# SUPPLEMENTAL MATERIAL

**Table S1**. **Definitions of symptomatic intracerebral hemorrhage.**

| sICH definition | NIHSS | Imaging |
|---|---|---|
| **PH** | None | Only PH |
| **NINDS** | Any clinical worsening | Any ICH |
| **ECASSII** | ≥4 NIHSS | Any ICH |
| **mSITS-MOST** | ≥4 NIHSS | Only PH |

sICH: symptomatic intracranial hemorrhage; NIHSS: National Institutes of Health Stroke Scale; PH: parenchymal hemorrhage; NINDS: National Institute of Neurological Disorders and Stroke; ECASSII: European-Australian Cooperative Acute Stroke Study 2; mSITS-MOST: modified Safe Implementation of Thrombolysis in Stroke Monitoring; ICH: intracranial hemorrhage.

**Table S2. Search strategy for each database.**

| **Scopus** | | |
|---|---|---|
| Step | Search query | Results |
| #1 | (TITLE(stroke*) AND TITLE(Ischemic or acute or cerebral OR infarct*)) OR TITLE(Large w/3 stroke*) or (TITLE(cerebrovascular) AND TITLE(injury or failure or arrest or accident OR infarct*)) OR TITLE("ischemic cerebral") OR (TITLE(Cerebral) AND TITLE(Apoplexia or "vascular accident" or insult)) | 1644 |
| #2 | ( ( TITLE( noac* OR "thrombin inhibitors" ) OR TITLE ( new W/3 anticoagulant* ) ) OR ( TITLE ( plasminogen W/1 activator ) OR TITLE ( alteplase OR tenecteplase OR "TNK tPA" OR tnkase ) ) ) OR ( ( TITLE ( "Factor Xa" W/2 inhibitor ) OR TITLE ( direct W/2 anticoagulant* ) ) OR ( TITLE ( intravenous W/3 thrombolysis ) ) OR ( TITLE ( direct W/2 anticoagulant* ) ) OR ( TITLE ( doac* OR *aban* AND rivaroxaban OR apixaban OR edoxaban OR betrixaban OR dabigatran ) ) ) | |
| Filters: | ( LIMIT-TO ( DOCTYPE , "ar" ) ) | |

| **Pubmed/Medline** | | |
|---|---|---|
| Step | Search query | Results |
| #1 | "Stroke"[Mh] or (stroke[ti] or "cerebrovascular"[ti] or "ischemic cerebral"[ti]) | 1620 |
| #2 | ("Tissue Plasminogen Activator"[Mh] or "Factor Xa Inhibitors"[Mh] or (noac* or 'thrombin inhibitors' OR rivaroxaban OR apixaban OR edoxaban OR betrixaban OR dabigatran or alteplase OR tenecteplase OR "TNK tPA" OR tnkase)) OR (((plasminogen[ti]) AND (activator[ti])) OR ((direct[ti]) and (anticoagulant*[ti]))) | |
| #3 | ((thrombol*[ti] OR treat*[ti] OR therap*[ti]) and (intravenous[ti])) | |
| #4 | #1 AND #2 | |
| #5 | #4 AND #3 | |
| **Embase** | | |
| Step | Search query | Results |
| #1 | (((ischemic OR acute OR cerebral) NEAR/3 stroke*):ti) OR 'ischemic cerebral':ti OR (((apoplexia OR 'vascular accident' OR insult) NEAR/3 cerebr*):ti) | 678 |
| #2 | noac*:ti OR 'thrombin inhibitors':ti OR rivaroxaban:ti OR apixaban:ti OR edoxaban:ti OR betrixaban:ti OR dabigatran:ti OR alteplase:ti OR tenecteplase:ti OR "TNK tPA":ti OR tnkase:ti ((direct NEAR/2 anticoagulant*):ti) OR (('factor xa' NEAR/2 inhibitor):ti) OR ((plasminogen NEAR/2 activator):ti) | |
| #3 | ((thrombol* OR treat* OR therap*) NEAR/4 intravenous) OR ((thromboly* NEAR/3 therap*):ti,ab) | |

| | | |
|---|---|---|
| #4 | #1 AND #2 | |
| #5 | #4 AND #3 | |

| **Web of Science** | | |
|---|---|---|
| Step | Search query | Results |
| #1 | TI=(stroke*) or (TI=(cerebrovascular) and TI=(injury or failure or arrest or accident OR infarct*)) OR ti=("ischemic cerebral") | 619 |
| #2 | TI=(Noac* or "thrombin inhibitors") or ti=(New near/3 anticoagulant*) or TI=(plasminogen NEAR/2 activator) OR TI=(alteplase OR tenecteplase OR "TNK tPA" OR tnkase) OR TI=("Factor Xa" NEAR/2 inhibitor) OR TI=(direct NEAR/2 anticoagulant*) OR TI=(doac* OR *aban* AND rivaroxaban OR apixaban OR edoxaban OR betrixaban OR dabigatran) OR TI=(antagonist near/3 anticoagulant*) | |
| #3 | TI=(Intravenous NEAR/3 Thrombolysis) OR AB=(Intravenous NEAR/3 Thrombolysis) OR TI=(Treat* near/3 intravenous) or AB=(Treat* near/3 intravenous) OR TI=(thromboly* near/3 therap*) or AB=(thromboly* near/3 therap*) | |
| #4 | #1 AND #2 | |
| #5 | #4 AND #3 | |
| **Scielo** | | |
| #1 | TI=(stroke*) or (TI=(cerebrovascular) and TI=(injury or failure or arrest or accident OR infarct*)) OR ti=("ischemic cerebral") | 11 |
| #2 | TI=(Noac* or "thrombin inhibitors") or ti=(New near/3 anticoagulant*) or TI=(plasminogen NEAR/2 activator) OR TI=(alteplase OR tenecteplase OR "TNK tPA" OR tnkase) OR TI=("Factor Xa" NEAR/2 inhibitor) OR TI=(direct NEAR/2 anticoagulant*) OR TI=(doac* OR *aban* AND rivaroxaban OR apixaban OR edoxaban OR betrixaban OR dabigatran) OR TI=(antagonist near/3 anticoagulant*) | |
| #3 | #1 AND #2 | |

| **CENTRAL (Cochrane Library Central Register of Controlled Trials)** | | |
|---|---|---|
| Step | Search query | Results |
| #A | #1 (stroke):ti<br>#2 MeSH descriptor: [Stroke] explode all trees<br>#3 ((noac* or 'thrombin inhibitors' OR rivaroxaban OR apixaban OR edoxaban OR betrixaban OR dabigatran or alteplase OR tenecteplase OR "TNK tPA" OR tnkase)):ti<br>#4 ((Oral and anticoagulants)):ti<br>#5 ((thrombol* OR treat* OR therap* or recombinant)):ti<br>#6 #1 or #2<br>#7 #3 or #4<br>#8 #6 and #7 | 331 |

| | | |
|---|---|---|
| | #9 #8 and #5 | |

***Results until March 2023**

**Table S3. Summary of certainty of the evidence.**

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Pooled Effect Size (95% CI) |
|---|---|---|---|
| sICH (comparison) | 246933 (8 observational studies) | ⊕⊕⊕◯ Moderate[a] | OR 0.95 (0.67 – 1.36) |
| sICH (proportion) | 3610 (14 observational studies) | ⊕⊕⊕◯ Moderate[a] | 3% (3% – 4%) |
| Any ICH (comparison) | 33816 (3 observational studies) | ⊕⊕⊕◯ Moderate[a] | OR 1.23 (0.61 – 2.48) |
| Any ICH (proportion) | 1062 (11 observational studies) | ⊕⊕⊕◯ Moderate[a] | 12% (7% – 19%) |
| Systemic Bleeding (comparison) | 205218 (3 observational studies) | ⊕⊕⊕◯ Moderate[a] | OR 1.27 (0.79 – 2.02) |
| Systemic Bleeding (proportion) | 2602 (7 observational studies) | ⊕⊕⊕◯ Moderate[a] | 1% (0% – 1%) |
| mRS at 90 days (comparison) | 30687 (3 observational studies) | ⊕⊕⊕◯ Moderate[a,b] | OR 1.22 (0.4 – 3.69) |
| mRS at 90 days (proportion) | 776 (7 observational studies) | ⊕◯◯◯ Very low[a,b,c] | 57% (43% – 70%) |

Explanations

a. Measured with the ROBINS-I tool.

b. Wide confidence interval.

c. Tau squared.

**Table S4. Table of studies excluded.**

| Author | Title | Reason for exclusion |
|---|---|---|
| Emberson et al | Details of a Prospective Protocol for a Collaborative Meta-Analysis of Individual Participant Data from all Randomized Trials of Intravenous rt-PA vs. Control: Statistical Analysis Plan for the Stroke Thrombolysis Trialists' Collaborative Meta-Analysis 2013 | Irrelevant to the topic |
| AAorn S et al | Acute Ischemic Stroke in Term Pregnancy Treated with Recombinant Tissue Plasminogen Activator 2020 | Irrelevant to the topic |
| AbdelRazek et al | Intravenous Thrombolysis for Stroke and Presumed Stroke in Human Immunodeficiency Virus-Infected Adults: A Retrospective, Multicenter US Study 2018 | Irrelevant to the topic |
| Abdullah et al: | Advance hospital notification by EMS in acute stroke is associated with shorter door-to-computed tomography time and increased likelihood of administration of tissue-plasminogen activator 2008 | Irrelevant to the topic |
| Abraham et al | The need for a population-based, dose optimization study for recombinant tissue plasminogen activator in acute ischemic stroke: A study from a tertiary care teaching hospital from South India 2017 | Irrelevant to the topic |
| Agarwal et al | Redefined Measure of Early Neurological Improvement Shows Treatment Benefit of Intravenous Tissue Plasminogen Activator Treatment in NINDS Rt-PA Acute Stroke Trial at 24 Hours 2020 | Irrelevant to the topic |
| Alamowitch et al | European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke 2023 | Irrelevant to the topic |
| Alberts et al | Risks of Stroke and Mortality in Atrial Fibrillation Patients Treated With Rivaroxaban and Warfarin 2020 | Irrelevant to the topic |
| Balogun et al | A Stroke Registry Data on the Use of Intravenous Recombinant Tissue Plasminogen Activator in Stroke of Unknown Time of Onset 2016 | Irrelevant to the topic |
| Broocks et al | Benefit and risk of intravenous alteplase in patients with acute large vessel occlusion stroke and low ASPECTS 2022 | Irrelevant to the topic |
| Calleja et al | Collateral circulation on perfusion-computed tomography-source images predicts the response to stroke intravenous thrombolysis 2013 | Irrelevant to the topic |
| Chen et al: | Neutrophil Counts to High-Density Lipoprotein Cholesterol Ratio: a Potential Predictor of Prognosis in Acute Ischemic Stroke Patients After Intravenous Thrombolysis 2020 | Irrelevant to the topic |
| Deitelzweig et al | An early evaluation of bleeding-related hospital readmissions among hospitalized patients with nonvalvular atrial fibrillation treated with direct oral anticoagulants 2016 | Irrelevant to the topic |

| | | |
|---|---|---|
| Demir et al | The relationship between serum bilirubin levels and early neurological improvement in patients with acute ischemic stroke treated with intravenous tissue plasminogen activator 2022 | Irrelevant to the topic |
| Dicpingaitis et al | Intravenous thrombolysis for treatment of pediatric acute ischemic stroke: Analysis of 20 years of population-level data in the United States 2022 | Irrelevant to the topic |
| Ellis et al | Bleeding in patients with atrial fibrillation treated with dabigatran, rivaroxaban or warfarin: A retrospective population-based cohort study 2016 | Irrelevant to the topic |
| Eryilidiz et al | The role of leukoaraiosis on outcomes and recombinant tissue-plasminogen activator-related symptomatic intracerebral hemorrhages in acute stroke 2020 | Irrelevant to the topic |
| Escudero-Martinez et al | Dabigatran initiation in patients with non-valvular AF and first acute ischaemic stroke: a retrospective observational study from the SITS registry 2020 | Irrelevant to the topic |
| Alvarez et al | Intravenous Fibrinolysis in ischemic stroke of large vessel after reversing effect with idraucizumab 2017 | Abstract |
| Binet et al | Systemic thrombolysis and endovascular thrombectomy in severe ischmeic stroke after dabigatran reversal with idarucizumab 2018 | Abstract |
| Frontera et al | Recent use of Non-vitamin K antagonist oral anticoagulants and intracranial Hemorrhage Among patients with acute ischemic stroke treated with Alteplase 2022 | Abstract |
| Kawiorski et al | Successful intravenous thrombolysis in acute ischaemic stroke in a patient on rivaroxaban treatment 2013 | Abstract |
| Marsch et al | Acute ischemic stroke in patient on treatment with non-vitamin K oral anticoagulants-safety and efficacy of NOAC plasma-level-guided therapy 2018 | Abstract |
| Neumann et al | Intravenous thrombolysis for ischemic stroke in patients receiving dabigatran 2014 | Abstract |
| Seiffge et al | Emergency measurement of plasma levels for rivaroxaban in patients with acute stroke is feasible in median of 34 minutes | Abstract |
| Steinberger et al | Successful intravenous alteplase use in four patients with acute ischemic stroke after dabigatran reversal with idarucizumab 2018 | Abstract |
| Suzuki et al | Revascularization therapy in acute stroke patients treated with NOAC should be safe 2016 | Abstract |

| | | |
|---|---|---|
| Bartoli et al | Early Carotid Endarterectomy after Intravenous Thrombolysis for Acute Ischaemic Stroke 2009 | Case Report |
| Berliner et al | Successful Outcome in an Adolescent with Artery of Percheron Occlusion who was Treated with Tissue Plasminogen Activator 2022 | Case Report |
| Bornkamm et al | Safe intravenous thrombolysis in acute stroke despite treatment with rivaroxaban 2014 | Case Report |
| Bouchal et al | Repeated intravenous thrombolysis in early recurrent stroke secondary to carotid web: Case report 2021 | Case Report |
| Bourdial et al | Intravenous thrombolysis in pediatric arterial ischemic stroke: A Case Report and a review of the literature 2008 | Case Report |
| Camara-Lemarroy et al | Successful intravenous thrombolysis in a patient with antiphospholipid syndrome, acute ischemic stroke and severe thrombocytopenia 2016 | Case Report |
| Cao et al | Successful intravenous thrombolysis for acute ischemic stroke caused by aortic dissection with severe hypofibrinogenemia: a case report and Literature review 2022 | Case Report |
| Chao et al | Thrombolysis in an acute ischemic stroke patient with rivaroxaban anticoagulation A case report 2019 | Case Report |
| Folyovich et al | Dilemma of indication for thrombolysis in a patient with acute ischemic stroke treated with a novel oral anticoagulant | Case Report |
| Fontaine et al | Alteplase for Acute Ischemic Stroke after Heparin Reversal with Protamine: A case report and Review 2017 | Case Report |
| Haghighi et al | Fibrinolytic treatment for acute ischaemic stroke in a patient on dabigatran etexilate | Case Report |
| Giannandrea et al | Intravenous thrombolysis in stroke after dabigatran reversal with idarucizumab | Case Report |

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|---|---|---|
| Von Wowern et al | 2017 REVERSAL OF THE ANTICOAGULATION EFFECTS OF DABIGATRAN ETEXILATE BY IDARUCIZUMAB IN THREE PATIENTS NEEDING URGENT SURGICAL INTERVENTION AND ONE CASE OF INTRAVENOUS THROMBOLYSIS IN ISCHAEMIC STROKE | Case Report |
| Bissig et al | Acute Stroke Despite Dabigatran Anticoagulation Treated with Idarucizumab and Intravenous Tissue Plasminogen Activator 2017 | Case Report |
| Acampa et al | Safety of Intravenous Thrombolysis and Mechanical Thrombectomy in Bilateral Posterior Cerebral Artery Territory Infarction 2022 | Case Report |
| Esmaeili et al | Intravenous thrombolysis for acute ischemic stroke due to cardiac myxoma 2020: | Case Report |
| Chen et al | Outcome of Patients Receiving Thrombolytic Therapy While on Rivaroxaban for Nonvalvular Atrial Fibrillation (from Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) 2017 | Wrong population |
| Goldhoorn et al | Endovascular Treatment for Acute Ischemic Stroke in Patients on Oral Anticoagulants 2020: wrong population | Wrong population |
| Kate et al | Proposed approach to thrombolysis in dabigatran-treated patients presenting with ischemic stroke 2014 | Wrong population |
| Purrucker et al | Coagulation Testing in Acute Ischemic Stroke Patients Taking Non–Vitamin K Antagonist Oral Anticoagulants 2016 | Wrong population |
| Seiffge et al | Recanalization therapies in acute ischemic stroke patients: impact of prior treatment with novel oral anticoagulants on bleeding complications and outcome 2015 | Wrong population |
| Seiffge et al | Feasibility of rapid measurement of Rivaroxaban plasma levels in patients with acute stroke 2016 | Wrong population |
| Teow et al | Trends in direct oral anticoagulant use in patients presenting with acute stroke 2022 | Wrong population |

| | | |
|---|---|---|
| Jin et al | Intravenous tPA (Tissue-Type Plasminogen Activator) in Patients With Acute Ischemic Stroke Taking Non–Vitamin K Antagonist Oral Anticoagulants Preceding Stroke 2018: Systematic review | Review article |
| Frol et al | Intravenous Thrombolysis After Dabigatran Reversal by Idarucizumab: A Systematic Review of the Literature 2021: review | Review article |
| Atti et al | Meta-analysis of the efficacy and safety of intravenous alteplase in the treatment of acute minor ischemic stroke 2022: meta-analysis | Review article |
| Moroni et al | Confidence in the Use of Direct Oral Anticoagulants in the Acute Phase of Nonvalvular Atrial Fibrillation–Related Ischemic Stroke Over the Years: A Real-World Single-Center Study 2018: Review | Review article |
| Seiffge et al | Management of patients with stroke treated with direct oral anticoagulants 2018: Review | Review article |
| Shahjouei et al | Safety of Intravenous Thrombolysis Among Patients Taking Direct Oral Anticoagulants: A Systematic Review and Meta-Analysis | Review article |
| Liu et al | Safety of Recanalization Therapy in Patients with Acute Ischemic Stroke Under Anticoagulation: A Systematic Review and Meta-Analysis | Review article |
| Kam et al | Recent Use of Non–Vitamin K Antagonist Oral Anticoagulants and Intracranial Hemorrhage Among Patients With Acute Ischemic Stroke Treated With Alteplase 2022 | Experts' statements and guidelines |
| Testai 2017 | Intravenous thrombolysis in a stroke patient taking dabigatran | Experts' statements and guidelines |
| Tsivgoulis et al | 2017 Intravenous Thrombolysis in Acute Ischemic Stroke Patients Pretreated With Non–Vitamin K Antagonist Oral Anticoagulants | Experts' statements and guidelines |
| WEBB ET AL | 2022 Recent Use of Non-Vitamin K Antagonist Oral Anticoagulants and Intracranial Hemorrhage Among Patients With Acute Ischemic Stroke Treated With Alteplase | Experts' statements and guidelines |
| Adams H. P. et al | Emergency management of acute ischemic stroke: the evolving roles of intravenous and endovascular therapies 2013 | Experts' statements and guidelines |

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|---|---|---|
| Xian et al | Clinical Effectiveness of Direct Oral Anticoagulants vs Warfarin in Older Patients with Atrial Fibrillation and Ischemic Stroke: Findings from the Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) Study 2019 | Overlapping population |
| Oblak et al | Intravenous Thrombolysis After Idarucizumab Application in Acute Stroke Patients—A Potentially Increased Sensitivity of Thrombi to Lysis? 2019 | Overlapping population |
| Frol et al | Revascularization outcomes following acute ischemic stroke in patients taking direct oral anticoagulants: a single hospital cohort study. Journal of Thrombosis and Thrombolysis | Overlapping population |

**Table S5. Additional characteristics of studies.**

| Study | Study design | Country | Study period | sICH definition |
|---|---|---|---|---|
| Meinel et al. (2023) [32] | Retrospective MC | Australia, Canada, China, England, Germany, Hong Kong, Israel, Italy, Japan, New Zealand, Norway, South Korea, Switzerland | 2008 - 2021 | Any ICH as reported by the site investigators within 36 hours after IVT with worsening NIHSS score of at least 4 points |
| Kam et al. (2022) [33] | Retrospective MC | United States | April 1, 2015 - March 31, 2020 | Any ICH within 36 hours by either CT or MRI, with noting a clinical deterioration from that hemorrhage |
| Kikule et al. (2022) [39] | Retrospective SC | Latvia | 2018 - 2022 | NR |
| Okada et al. (2022) [34] | Prospective SC | Japan | March 2011 - January 2021 | ECASS-III |
| Frol et al. (2021) [35] | Prospective SC | Slovenia | September 2016 – March 2020 | ECASS-II |
| Beharry et al. (2020) [37] | Retrospective MC | New Zealand and Australia | Unknown | PH2 |
| Kermer et al. (2020) [40] | Retrospective MC | Germany | January 2016 – August 2018 | Any ICH with clinical deterioration (indicated by increase in NIHSS) with follow-up CT scan |
| Fang et al. (2019) [38] | Retrospective MC | Taiwan | May 2016 – May 2018 | ICH that causes at least a 4-point increase of the NIHSS score or mortality |
| Šaňák et al. (2018) [41] | Retrospective MC | Czech Republic | Unknown | SITS-MOST |
| Xian et al. (2017) [36] | Retrospective MC | United States | October 2012 – March 2015 | Like Kam et al 2022 |
| Seiffge et al. (2017) [22,23] | Prospective SC | Switzerland | September 2012 – November 2016 | ECASS-II or NINDS |
| Tse et al. (2017) [42] | Retrospective MC | New Zealand | July 1, 2016 – December 31, 2016 | PH2 and ≥4point increase in NIHSS score |

| | | | | |
|---|---|---|---|---|
| Suzuki et al. (2017) [43] | Retrospective MC | Japan | March 2011 – February 2015 | ECASS-II |
| Shahjouei et al. (2015) [44] | Retrospective MC | United States, Greece | October 2010 – October 2014 | NINDS and Stroke tPA trial definition |

MC: Multicenter; SC: Single center; sICH: symptomatic intracranial hemorrhage; NIHSS: National Institutes of Health Stroke Scale; PH: parenchymal hemorrhage; NINDS: National Institute of Neurological Disorders and Stroke; ECASS II or III: European-Australian Cooperative Acute Stroke Study 2 or 3; mSITS-MOST: modified Safe Implementation of Thrombolysis in Stroke Monitoring. CT: computed tomography; MRI: magnetic resonance imaging; ICH: intracranial hemorrhage; NR: not reported.

**Table S6. Characteristics of Direct oral anticoagulants.**

| Study | Dabigatran (n) | Rivaroxaban (n) | Apixaban (n) | Edoxaban (n) | Not specified (n) | DOAC within 48 hours of onset (n) | DOAC within 24 hours of onset (n) | Idarucizumab (n) |
|---|---|---|---|---|---|---|---|---|
| **Meinel et al. 2023** [32] | 342 | 258 | 163 | 68 | 1 | 832 | 400 | 252 |
| **Kam et al. 2022** [33] | - | - | - | - | 2207 | 25 | 8 | 0 |
| **Kikule et al. 2022** [39] | 9 | 0 | 0 | 0 | 0 | - | - | 9 |
| **Okada et al. 2022** [34] | 6 | 8 | 16 | 10 | 0 | 40 | 40 | 2 |
| **Frol et al. 2021** [35] | 22 | 0 | 0 | 0 | 0 | - | - | 22 |
| **Beharry et al. 2020** [37] | 13 | 0 | 0 | 0 | 0 | 7 | 7 | 13 |
| **Kermer et al. 2020** [40] | 80 | 0 | 0 | 0 | 0 | - | - | 80 |
| **Fang et al. 2019** [38] | 10 | 0 | 0 | 0 | 0 | 9 | 9 | 10 |
| **Šaňák et al. 2018** [41] | 13 | 0 | 0 | 0 | 0 | 13 | 13 | 13 |
| **Xian et al. 2017** [36] | 87 | 129 | 35 | 0 | 0 | - | - | 0 |
| **Seiffge et al. 2017** [22-23] | 0 | 18 | 0 | 0 | 33 | 51 | 18 | 0 |
| **Tse et al. 2017** [42] | 6 | 0 | 0 | 0 | 0 | - | - | 6 |
| **Suzuki et al. 2017** [43] | - | - | - | - | 71 | 56 | - | 0 |
| **Shahjouei et al. 2015** [44] | 5 | 0 | 0 | 0 | 0 | 5 | 5 | 0 |

**Table S7. Assessment of publication bias using the Egger's test for studies including each outcome.**

| Metanalysis of proportions | |
|---|---|
| | **p-value** |
| **sICH** | 0.40 |
| **Any ICH** | 0.11 |
| **Systemic Bleeding** | 0.10 |
| **Mortality at 90 days** | 0.19 |
| **mRS 0-2 at 90 days** | 0.15 |
| **Comparative analysis** | |
| | **p-value** |
| **sICH** | 0.54 |
| **Any ICH** | 0.70 |
| **Systemic Bleeding** | 0.84 |
| **Mortality at 90 days** | 0.84 |
| **mRS 0-2 at 90 days** | 0.23 |

sICH: symptomatic intracranial hemorrhage
ICH: intracranial hemorrhage
mRS: modified Rankin Scale

**Table S8. Sensitivity analyses, MA of proportions.**

| Outcome | No of studies | No of participants | Pooled rate (95% CI) |
|---|---|---|---|
| **DOAC use < 48 hours of stroke onset** | | | |
| sICH | 9 | 1038 | 0.03 (0.02 to 0.04) |
| Any ICH | 6 | 869 | 0.17 (0.15 to 0.20) |
| Systemic Bleeding | 4 | 83 | 0.01 (0.00 to 0.08) |
| mRS 0-2 at 90 days | 4 | 735 | 0.46 (0.42 to 0.49) |
| **DOACs use < 48 hours of stroke onset + no idarucizumab** | | | |
| sICH | 5 | 717 | 0.03 (0.02 to 0.05) |
| **Idarucizumab was given < IVT** | | | |
| sICH | 8 | 405 | 0.03 (0.01 to 0.07) |
| **Idarucizumab was not given < IVT** | | | |
| sICH | 6 | 3150 | 0.04 (0.03 to 0.04) |

No: number; MA: meta-analysis; DOAC: direct oral anticoagulant; mRS: modified Rankin Scale; sICH: symptomatic intracranial hemorrhage; ICH: intracranial hemorrhage; <: prior to; IVT: intravenous thrombolysis; CI: confidence interval

**Table S9. Sensitivity analyses, pairwise comparison.**

| Outcome | No of studies | DOAC: events/total | No DOAC: events/total | Odds ratio (95% CI) |
|---|---|---|---|---|
| **DOAC use in last 48 hours < stroke onset** | | | | |
| **sICH** | 6 | 27/1009 | 7024/202151 | 0.79 (0.45 to 1.37) |
| **DOAC use in last 48 hours < stroke onset + no idarucizumab was given < IVT** | | | | |
| **sICH** | 5 | 23/717 | 7006/201398 | 0.83 (0.55 to 1.25) |

No: number; DOAC: direct oral anticoagulant; <: prior to

**Table S10. Summary of certainty of the evidence.**

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Pooled Effect Size (95% CI) |
|---|---|---|---|
| sICH (comparison) | 246933 (8 observational studies) | ⊕⊕⊕◯ Moderate[a] | OR 0.95 (0.67 – 1.36) |
| sICH (proportion) | 3610 (14 observational studies) | ⊕⊕⊕◯ Moderate[a] | 3% (3% – 4%) |
| Any ICH (comparison) | 33816 (3 observational studies) | ⊕⊕⊕◯ Moderate[a] | OR 1.23 (0.61 – 2.48) |
| Any ICH (proportion) | 1062 (11 observational studies) | ⊕⊕⊕◯ Moderate[a] | 12% (7% – 19%) |
| Systemic Bleeding (comparison) | 205218 (3 observational studies) | ⊕⊕⊕◯ Moderate[a] | OR 1.27 (0.79 – 2.02) |
| Systemic Bleeding (proportion) | 2602 (7 observational studies) | ⊕⊕⊕◯ Moderate[a] | 1% (0% – 1%) |
| mRS at 90 days (comparison) | 30687 (3 observational studies) | ⊕⊕⊕◯ Moderate[a,b] | OR 1.22 (0.4 – 3.69) |
| mRS at 90 days (proportion) | 776 (7 observational studies) | ⊕◯◯◯ Very low[a,b,c] | 57% (43% – 70%) |

Explanations
a. Measured with the ROBINS-I tool.
b. Wide confidence interval.
c. Tau squared.

**Table S11. Tau-squared for evaluation of heterogeneity.**

| Outcomes | Tau2 (95% CI) |
|---|---|
| **Meta-analyses of binary outcomes** | |
| Symptomatic ICH | 0.02 (0.00 – 1.62) |
| Any ICH | 0.42 (0.00 – 29.36) |
| Systemic Bleeding | 0 (0.00 – 25.58) |
| Mortality at 90 days | 0 (0.00 – 5.66) |
| mRS 0-2 at 90 days | 0.93 (0.08 – 47.13) |
| sICH (Only 48 hours) | 0.05 (0.00 – 5.79) |
| sICH (Only 48 hours, no idarucizumab) | 0.08 (0.25 – 3.19) |
| **Meta-analyses of proportions*** | |
| Symptomatic ICH | 0.00 |
| sICH (Only 48 hours) | 0.00 |
| Any ICH | 0.42 |
| Any ICH (Only 48 hours) | 0.00 |
| Systemic Bleeding | 0.00 |
| Systemic Bleeding (Only 48 hours) | 0.00 |
| Mortality at 90 days | 0.00 |
| Mortality at 90 days (Only 48 hours) | 0.00 |
| mRS 0-2 at 90 days | 0.34 |
| mRS 0-2 at 90 days (Only 48 hours) | 0.00 |
| sICH (Only 48 hours, no idarucizumab) | 0.00 |

mRS: modified Rankin Scale; sICH: symptomatic intracranial hemorrhage; ICH: intracranial hemorrhage; CI: confidence interval.

*No method available to calculate the tau-squared CI.

**Figure S1. Flow chart of study selection.**

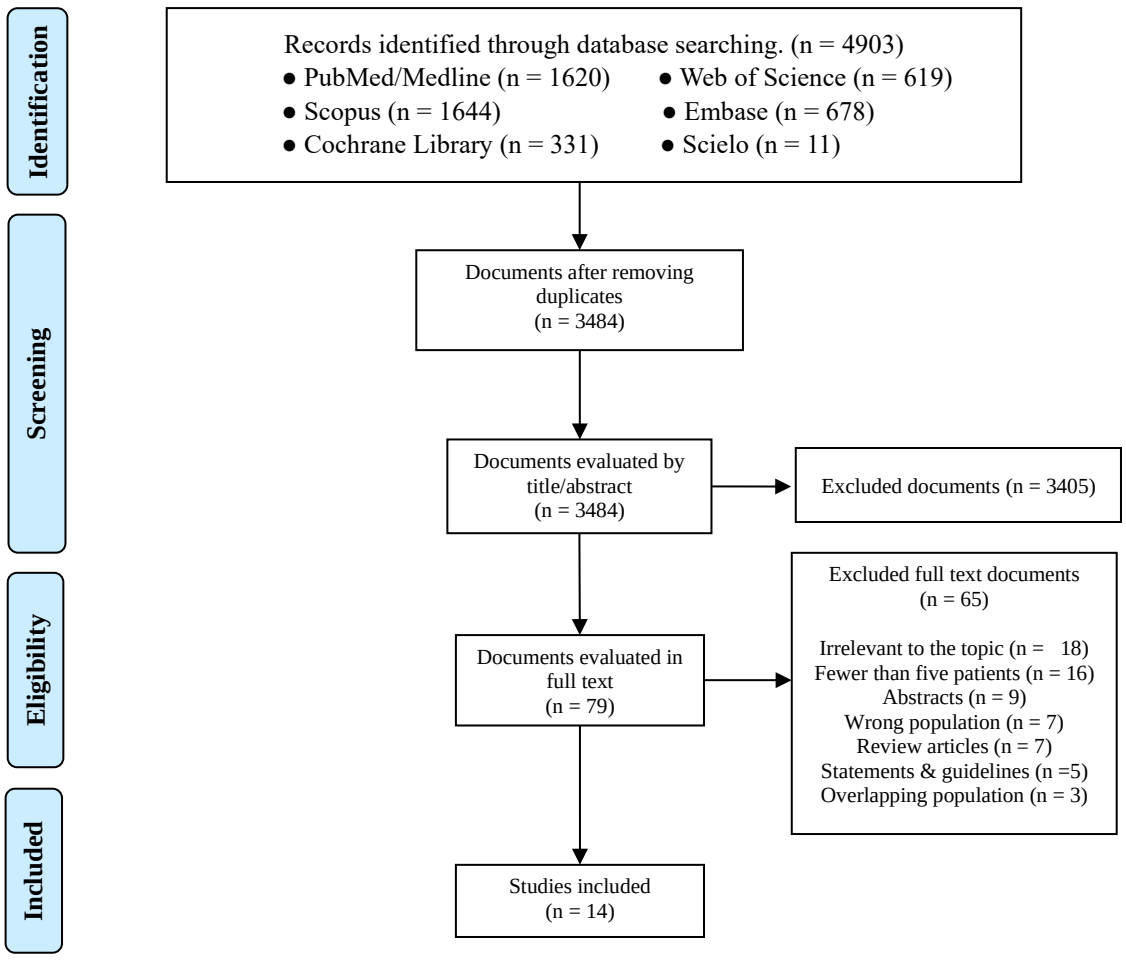
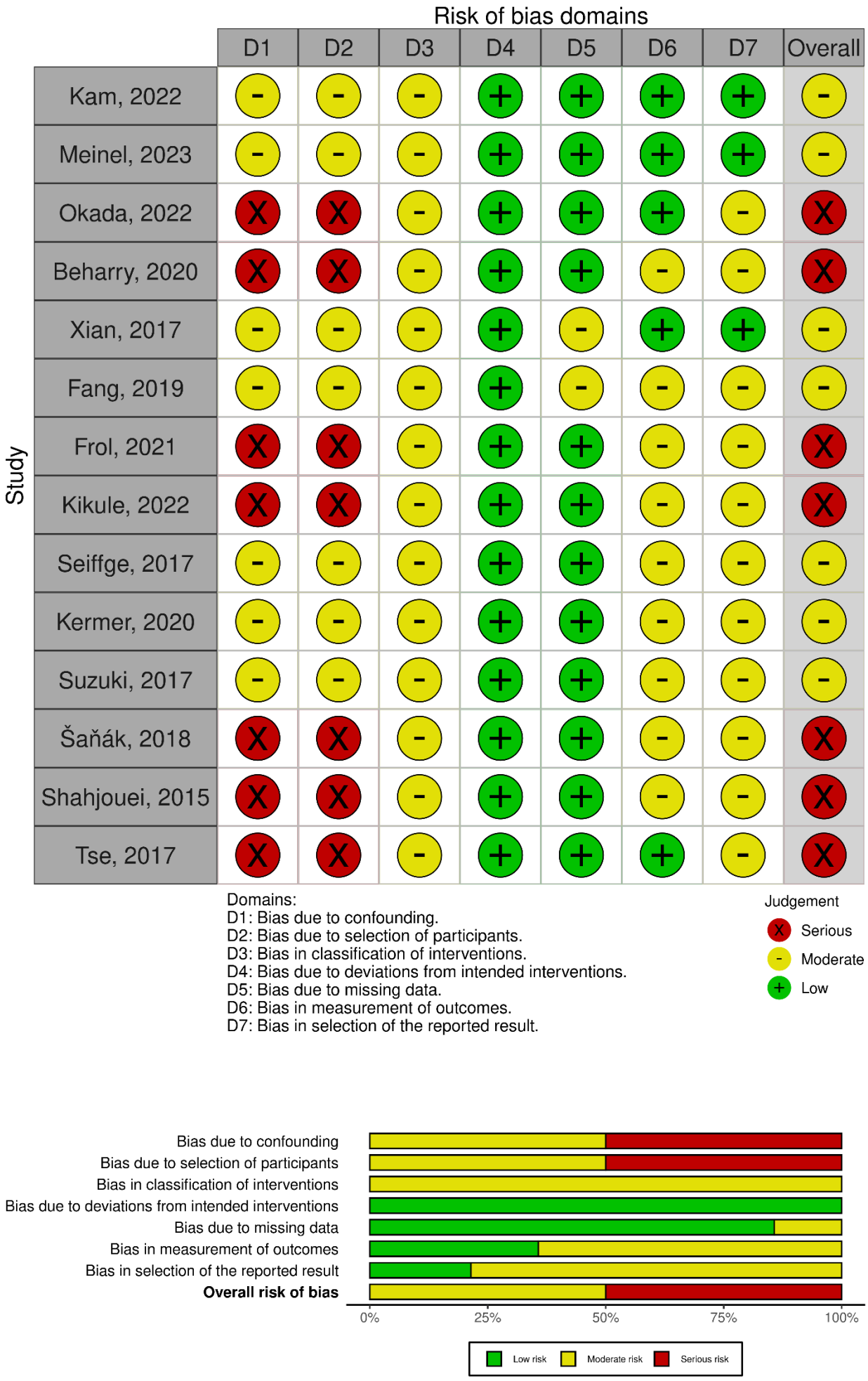


**Figure S2. Traffick-light and summary plots of risk of bias of non-interventional studies, using the ROBINS-I tool.**



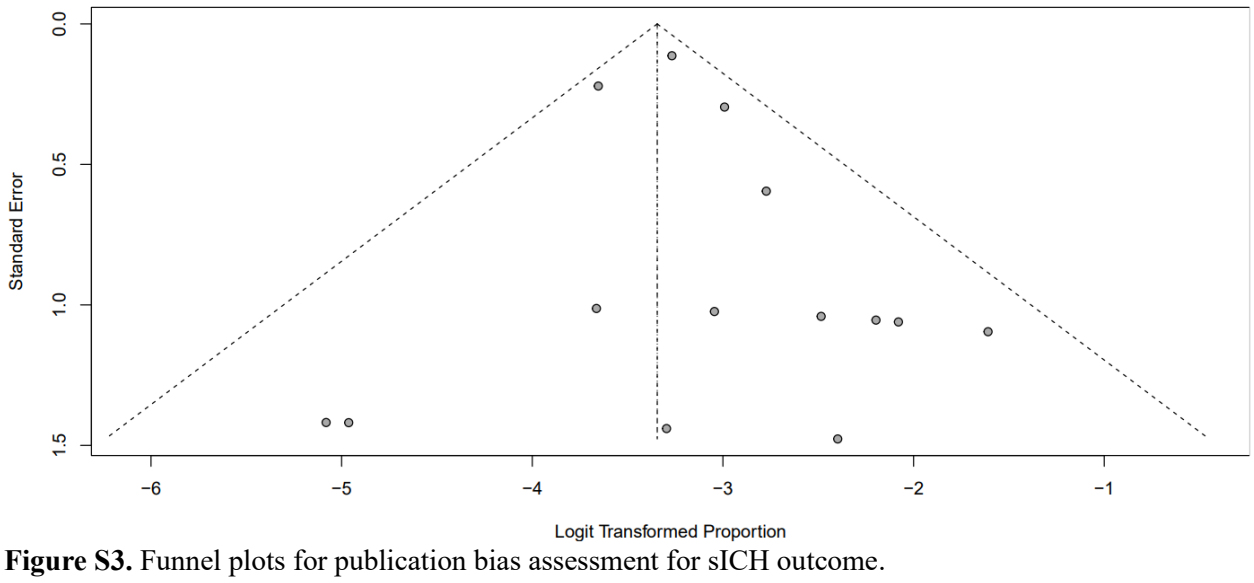



**Figure S3.** Funnel plots for publication bias assessment for sICH outcome.

sICH: symptomatic intracranial hemorrhage

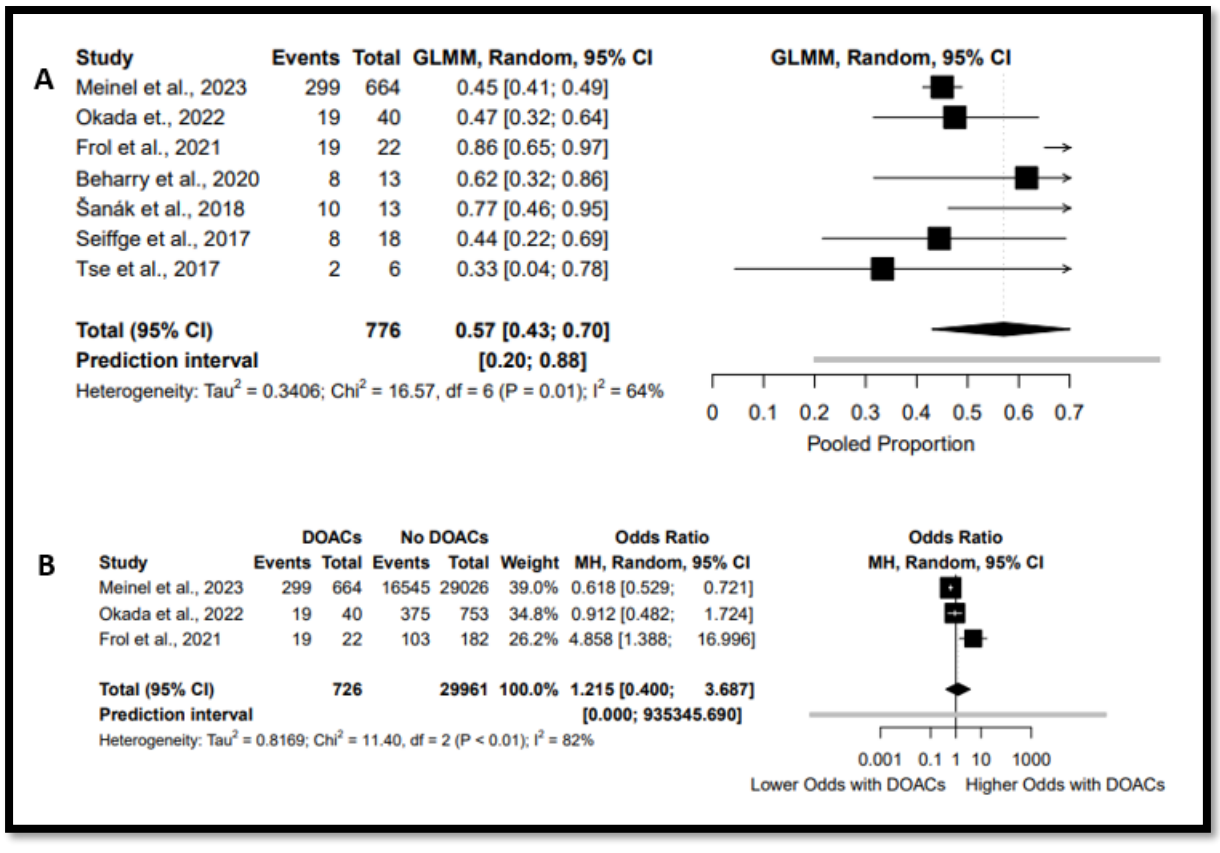



**Figure S4**. Forest plot for IVT in patients were taking DOAC for functional independence at 90 days.

A: referring to the meta-analysis of proportions. B: referring to the comparative analysis.

CI: confidence interval; DOAC: direct oral anticoagulant

sICH: symptomatic intracranial hemorrhage

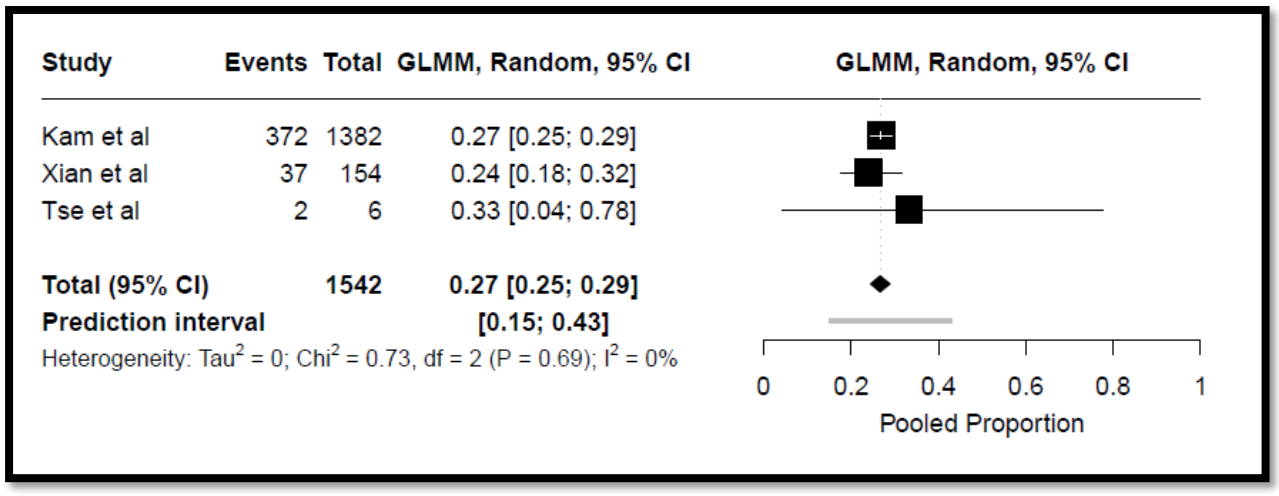



**Figure S5**. Forest plot for IVT in patients were taking DOAC for excellent outcome (mRS 0-1) at 90 days.

CI: confidence interval

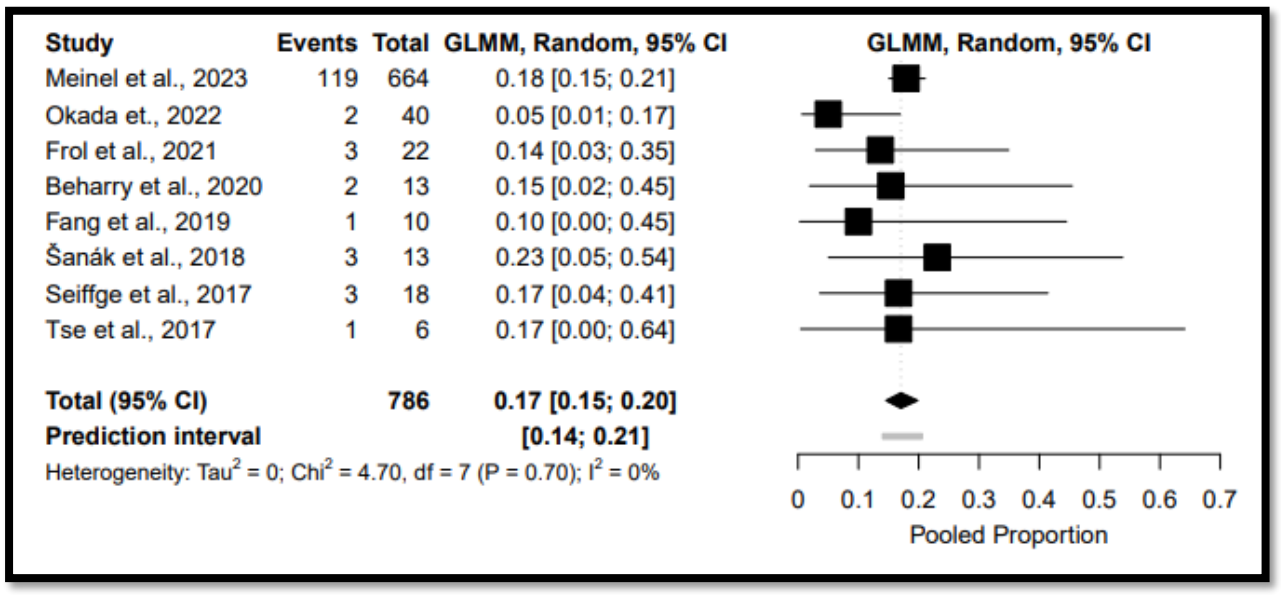



**Figure S6**. Forest plot for proportion of mortality at 90 days in patients who received IVT and were taking DOAC.

CI: confidence interval

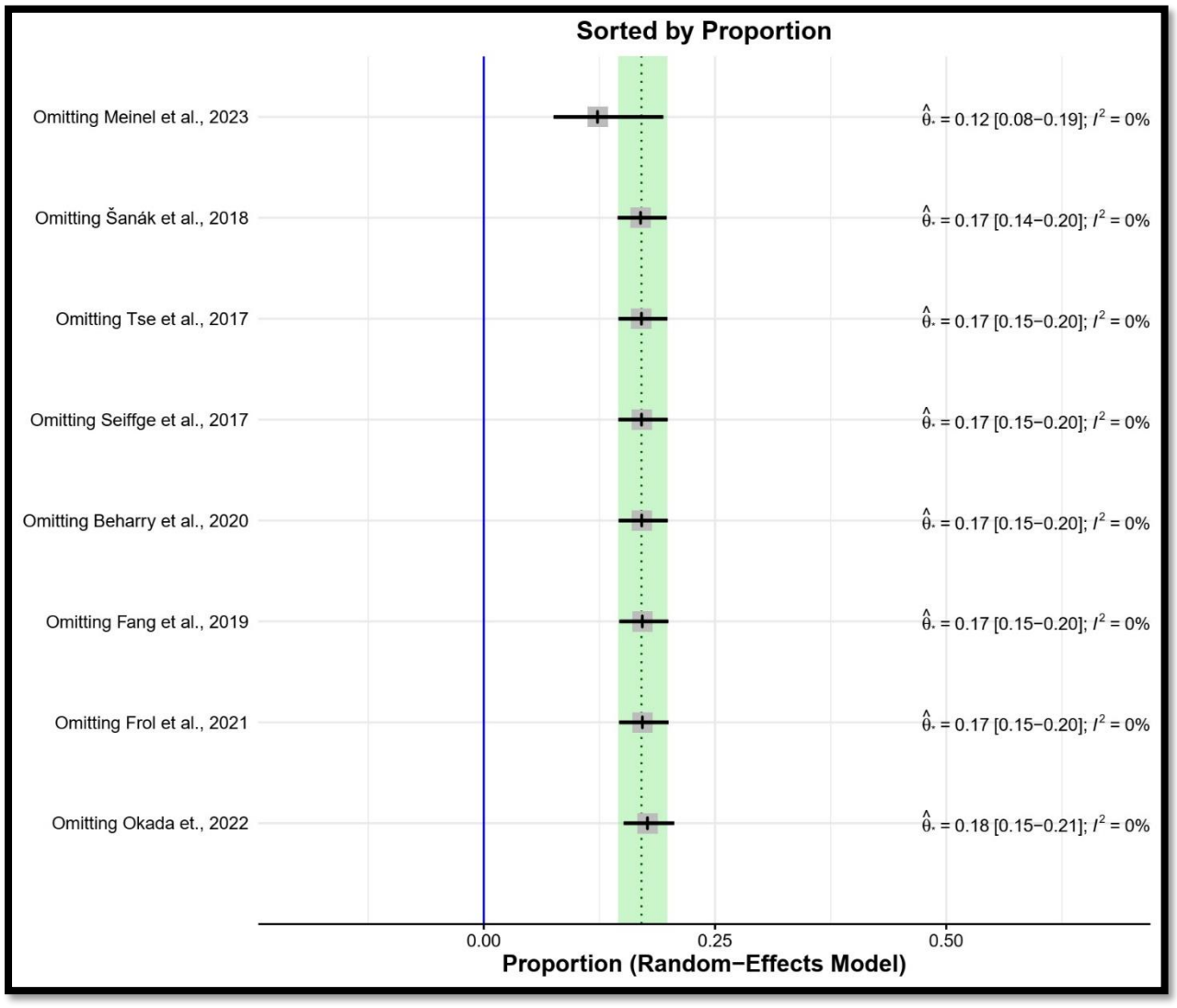



**Figure S7.** Sensitivity analysis for proportion of mortality at 90 days in patients who received IVT and were taking DOAC.

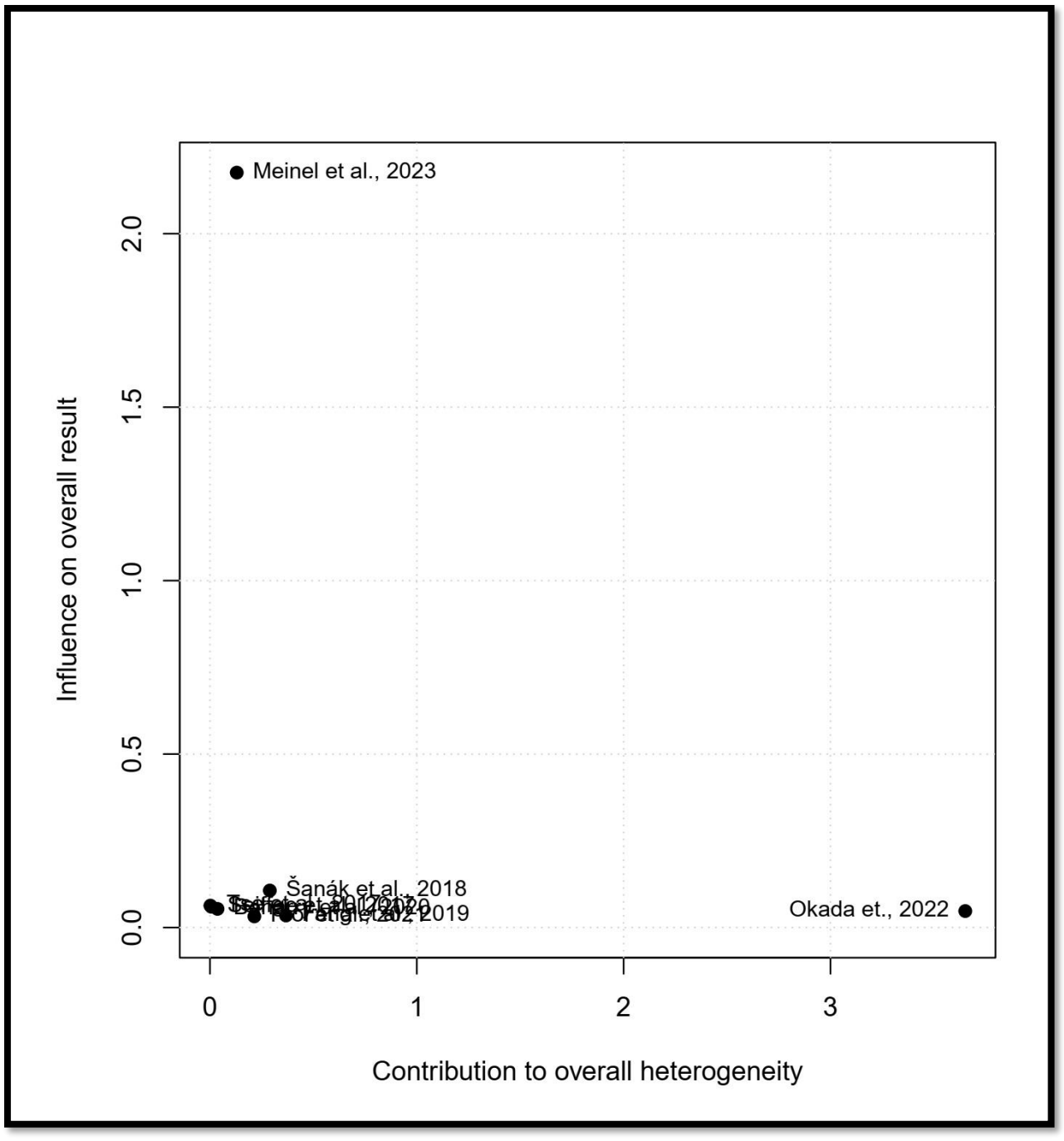



**Figure S8.** Baujat plot for proportion of mortality at 90 days in patients who received IVT and were taking DOAC.

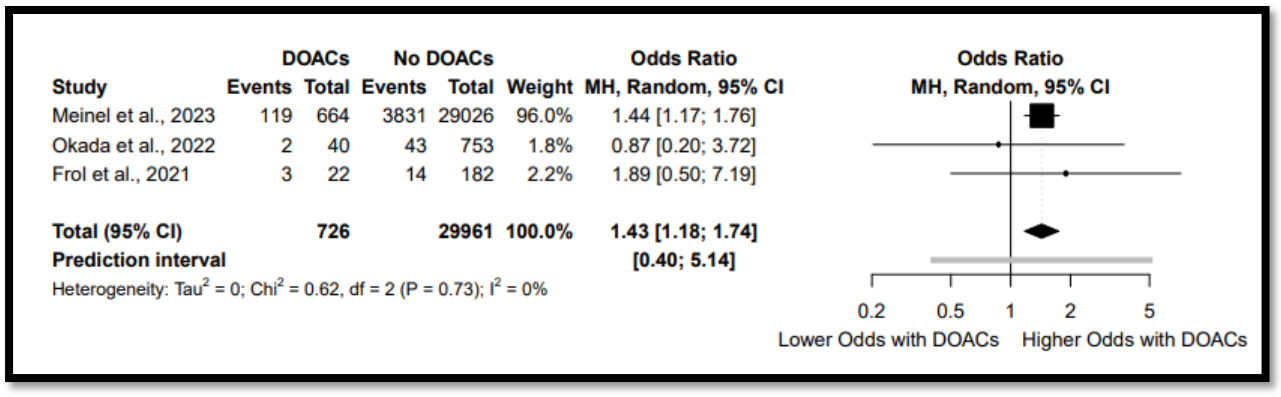



**Figure S9.** Forest plot for comparison in mortality rate for IVT between patients were taking DOAC vs who were not taking DOAC.

CI: confidence interval

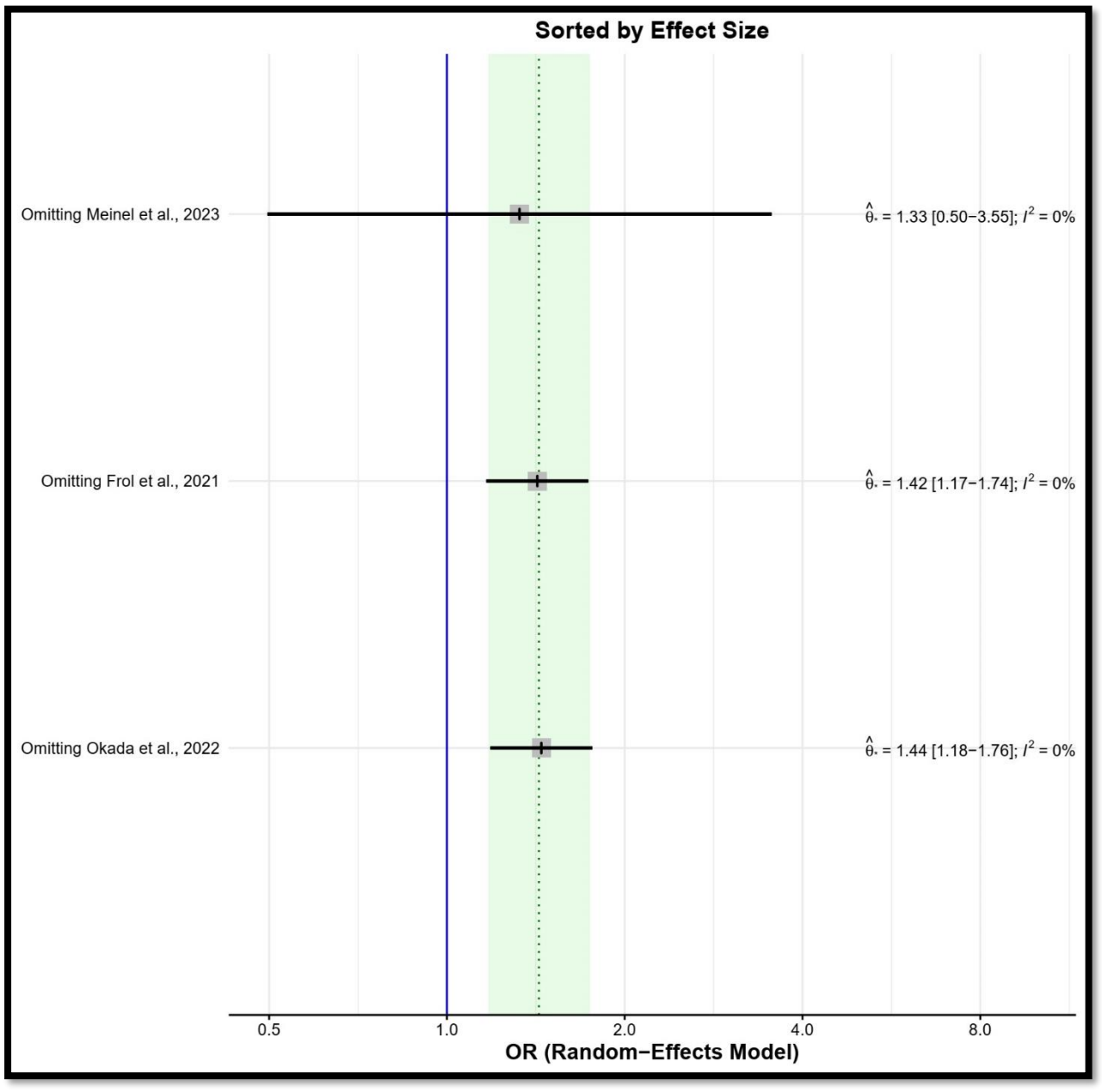



**Figure S10.** Sensitivity analysis for comparison of mortality at 90 days in patients who received IVT and were taking DOAC as compared to none.

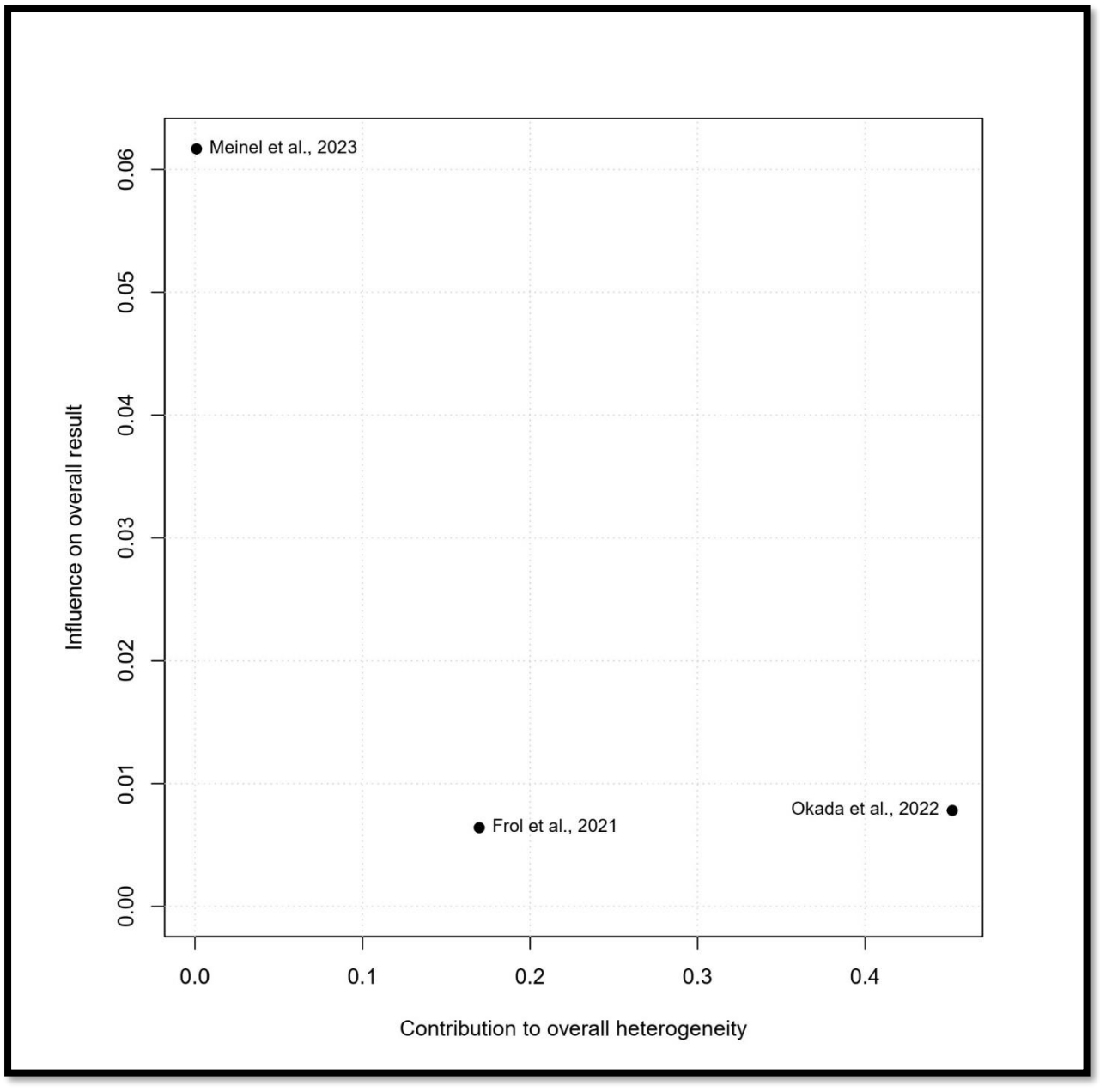
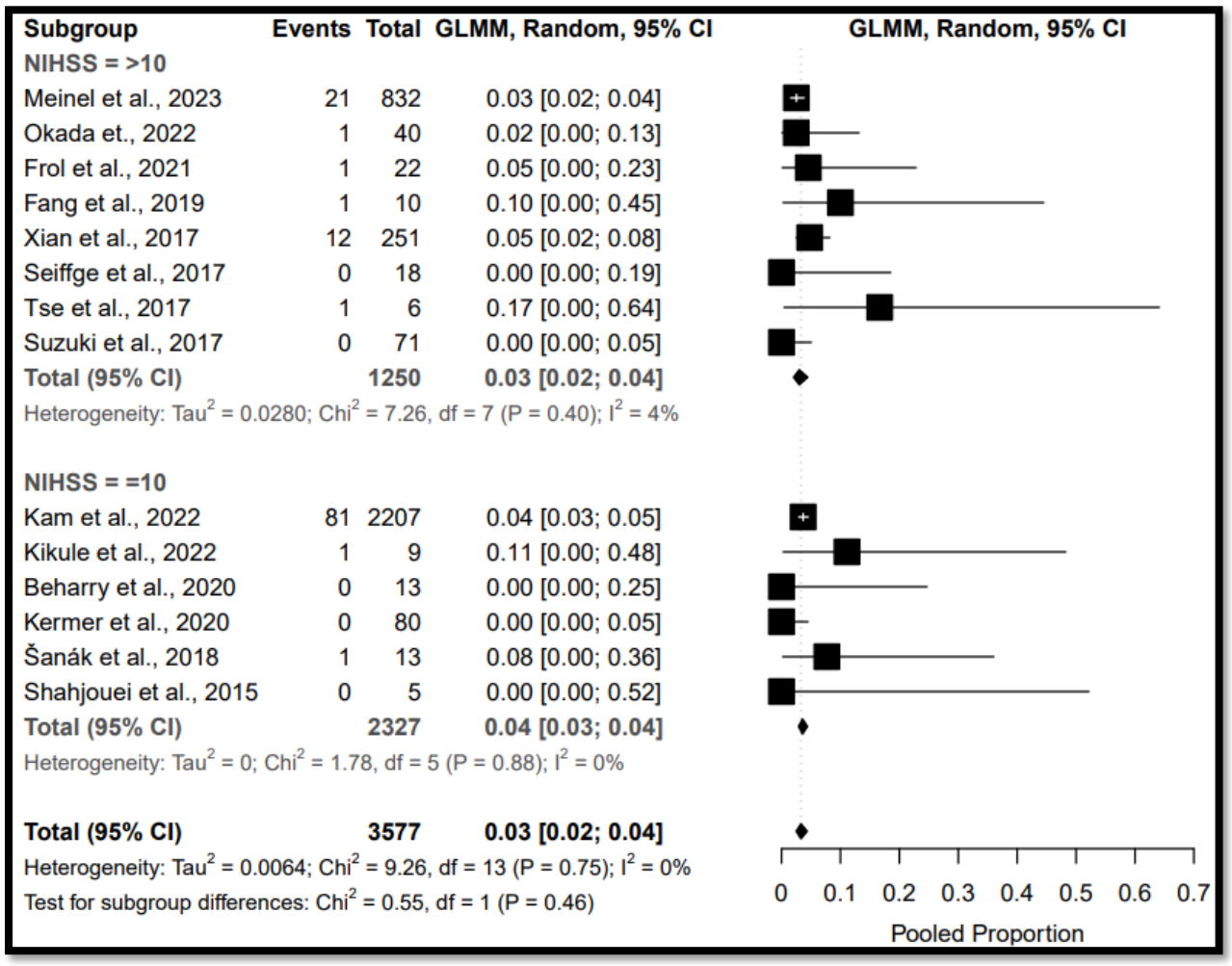



**Figure S11**. Baujat plot for comparison of mortality at 90 days in patients who received IVT and were taking DOAC as compared to none.

**A**




**B**

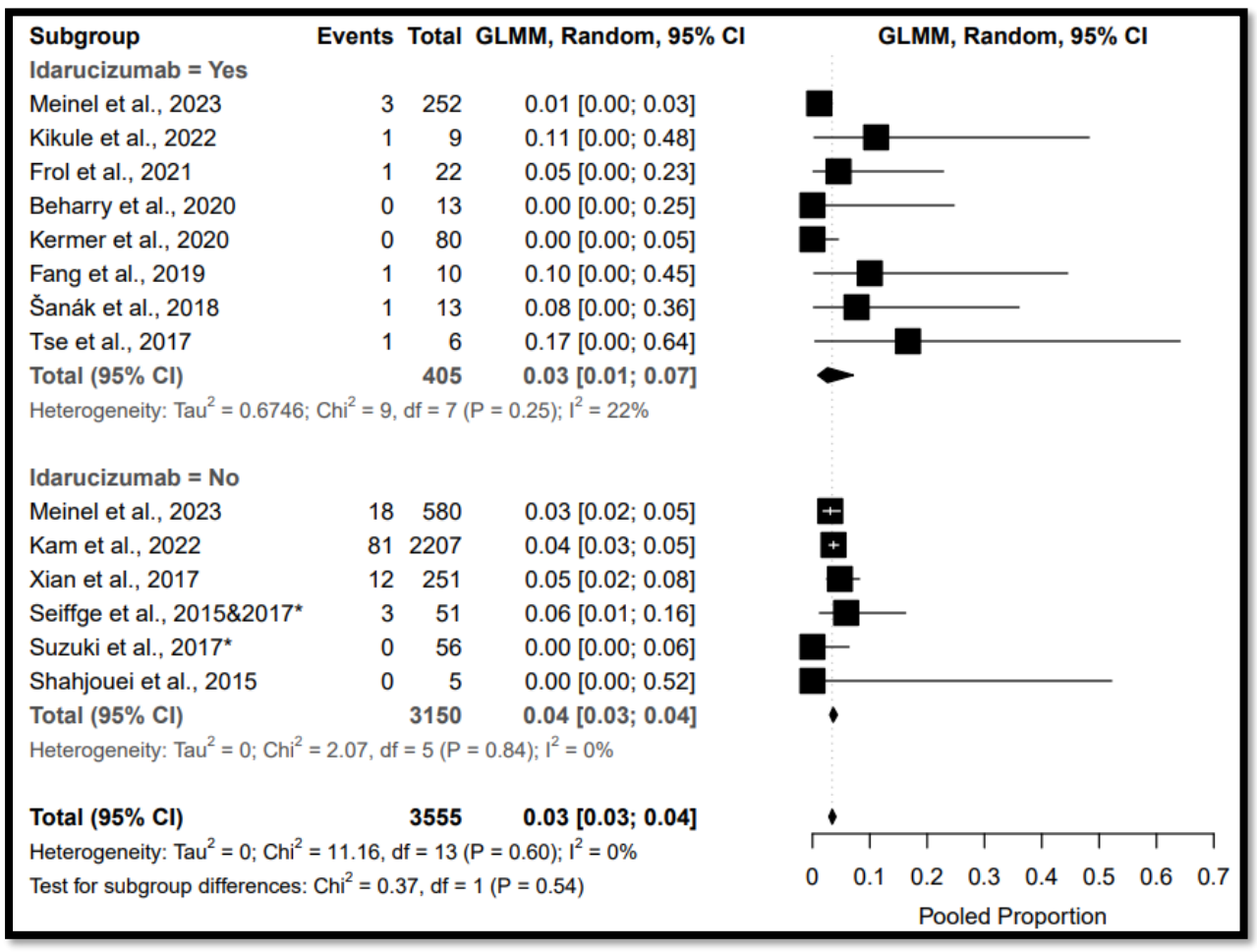



**Figure S12.** Forest plot for subgroup analysis for sICH.

A: NIHSS >10 vs. ≤10. B: received idarucizumab vs. no idarucizumab. *: direct communication with the authors.
sICH: symptomatic intracranial hemorrhage; NIHSS: National Institutes of Health Stroke Scale; CI: confidence interval.