46.5	2.3	24.4	NR	NR	NR	NR
Halvorsen 2017 (AF-Riva)	18,244	14.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	56.5	53.1	3.4	23.2	NR	NR	NR	NR
Halvorsen 2017 (AF-Api)	17,933	15.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	53.7	50.8	2.9	23.0	NR	NR	NR	NR
Li 2017 (AF)	76,940	16.6	NR	58.6	60.1	NR	NR	NR	11.0	NR	NR	NR	56.5	15.8	NR	NR	23.5	27.6	5.2	NR	NR
Go 2017 (AF)	50,578	2.1	1.1	60.1	71.5	NR	NR	40.9	NR	NR	NR	34.5	53.2	13.2	0.9	NR	21.1	25.2	NR	NR	NR
Chan 2017 (AF-Dabi)	14,838	2.0	NR	62.0	50.0	20.0	NR	NR	17.0	NR	26.0	NR	28.0	NR	NR	NR	24.0	5.0	NR	NR	NR
Chan 2017 (AF-Riva)	7783	5.0	NR	59.0	53.0	22.0	NR	NR	13.0	NR	26.0	NR	25.0	NR	NR	NR	20.0	7.0	NR	NR	NR
Amin 2017 (AF-Dabi)	33,462	19.5	NR	63.2	53.8	NR	NR	NR	8.6	NR	NR	NR	57.4	15.1	NR	NR	NR	29.6	6.5	NR	NR
Amin 2017 (AF-Riva)	104,952	22.5	NR	61.3	54.1	NR	NR	NR	8.0	NR	NR	NR	57.5	16.9	NR	NR	NR	31.6	6.8	NR	NR
Amin 2017 (AF-Api)	41,606	21.9	NR	62.4	57.1	NR	NR	NR	10.4	NR	NR	NR	61.5	19.7	NR	NR	NR	33.2	7.0	NR	NR
Adeboyeje 2017 (AF-Dabi)	31,970	14.9	NR	NR	NR	NR	NR	NR	18.1	NR	NR	NR	NR	10.4	NR	NR	9.8	34.0	NR	NR	NR
Adeboyeje 2017 (AF-Riva)	31,829	14.9	NR	NR	NR	NR	NR	NR	18.1	NR	NR	NR	NR	10.4	NR	NR	9.8	34.0	NR	NR	NR
Adeboyeje 2017 (AF-Api)	27,120	14.9	NR	NR	NR	NR	NR	NR	18.1	NR	NR	NR	NR	10.4	NR	NR	9.8	34.0	NR	NR	NR
Zoppellaro 2018 (AF)	15,136	4.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	49.9	NR	NR	17.5	NR	NR	NR	NR
Streiff 2018 (cancer and VTE)	1367	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mayer 2018 (AF)	10,742	2.2	0.9	89.9	67.2	NR	NR	37.6	NR	NR	NR	42.0	43.0	10.2	48.2	13.7	53.5	81.6	4.2	11.1	24.2
Martinez 2018 (AF-Dabi)	2700	1.3	1.0	46.0	59.0	12.9	2.0	23.1	6.1	1.2	10.9	4.0	49.0	16.7	NR	NR	19.2	23.5	4.6	17.7	20.0
Martinez 2018 (AF-Riva)	5270	2.7	2.2	56.9	58.6	12.4	1.8	30.0	6.2	0.8	8.9	4.1	52.6	16.1	NR	NR	19.2	28.1	5.5	19.0	22.2
Martinez 2018 (AF-Api)	2784	3.4	3.1	49.3	62.2	108.0	1.5	29.4	6.2	0.4	7.1	3.8	53.1	17.1	NR	NR	17.7	30.8	6.0	18.8	21.6
Li 2018 (AF-Api 2.5 mg)	13,200	22.1	NR	60.7	61.5	NR	NR	NR	14.6	NR	NR	NR	60	21.6	NR	NR	21.2	33.2	6.9	NR	NR
Li 2018 (AF-Api 5 mg)	63,654	15.5	NR	58.3	59.9	NR	NR	NR	10.3	NR	NR	NR	56.2	15	NR	NR	24.1	26.5	4.8	NR	NR
Lee 2018 (AF-Riva 15 mg)	30,971	2	NR	14	56	25	NR	NR	27	6	22	NR	11	NR	NR	NR	25	11	32	NR	NR
Lee 2018 (AF-Riva 10 mg)	27,029	3	NR	14	56	25	NR	NR	27	6	22	NR	10	NR	NR	NR	25	11	32	NR	NR
Hohnloser 2018 (AF-Dabi)	28,945	7.2	NR	NR	82.3	NR	NR	NR	4.1	NR	NR	NR	NR	25.1	19.3	NR	35.5	44.0	NR	NR	NR
Hohnloser 2018 (AF-Riva)	45,966	7.6	NR	NR	82.6	NR	NR	NR	5.1	NR	NR	NR	NR	22.5	18.1	NR	36.9	43.6	NR	NR	NR
Hohnloser 2018 (AF-Api)	33,940	9.3	NR	NR	81.9	NR	NR	NR	5.0	NR	NR	NR	NR	26.5	21.2	NR	35.8	46.0	NR	NR	NR

Supplementary Table 7. Continued

Study	Prior bleeding	Prior GI bleeding	ACEI/ ARB	Beta-blocker	Dil	Vera	CCB	Amio	Dron	Digoxin	Antia-drugs	Statin	Antip-drugs	Asp	Clo	NSAIDS	PPI	H2	SSRI	Glu	Estr
Coleman 2018 (VTE-Riva)	6869	NR	NR	48.8	44.4	NR	NR	32.9	NR	NR	1.9	NR	47.2	33.1	NR	NR	NR	30.6	NR	NR	NR
Coleman 2018 (AF)	11,034	4.0	1.0	69.2	61.6	12.9	2.2	29.5	5.2	1.8	8.0	6.3	65.5	15.7	NR	NR	21.5	26.0	4.6	16.1	20.7
Lai 2018 (AF)	4774	NR	NR	59.5	41.7	21.3	2.7	39.7	15.7	2.2	20.3	NR	17	54.9	44.7	10.2	52.9	12	32	NR	NR
Chan 2018 (AF-Dabi)	39,454	2.0	NR	6.0	59.0	24.0	NR	NR	28.0	5.0	20.0	NR	4.0	NR	NR	NR	27.0	11.0	31.0	NR	NR
Chan 2018 (AF-Riva)	47,152	2.0	NR	6.0	59.0	24.0	NR	NR	28.0	5.0	20.0	NR	4.0	NR	NR	NR	27.0	11.0	31.0	NR	NR
Chan 2018 (AF-Api)	25,218	2.0	NR	6.0	59.0	25.0	NR	NR	28.0	5.0	20.0	NR	4.0	NR	NR	NR	27.0	11.0	31.0	NR	NR
Briasoulis 2018 (NVAF-Dabi)	26,814	29.0	24.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	44.0	NR	NR	4.4	13.0	20.0	NR	NR	NR
Briasoulis 2018 (NVAF-Riva)	26,814	30.0	24.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	45.0	NR	NR	4.5	13.0	20.0	NR	NR	NR
Briasoulis 2018 (VAF-Dabi)	3914	38.0	32.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	43.0	NR	NR	7.0	12.0	20.0	NR	NR	NR
Briasoulis 2018 (VAF-Riva)	3914	39.0	33.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	43.0	NR	NR	6.0	12.0	21.0	NR	NR	NR
Vinogradova 2018 (AF-Dabi)	76,122	25.9	13.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	53.6	23.3	NR	NR	8.5	44.1	NR	NR	11.2
Vinogradova 2018 (AF-Riva)	87,132	26.0	13.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	51.3	19.8	NR	NR	7.3	41.1	NR	NR	10.7
Vinogradova 2018 (AF-Api)	81,186	27.1	14.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	54.1	17.4	NR	NR	5.7	44.1	NR	NR	9.9
Vinogradova 2018 (VTE-Dabi)	63,853	22.7	12.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	49.1	21.6	NR	NR	17.2	45.0	NR	NR	9.2
Vinogradova 2018 (VTE-Riva)	82,962	23.3	13.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	35.3	16.4	NR	NR	13.2	40.4	NR	NR	10.5
Vinogradova 2018 (VTE-Api)	69,268	23.8	13.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	51.2	17.8	NR	NR	5.7	42.7	NR	NR	9.4
Ujeyl 2018 (AF-Dabi)	47,308	8.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	16.0	NR	NR	17.2	33.6	1.2	5.3	NR
Ujeyl 2018 (AF-Riva)	118,898	8.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	16.0	NR	NR	17.2	33.6	1.2	5.3	NR
Ujeyl 2018 (AF-Api)	9788	8.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	16.0	NR	NR	17.2	33.6	1.2	5.3	NR
Siontis 2018 (AF)	9404	9.2	10.6	15.7	39.3	NR	NR	22.5	NR	NR	NR	22.9	23.5	6.6	NR	NR	1.4	17.4	NR	NR	NR
Coleman 2018 (VTE)	36,853	0.6	NR	33.8	23.8	NR	NR	18.6	NR	NR	0.6	NR	29.9	27.8	NR	NR	NR	NR	NR	NR	NR

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; Amio, amiodarone; Antia-drugs, antiarrhythmic drugs; antip-drugs, antiplatelet agents; Api, apixaban; ARB, angiotensin receptor inhibitor; Asp, aspirin; CCB, calcium channel blocker; Clo, clopidogrel; Dabi, dabigatran; Dil, diltiazem; Dron, dronedarone; Estr, estrogen; GI, gastrointestinal tract; Glu, glucocorticoids; H2, H2-receptor antagonist; NR, not reported; NSAIDS, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; Riva, rivaroxaban; SSRI, serotonin receptor antagonist; Vera, verapamil; VTE, venous thromboembolism.

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Supplementary Table 8. Quality Assessment of Randomized Controlled Trials

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
ODIXa-HIP 2006	Low	Unclear	Low	Low	Low	Unclear	Low
RE-NOVATE 2007	Low	Low	Low	Low	Low	Low	Low
RE-MODEL 2007	Low	Low	Low	Low	Low	Low	Low
PETRO 2007	Unclear	Unclear	Unclear	Low	Low	Low	Low
RECORD1 2008	Low	Low	Low	Low	Low	Low	Low
RECORD2 2008	Low	Low	Low	Low	Low	Low	Low
RECORD3 2008	Low	Low	Low	Low	Low	Low	Low
RE-LY 2009	Low	Low	High	Low	Low	Low	Low
RE-COVER 2009	Low	Low	Low	Low	Low	Low	Low
RECORD4 2009	Low	Low	Low	Low	Unclear	Low	Low
ADVANCE-1 2009	Low	Low	Low	Low	Low	Low	Low
ADVANCE-2 2010	Low	Low	Low	Low	Low	Low	Low
ADVANCE-3 2010	Low	Low	Low	Low	Low	Low	Low
Weitz 2010	Low	Low	High	Unclear	Low	Low	Low
EINSTEIN 2010	Low	Unclear	High	Low	Low	Low	Low
Raskob 2010	Low	Low	Low	Low	Low	Low	Low
ROCKET AF 2011	Low	Low	Low	Low	Low	Unclear	Low
ARISTOTLE 2011	Low	Low	Low	Low	Low	Unclear	Low
Chung 2011	Low	Low	High	Low	Low	Low	Low
AVERROES 2011	Low	Low	Low	Low	Low	Low	Low
ADOPT 2011	Low	Unclear	Low	Low	Low	Low	Low
J-ROCKET AF 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
EINSTEIN–PE 2012	Low	Unclear	High	Low	Low	Low	Low
RE-MEDY 2013	Low	Low	Low	Low	Unclear	Low	Low
ENGAGE AF-TIMI 48 2013	Low	Low	Low	Low	Low	Low	Low
Hokusai-VTE 2013	Low	Unclear	Low	Low	Low	Low	Low
AMPLIFY 2013	Low	Low	Low	Low	Low	Low	Low
MAGELLAN 2013	Low	Low	Low	Low	Low	Low	Low
RE-COVER II 2014	Low	Unclear	Low	Low	Low	Low	Low
Boehringer Ingelheim 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
X-VeRT 2014	Low	Unclear	High	Low	Low	Low	Low
Daiichi Sankyo 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
J-EINSTEIN DVT and PE 2015	Low	Low	High	Low	Low	Low	Low
APEX 2016	Low	Low	Low	Low	Low	Low	Low
PIONEER AF-PCI 2016	Low	Low	High	Low	Low	Low	Low
RE-DUAL PCI 2017	Low	Low	High	Low	Low	Low	Low
COMPASS 2017	Low	Low	Low	Low	Low	Low	Low
EINSTEIN CHOICE 2017	Low	Low	Low	Low	Low	Low	Low
ENSURE-AF 2017	Low	Unclear	High	Low	Low	Low	Low
Hokusai VTE Cancer 2018	Low	Unclear	High	Low	Low	Low	Low
SELECT-D 2018	Low	Low	High	Low	Low	Low	Low
RE-CIRCUIT 2018	Low	Low	High	Low	Low	Low	Low
EMANATE 2018	Low	Unclear	High	Low	Low	Low	Low

High, high risk; Low, low risk; unclear, unclear risk.

Supplementary Table 9. Quality Assessment of Real-World Studies

Study	Selection bias	Bias due to residual confounding	Bias due to time-varying covariates/information censoring	Bias due to selective reporting of study outcomes
Laliberté 2014	Low	Moderate	Moderate	Low
Larsen 2014	Low	Moderate	Moderate	Low
Graham 2015	Low	Low	Low	Low
Hernandez 2015	Low	Low	Low	Low
Abraham 2015	Low	Low	Low	Low
Villines 2015	Low	Low	Moderate	Low
Chang 2015	Low	Low	Moderate	Low
Yao 2016	Low	Low	Moderate	Low
Chan 2016	Low	Moderate	Moderate	Low
Avgil-Tsadok 2016	Low	Low	Low	Low
Nishtala 2016	Low	Moderate	Moderate	Low
Kalil 2016	Low	Moderate	Low	Low
Bengtson 2017	Low	Moderate	Moderate	Low
Norby 2017	Low	Low	Moderate	Low
Friberg 2017	Low	Moderate	Moderate	Low
Palamaner Subash Shantha 2017	Low	Low	Moderate	Low
Hernandez 2017	Low	Moderate	Moderate	Low
Gieling 2017	Low	Low	Moderate	Low
Deitelzweig 2017	Low	Low	Low	Low
Halvorsen 2017	Low	Moderate	Moderate	Low
Li 2017	Low	Low	Moderate	Low
Go 2017	Low	Low	Moderate	Low
Chan 2017	Low	Moderate	Moderate	Low
Amin 2017	Low	Low	Moderate	Low
Adeboyeje 2017	Low	Moderate	Moderate	Low
Zoppellaro 2018	Low	Moderate	Low	Low
Streiff 2018	Low	Low	Low	Low
Mayer 2018	Low	Low	Moderate	Low
Martinez 2018	Low	Low	Moderate	Low
Li 2018	Low	Low	Moderate	Low
Lee 2018	Low	Low	Moderate	Low
Hohnloser 2018	Low	Moderate	Moderate	Low
Coleman 2018	Low	Low	Moderate	Low
Coleman 2018	Low	Low	Moderate	Low
Lai 2018	Low	Moderate	Moderate	Low
Chan 2018	Low	Low	Moderate	Low
Briasoulis 2018	Low	Moderate	Moderate	Low
Vinogradova 2018	Low	Low	Low	Low
Ujeyl 2018	Low	Moderate	Moderate	Low
Siontis 2018	Low	Low	Moderate	Low
Coleman 2018	Low	Moderate	Moderate	Low

Low, low risk; Moderate, moderate risk.

Supplementary Table 10. Sensitivity Analysis of RCTs and Real-World Studies

Omitted RCTs	RR (95% CI)	Omitted real-world studies	HR (95% CI)
ODIXa-HIP 2006	1.10 (0.91–1.32)	Laliberté 2014	1.01 (0.93–1.10)
RE-NOVATE 2007	1.10 (0.91–1.32)	Larsen 2014	1.02 (0.94–1.10)
RE-MODEL 2007	1.09 (0.91–1.31)	Graham 2015	1.01 (0.93–1.09)
PETRO 2007	1.09 (0.91–1.31)	Hernandez 2015	1.00 (0.93–1.08)
RECORD1 2008	1.09 (0.91–1.31)	Abraham 2015	1.02 (0.94–1.10)
RECORD2 2008	1.09 (0.91–1.31)	Villines 2015	1.02 (0.93–1.10)
RECORD3 2008	1.09 (0.91–1.31)	Chang 2015	1.01 (0.93–1.10)
RE-LY 2009	1.07 (0.88–1.31)	Yao 2016	1.02 (0.94–1.10)
RE-COVER 2009	1.08 (0.90–1.30)	Chan 2016	1.02 (0.94–1.10)
RECORD4 2009	1.08 (0.90–1.30)	Avgil-Tsadok 2016	1.01 (0.93–1.10)
ADVANCE-1 2009	1.11 (0.93–1.32)	Nishtala 2016	1.02 (0.94–1.10)
ADVANCE-2 2010	1.10 (0.91–1.32)	Kalil 2016	1.02 (0.94–1.10)
ADVANCE-3 2010	1.08 (0.91–1.30)	Bengtson 2017	1.02 (0.94–1.10)
Weitz 2010	1.09 (0.91–1.31)	Norby 2017	1.01 (0.93–1.10)
EINSTEIN 2010	1.08 (0.91–1.30)	Friberg 2017	1.01 (0.93–1.10)
Raskob 2010	1.09 (0.91–1.31)	Palamaner Subash Shantha 2017	1.02 (0.94–1.10)
ROCKET AF 2011	1.05 (0.87–1.27)	Hernandez 2017	1.01 (0.93–1.09)
ARISTOTLE 2011	1.12 (0.92–1.36)	Gieling 2017	1.02 (0.95–1.10)
Chung 2011	1.10 (0.92–1.32)	Deitelzweig 2017	1.01 (0.93–1.09)
AVERROES 2011	1.12 (0.94–1.35)	Halvorsen 2017	1.02 (0.94–1.10)
ADOPT 2011	1.08 (0.90–1.30)	Li 2017	1.02 (0.94–1.10)
J-ROCKET AF 2012	1.12 (0.94–1.34)	Go 2017	1.03 (0.95–1.10)
EINSTEIN–PE 2012	1.09 (0.90–1.31)	Chan 2017	1.02 (0.94–1.10)
RE-MEDY 2013	1.11 (0.92–1.33)	Amin 2017	1.02 (0.94–1.10)
ENGAGE AF-TIMI 48 2013	1.11 (0.91–1.36)	Adeboyeje 2017	1.02 (0.94–1.10)
Hokusai-VTE 2013	1.09 (0.90–1.31)	Zoppellaro 2018	1.02 (0.94–1.10)
AMPLIFY 2013	1.13 (0.95–1.35)	Streiff 2018	1.02 (0.94–1.10)
MAGELLAN 2013	1.08 (0.90–1.30)	Mayer 2018	1.02 (0.94–1.10)
RE-COVER II 2014	1.11 (0.92–1.33)	Martinez 2018	1.02 (0.94–1.10)
Boehringer Ingelheim 2014	1.09 (0.91–1.31)	Li 2018	1.02 (0.94–1.10)
X-VeRT 2014	1.09 (0.91–1.31)	Lee 2018	1.02 (0.94–1.10)
Daiichi Sankyo 2015	1.10 (0.92–1.32)	Hohnloser 2018	1.04 (0.96–1.12)
J-EINSTEIN DVT and PE 2015	1.09 (0.91–1.31)	Coleman 2018	1.00 (0.92–1.09)
APEX 2016	1.06 (0.89–1.26)	Coleman 2018	1.02 (0.94–1.11)
PIONEER AF-PCI 2016	1.11 (0.92–1.33)	Lai 2018	1.01 (0.93–1.10)
RE-DUAL PCI 2017	1.12 (0.93–1.35)	Chan 2018	1.02 (0.94–1.10)
COMPASS 2017	1.07 (0.89–1.30)	Briasoulis 2018	1.02 (0.94–1.10)
EINSTEIN CHOICE 2017	1.09 (0.91–1.31)	Vinogradova 2018	1.02 (0.93–1.10)
ENSURE-AF 2017	1.09 (0.91–1.31)	Ujeyl 2018	1.01 (0.93–1.10)
Hokusai VTE Cancer 2018	1.06 (0.89–1.26)	Siontis 2018	1.02 (0.94–1.10)
SELECT-D 2018	1.08 (0.90–1.30)	Coleman 2018	1.01 (0.93–1.09)
RE-CIRCUIT 2018	1.10 (0.91–1.32)	Excluding special clinical scenarios[b]	1.00 (0.93–1.08)
EMANATE 2018	1.09 (0.91–1.31)		
Excluding special clinical scenarios[a]	1.00 (0.83–1.21)		

CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk.

[a]Studies of special clinical scenarios including ADOPT 2011, MAGELLAN 2013, APEX 2016, PIONEER AF-PCI 2016, RE-DUAL PCI 2017, COMPASS 2017, Hokusai VTE Cancer 2018, and SELECT-D 2018.

[b]Studies of special clinical scenarios including Streiff 2018 and Siontis 2018.

Supplementary Table 11. Meta-Regression Analysis of RCTs and Real-World Studies

Variable	*P* value for RCTs
Mean age (*y*)	.075
Female (%)	.134
Weight (*kg*)	.503
Body mass index (kg/m^2)	.225
Heart failure (%)	.529
Hypertension (%)	.252
Diabetes (%)	.743
Stroke/transient ischemic attack (%)	.546
Prior myocardial infarction (%)	.887
Cancer (%)	.917
Creatinine clearance rate (*mL/min*)	.148
Creatinine clearance rate >80 mL/min (%)	.059
Antiplatelet agents (%)	.699

Variable	*P* value for real-world studies
Mean age (*y*)	.969
Female (%)	.855
Obesity (%)	.509
Heart failure (%)	.442
Hypertension (%)	.459
Diabetes (%)	.409
Stroke/transient ischemic attack (%)	.733
Prior myocardial infarction (%)	.798
Renal disease (%)	.892
Liver disease (%)	.182
Anemia (%)	.805
Cancer (%)	.810
CHADS2 (mean)	.723
CHADS2-VASc (mean)	.899
HAS-BLED (mean)	.573
HAS-BLED >3 (%)	.992
Prior bleeding (%)	.923
Prior gastrointestinal tract bleeding (%)	.876
Angiotensin-converting enzyme inhibitor/ angiotensin receptor inhibitor (%)	.587
Beta-blocker (%)	.573
Diltiazem (%)	.527
Verapamil (%)	.904
Dihydropyridine calcium channel blocker (%)	.556
Amiodarone (%)	.604
Dronedarone (%)	.500
Digoxin (%)	.942
Other antiarrhythmic drugs (%)	.733
Statin (%)	.418
Antiplatelet agents (%)	.342
Aspirin (%)	.367
Clopidogrel (%)	.890
Nonsteroidal anti-inflammatory drugs (%)	.869
Proton pump inhibitor (%)	.409
H2-receptor antagonist (%)	.400
Serotonin receptor antagonist (%)	.283
Glucocorticoids (%)	.573
Estrogen (%)	.412

RCT, randomized controlled trial.