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ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

«Η Ασφάλεια Χρήσης των Αμέσων Δρώντων Αντιπηκτικών αναφορικά με Ενδοκράνια Αιμορραγία σε ασθενείς με Μη-Βαλβιδική Κολπική Μαρμαρυγή: Μια Ανασκόπηση και Μετα-ανάλυση»

«Safety of Direct Oral Anticoagulants concerning Intracranial Hemorrhage in Non-Valvular Atrial Fibrillation: A Systematic Review and Meta-analysis of Real-World Studies»

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Περίληψη

Εισαγωγή

Από την εισαγωγή των Αμέσως Δρώντων Αντιπηκτικών (ΑΔΑ) στην κλινική πράξη και έκτοτε, μελέτες από τον πραγματικό κόσμο έχουν ερευνήσει την ασφάλεια χρήσης τους αναφορικά με τον κίνδυνο Ενδοκράνιας Αιμορραγίας σε ασθενείς με Μη-Βαλβιδική Κολπική Μαρμαρυγή.

Στόχοι

Πραγματοποιήσαμε μια συστηματική ανασκόπηση και μετα-ανάλυση για να συγκεντρώσουμε και να συνοψίσουμε τα δεδομένα αυτά με βάση τις οδηγίες PRISMA.

Μέθοδοι

Έγινε συστηματική αναζήτηση στις βάσεις δεδομένων Medline και Embrace μέχρι τον Απρίλιο του 2020. Συλλέχθηκαν μελέτες παρατήρησης και εξάχθηκαν οι Αναλογίες Κινδύνου (HR) μαζί με το Διάστημα Εμπιστοσύνης 95% (95% CI). Πραγματοποιήθηκε ανάλυση επιμέρους υποσυνόλων με βάση τη δόση των ΑΔΑ, το ιστορικό χρόνιας νεφρικής νόσου, το ιστορικού εγκεφαλικού επεισοδίου, την προηγούμενη χρήση Αναστολέα Βιταμίνης Κ (ΑΒΚ), την ηλικία και το φύλλο.

Αποτελέσματα

Στην έρευνα μας συμπεριλήφθηκαν 57 μελέτες και πραγματοποιήθηκαν 34 συγκρίσεις. Το Dabigatran σχετίστηκε με χαμηλότερη πιθανότητα Ενδοκράνιας Αιμορραγίας (HR: 0.48, 95% CI: 0.44 - 0.52, I2: 0.00%) σε σχέση με τους ΑΒΚ. Το Rivaroxaban σχετίστηκε με χαμηλότερη πιθανότητα Ενδοκράνιας Αιμορραγίας (HR: 0.73, 95% CI: 0.65 - 0.81, I2: 51.71%) σε σχέση με τους ΑΒΚ. Το Apixaban σχετίστηκε με χαμηλότερη πιθανότητα Ενδοκράνιας Αιμορραγίας (HR: 0.60, 95% CI: 0.49 - 0.73, I2: 72.93%) σε σχέση με τους ΑΒΚ. Το Rivaroxaban σχετίστηκε με υψηλότερη πιθανότητα Ενδοκράνιας Αιμορραγίας (HR: 1.58, 95% CI: 1.31 - 1.89, I2: 0.00%) σε σχέση με το Dabigatran. Το Apixaban σχετίστηκε με υψηλότερη πιθανότητα Ενδοκράνιας Αιμορραγίας (HR: 1.32, 95% CI: 1.03 -

1.68, I2: 7.04%) σε σχέση με το Dabigatran. Παρόμοια αποτελέσματα βρέθηκαν και στην ανάλυση των υποσυνόλων.

Συμπέρασμα

Η μελέτη μας δείχνει ότι τα ΑΔΑ σχετίζονται με μείωση του κινδύνου Ενδοκράνιας Αιμορραγίας σε σχέση με τους ΑΒΚ. Επίσης, το Dabigatran σχετίζεται με μείωση τους κινδύνου Ενδοκράνιας Αιμορραγίας σε σχέση τόσο με το Rivaroxaban και με το Apixaban.

Abstract

Introduction

Since the introduction of Direct Oral Anticoagulants (DOACs), real-world studies have investigated their safety profile on Intracranial Hemorrhage (ICH) in patients with Non-Valvular Atrial Fibrillation (NVAF).

Aim

We performed a systematic review and meta-analysis to compile and summarize this data following PRISMA guidelines.

Methods

Medline and Embrace were systematically searched until April 27th, 2020. Observational studies were gathered and hazard ratios (HRs) with 95% confidence intervals (CI) were extracted. Subgroup analyses based on DOAC doses, history of chronic kidney disease, stroke, prior exposure to VKA (Vitamin K Antagonist), age and gender were performed. A random-effects model was used.

Results

We included 57 studies and performed 34 comparisons. Dabigatran was associated with lower rate of ICH (HR: 0.48, 95% CI: 0.44 - 0.52, I2: 0.00%) compared to VKA. Rivaroxaban was associated with lower rate of ICH (HR: 0.73, 95% CI: 0.65 - 0.81, I2: 51.71%) compared to VKA. Apixaban was associated with lower rate of ICH (HR: 0.60, 95% CI: 0.49 - 0.73, I2: 72.93%) compared to VKA. Rivaroxaban was associated with higher rate of ICH (HR: 1.58, 95% CI: 1.31 - 1.89, I2: 0.00%) compared to Dabigatran. Apixaban was associated with higher rate of ICH (HR: 1.32, 95% CI: 1.03 - 1.68, I2: 7.04%) compared to Dabigatran. Similar effects were appreciated in subgroup analysis.

Conclusion

Our study shows that individual DOACs were associated with a reduction of ICH risk compared to VKA. Also, Dabigatran was associated with a reduction of ICH risk compared to both Rivaroxaban and Apixaban.

Key Points (Ελληνικά)

• Μη-βαλβιδική Κολπική Μαρμαρυγή

• Ενδοκράνια Αιμορραγία

• Άμεσα Δρώντα Αντιπηκτικά

• Αναστολείς της Βιταμίνης Κ

Key Points (English)

• Non-Valvular Atrial Fibrillation

• Intracranial Hemorrhage

• Direct Oral Anticoagulants

• Vitamin K Antagonists

Introduction

Non-Valvular Atrial Fibrillation (NVAF) is the most common cardiac arrhythmia. (1) In addition, NVAF is associated with increased risk of stroke and other thromboembolic phenomena, of the total number of which at least a third is attributed to NVAF. (2, 3) As such, prevention of thromboembolism (TE) via systemic anticoagulation has been the main focus of AF management. (4) In addition to warfarin and other Vitamin K Antagonists (VKAs), Direct Oral Anticoagulants (DOACs) have been introduced since the 2000s. (5) Benefits from their use, both concerning their efficacy and their safety profile, are well known by published clinical trials. (6-9) According to those, DOACs seem to have a superior safety profile in the context of decreased hemorrhage rates, including Intracranial Hemorrhage (ICH).

Apart from the aforementioned trials, real-world studies were performed on the subject. They not only compared a DOAC to VKA but also a DOAC to another DOAC, a subject on which no clinical trial has been attempted. These studies have investigated different outcomes (including stroke prevention rates and safety outcomes, such as intracranial hemorrhage, major hemorrhage and gastrointestinal hemorrhage), dosing regimens, specific comorbidities affecting the users apart from NVAF, different age groups and different ethnicities.

In order to investigate and quantify the safety profile on ICH of different DOACs compared to VKA and to other DOACs, we performed a systematic review of the literature and meta-analyzed the observational (prospective and retrospective) studies that provided details on these outcomes in patients with NVAF.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). (10)

Study Selection and Eligibility Criteria

Medline and Embrace were systematically searched until April 27th, 2020 by two independent investigators (Damianos G. Kokkinidis, Weijia Lee) for eligible studies. In case of disagreement, a third, also independent investigator (Paraschos Archontakis Barakakis) intervened to reach consensus. The utilized algorithm was ("novel oral anticoagulants" OR "direct oral anticoagulants" OR "non-vitamin K antagonist oral anticoagulants" OR NOAC OR DOAC OR dabigatran OR rivaroxaban OR apixaban OR warfarin OR coumadin OR "vitamin K antagonist") AND (atrial fibrillation OR AF OR AFIB) AND (real-world OR "real world" OR observational OR cohort OR post-approval). Edoxaban was excluded from our analysis because of its decreased availability in most European countries and thus scarce studies on it from this region. In addition, references from pertinent reviews and observational studies were also used to investigate for further potential eligible studies. The processing of studies continued with pre-specified inclusion criteria: i) retrospective or prospective observational studies, ii) studies comparing one of the DOACs to warfarin or studies comparing different DOACs, iii) studies examining the outcome of interest (ICH), and iv) studies providing Hazard Ratio (HR) with 95% Confidence Intervals (95% CI) as the effect estimate. Randomized control trials, studies with participants suffering from valvular AF and studies where DOACs were used for different primary indications (such as deep vein thrombosis, pulmonary embolism or peripheral artery disease) were excluded.

Data Extraction and Outcomes

Data extraction was performed on a pre-constructed data extraction form by two independent investigator teams (led by Paraschos Archontakis Barakakis and Weijia Lee) blinded to each other. Disagreements were resolved via consensus and with the intervention of a reviewer (Damianos G. Kokkinidis).

The primary and only outcome for this study was ICH occurring during the study follow up period, as defined by the authors of the individual studies. In the case of studies using databases for their study

population assembly, the documented in the studies International Statistical Classification of Diseases and Related Health Problems (ICD) codes were investigated for accurate inclusion.

HRs with 95% CIs comparing DOACs (as a whole) to VKA, Dabigatran to VKA, Rivaroxaban to VKA, Apixaban to VKA, Dabigatran to Rivaroxaban, Apixaban to Dabigatran and Apixaban to Rivaroxaban were collected. Considering the different dosing regimens available for each DOAC, HRs on the specific doses were collected and registered under different categories. If the effect of the lower dose regimen of a specific DOAC was provided by a study, e.g. 110 mg of dabigatran twice daily, it was registered under the “Low Dose” category. If the effect of the higher dose was provided, it was registered under the “High Dose” category. If a study provided a result (HR) using data from patients taking either dosing regimen or no clear distinction of dosing was stated in the study, the result was categorized in the “Combined” analysis category.

In addition to the main data collection, separate HRs were collected on pre-determined subgroups of interest, more specifically i) patients with chronic kidney disease (CKD), ii) post-stroke patients, iii) DOAC users who were previously on VKA prior to switching to a DOAC (Experienced users), ii) elderly users (patients aged >65 years old), iii) very elderly users (patients aged >75 years old), iv) male users and v) female users.

Risk of Bias Assessment

Two independent reviewers (Dimitrios Kalaitzoglou, Lazaros Tzelves) assessed the risk of bias of the included studies with the Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) tool. (11) Studies were assessed as having low, moderate, serious or critical risk of bias in the following domains: confounding measurement and account, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and results reporting.

Statistical Analysis

In order to avoid including duplicate population samples in our study and when such potentially duplicate study populations were encountered (among included studies using the same source/database, demonstrating the same investigation period, documenting no mutually exclusive inclusion criteria), the respective, extracted HRs were not analyzed together under the same comparison and outcome. The utmost care was given to ensure that the under-investigation population was best represented, e.g. when two studies derived their study population from the same database, the larger one of the two studies was prioritized.

Because of the aforementioned division of extracted data into categories but also the different methodologies used by the researchers, we decided to process the different mutually exclusive subgroups from a study (e.g. males and females or patients taking the lower dose regimen and patients taking the higher dose regimen) independently among other studies or even among other groups from the same study. This method was used in order to ensure that, first, no duplicated patients would be included and, second, that the meta-analysis for each outcome and comparison would include the largest possible number of patients and studies.

Because of the scope of our approach to include populations that by defaults varied significantly as per their country of origin, age group, etc., a random effects model was used by default to account for heterogeneity. Heterogeneity was quantified with the Higgins I-square (I^2) statistic, although both the Q value and accompanied p-value for Q are documented in the forest plot for each comparison. A cutoff of I^2 >75% was used to indicate significant heterogeneity. Forest plots were used to graphically display the effect size in each study and the pooled estimates. The Egger's test was used for assessment of publication bias and Funnel plots were created only when the number of included number of studies was more than ten. A p value of <0.05 was considered statistically significant for all comparisons. The statistical analysis was performed with R (version 4.0.2) with the assistance of RStudio (version 1.3.1073).

Results

In total, 7,014 records were screened and 135 full text articles were assessed for eligibility. Of these, 57 studies met all the inclusion criteria, survived the potential duplicate removal process and were advanced to qualitative and quantitative analysis. (12-68) A PRISMA flow diagram with the selection process was created to depict this work. **(Figure 1)**

From the processed studies, more than 2,690,000 patients were collectively included. Extensive details on baseline characteristics as provided by the individual studies are presented in **supplementary Table 1**.

Because of the large number of studies included, equally large number of outcomes and subgroups investigated and analyses performed, all the results are presented in the comprehensive **Table 1.** The data are presented in the form of Number of Studies included in the specific analysis, Hazard Ratio (HR), 95% Confidence Interval (CI), Heterogeneity (I^2). In this section, we focus on most statistically significant comparisons.

Dabigatran vs. VKA

Our main analysis (Combined: HR: 0.48, 95% CI: 0.44 - 0.52, I2: 0.00% / Low dose: HR: 0.50, 95% CI: 0.43 - 0.58, I2: 0.00% / High Dose: HR: 0.47, 95% CI: 0.38 - 0.58, I2: 8.69%) **(Figure 2A, supplementary Figures 2A-B)** and most subgroup analyses (Elderly users: HR: 0.52, 95% CI: 0.45 - 0.61, I2: 0.00% / Very Elderly users: HR: 0.50, 95% CI: 0.42 - 0.61, I2: 10.69% / Male users: HR: 0.38, 95% CI: 0.29 - 0.50, I2: 0.00% / Female users: HR: 0.42, 95% CI: 0.30 - 0.60, I2: 25.47%) **(supplementary Figures 2C-J)** found that Dabigatran was associated with significantly lower risk of ICH compared to VKA. Of note, the main analysis for the Combined category demonstrated a positive Egger's test ($p < 0.05$).

Rivaroxaban vs. VKA

Rivaroxaban was associated with lower rates of ICH (Combined category: HR: 0.73, 95% CI: 0.65 - 0.81, I2: 51.71% / Low Dose: HR: 0.71, 95% CI: 0.57 - 0.88, I2: 36.74% / High Dose: HR: 0.66, 95% CI: 0.59 - 0.73, I2: 0.00%) **(Figure 2B, supplementary Figures 3A-B)** compared to VKA in the main group analysis.

Subgroup analyses produced relatively similar results. CKD patients taking Rivaroxaban had lower rates of ICH (Combined category: HR: 0.64, 95% CI: 0.45 - 0.89, I2: 0.00%) compared to CKD patients taking VKA. Elderly users of anticoagulation had lower rates of ICH (Combined category: HR: 0.62, 95% CI: 0.49 - 0.80, I2: 0.00%) compared to elderly taking VKA. Male users of Rivaroxaban had lower rates of ICH (Combined category: HR: 0.52, 95% CI: 0.38 - 0.73, I2: 0.00%) compared to Male users of VKA. **(supplementary Figures 3C-3H)**

Apixaban vs. VKA

Apixaban was associated with significantly lower risk for ICH compared to VKA (Combined category: HR: 0.60, 95% CI: 0.49 - 0.73, I2: 72.93% / Low Dose: HR: 0.57, 95% CI: 0.45 - 0.72, I2: 0.00% / High Dose category: HR: 0.54, 95% CI: 0.43 - 0.68, I2: 17.33%) with our main analysis. **(Figure 2C, supplementary Figures 4A-B).**

In the Elderly users subgroup, Apixaban was associated with lower rates of ICH (Combined category: HR: 0.60, 95% CI: 0.49 - 0.73, I2: 4.57%). In the Very elderly users subgroup, Apixaban was associated with lower rates of ICH (Combined category: HR: 0.57, 95% CI: 0.38 - 0.85, I2: 13.15%) compared to VKA. **(supplementary Figures 4C-4D)**

DOACs vs. VKA

The main analysis of studies comparing DOACs in general (without specifying a particular agent) vs VKA showed that DOACs were associated with lower rates of ICH (Combined category: HR: 0.57, 95% CI: 0.50 - 0.65, I2: 28.78%). The same finding was identified for the Elderly users (Combined

category: HR: 0.53, 95% CI: 0.46 - 0.61, I2: 35.14%) and Very Elderly users (Combined category: HR: 0.57, 95% CI: 0.44 - 0.72, I2: 45.53%). **(supplementary Figures 5A-5C)**

Rivaroxaban vs. Dabigatran

Our head-to-head comparison between Rivaroxaban and Dabigatran identified statistically significant higher rates of ICH when using Rivaroxaban (Combined category: HR: 1.58, 95% CI: 1.31 - 1.89, I2: 0.00%). Similarly, the same trend was identified for the Low Dose (HR: 1.70, 95% CI: 1.23 - 2.36, I2: 0.00%) and High Dose (HR: 1.64, 95% CI: 1.35 - 2.00, I2: 0.00%) of both medications. **(Figure 3A, supplementary Figures 6A-6B)**

Apixaban vs. Dabigatran

The main analysis demonstrated higher ICH rates with Apixaban use versus Dabigatran use (Combined category: HR: 1.32, 95% CI: 1.03 - 1.68, I2: 7.04% / High Dose category: HR: 1.41, 95% CI: 1.10 - 1.80, I2: 0.00%). **(Figure 3B, supplementary Figure 7A)**

Apixaban vs. Rivaroxaban

The comparison of ICH rates for patients taking Apixaban and Rivaroxaban did not reveal any statistically significant difference between the agents (Combined category: HR: 0.89, 95% CI: 0.69 - 1.17, I2: 41.70%). **(Figure 3C)**

Post Stroke Patients and Experienced Users

Our data collection and duplicate population elimination processes resulted in insufficient number of studies (for each medication comparison and category) compared to our predetermined cut off number in order to perform any analysis.

Publication Bias

Funnel Plots were constructed for all studies that demonstrated a number of included studies of ten (10) or more. **(supplementary Figures 8A-8G)** Of note and as expected by the nature of included

studies (observational studies), a certain level of publication bias was generally observed in favor of DOACs versus VKA.

Publication bias was also assessed the Egger's test. This test was performed for all comparisons. No evidence of publication bias was found in the vast majority of the comparisons with the exceptions of the presented in **supplementary Table 2.**

Other Risks of Bias Assessment

Our risk of bias assessment based on the (ROBINS-I) tool revealed at least moderate risk of bias for all included studies. The explanation of this phenomenon is presented in Discussion.

Discussion

This study was a systematic review and meta-analysis of 57 observational studies comparing the ICH risk associated with the use of DOACs versus the use of VKA and other DOACs. To the best of our knowledge, this is the largest real-world observational studies meta-analysis to focus on and investigate this very specific question.

Our results indicate that i) DOACs as a whole were associated with a lower ICH risk compared to VKA ii) Dabigatran was associated with a lower ICH risk compared to VKA in our main analysis (Combined Dose, Low Dose and High Dose categories) and several subgroups (Elderly users, Very Elderly users, Male users, Female Users) iii) Rivaroxaban was associated with a lower ICH risk compared to VKA in our main analysis (Combined Dose, Low Dose and High Dose categories) and several subgroups (CKD patients, Elderly users, Male users) iv) Apixaban was associated with a lower ICH risk compared to VKA in our main analysis (Combined Dose, Low Dose and High Dose categories) and two subgroups (Elderly users, Very Elderly users) v) Rivaroxaban was associated with higher ICH risk compared to Dabigatran vi) Apixaban was associated with higher ICH risk compared to Dabigatran vii) there was no difference identified in the risk for ICH between Apixaban and Rivaroxaban.

Our results comparing DOACs to VKA align to a great degree with the results that the worldwide bibliography has already established. The initial landmark trial that led to the approval and wide use of dabigatran (the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study) showed lower rates of ICH with the use of both the Low and High Dose of Dabigatran compared to VKA. (6) Our study reinforces this finding with our main and several subgroup analyses in the real-world setting. The second major DOAC trial, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial (7), showed significantly lower ICH hemorrhage risk in the rivaroxaban group as compared to the warfarin group, a result also in total agreement with our findings. Finally, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial showed that patients with non-valvular AF taking Apixaban had lower ICH events rates compared to warfarin group. Our results reinforce these findings as well. (8) Except for these milestone trials, both observational studies, such as those included in our study, and smaller meta-analyses showed similar but not as robust results. For example, Proietti et al. showed that the risk for ICH was lower for apixaban than warfarin. (69) All in all, it seems that results on the safety of DOACs compared to VKA as produced by the aforementioned clinical trials are adequately reinforced by results produced by real-world, observational studies and meta-analyses including ours.

While our knowledge on the superiority of DOACS in general compared to VKA is evolving, the major question focuses on the comparisons among the different DOAC agents themselves. As mentioned above, no trial has investigated this specific question and our study provides valuable input on the matter. Our results demonstrate that Dabigatran is associated with a lower risk for ICH compared to both Rivaroxaban and Apixaban. There was no difference appreciated between Rivaroxaban and Apixaban. Those findings were not deemed to suffer from any major biases.

Strengths and Limitations

Our study demonstrates a number of strengths, including strict adherence to the systematic review methodology and the narrow focus on one type of outcome and thus attempting to answer one main question. Because of this methodology we were able to search, collect, screen and analyze a large number of studies and thus a substantial patient population size. To the best of our knowledge, this is the first real-world data meta-analysis to investigate this topic to this extent.

On the contrary, our study exhibits certain limitations as well. Firstly, this is a meta-analysis of real-world studies and thus is limited by the inherent limitations of observational research. More specifically, most of the included studies collected data from databases in which documentation was performed via ICD codes. As such, unmeasured and residual confounding factors were deemed likely to exist in the source studies, persist the transfer to our study and translate to different types of bias. Outstanding types of such bias would be selection bias and bias by indication. For example, there is scarce information to determine the appropriate dosing of each NOAC, despite dividing the included patients in low and high dose subgroups. Our goal with this study was to summarize and present the available data on DOACs in the real-world setting and, thus, we accepted this possibility of bias. Second, because of the aforementioned inability to collect accurate and unified baseline data, a meta-regression analysis was deemed methodologically improper. Third, some of our comparisons were dominated by a limited number of studies or study populations either because of the weight attributed to the study or because of the paucity of similar data in other included studies.

Conclusions

In conclusion, this is the largest systematic review and meta-analysis up to date on the comparison of DOACs vs VKA and vs other DOACs for ICH risk. Our results show that all individual DOACs were associated with an improved safety profile concerning ICH risk as compared to VKA. DOACs were consistently superior to VKA in the subgroup analyses among elderly and very elderly patients. Finally, Dabigatran was found to have significantly lower ICH risk against both Rivaroxaban and Apixaban.

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Table 1

ICH: (part 1)	Dabigatran (Combined) vs. VKA	Dabigatran (Low Dose) vs VKA	Dabigatran (High Dose) vs. VKA	Rivaroxaban (Combined) vs. VKA	Rivaroxaban (Low Dose) vs. VKA	Rivaroxaban (High Dose) vs. VKA	Apixaban (Combined) vs. VKA	Apixaban (Low Dose) vs. VKA
Gen. Population	23; 0.48 (0.44 - 0.52); I2: 0.00%	10; 0.50 (0.43 - 0.58); I2: 0.00%	9; 0.47 (0.38 - 0.58); I2: 8.69%	16; 0.73 (0.65 - 0.81); I2: 51.71%	8; 0.71 (0.57 - 0.88); I2: 36.74%	8; 0.66 (0.59 - 0.73); I2: 0.00%	17; 0.60 (0.49 - 0.73); I2: 72.93%	5; 0.57 (0.45 - 0.72); I2: 0.00%
CKD Patients	3; 0.66 (0.42 - 1.05); I2: 0.00%			4; 0.64 (0.45 - 0.89); I2: 0.00%	3; 0.71 (0.46 - 1.09); I2: 55.23%			
Elderly (>65) Users	10; 0.52 (0.45 - 0.61); I2: 0.00%	4; 0.49 (0.40 - 0.61); I2: 0.00%	3; 0.46 (0.27 - 0.76); I2: 78.17%	4; 0.62 (0.49 - 0.80); I2: 0.00%			6; 0.60 (0.49 - 0.73); I2: 4.57%	
Very Elderly (>75) Users	11; 0.50 (0.42 - 0.61); I2: 10.69%	4; 0.49 (0.40 - 0.61); I2: 0.00%		5; 0.69 (0.45 - 1.05); I2: 62.58%			4; 0.57 (0.38 - 0.85); I2: 13.15%	
Male Users	7; 0.38 (0.29 - 0.50); I2: 0.00%			3; 0.52 (0.38 - 0.73); I2: 0.00%				
Female Users	7; 0.42 (0.30 - 0.60); I2: 25.47%			3; 0.91 (0.56 - 1.50); I2: 55.85%				

ICH: (part 2)	Apixaban (High Dose) vs. VKA	DOACs (Combined) vs. VKA	Rivaroxaban (Combined) vs. Dabigatran	Rivaroxaban (Low Dose) vs. Dabigatran	Rivaroxaban (High Dose) vs. Dabigatran	Apixaban (Combined) vs. Dabigatran	Apixaban (High Dose) vs. Dabigatran	Apixaban (Combined) vs. Rivaroxaban
Gen. Population	5; 0.54 (0.43 - 0.68); I2: 17.33%	12; 0.57 (0.50 - 0.65); I2: 28.78%	6; 1.58 (1.31 - 1.89); I2: 0.00%	4; 1.70 (1.23 - 2.36); I2: 0.00%	4; 1.64 (1.35 - 2.00); I2: 0.00%	6; 1.32 (1.03 - 1.68); I2: 7.04%	3; 1.41 (1.10 - 1.80); I2: 0.00%	6; 0.89 (0.69 - 1.17); I2: 41.70%
CKD Patients								
Elderly (>65) Users		5; 0.53 (0.46 - 0.61); I2: 35.14%						
Very Elderly (>75) Users		4; 0.57 (0.44 - 0.72); I2: 45.53%						
Male Users								
Female Users								

Figure 1

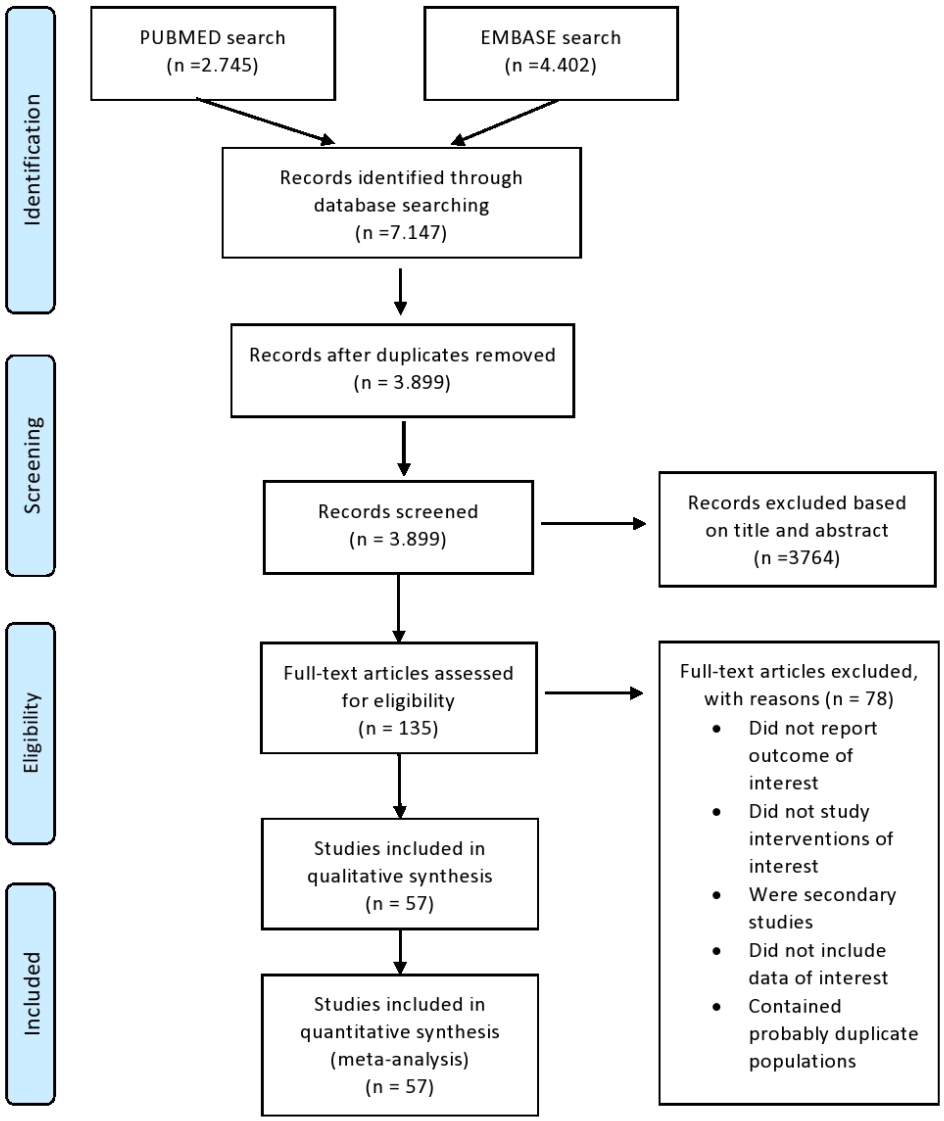

Figure 2

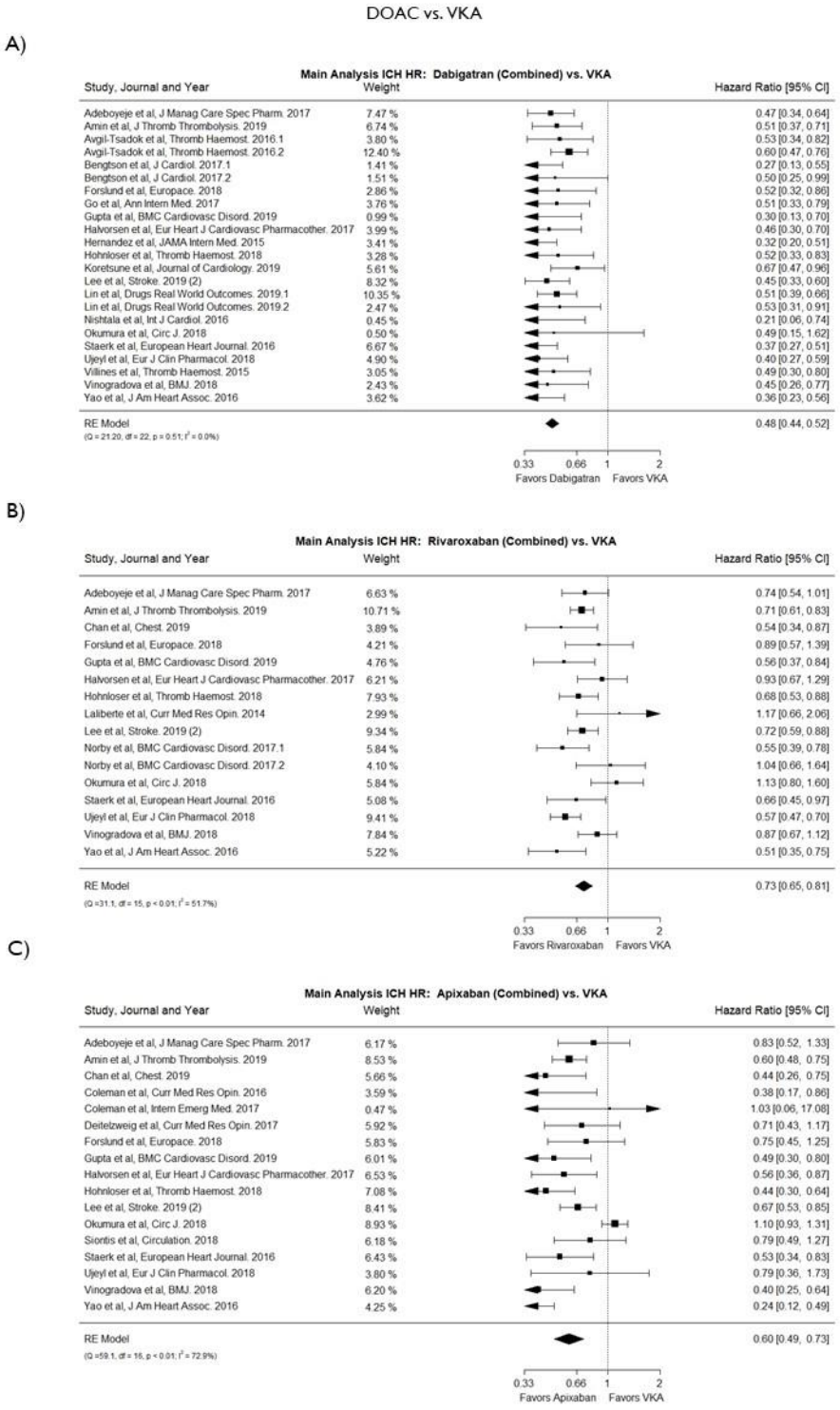

Figure 3