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Μεταπτυχιακή Διπλωματική Εργασία

"Αντιθρομβωτική αγωγή σε διαχωρισμό αυχενικών αρτηριών: Συστηματική ανασκόπηση και Μετα-ανάλυση"

υπό

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Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

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FACULTY OF MEDICINE
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MSc COURSE
THROMBOSIS AND ANTITHROMBOTIC TREATMENT

Master of Science Thesis

" Antithrombotic treatment of cervical artery dissection: A Systematic review and Meta-analysis "

by

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Περίληψη

Υπόβαθρο: Ενώ η αντιπηκτική θεραπεία αποτελεί καλά εδραιωμένη θεραπεία για την πρόληψη του εγκεφαλικού επεισοδίου μετά από διαχωρισμό των αυχενικών αρτηριών, πρόσφατες μελέτες έχουν προτείνει τη χρήση αντιαιμοπεταλιακών φαρμάκων λόγω της συγκρίσιμης αποτελεσματικότητάς τους και του χαμηλότερου κινδύνου αιμορραγίας. Η έρευνά μας αξιολογεί τη συχνότητα των εγκεφαλικών και αιμορραγικών επεισοδίων μετά από διάφορες αντιθρομβωτικές θεραπείες σε αυτούς τους ασθενείς.

Μέθοδοι: Πραγματοποιήσαμε συστηματική αναζήτηση στις βάσεις δεδομένων PubMed, Scopus και Cochrane για συγκριτικές μελέτες που αφορούν ασθενείς με διαχωρισμό αυχενικών αρτηριών οι οποίοι έλαβαν αντιπηκτικά και αντιαιμοπεταλιακά φάρμακα. Τα κύρια αποτελέσματα ήταν τα ποσοστά εγκεφαλικών επεισοδίων και αιμορραγικών γεγονότων. Οι συγκεντρωτικές εκτιμήσεις των αποτελεσμάτων ενδιαφέροντος προήλθαν μέσω του μοντέλου τυχαίων επιδράσεων. Διενεργήθηκε ανάλυση υποομάδων για να εξεταστεί η επίδραση διαφορετικών τύπων αντιπηκτικών και διαφόρων σχημάτων αντιαιμοπεταλιακής θεραπείας.

Αποτελέσματα: 22 μελέτες, συνολικά με 5.180 ασθενείς που έλαβαν αντιαιμοπεταλιακά φάρμακα, ανταγωνιστές βιταμίνης Κ (VKA) και νέους από του στόματος αντιπηκτικούς παράγοντες (NOACs) για την πρόληψη του δευτερογενούς εγκεφαλικού επεισοδίου, πληρούσαν τα κριτήρια ένταξης. Η συχνότητα των εγκεφαλικών επεισοδίων (OR: 0.85, 95% CI: 0.62-1.19, p=0.35), της ενδοκρανιακής (OR: 0.70, 95% CI: 0.32-1.55, p=0.38) και εξωκρανιακής αιμορραγίας (OR: 0.74, 95% CI: 0.23-2.41, p=0.62), καθώς και τα ποσοστά θνησιμότητας (OR: 1.09, 95% CI: 0.33-3.59, p=0.89), δεν παρουσίασαν στατιστικά σημαντικές διαφορές μεταξύ της ομάδας αντιπηκτικών και της ομάδας αντιαιμοπεταλιακών. Η σύγκριση των

αντιαιμοπεταλιακών με τους VKA (OR: 1.46, 95% CI: 0.79-2.72, p=0.23) και αποκλειστικά της ασπιρίνης με τους VKA (OR: 1.26, 95% CI: 0.48-3.29, p=0.64) δεν δείχνει σημαντικές διαφορές ως προς τα εγκεφαλικά επεισόδια. Συνολικά, τα αιμορραγικά επεισόδια ήταν λιγότερο συχνά στην ομάδα των αντιαιμοπεταλιακών συγκριτικά με την ομάδα VKA (OR: 0.40, 95% CI: 0.17-0.91, p=0.03). Οι ομάδες των VKA και NOACs δεν φαίνεται να παρουσιάζουν διαφορετικά ποσοστά επανακαναλοποίησης και αιμορραγικών επεισοδίων.

Συμπεράσματα: Η αντιπηκτική θεραπεία παρουσιάζει συγκρίσιμα ποσοστά εγκεφαλικών επεισοδίων, ενδοκρανιακής και εξωκρανιακής αιμορραγίας και θνησιμότητας με την αντιαιμοπεταλιακή θεραπεία. Η ατομική προσέγγιση, λαμβάνοντας υπόψη τον κίνδυνο αιμορραγίας και θρόμβωσης του ασθενούς, για τον καθορισμό της αντιθρομβωτικής θεραπείας παραμένει η ιδανική προσέγγιση.

Λέξεις-κλειδιά: Διαχωρισμός αυχενικών αρτηριών, καρωτιδική αρτηρία, σπονδυλική αρτηρία, αντιπηκτικά, αντιαιμοπεταλιακά, αντιθρομβωτική θεραπεία

Abstract

Background: While anticoagulation is a well-established treatment for secondary stroke prevention in cervical artery dissection, recent studies have suggested antiplatelet agents as treatment due to their comparable effectiveness and lower risk of bleeding. Our research assesses the incidence of stroke and hemorrhagic events following various antithrombotic treatment in these patients.

Methods: We systematically searched PubMed, Scopus and Cochrane for comparative studies reporting on patients with cervical artery dissection who received anticoagulants and antiplatelet agents. The primary outcomes were the stroke rates and the hemorrhagic events. Pooled effect estimates for the outcomes of interest were derived using the random-effects model. A subgroup analysis was conducted to examine the impact of different types of anticoagulants and various antiplatelet treatment schemes.

Results: 22 studies involving on a total of 5180 patients treated with antiplatelets, vitamin K antagonist (VKA) and new oral anticoagulants (NOACs) for prevention of secondary stroke, fulfilled the inclusion criteria. The incidence of stroke events OR: 0.85, 95% CI: 0.62-1.19, p=0.35), intracranial (OR: 0.70, 95% CI: 0.32-1.55, p=0.38) and extracranial hemorrhage (OR:0.74, 95% CI: 0.23-2.41, p=0.62), and the mortality rates (OR:1.09, 95% CI: 0.33-3.59, p=0.89) were not statistically significant different between the anticoagulant and antiplatelet group. The comparison of antiplatelets to VKA (OR: 1.46, 95%CI: 0.79-2.72, p=0.23) and exclusively aspirin to VKA (OR: 1.26, 95%CI: 0.48-3.29, p=0.64) shows non significantly difference in terms of stroke Overall hemorrhagic events were less frequent in the antiplatelet compared to VKA

group (OR: 0.40, 95%CI:0.17-0.91, p=0.03). The groups of VKA and NOACs do not seem to present different recanalization and hemorrhagic events rates.

Conclusions

Anticoagulation demonstrates comparable rates of stroke, intra and extracranial haemorrhage and mortality with antiplatelet therapy. Individual approach considering patient's bleeding and thrombotic risk in order to define the antithrombotic treatment remains reasonable.

Keywords: Cervical dissection, carotid artery, vertebral artery, anticoagulants, antiplatelets, antithrombotic treatment

Abbreviations

EAD: extracranial artery dissection

INR: International normalized ratio

LMWH: Low molecular weight heparin

MRI: Magnetic Resonance

mRS: modified Rankin Score

NOAC: Novel oral anticoagulants

RCTs: Randomized controlled trials

SAH: subarachnoid hemorrhage

VKA: Vitamin K antagonist

UFH: Unfractionated heparin

ΠΕΡΙΕΧΟΜΕΝΑ

ΓΕΝΙΚΟ ΜΕΡΟΣ

ΕΙΔΙΚΟ ΜΕΡΟΣ

General Section

Introduction

The occurrence of cervical artery dissection is responsible for approximately 1-2% of all ischemic cerebrovascular events overall. However, in younger patients, it accounts for 10-25% of strokes[1,2]. It follows an intimal tear or rupture of the vasa vasorum. The dissection can extend either to the carotid or the vertebral artery. This can lead to an intraluminal thrombus, vascular stenosis, occlusion, or dissecting aneurysm formation. Studies suggest a heightened risk of secondary stroke (15-20%) in individuals with carotid dissection, presenting either localized symptoms such as headaches or Horner's syndrome, or experiencing transient ischemic attacks[3]. Alternatively, it may lead to less frequent occurrences of retinal or spinal cord ischemia, usually emerging several hours or days after the initial localized symptoms appear. The occurrence of subarachnoid hemorrhage (SAH) in extracranial artery dissection (EAD) is extremely rare and typically occurs when the dissection extends into the intradural portion of the artery[3].

Most strokes seem to manifest shortly after the initial symptoms due to embolic events following a thrombus formation at the dissection site. The significant rate of early recurrence has led to the adoption of antithrombotic therapy to reduce the risk of subsequent strokes[4]. While some argue for anticoagulant therapy as more effective in preventing embolic events resulting from soft thrombus formation, others advocate for antiplatelet therapy, citing comparable effectiveness and a lower risk of significant bleeding[5–8]. Despite the abundance of studies, the available data remain unclear.

The CADISS study (Cervical Artery Dissection in Stroke Study), is a prospective randomized trial comparing the effects of anticoagulant and antiplatelet therapy on stroke occurrence following dissection of the extracranial carotid or

vertebral artery and involves 250 patients randomized into two groups of antithrombotic treatment[5,9]. One group received anticoagulant therapy (initially heparin and later warfarin with a target INR of 2-3), while the other received antiplatelet therapy for a minimum of 3 months. A total of 22% of patients received exclusively aspirin, 28% received both aspirin and clopidogrel, 33% received clopidogrel alone, 16% received aspirin and dipyridamole, and one patient had only dipyridamole. The risk of stroke within the first year was 2.4% in the overall population, with no significant differences in stroke occurrence at both 3 months and the first year of follow-up. In the 181 patients with diagnosed dissection and comprehensive imaging, no variation was observed in the incidence of stenosis or occlusion between the two therapy groups. Therefore, antiplatelet therapy with clopidogrel (75 mg daily), aspirin (75-150 mg daily), or their combination may serve as the primary antithrombotic treatment in acute internal carotid or vertebral artery dissection, considering its simplicity and potentially superior bleeding profile compared to anticoagulant therapy with coumarin drugs.

Special Section

Objective

Various meta-analyses have consistently highlighted the comparability between antiplatelet therapy and VKA regarding stroke prevention, major intra- or extracranial hemorrhage, and death[10–12]. To summarize the most updated data from the current literature on the major clinical outcomes in patients with cervical artery dissection treated with antithrombotic therapy, we conducted a systematic review and meta-analysis with direct comparison of the efficacy of antiplatelets, VKA and NOACs. Our research aims to provide conclusive evidence and assess the efficacy of various antithrombotic therapies through rigorous mathematical methodology.

Methods

Study design and PICO criteria

The present systematic review and meta-analysis are in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[13] and were submitted in advance in the International Prospective Register of Systematic Review (PROSPERO) database with registration number: CRD42024535906. The research question was defined by applying the PICO (Population, Intervention, Comparison, and Outcome) criteria:

1. Population: Patients with cervical artery dissection (extracranial carotid artery, vertebral artery).
2. Intervention: Antiplatelet agents
3. Comparison group: Anticoagulant agents (DOACs, VKA)
4. Outcomes: The primary outcomes were the stroke rates and the hemorrhagic events. The secondary outcomes were the rates of mortality, recanalization rate, and modified Rankin score (mRS).

Stroke events were classified as either ipsilateral or contralateral, cortical, vertebrobasilar or ischemic. The hemorrhagic strokes were included in the hemorrhagic events. The review included original clinical studies, both randomized clinical trials and non-randomized prospective or retrospective comparative studies, reporting on the secondary prevention of outcomes of interest in patients with diagnosed cervical artery dissection treated with antiplatelets and anticoagulant agents. The exclusion criteria were defined as follows: (i) irrelevant articles, (ii) non-comparative studies with fewer than two arms, (iii) studies not referring to the outcomes of interest, (iv) studies reporting on patients with intracranial artery dissection (v) animal or in-vitro studies, (vi) case reports, (vii) case series with less than 5 patients in each group, (viii) narrative

or systematic reviews and meta-analyses, letters to the editor and comments, (ix) non-English language articles and (x) published abstracts without published full text. The identified studies were systematically assessed for overlap and in cases where multiple studies covered the same population, only the larger study, in terms of participants, or with the highest quality of data was included in the meta-analysis.

Literature search strategy

Systematic search through the MEDLINE (via PubMed), Scopus, and Cochrane Library databases, with last search: Mars[25th], 2024, was conducted using the following qalgorithm: ((antithrombic drugs[MeSH Terms]) OR (agents, antiplatelet[MeSH Terms])) OR (anticoagulant drugs[MeSH Terms])) OR (anticoag*)) OR (antiplatel*)) OR (antiagreg*)) OR (antithromb*)) OR (platelet antiaggregants[MeSH Terms])) AND (((artery dissection, vertebral[MeSH Terms]) OR (carotid artery dissection[MeSH Terms])) OR ("cervical artery dissection")). We did not apply any filter in our search. Two independent investigators screened titles and abstracts and assessed their full-text eligibility. We resolved the disagreements through discussion with a third reviewer. Additionally, the reference list of the included studies was ultimately searched for potentially eligible studies using the snowball methodology[14]. The Covidence reference and article manager software was used in the title, abstract and full text screening attaining the final study selection[15].

Data extraction and assessment of the risk of bias

Patients' baseline characteristics and the outcomes of interest were independently extracted and collected by two investigators into a pre-designed standardized table. Concerning the Randomized controlled trials (RCTs) we used the data from the intention to treat analysis. The Risk of Bias in Non-Randomized Studies of

Interventions tool (ROBINS-I) was systematically used to assess the quality and address the risk of bias in non-randomized studies, while the revised Cochrane risk of bias tool for randomized trials (RoB 2) was applied to evaluate the RCTs[16,17]. The studies were categorized based on their characteristics into low, moderate, serious, or critical risk of bias using the ROBINS-I tool and low, some concerns or high risk of bias with RoB2 tool. Two independent reviewers assessed the risk for bias and any disagreements were resolved by a third reviewer who evaluated the data making the final decision.

Statistical Analysis

Data Pooling

Continuous and categorical variables were summarized as means with standard deviations (SDs) and frequencies with percentages, respectively. When medians and ranges were provided, the means and SDs of continuous variables were estimated using the methods of Hozo et al. and the Wan et al. for median and interquartile ranges, respectively[1819]. The outcomes of interest were extracted and entered into tables. While the data were analyzed cumulatively.

Meta-Analysis

We derived odds ratios (ORs) and 95% confidence intervals (CIs) concerning the outcomes of interest of each individual study based on the extracted data, using 2 x 2 tables categorical outcomes. OR greater than 1 indicated a higher frequency of the outcome in the antiplatelets group. For studies with zero cell frequencies, we applied treatment arm continuity correction[20]. Heterogeneity among studies was assessed through Cochran Q statistic and the I^2 statistic, with I^2 greater than 50% and $p<0.1$ denoting significant heterogeneity. Due to the significant heterogeneity across studies, we used the random-effects model (DerSimonian–Laird) to calculate the pooled effect

estimates for all outcomes[21]. For each outcome we created graphically a forest plot to display visually the pooled estimates. To confront with potentials distortions from exaggerated effect sizes we used the leave-one-out statistical methodology conducting multiple meta-analyses by systematically excluding one study at a time. Publication bias were evaluated via funnel plots and Egger's test was employed when at least 10 studies were included for a particular outcome with a p value less than 0.10 indicating potential publication bias. Subgroup analyses were performed according to the comparison of antiplatelets versus vitamin K antagonists, aspirin versus vitamin K antagonists, NOACs versus vitamin K antagonists, and the expansion of the dissection only in the carotid artery. Statistical analysis was conducted using Stata/SE version 18 (Stata Corp, College Station, TX, USA).

Results

Study and Patient characteristics

The literature search identified 1369 possible eligible articles after duplicates were removed, of which 38 underwent full-text evaluation. A total of 3 studies were excluded due to overlapping populations, including 2 which were subgroup and long-term analysis of CADISS and TREAT-CAD trials[9,22,23]. We identified no study reporting on propensity matched pair of patients. 1 study was excluded because the available full text was written in Russian language, and through the abstract, the data extraction and the assessment of risk of bias were not feasible[24]. Also, 2 studies were excluded due to non extractable data and missing outcomes of interest[25,26]. 1 study was detected through the snowball methodology[27]. Finally, 22 studies reporting on a total of 5180 patients with cervical artery dissection treated with antiplatelets, VKA and NOACs for secondary stroke prevention, met the inclusion criteria and were analyzed in our quantitative data synthesis, as indicated in the PRISMA flowchart **(Figure 1)**[4–

[6,27–45]. The baseline characteristics of the included studies and the patient's demographics **Table 1** and **Supplementary Table 1**, respectively.

Study quality and publication bias assessment

Of the 22 studies included in the final analysis, 20 were non-randomized observational studies (4 prospective and 16 retrospective)[4,27–45] and 2 were randomized controlled trials[5,6]. All the 20 observational studies were considered with moderate risk of bias, with four of them containing domains with no information given (**Supplemental Figure 1).** The two RCTs were considered with some concerns in terms of deviation from the intended intervention (**Supplemental Figure 2).** The funnel plots assessing for publication bias are presented in **Supplemental Figures 3-5.** While the Egger's test and the visual assessment of the funnel plots did not identify any potential publication bias concerning the mortality, possible bias were indicated regarding the stroke and hemorrhagic events **(Supplemental Figure 3-5).**

Outcomes of interest

Stroke

The overall secondary stroke rates were available in 18 studies, reporting on a total of 4925 patients, 3458 treated with antiplatelets and 1467 with anticoagulation[5,6,27,29–32,34–37,39–45]. In the pooled analysis, the incidence rate of stroke between antiplatelets and anticoagulation was 4.8% (167/3458) and 3.7% (55/1467), respectively, with no statistically significant difference between the two groups (OR: 0.85, 95% CI: 0.62-1.19, p=0.35) **(Figure 2)**. There was found no statistical heterogeneity (I^2= 0.00%). Even though excluding the large study by Yaghi S. et al [29] increases the OR from 0.85 to 1.15 in favor of antiplatelets, the non-significant difference remains (95% CI: 0.85-2.65, p=0.17) **(Supplemental Figure 6).**

Intracranial Hemorrhage

Eleven studies reported on the events of intracranial hemorrhage[4–6,27,30,31,35,40–42,45]. The rate of intracranial hemorrhage was not statistically different between the antiplatelet (1.6%, 9/566) and the anticoagulation group (1.5%, 10/653) (OR: 0.70, 95% CI: 0.32-1.55, p=0.38) **(Figure 3)**. The statistical heterogeneity was not considerable (I^2=0.00%).

Extracranial Hemorrhage

The overall rates of extracranial hemorrhage were available in 9 studies, including 1 hemorrhagic event in antiplatelet group (0.2%, 1/486) and 4 in anticoagulation group (0.7%, 4/570)[5,6,27,30,35,37,41,42,45]. There was no statistically significant difference between the two treatments (OR:0.74, 95% CI: 0.23-2.41, p=0.62) and the heterogeneity remained low (I^2=0.00%) **(Figure 4)**.

Any Hemorrhage

The overall hemorrhagic events following the antithrombotic treatment were reported in 12 studies, including 30 events following antiplatelets (0.9%, 30/3202) and 37 in anticoagulation (3.7%, 37/1005)[5,6,27,29,31,34,35,39,41–43,45]. Patients under antiplatelets had a significantly lower risk of any hemorrhagic event compared to those receiving anticoagulation and the statistical heterogeneity was low (OR: 0.34, 95%CI: 0.20-0.56, p<0.001, I^2=0.00%) **(Figure 5)**. By excluding the large study by Yaghi S. et al [29] the statistical significance remains with higher odds of any hemorrhagic event in the antiplatelets group (OR: 0.49, 95% CI: 0.25-0.97, p=0.041) **(Supplemental Figure 7)**.

Mortality

The overall mortality rates were reported in 10 studies[5,6,31,34,38,40–42,44,45]. In the pooled analysis, the incidence of mortality rates of treatment with antiplatelets

compared to anticoagulation was 1.1% (6/560) and 0.8% (4/509), respectively, with no statistically significant difference between the two groups (OR:1.09, 95% CI: 0.33-3.59, p=0.89) **(Supplemental Figure 8)**. There was no found statistical heterogeneity (I^2= 0.00%).

Modified Rankin Score

In total 6 studies provided sufficient data regarding the modified Rankin Score[6,31,36,39,40,42]. 386 (72.8%, 386/530) patients in the antiplatelet and 285 (84.1%, 285/339) in the anticoagulation group were reported with mRS from 0 to 2, with statistically significant lower rates in the antiplatelet arm (OR: 0.53, 95% CI: 0.36-0.79, p<0.001) **(Supplemental Figure 9)**. There statistical heterogeneity remained low (I^2= 0.00%).

Subgroup Analysis

Single or Dual Antiplatelet treatment versus Vitamin K Antagonists

Thirteen studies reported data regarding stroke events in patients treated with single or dual antiplatelet therapy compared to exclusively vitamin K antagonists[5,6,30–32,34,36,37,40–44] and 7 studies included data in terms of any hemorrhagic event[5,6,31,34,41–43]. Stroke rates were 4.1% (30/773) in antiplatelets versus 3.1% (21/896) in vitamin K antagonists' group and hemorrhagic rates 1.5% (8/547) in antiplatelets versus 4.4% (19/434) in the vitamin K antagonists with no statistically significant difference was detected in terms of stroke (OR: 1.46, 95%CI: 0.79-2.72, p=0.23) **(Supplemental Figure 10)**. The overall hemorrhagic events were significantly lower in the antiplatelets group (OR: 0.40, 95%CI:0.17-0.91, p=0.03) **(Supplemental Figure 11).** The heterogeneity remained in both endpoints low (I^2=0.00%).

Exclusively Aspirin treatment versus Vitamin K Antagonists

Eight studies reported data regarding stroke events in patients treated exclusively with aspirin compared to exclusively vitamin K antagonist[5,6,30,37,40–42,44] and 4 studies included data in terms of hemorrhagic events[5,6,41,42]. Stroke rates were 3.1% (14/445) in aspirin versus 1.5% (9/582) in vitamin K antagonists group and hemorrhagic rates 0% (0/312) in aspirin versus 0.7% (2/272) in the vitamin K antagonists with no statistically significant difference was detected in terms of stroke (OR: 1.26, 95%CI: 0.48-3.29, p=0.64) **(Supplemental Figure 12)** and overall hemorrhagic events (OR: 0.49, 95% CI:0.08-2.97, p=0.44) **(Supplemental Figure 13).** The heterogeneity remained in both endpoints low (I^2=0.00%).

Vitamin K antagonist versus NOACs

There were two studies with direct head-to-head comparison between vitamin K antagonists and NOACs[33,43], with a total of 132 and 45 patients in each group, respectively. Only one of them provided data regarding the recurrent stroke events[43]. Complete recanalization rates were 46.3% (57/123) in vitamin K antagonists and 39%, (16/41) in NOACs group (OR: 0.78, 95% CI:0.17-3.62, p=0.75) with moderate statistical heterogeneity (I^2 = 48.82%) **(Supplemental Figure 14).** Hemorrhagic events were reported in 9.1% (12/132) patients in vitamin K antagonists and 4.6% (2/43) in NOACs (OR: 3.37, 95% CI:0.73-15.43, p=0.12) with no statistical heterogeneity (I^2=0.00%) **(Supplemental Figure 15).** No statistically significant difference was identified between the two treatments regarding the complete recanalization and the overall hemorrhagic events.

Aspirin versus vitamin K antagonists in carotid artery dissection

In total 4 studies provided data regarding the stroke rates in patients with carotid artery dissection[30,37,40,42], comparing the aspirin to the vitamin K antagonists. Stroke rates were 1.9% (3/155) in aspirin and 2% (5/252) in vitamin K antagonists group, with

no observed statistically significant difference between (OR: 0.42, 95%CI: 0.1-1.84, p=0.25) and low statistical heterogeneity (I^2=0.00%) **(Supplemental Figure 16).**

Discussion

Our research included a total of 22 studies reporting on 5180 patients with cervical artery dissection, comparing directly different types of antithrombotic treatment, aspirin, VKA and NOACs as secondary stroke prevention. The results of this meta-analysis suggest that the incidence of stroke events, intracranial and extracranial hemorrhage, and the mortality rates were not statistically significantly different between the two treatment groups. Otherwise, the rate of the combined overall hemorrhagic events appears to be significantly higher in the group of anticoagulants. To address the heterogeneity between studies, we performed subgroup analyses based on the particular antiplatelet and anticoagulation agent. The comparison of antiplatelets to VKA and aspirin to VKA shows no significant difference in terms of stroke. Overall hemorrhagic events were less frequent in the antiplatelet group compared to VKA. Meanwhile, the groups of VKA and NOACs do not seem to present different recanalization and hemorrhagic events rates.

The results of our study seem to be in accordance with the previously published meta-analysis by Chowdhuri M et al, indicating no difference between anticoagulant and antiplatelet agents in terms of stroke, mortality, intra and extracranial hemorrhage[11]. However, the rates of the reported stroke in the antiplatelet compared to anticoagulants group, 1.74% and 1.43%, respectively, were lower compared the results from our study, 4.8% in antiplatelets versus 3.7% in anticoagulants. Moreover, in our study, we proceeded to a further analysis of the total hemorrhagic events, intracranial and extracranial, concluded in statistically significant difference with higher odds in the anticoagulant group. Additionally, all of the included studies were observational case

series, as it is with all the meta-analyses conducted before 2015, date of publication of the first RCT regarding the antithrombotic treatment in cervical artery dissection[46–49].

The meta-analysis by Hagrass A et al. proceeded to a different analysis of primary and recurrent stroke events, finding no statistically significant difference between the two-treatment therapies [50]. However, this distinction was only available in 8 studies, all of which are retrospective observational studies. Thus, we are under the impression, that such a distinction may be subject to clinical errors, due to the accuracy of the existing data. However, the clinical influence of the symptoms, with which the patient appeared in the hospital and their respective antithrombotic treatment, would be of great interest and it should be in the analysis of future clinical trials. We choose, also, to not proceed to the subgroup analysis according to the type of study, like the RCTs, as it is already analysed in previous systematic reviews and meta-analyses[51], and the data from only two RCTs are not sufficient for a safe conclusion.

In order to address the impact of the location of the dissection, we decided to do a subgroup analysis in terms of stroke events, in patients with only carotid artery dissection, and no statistically significant difference was indicated between antiplatelet agents and anticoagulation. Unfortunately, data for a similar analysis in patients with vertebral artery dissection alone were scarce and were only provided by one study[42]. Our result is in accordance with the previous meta-analysis of The EZ et al., but it is noteworthy to mention that in their analysis they included 24 studies with a total number of patients, in the two groups, less than 10[52]. Thus, by including studies with such a small number of patients, we considered their analysis as with great heterogeneity and very difficult generalized results in clinical practice. Moreover, the severity of the initial presentation and the different types of dissection aneurysmal, stenotic, or occlusive, when comparing the effects of antiplatelets and anticoagulants in the medical treatment,

could affect the rates of the final outcomes of interest. Unfortunately, the existing data are not adequate to perform a subgroup analysis and examine the heterogeneity of the aforementioned factors between the two treatment groups.

In real-world clinical settings, novel oral anticoagulants (NOACs) have been favored over warfarin. This preference stems from several factors, including warfarin's slower onset of action, increased susceptibility to drug interactions, the requirement for routine laboratory monitoring, and potentially elevated rates of major bleeding events compared to NOACs[53–55]. The STOP-CAD (Antithrombotic Treatment for Stroke Prevention in Cervical Artery Dissection) study is a recent multicenter observational retrospective study that was conducted in 16 countries, comprised of 1918 in single antiplatelet therapy, 535 in double antiplatelet, 350 in NOACs, 674 in VKA or parenteral anticoagulation and 159 in combination therapy. The NOACs were associated with a non significant lower risk of ischemic stroke at 1, 3 and 6 months of follow up[29]. We have identified only two studies with a direct head-to-head comparison between vitamin K antagonists and NOACs, showing no statistically significant difference between the two treatments in terms of recanalization rate and hemorrhagic events[33,43]. The missing data concerning the stroke rate and the small number of studies in combination with the moderate heterogeneity and the moderate risk of bias preclude a safe conclusion. The meta-analysis of Essibayi MA et al., incorporated total 11 single and double arm studies comparing the vitamin K antagonists and NOACs, identified no statistically significant difference between the two groups regarding secondary stroke events, minor and major bleeding and mortality[10]. In this context, the imperative for a head-to-head randomized clinical trial becomes evident to decisively ascertain the suitability of regular NOAC use for stroke prevention in patients with cervical artery dissection.

The TREAT-CAD was a randomized controlled non inferiority multicenter trial, testing the non-inferiority of aspirin compared to vitamin K antagonists in patients diagnosed with cervical artery dissection[6]. Individuals were randomly allocated to either receive aspirin (300 mg daily) or VKA (with or without bridging using UFH or LMWH) for 3 months. The clinical endpoints of acute ischemic stroke, major intra- or extracranial hemorrhage, and death as well as the new cerebral lesions in Magnetic Resonance Imaging (MRI) were analyzed in per protocol and intention to treat analysis. The primary analyses comprised 194 patients of which 100 were allocated to aspirin and 94 were allocated to VKA. The clinical endpoint of stroke occurred in 7 (7%) patients in the aspirin group and in 0 (0%) in the VKA group[6]. Comparing the effect of aspirin and vitamin K antagonist treatment in our pooled analysis the stroke rates were 3.1% (14/445) and 1.5% (9/582), respectively. Our findings appear to be significantly lower compared to the results observed in the TREAT-CAD study. It remains unclear the difference in this outcome could be attributed to the higher dose of Aspirin, 300 mg, used in the TREAT-CAD trial.

The limitations of our research should be addressed. Firstly, as a study-level meta-analysis we did not have access to patient-level covariates that might confound our findings. Most of the studies did not provide critical data on revascularization procedures at the first 24 hours, such as thrombolysis, stenting or thrombectomy, that could influence the clinical outcomes. Moreover, it is noteworthy to mention that the difference of points in time at which the outcomes of interest are reported may have contributed to high heterogeneity between the studies. This fact, along with the variations in the follow-up schemes and the doses of the treatment across the studies, might have affected the generalizability of our results. Furthermore, the 20 of the 22 included studies are not randomized. The lack of randomization, allocation

concealment, and blinding increases the chances of confounding and selection bias. In addition, there is no existing data regarding the appropriate duration of the antithrombotic treatment.

Conclusions

This meta-analysis attempts through rigorous mathematical methodology to provide concrete evidence and compare the efficacy of different antithrombotic therapies. Our research indicates comparable rates of stroke, intra and extracranial hemorrhage and mortality between anticoagulant and antiplatelet arms. An individual approach considering the patient's bleeding and thrombotic risk, to define the antithrombotic treatment remains reasonable.

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Figures

Figure 1. PRISMA flow diagram

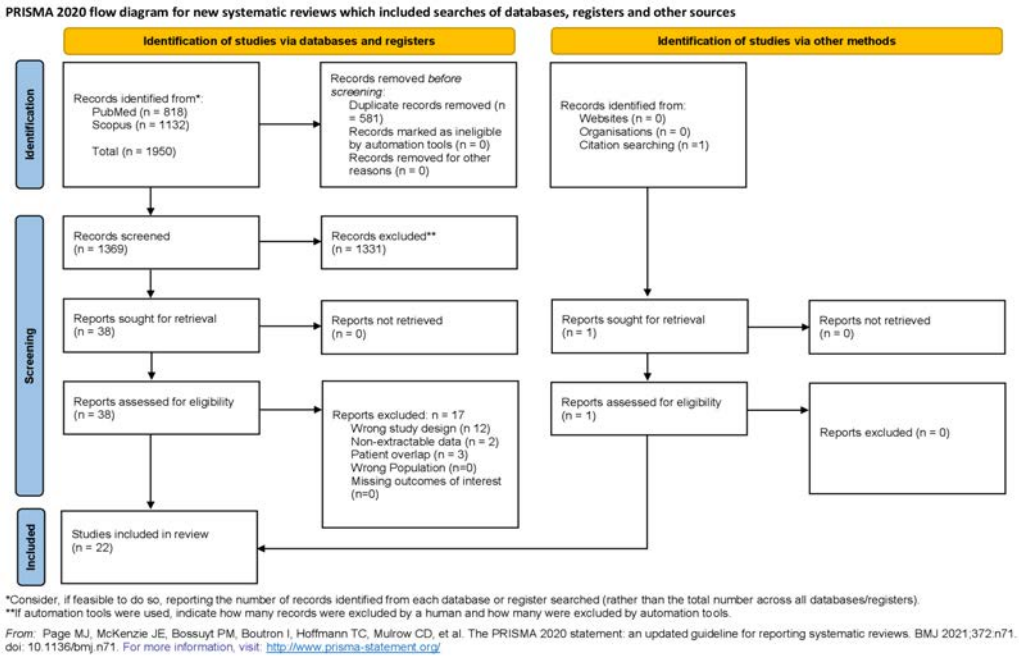


Figure 2. Forest plot regarding stroke events of antiplatelets versus anticoagulants agents

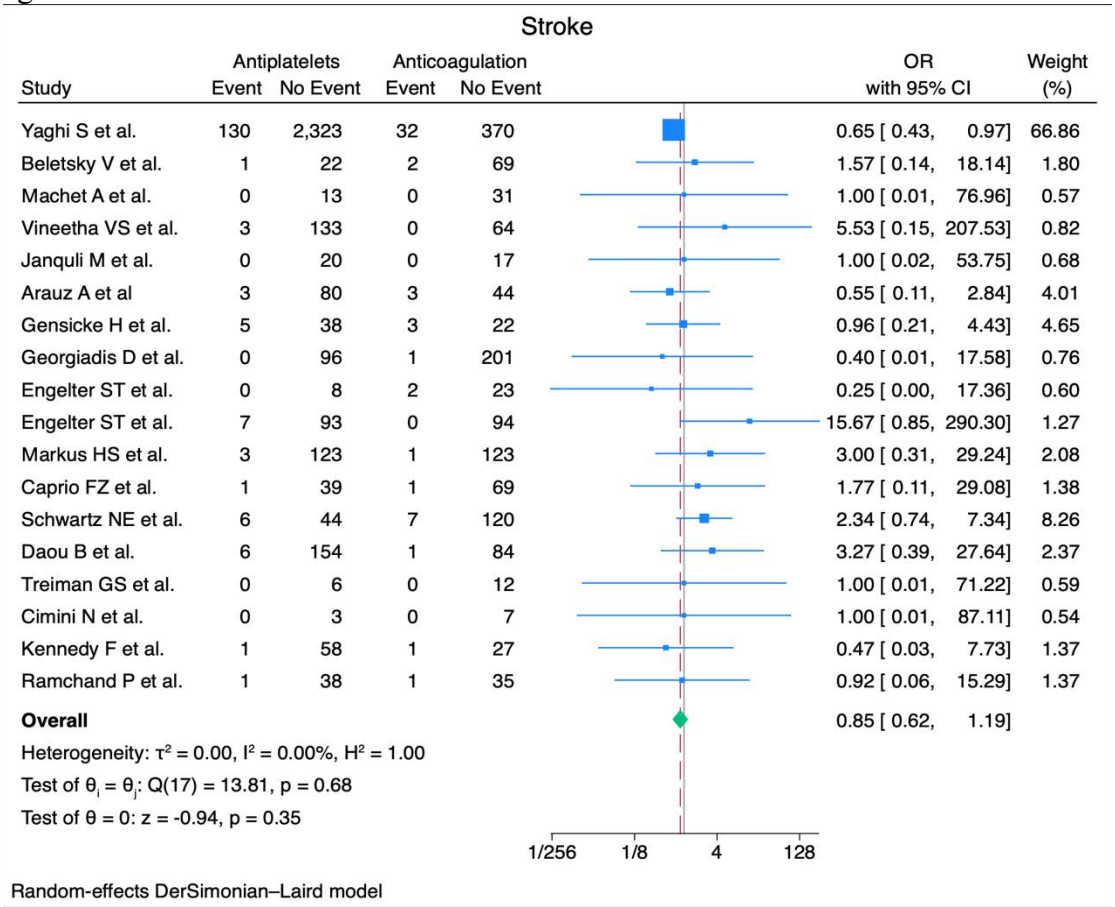


Figure 3. Forest plot regarding intracranial hemorrhage of antiplatelets versus anticoagulants agents

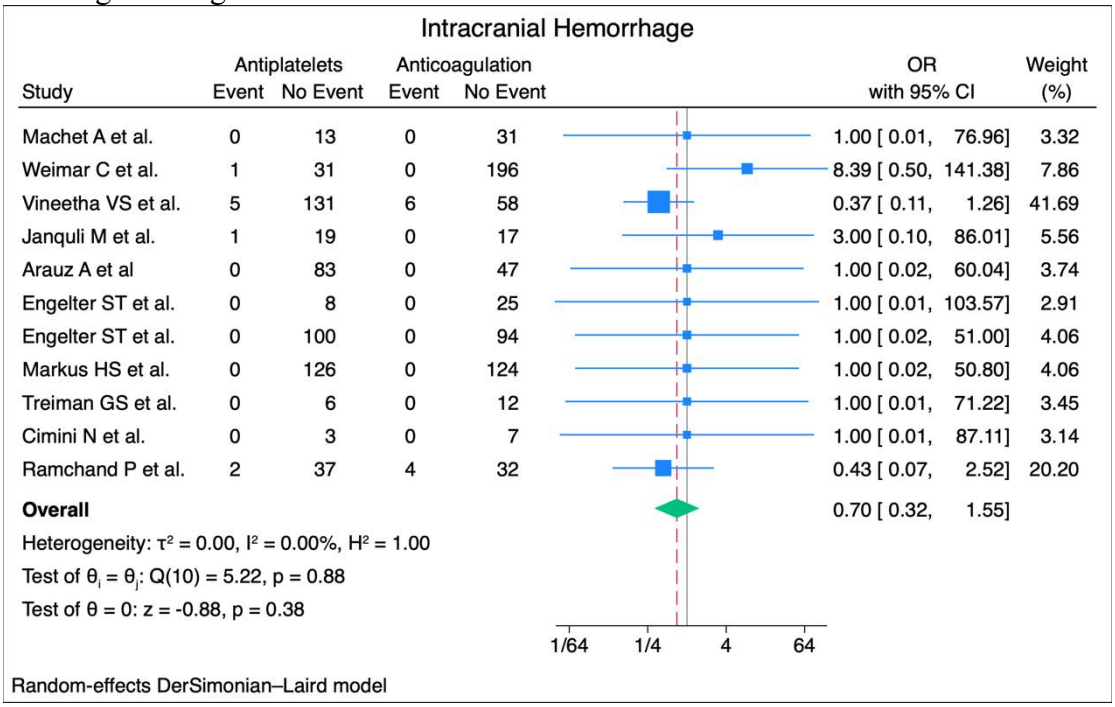


Figure 4. Forest plot regarding extracranial hemorrhage of antiplatelets versus anticoagulants agents

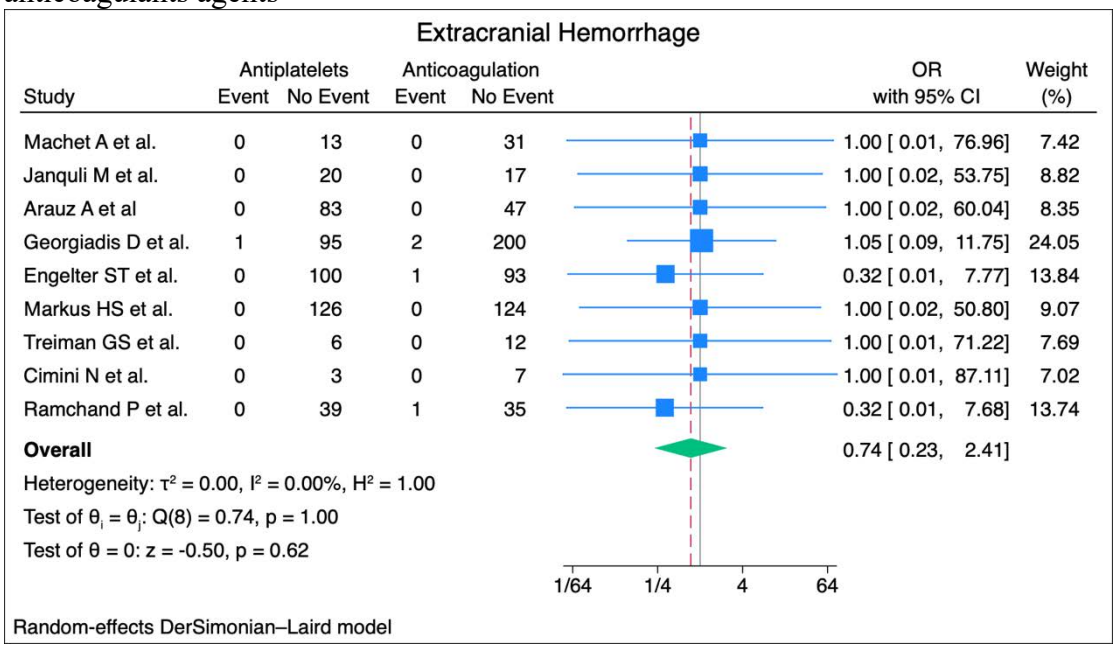
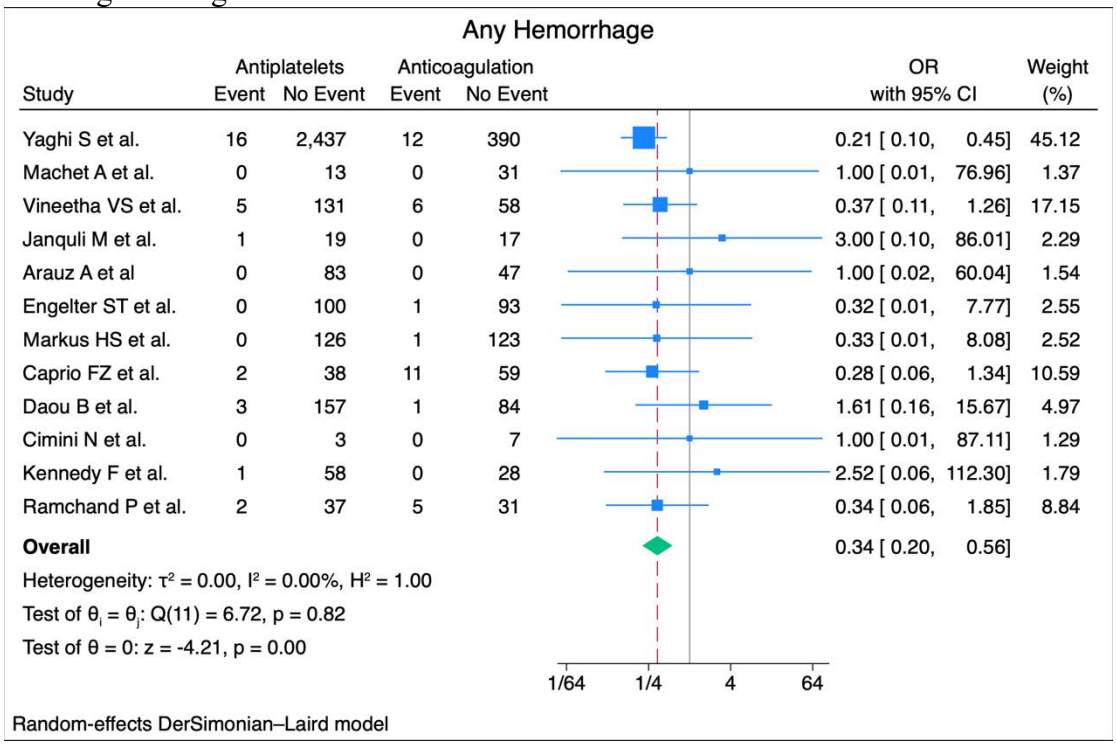


Figure 5. Forest plot regarding any hemorrhagic event of antiplatelets versus anticoagulants agents



Tables

Table 1. Study characteristics

Author	Year	Center	Country	Design	Study period	Comparison	Carotid	Vertebral	Multiple Vessels
Yaghi S et al.	2024	63 sites	16 countries	Retrospective	2006 - 2023	Antiplatelets vs Antagonist vit K vs NOACs	1437	1418	-
Beletsky V et al.	2003	Collaborating members of the Canadian Stroke Consortium	Canada	Retrospective	>2000 and <2003	Aspirin vs Antagonist Vit K	49	67	2
Machet A et al.	2013	Université Paris-Descartes, Sorbonne Paris Cité, INSERM UMR 894, Centre Hospitalier Sainte-Anne, Paris	France	Retrospective	2004-2008	Aspirin vs Heparin sc	-	-	-
Weimar C et al.	2010	30 neurology centers	Germany	Prospective	September 2002-December 2006	Antiplatelets vs Antagonist Vit K	130	117	3
Vineetha VS et al.	2019	Department of Neurology, Sree Chitra Tirunal Institute	India	Retrospective	January 2005-October 2015	Antiplatelets vs Antagonist Vit K	132	68	14
Janquli M et al.	2023	University Hospital Limerick	Ireland	Retrospective	January 2017-April 2022	Antiplatelets vs Anticoag	25	14	3
Arauz A et al	2006	Stroke Clinic of the Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City	Mexico	Retrospective	10-year period	Aspirin vs Antagonist Vit K	58	72	0
Gensicke H et al.	2014	Department of Neurology and Stroke Center, University Hospital Basel, Department of Neurology,	Switzerland	Prospective	November 2009-may 2013	Antiplatelets vs Antagonist Vit K	37	26	5

		Inselspital, University Hospital Bern							
Georgiadis D et al.	2009	Neurological Departments of the University Hospitals of Bern and Zurich	Switzerland	Retrospective	December 1987-November 2005	Aspirin vs Antagonist Vit K	298	0	0
Engelter ST et al.	2000	Department of Neurology, University Hospital Basel	Switzerland	Retrospective	<2000	Aspirin vs Antagonist Vit K	33	0	0
Engelter ST et al.	2021	University Hospital, Stroke Center Bispebjerg Hospital Copenhagen, University Hospital, Stroke Center Charite Berlin, University Hospital, Stroke Center LMU Munich, Kantonsspital, Stroke Center Aarau, University Hospital, Stroke Center Basel, University Hospital, Stroke Center Inselspital Berne, University Hospital, Stroke Center Geneva, University Hospital, Stroke Center CHUV Lausanne, Switzerland	Switzerland, Germany, Denmark	RCT	September 2013-October 2018	Aspirin vs Antagonist Vit K	130	67	14
Markus HS et al.	2019	39 strokes center UK and 7 in Australia	UK, Australia	RCT	24 Februar y 2006-	Aspirin vs Antagonist Vit K	118	132	-

					17 June 2013				
Yaghi S et al.	2011	Department of Neurology, University of Arkansas for Medical Sciences, Little Rock, Arkansas	USA	Retrospective	January 2004-December 2009	Antiplatelets vs Antagonist Vit K	30	17	0
Caprio FZ et al.	2014	Northwestern Healthcare System	USA	Retrospective	January 2010-August 2013	Antiplatelets vs Antagonist Vit K vs NOACs	55	105	11
Schwartz NE et al.	2009	Stanford Stroke Center, Department of Neurology and Neurological Sciences, Stanford University, Palo Alto, California	USA	Retrospective	January 1992-December 2006	Antiplatelets vs Antagonist Vit K	118	93	27
Daou B et al.	2017	Department of Neurosurgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience, Philadelphia, Pennsylvania	USA	Retrospective	January 2005-January 2014	Antiplatelets vs Anticoag vs Combination	161	118	15
Treiman GS et al.	1996	Division of Vascular Surgery, Cedars-Sinai Medical Center, CA	USA	Retrospective	1976-1995	Aspirin vs Antagonist Vit K	21	0	4
Gonzalles Portillo F et al.	2002	Indiana University Medical Center	USA	Retrospective	September 1995-August 2001	Antiplatelets vs Antagonist Vit K	17	8	2
Cimini N et al.	2004	Neurology Department of the Belluno General Hospital	Italy	Prospective	<2004	Aspirin vs Antagonist Vit K	8	2	0
Kennedy F et al.	2012	CADISS non randomized arm	UK, Australia	Prospective	-	Antiplatelets vs Anti K	-	-	-

Ramchand P et al.	2017	Hospital of the University of Pennsylvania, Perelman School of Medicine, Pensylvannia	USA	Retrospective	Janury 1999-December 2013	Antiplatelets vs Anticoag	-	-	9
Mustanoja S et al.	2015	Department of Neurology, Helsinki University Central Hospital, Helsinki	Finland	Retrospective	November 2011-January 2014	Antagonist Vit K vs NOACs	31	40	-

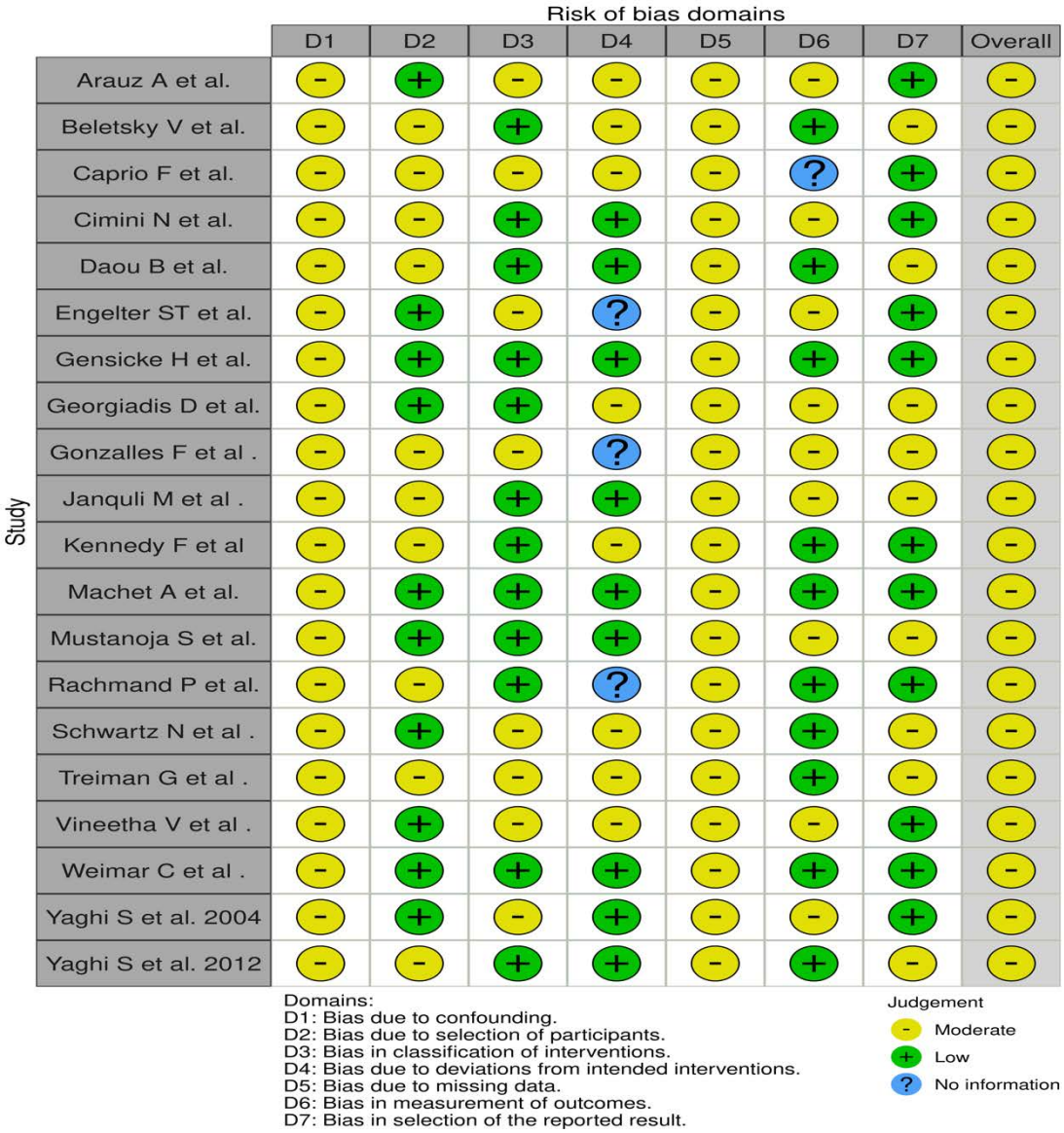
Supplemental Data

Supplemental Table 1. Patients' characteristics

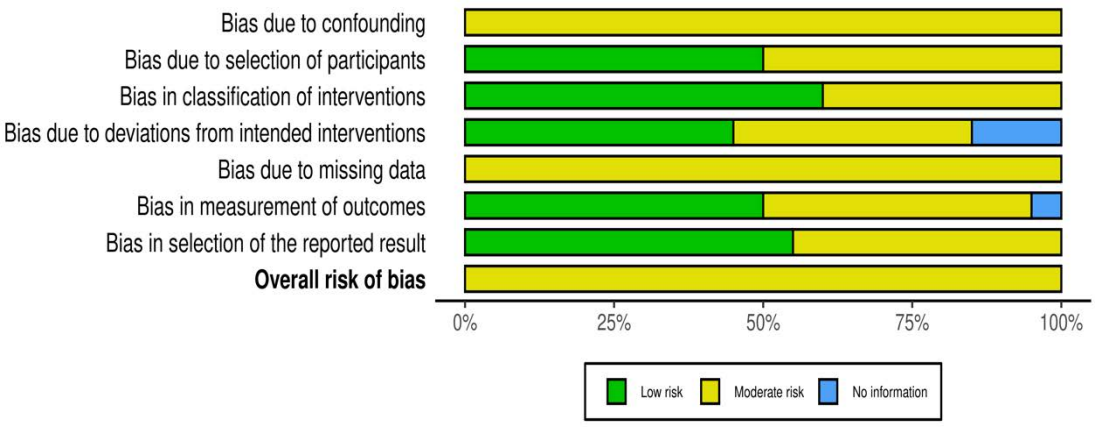
Authors	AP Age (years)	AC Age (years)	AP Males no.	AC Males no.	AP Diabetes no.	AC Diabetes no.	AP HTN no.	AC HTN no.	AP Stroke at admission no.	AC Stroke at Admission No.
Yaghi S et al.	47±13.3	47±13.3	1342	197	207	26	865	137	1492	239
Beletsky V et al.	-	-	-	-	-	-	-	-	-	-
Machet A et al.	41.8±9.6	45.7±8.5	-	-	-	-	-	-	10	19
Weimar C et al.	50.4	47.7	20	118	9	19	18	74	-	-
Vineetha VS et al.	43.4±13.1	43.5±12.9	103	50	31	20	60	32	104	45
Janquli M et al.	-	-	-	-	-	-	-	-	-	-
Arauz A et al	-	-	-	-	-	-	-	-	83	47
Gensicke H et al.	45.2±3.7	48±4	29	18	-	-	-	-	20	13
Georgiadis D et al.	-	-	-	-	-	-	-	-	60	150
Engelter ST et al.	47.8±12.6	44.5±9.3	5	18	-	-	1	7	5	15
Engelter ST et al.	46.6±10.6	45.5±11.6	62	61	1	3	32	28	52	49
Markus HS et al.	49±12	49±12	87	87	5	5	29	26	93	101
Yaghi S et al.	44.5±12.7	44.5±12.7	-	-	-	-	-	-	-	-
Caprio FZ et al.	48.1±13.2	41.4±15	17	21	1	1	8	10	18	38 (25)
Schwartz NE et al.	44±11.1	44±11.1	-	-	0	-	-	-	-	-
Daou B et al.	-	-	-	-	-	-	-	-	-	-
Treiman GS et al.	-	-	-	-	-	-	-		-	-
Gonzalles Portillo F et al.	-	-	-	-	-	-	-	-	-	-
Cimini N et al.	-	-	-	-	-	-	-	-	-	-
Kennedy F et al.	-	-	34	17	4	0	12	1	34	23
Ramchand P et al.	47±15	47±15	-	-	-	-	-	-	-	-
Mustanoja S et al.	-	-	-	-	-	-	-	-	-	68

Supplemental Figure 1. ROBINS 1 tool for risk of bias assessment (A) traffic light plot and (B) summary plot.

A.

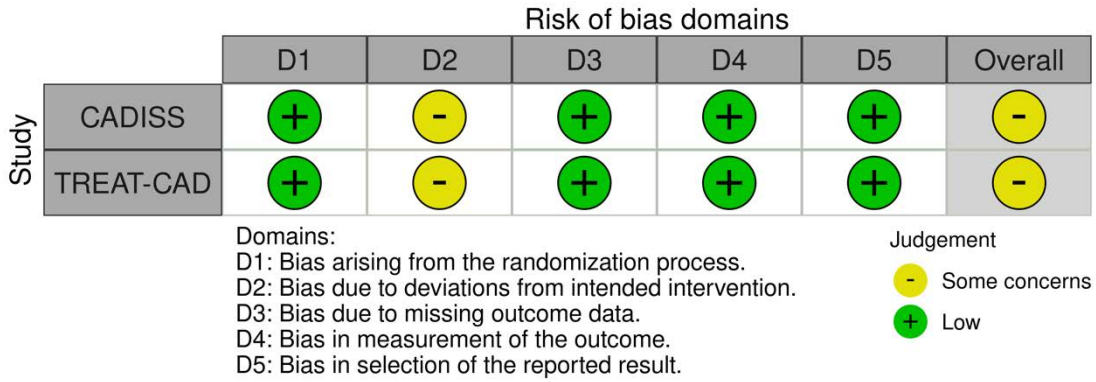


B.

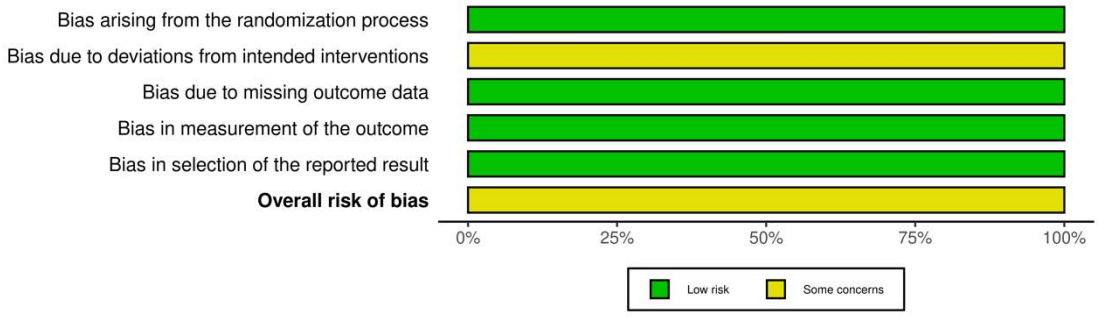


Supplemental Figure 2. RoB2 tool for risk of bias assessment (A) traffic light plot and (B) summary plot.

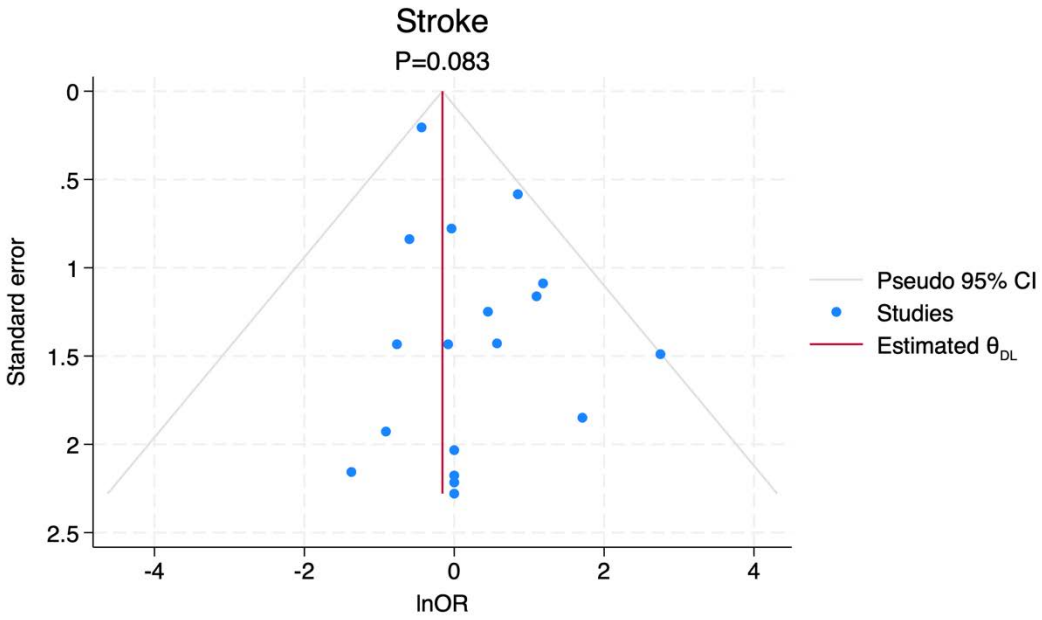
A.



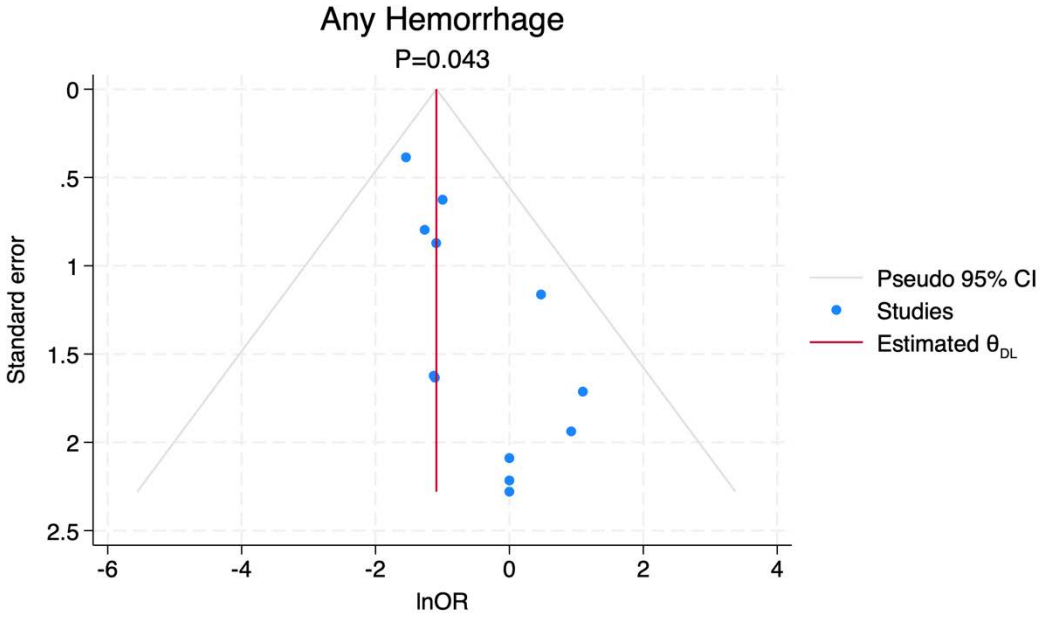
B.



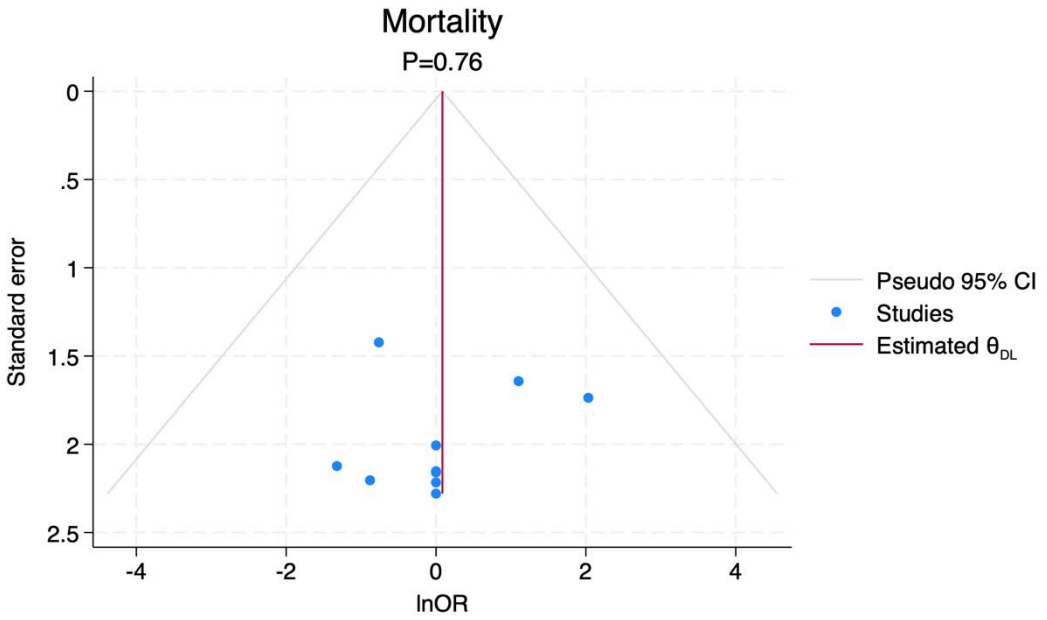
Supplemental Figure 3. Funnel plot regarding stroke events



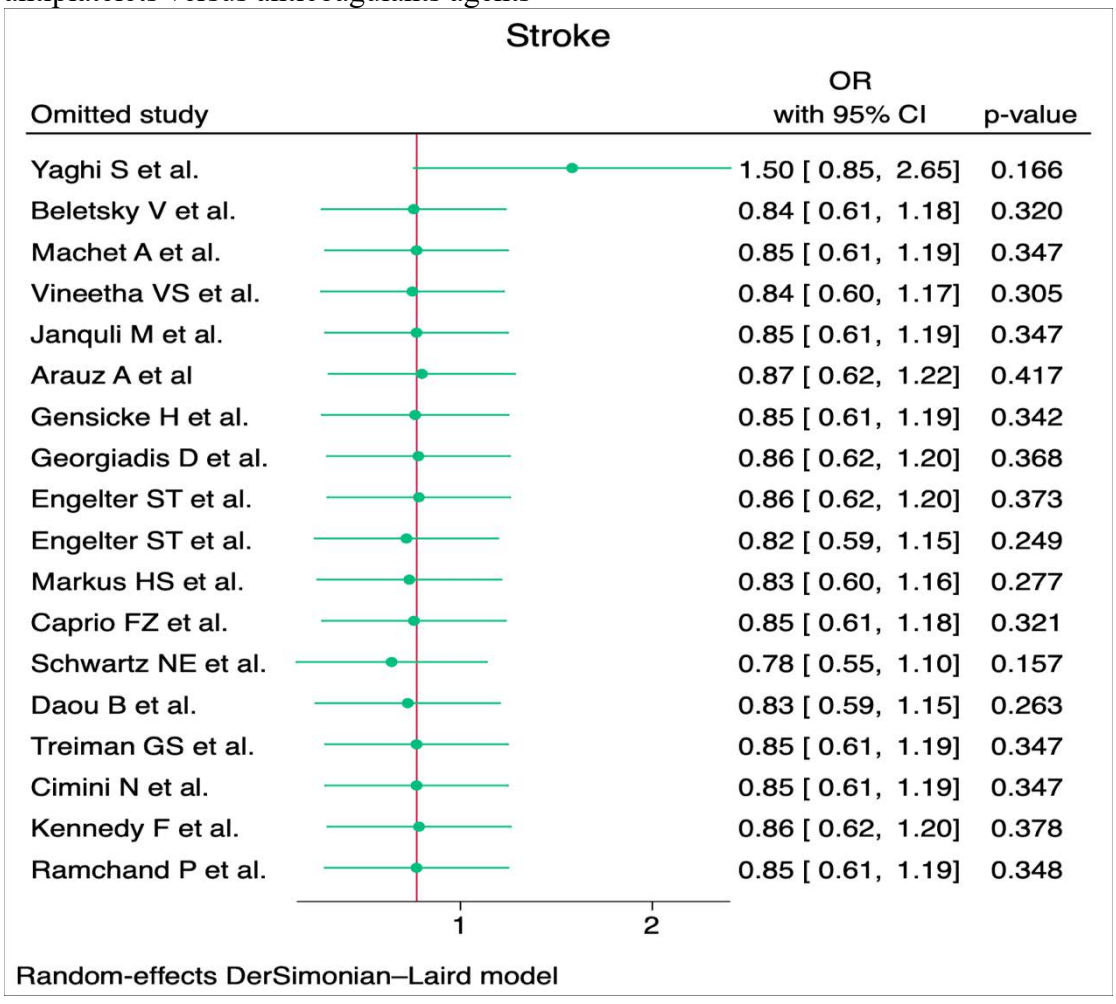
Supplemental Figure 4. Funnel plot regarding hemorrhagic events



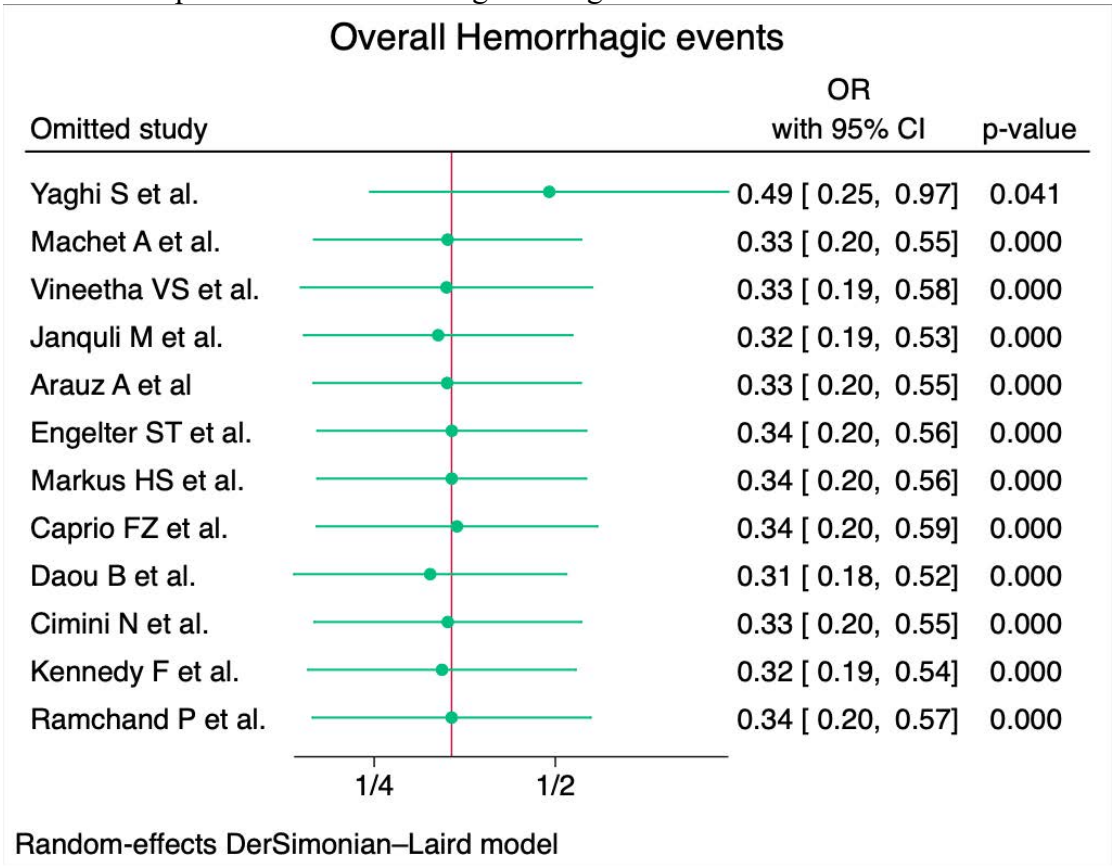
Supplemental Figure 5. Funnel plot regarding mortality rate



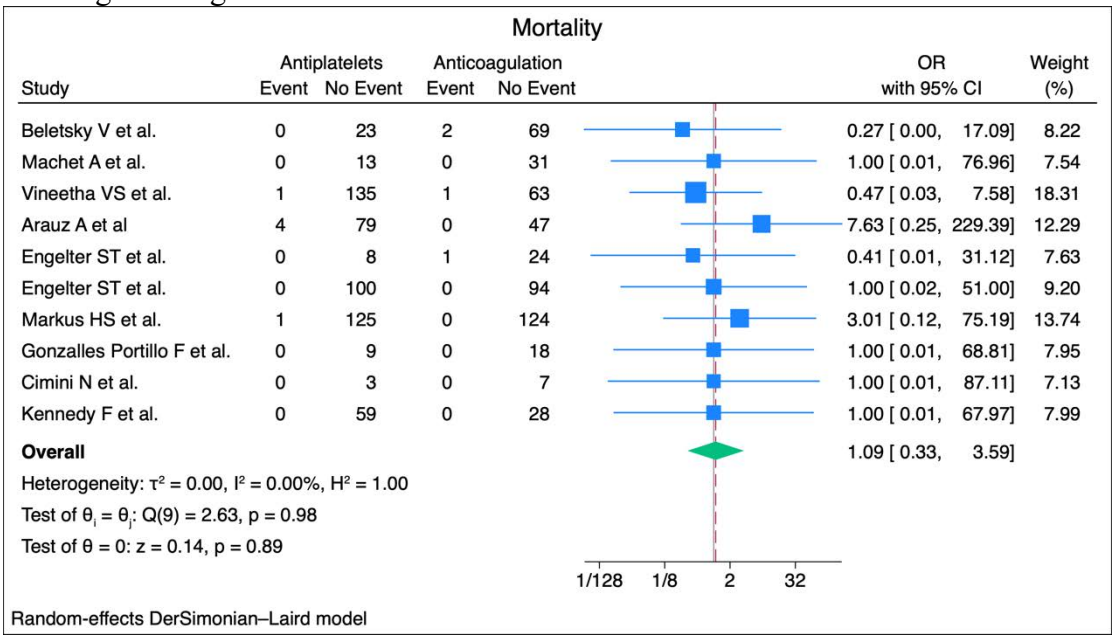
Supplemental Figure 6. Leave one out forest plot regarding stroke events of antiplatelets versus anticoagulants agents



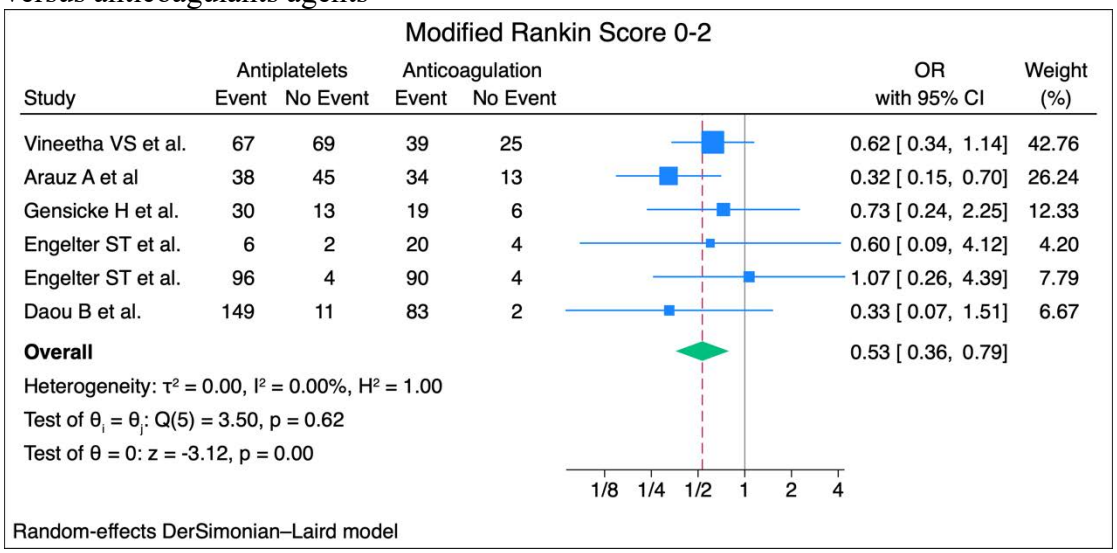
Supplemental Figure 7. Leave one out forest plot regarding overall hemorrhagic events of antiplatelets versus anticoagulants agents



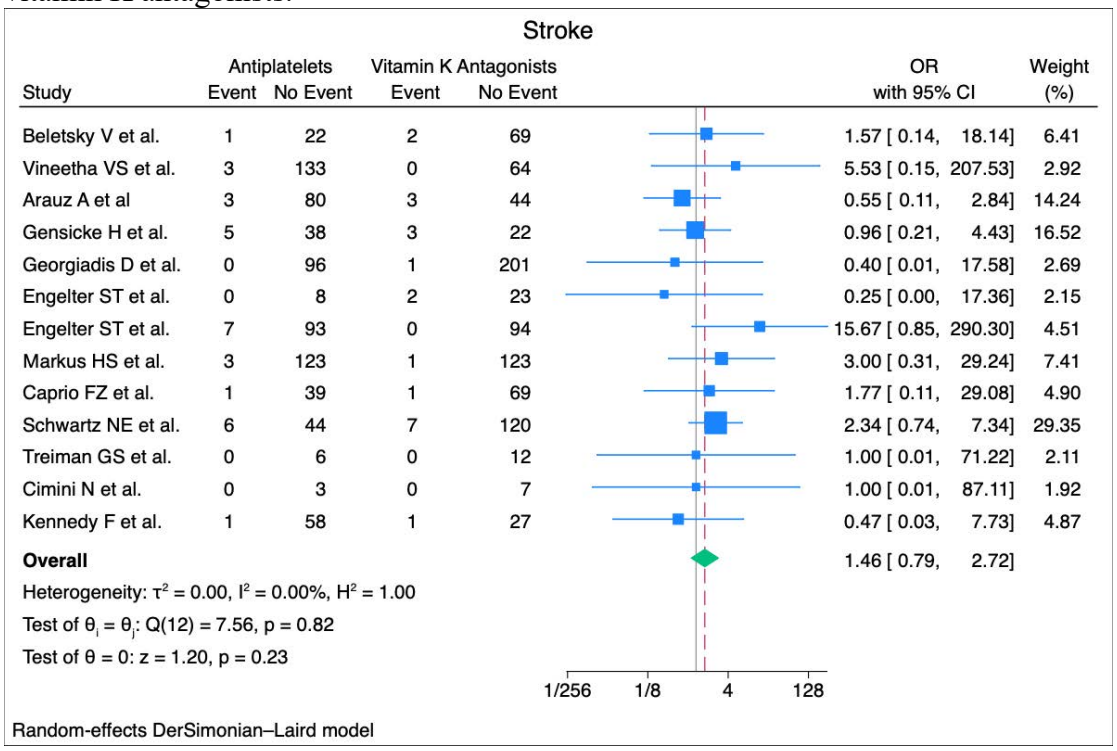
Supplemental Figure 8. Forest plot regarding mortality of antiplatelets versus anticoagulants agents



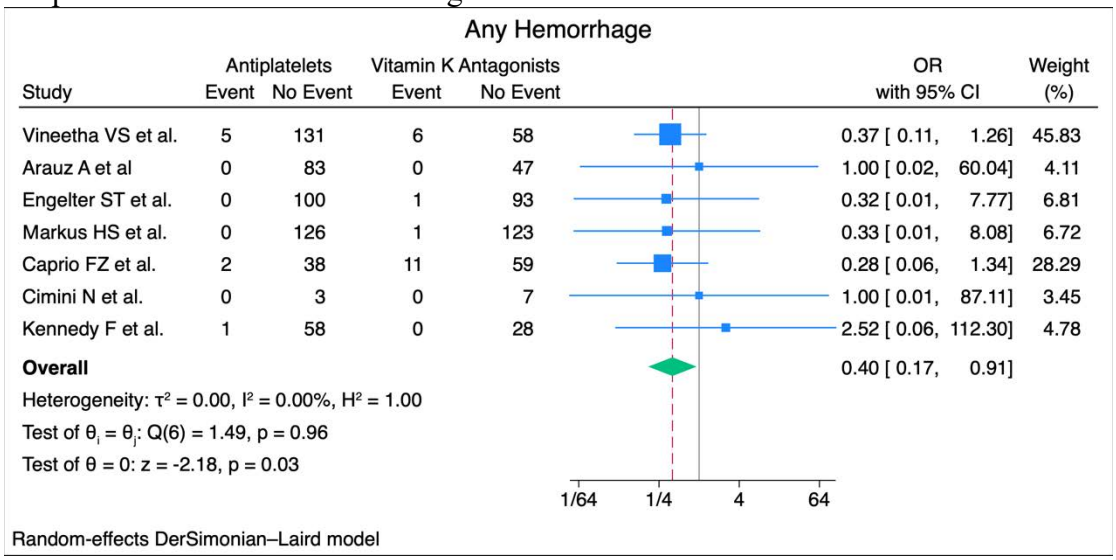
Supplemental Figure 9. Forest plot regarding modified Rankin Score of antiplatelets versus anticoagulants agents



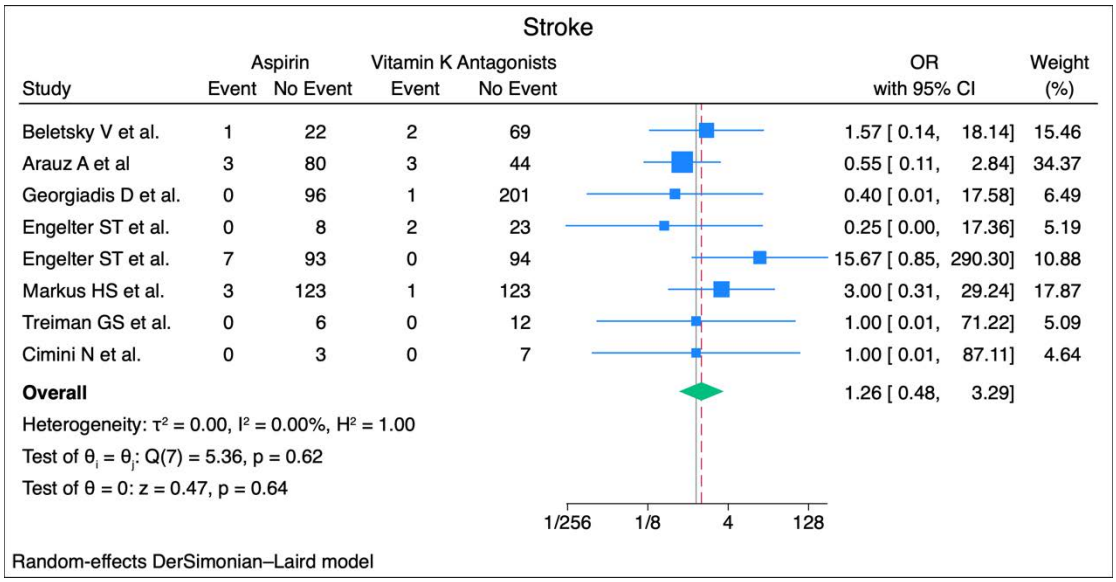
Supplemental Figure 10. Forest plot regarding stroke events of antiplatelets versus vitamin K antagonists.



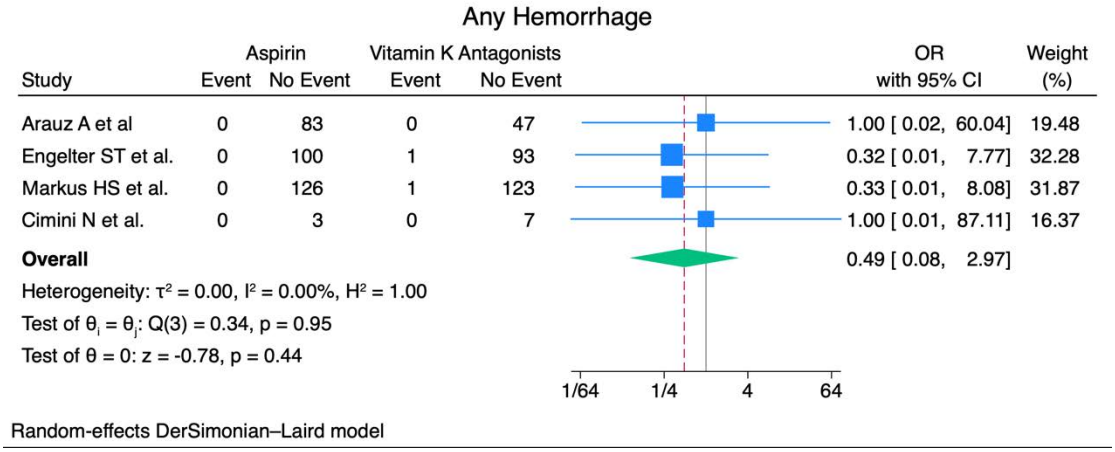
Supplemental Figure 11. Forest plot regarding any hemmorhagic event of antiplatelets versus vitamin K antagonists.



Supplemental Figure 12. Forest plot regarding stroke events of aspirin versus vitamin K antagonists.



Supplemental Figure 13. Forest plot regarding any hemmorhagic events of aspirin versus vitamin K antagonists.



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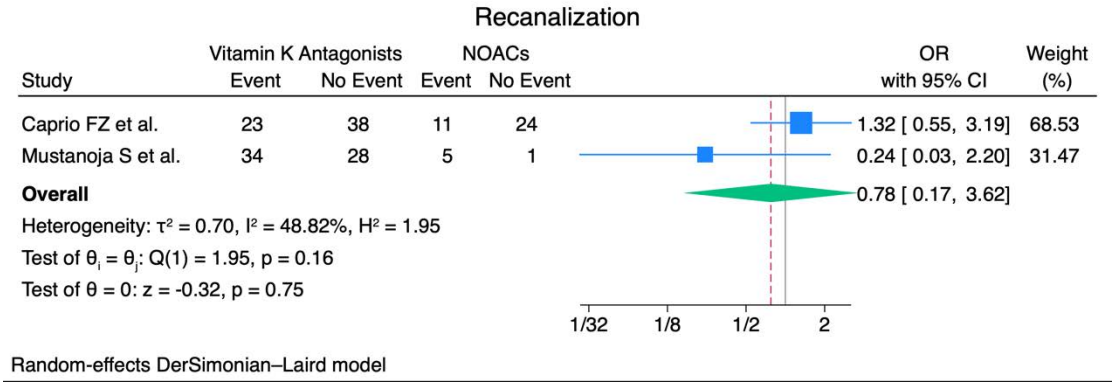
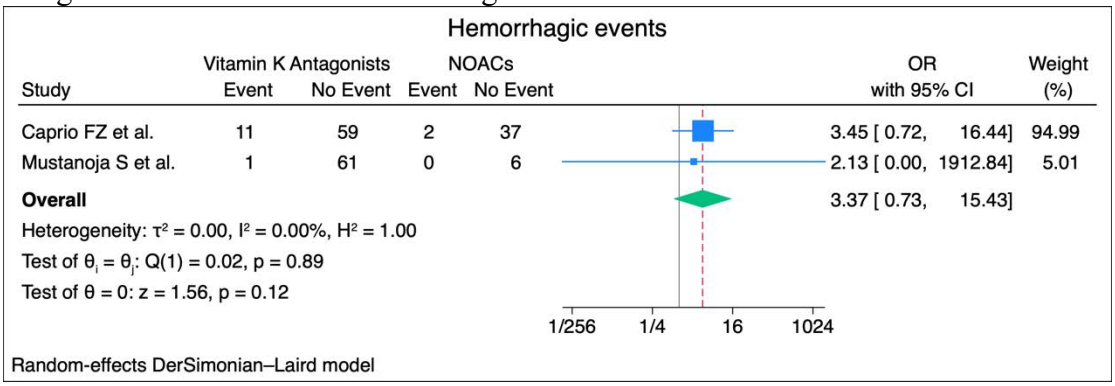
Supplemental Figure 14. Forest plot regarding complete recanalization of vitamin K antagonists versus Novel oral anticoagulants.



Supplemental Figure 15. Forest plot regarding hemorrhagic events of vitamin K antagonists versus Novel oral anticoagulants.



Supplemental Figure 16. Forest plot regarding stroke events of aspirin versus vitamin K antagonists in patients with only carotid artery dissection.