Supplementary Material

**Title:** Non-vitamin K Antagonist Oral Anticoagulants and Cognitive Impairment in Atrial Fibrillation: Insights from the Meta-analysis of Over 90,000 Patients of Randomized Controlled Trials and Real-World Studies

**Running Title**: Cognitive Impairment of NOACs in AF

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**Table S1. Randomized controlled trials excluded for a) one arm study and b) not reporting cognitive impairment data.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **NCT number** | **Phase** | **Study name** | **Drugs** | **Condition** | **Reason for exclusion** |
| NCT01546883 | 4 | DEPAF | Dabigatran | AF | a |
| NCT02348723 | 4 | RE-CIRCUIT | Dabigatran | AF | b |
| NCT00808067 | 3 | RELY-ABLE | Dabigatran | AF | a |
| NCT01896297 | 4 | NA | Dabigatran | AF and CKD | a |
| NCT01493557 | 4 | NA | Dabigatran | AF | b |
| NCT01868243 | 2, 3 | DAWA | Dabigatran | AF with bioprosthetic replacement | b |
| NCT01227629 | 2 | PETRO | Dabigatran | AF | b |
| NCT01136408 | 2 | AF-DABIG-VKA-JAPAN | Dabigatran | AF | b |
| NCT01674647 | 3 | X-VERT | Rivaroxaban | AF and cardioversion | b |
| NCT01729871 | 3 | VENTURE-AF | Rivaroxaban | AF with ablation | b |
| NCT00494871 | 3 | J-ROCKET-AF | Rivaroxaban | AF | b |
| NCT00412984 | 2 | ARISTOTLE-J | Apixaban | AF | b |
| NCT01706146 | 4 | REACT COM | Apixaban | AF | a |
| NCT01857622 | 3 | NA | Edoxaban | AF and CKD | a |
| NCT00829933 | 2 | AF-EDOX-VKA-JAPAN | Edoxaban | AF | b |
| NCT00806624 | 2 | AF-EDOX-VKA-ASIA | Edoxaban | AF | b |
| NCT00504556 | 2 | AF-EDOX-VKA-MULTI | Edoxaban | AF | b |
| NCT00742859 | 2 | EXPLORE-XA | Betrixaban | AF | b |
| [NCT01830543](http://clinicaltrials.gov/show/NCT01830543) | 4 | PIONEER AF-PCI | Rivaroxaban | AF and PCI | b |
| NCT02164864 | 4 | RE-DUAL PCI | Dabigatran | AF and PCI | b |

AF: atrial fibrillation; CKD: chronic kidney disease; NA: not available; PCI: percutaneous coronary intervention; a: one arm study; b: not reporting cognitive impairment

**Table S2. Database studies excluded for no cognitive impairment data reported**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study (year)** | **Indication** | **Country** | **Data Source** | **Inclusion Period** |
| Larsen (2013)([Larsen et al., 2013](#_ENREF_33)) | AF | Denmark | The Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 2011.8.1-2012.12.31 |
| Sørensen (2013)([Sorensen et al., 2013](#_ENREF_49)) | AF | Denmark | The Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 1995.1.1-2011.12..31 |
| Alonso (2014)([Alonso et al., 2014](#_ENREF_2)) | AF | U.S.A. | The Truven Health MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database | 2009.1.1-2012.12.31 |
| Larsen (2014)([Larsen et al., 2014a](#_ENREF_31)) | AF | Denmark | The Truven Health MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database | 2009.8.1-2013.3.30 |
| Larsen (2014)([Larsen et al., 2014b](#_ENREF_32)) | AF | Denmark | The Truven Health MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database | 2009.8.1-2013.3.30 |
| Vaughan Sarrazin (2014)([Vaughan Sarrazin et al., 2014](#_ENREF_54)) | AF | U.S.A. | National Veterans Affairs administrative encounter and pharmacy data | 2010-2012 |
| Abraham (2015)([Abraham et al., 2015](#_ENREF_1)) | AF | U.S.A. | Optum Labs Data Warehouse | 2010.12.1-2013.9.30 |
| Chang (2015)([Chang et al., 2015](#_ENREF_6)) | AF | U.S.A. | IMS Health Life Link Health Plan Claims Database | 2010.10.1-2012.3.31 |
| Hernandez (2015)([Hernandez et al., 2015](#_ENREF_20)) | AF | Spain | The Centers for Medicare and Medicaid Services | 2010.10.1-2011.10.31 |
| Ho (2015)([Ho et al., 2015](#_ENREF_24)) | AF | Hong Kong | Queen Mary Hospital (8754 patients) | 1997.7-2011.12 |
| Lauffenburger (2015)([Lauffenburger et al., 2015](#_ENREF_35)) | AF | U.S.A. | Truven Health MarketScan Commercial Claims and Encounters and Medicare Supplement databases | 2010.10-2012.12 |
| Maura (2015)([Maura et al., 2015](#_ENREF_41)) | AF | France | The French National Insurance information system; the French Hospital Discharge database | NA |
| Staerk (2015)([Staerk et al., 2015](#_ENREF_52)) | AF | Denmark | Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 2011.8.22-2012.12.31 |
| Avgil-Tsadok (2016)([Avgil-Tsadok et al., 2016](#_ENREF_3)) | AF | Canada | Provincial hospital discharge database, physician and prescription claims database | 1999.1.1-2013.3.31 |
| Chan (2016)([Chan et al., 2016](#_ENREF_5)) | AF | Taiwan | Taiwan National Health Insurance Research Database (NHIRD) | 1996.1.1-2013.12.31 |
| Ellis (2016)([Ellis et al., 2016](#_ENREF_11)) | AF | Israel | The computerized database of the Israeli Clalit Health Services Healthcare Organization | 2011.1.1-2013.12.1 |
| Gorst-Rasmussen (2016)([Gorst-Rasmussen et al., 2016](#_ENREF_16)) | AF | Denmark | Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 2012.2-2014.8 |
| Harel (2016)([Harel et al., 2016](#_ENREF_19)) | AF | Canada | The Ontario Public Drug Benefit Program Database, Canadian Institute for Health Information Discharge Abstract Database, National Ambulatory Care Reporting System | NA |
| Larsen (2016)([Larsen et al., 2016](#_ENREF_34)) | AF | Denmark | Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 2011.8.1-2015.12.30 |
| Lip (2016)([Lip et al., 2016b](#_ENREF_39)) | AF | U.S.A. | US Truven MarketScan data | 2013.1.1-2013.12.31 |
| Lip (2016)([Lip et al., 2016a](#_ENREF_38)) | AF | U.S.A. | US Truven MarketScan data | 2012.1.1-2014.12.31 |
| Nishtala (2016)([Nishtala et al., 2016](#_ENREF_44)) | AF | New Zealand | The National Minimum Dataset (NMDS) | 2011.7.1-2012.12.31 |
| Yao (2016)([Yao et al., 2016](#_ENREF_56)) | AF | U.S.A. | Optum Labs Data Warehouse | 2010.10.1-2015.6.30 |
| Yap (2016)([Yap et al., 2016](#_ENREF_57)) | AF | Malaysia | Single-center retrospective cohort registry | 2009.1-2013.12 |
| Yavuz (2016)([Yavuz et al., 2016](#_ENREF_58)) | AF | Turkey | Consecutive NVAF patients in 4 centers | 2013.3-2014.11 |
| Korenstra (2016)([Korenstra et al., 2016](#_ENREF_29)) | AF | Netherlands | Martini Hospital Groningen | 2010.1.1-2012.12.31 |
| Cha (2017)([Cha et al., 2017](#_ENREF_4)) | AF | Korea | The Korean National Health Insurance Service database | 2014.1-2015.12 |
| Coleman (2017)([Coleman et al., 2017](#_ENREF_8)) | AF | U.S.A. | US Truven MarketScan data | 2012.1-2015.6 |
| Friberg (2017)([Friberg and Oldgren, 2017](#_ENREF_12)) | AF | Sweden | The National Swedish Patient Register, Dispensed Drug Register, Cause of Death Register and the socioeconomic longitudinal integration database for health insurance and labor market studies (LISA) register | 2011.12.1-2014.12.31 |
| Gieling (2017)([Gieling et al., 2017](#_ENREF_14)) | AF | British | The Clinical Practice Research Datalink (CPRD) | 2008.3.18-2014.10.1 |
| Halvorsen (2017)([Halvorsen et al., 2017](#_ENREF_18)) | AF | Norway | The Norwegian Patient Registry and the Norwegian Prescription Database | 2013.1.1-2015.6.30 |
| Hernandez (2017)([Hernandez and Zhang, 2017](#_ENREF_21)) | AF | U.S.A. | The Centers for Medicare and Medicaid Services | 2010-2013 |
| Hernandez (2017)([Hernandez et al., 2017a](#_ENREF_22)) | AF | U.S.A. | The Centers for Medicare and Medicaid Services | 2010.10.19-2012.12.31 |
| Hernandez (2017)([Hernandez et al., 2017b](#_ENREF_23)) | AF | U.S.A. | The Centers for Medicare and Medicaid Services | 2013.1.1-2014.12.31 |
| Hohnloser (2017)([Hohnloser et al., 2017](#_ENREF_25)) | AF | Germany | German claims database | 2013.1.1-2015.3.31 |
| Kohsaka (2017)([Kohsaka et al., 2017](#_ENREF_28)) | AF | Japan | De-identified data from health claims and Diagnosis Procedure Combination | 2011.3.1-2016.3.31 |
| Lamberts (2017)([Lamberts et al., 2017](#_ENREF_30)) | AF | Denmark | Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 2011.8.22-2015.12.31 |
| Li (2017)([Li et al., 2017](#_ENREF_36)) | AF | Hong Kong | Hospital-based AF registry | 2008.1-2014.12 |
| Lin (2017)([Lin et al., 2017](#_ENREF_37)) | AF | U.S.A. | IMS Parametric Plus database | 2013.1.1-2015.9.30 |
| Lip (2017)([Lip et al., 2017](#_ENREF_40)) | AF | Denmark | Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | NA |
| Nielsen (2017)([Nielsen et al., 2017](#_ENREF_43)) | AF | Denmark | Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 2011.8-2016.2 |
| Palamaner Subash Shantha (2017)([Palamaner Subash Shantha et al., 2017](#_ENREF_46)) | AF | U.S.A. | The Centers for Medicare and Medicaid Services patient records and linked data sources | 2011.11.1-2013.10.31 |
| Song (2017)([Song et al., 2017](#_ENREF_48)) | AF | U.S.A. | MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases | 2010.1.1-2013.12.31 |
| Staerk (2017)([Staerk et al., 2017a](#_ENREF_50)) | AF | Denmark | Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 2011.8.22-2015.12.31 |
| Staerk (2017)([Staerk et al., 2017b](#_ENREF_51)) | AF | Denmark | Danish Civil Registration system; the National Patient Register; the Danish National Prescription Registry | 2012.3.1-2016.12.31 |
| Stolk (2017)([Stolk et al., 2017](#_ENREF_53)) | AF | British | The Clinical Practice Research Datalink (CPRD) | 2008.3.18-2014.6.30 |
| Yamashita (2017)([Yamashita et al., 2017](#_ENREF_55)) | AF | Japan | The Fushimi AF Registry | 2011.3-2015.11 |
| Naganuma (2017)([Naganuma et al., 2017](#_ENREF_42)) | AF | Japan | NA | 2011.3-2013.12 |
| Coleman (2016)([Coleman et al., 2016](#_ENREF_7)) | AF | U.S.A. | US Truven MarketScan data | 2012.1-2014.10 |
| Norby (2017)([Norby et al., 2017](#_ENREF_45)) | AF | U.S.A. | Truven Health MarketScan Commercial Claims and Encounters Database | 2010.1.1-2014.12.31 |

**Table S3. Quality assessment of RCTs**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Random sequence generation** | **Allocation concealment** | **Blinding of participants and personnel** | **Blinding of outcome assessment** | **Incomplete outcome data** | **Selective reporting** | **Other bias** |
| RE-LY (2009)([Connolly et al., 2009](#_ENREF_10)) | Low | Low | High | Low | Low | Low | Low |
| ROCKET-AF (2011)([Patel et al., 2011](#_ENREF_47)) | Low | Low | Low | Low | Low | Low | Low |
| ARISTOTLE (2011)([Granger et al., 2011](#_ENREF_17)) | Low | Low | Low | Low | Low | Low | Low |
| AVERROES (2011)([Connolly et al., 2011](#_ENREF_9)) | Low | Low | Low | Low | Low | Low | Low |
| EngageAF-TIMI48 (2013)([Giugliano et al., 2013](#_ENREF_15)) | Low | Low | Low | Low | Low | Low | Low |
| AXAFA-AFNET 5 (2018)([Kirchhof et al., 2018](#_ENREF_27)) | Low | Low | High | Low | Low | Low | Low |

Low: low risk; unclear: unclear risk; High: high risk

**Table S4. Quality assessment of database studies**

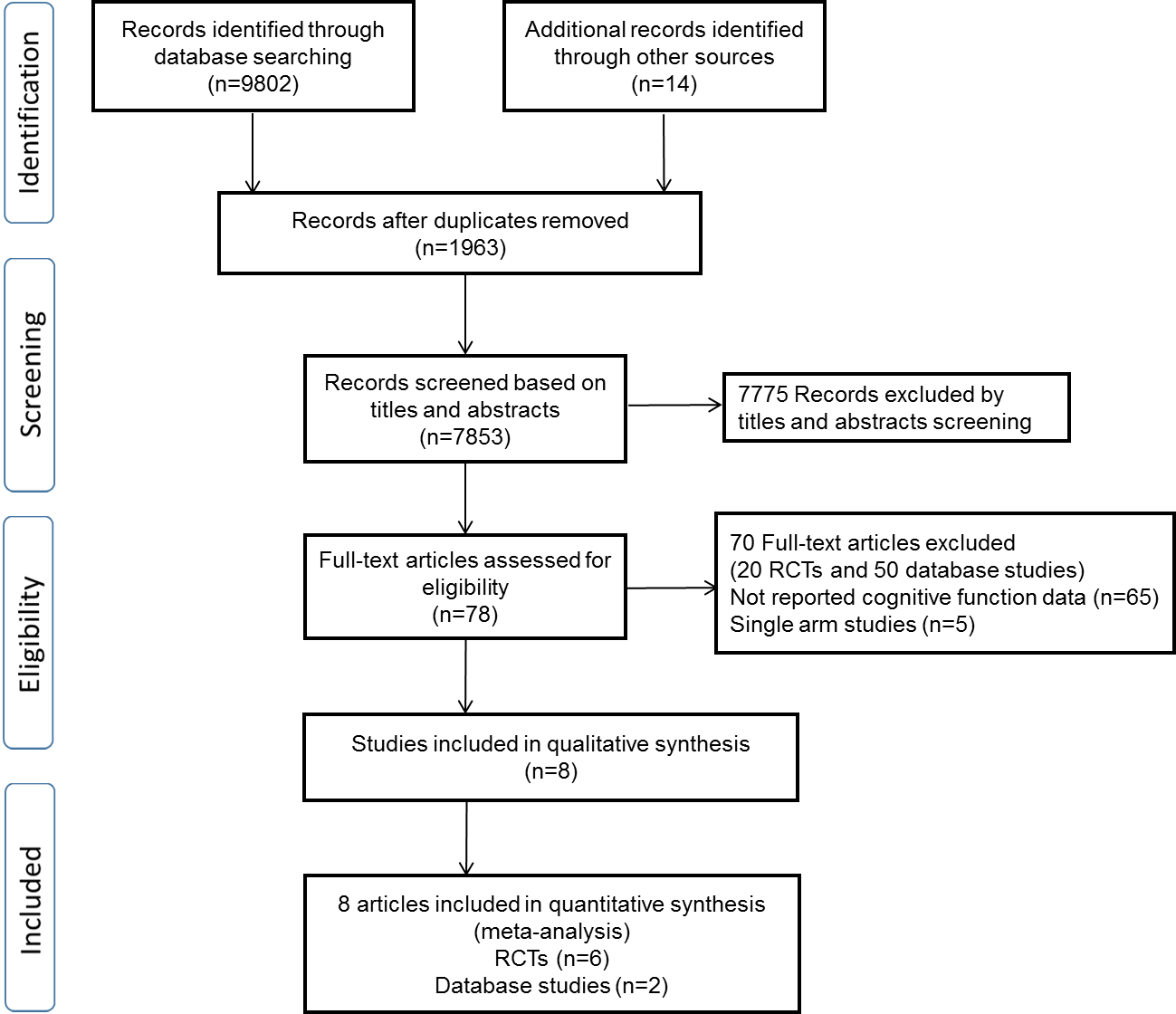
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Selection bias** | **Bias due to residual confounding** | **Bias due to time-varying covariates/information censoring** | **Bias due to selective reporting of study outcomes** |
| Victoria Jacobs (2016)([Jacobs et al., 2016](#_ENREF_26)) | Low | Moderate | Moderate | Low |
| Leif Friberg (2018)([Friberg and Rosenqvist, 2018](#_ENREF_13)) | Low | Low | Low | Low |

Low: low risk; Moderate: moderate risk: unclear risk; High: high risk

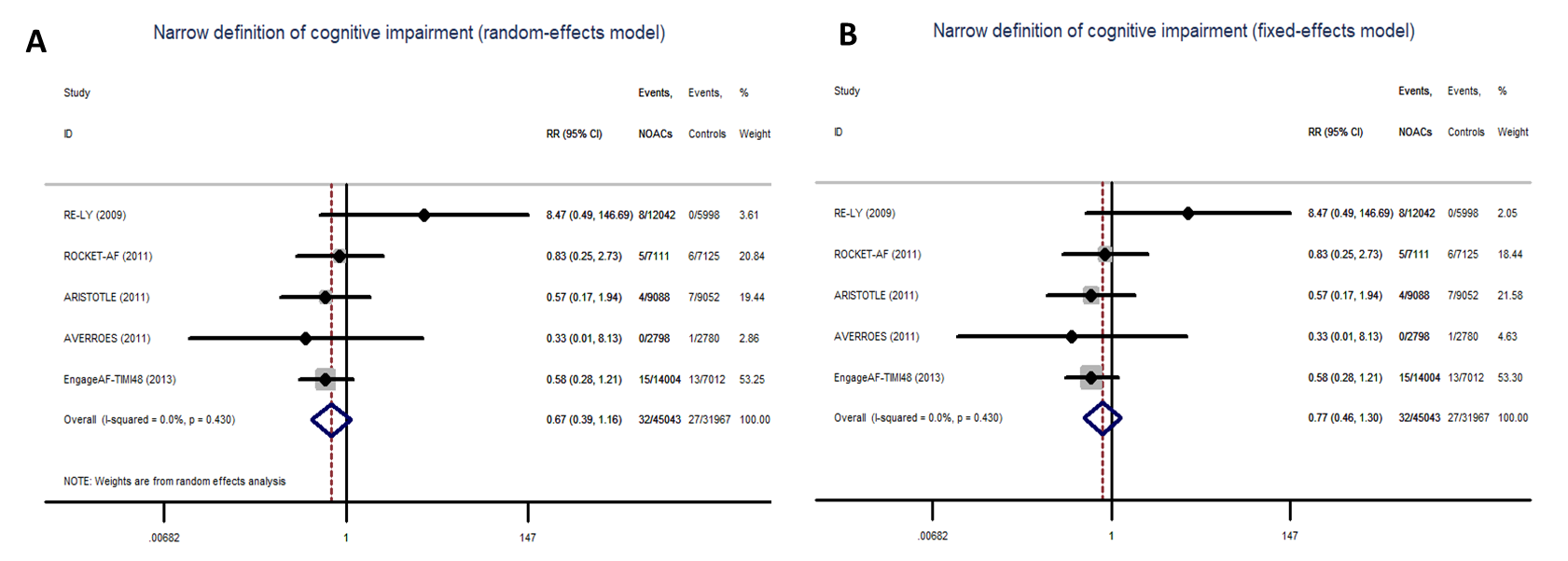
**Table S5. Meta-regression analysis**

|  |  |
| --- | --- |
| **Variable** | **P value** |
| Mean age (year) | 0.61 |
| Male (%) | 0.58 |
| Heart failure | 0.54 |
| Hypertension | 0.93 |
| Diabetes | 0.42 |
| Stroke/ transient ischemic attack/SE | 0.56 |
| Prior myocardial infarction | 0.84 |
| CHADS2/ CHA2DS2-VAS | 0.92 |
| Follow-up | 0.84 |

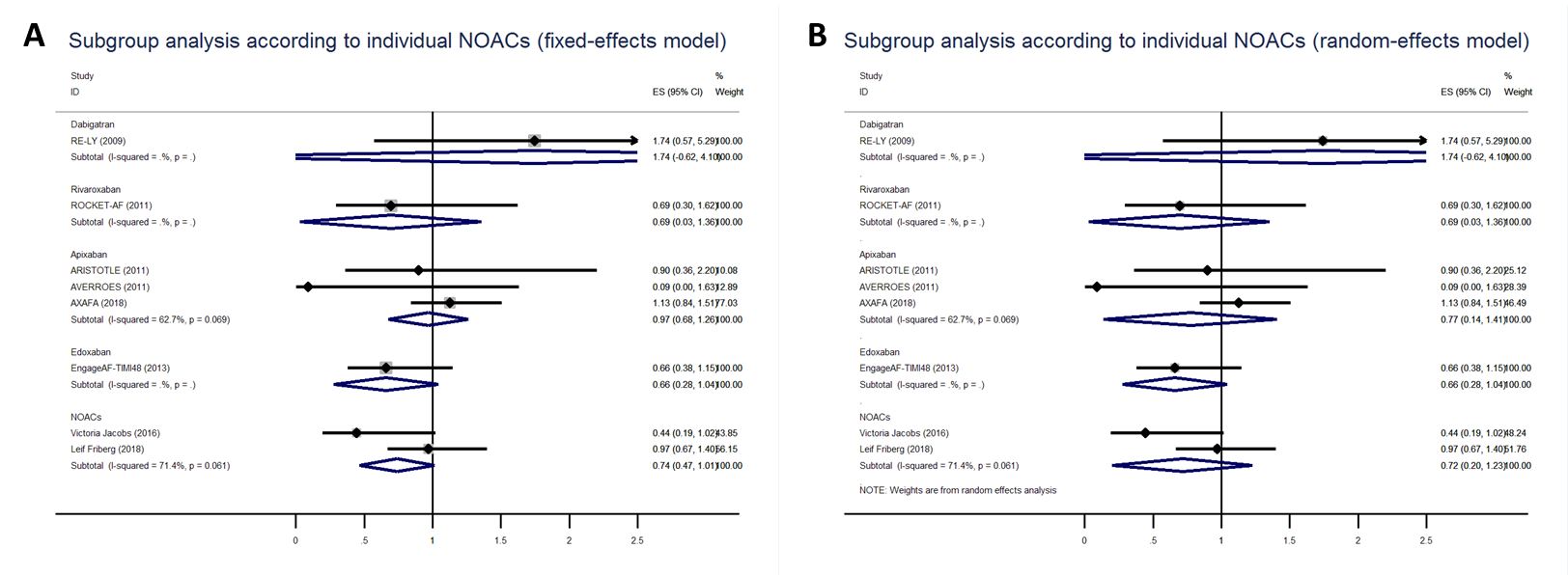
P values: it is the results of meta-regression for the relationship between each variable and the outcome

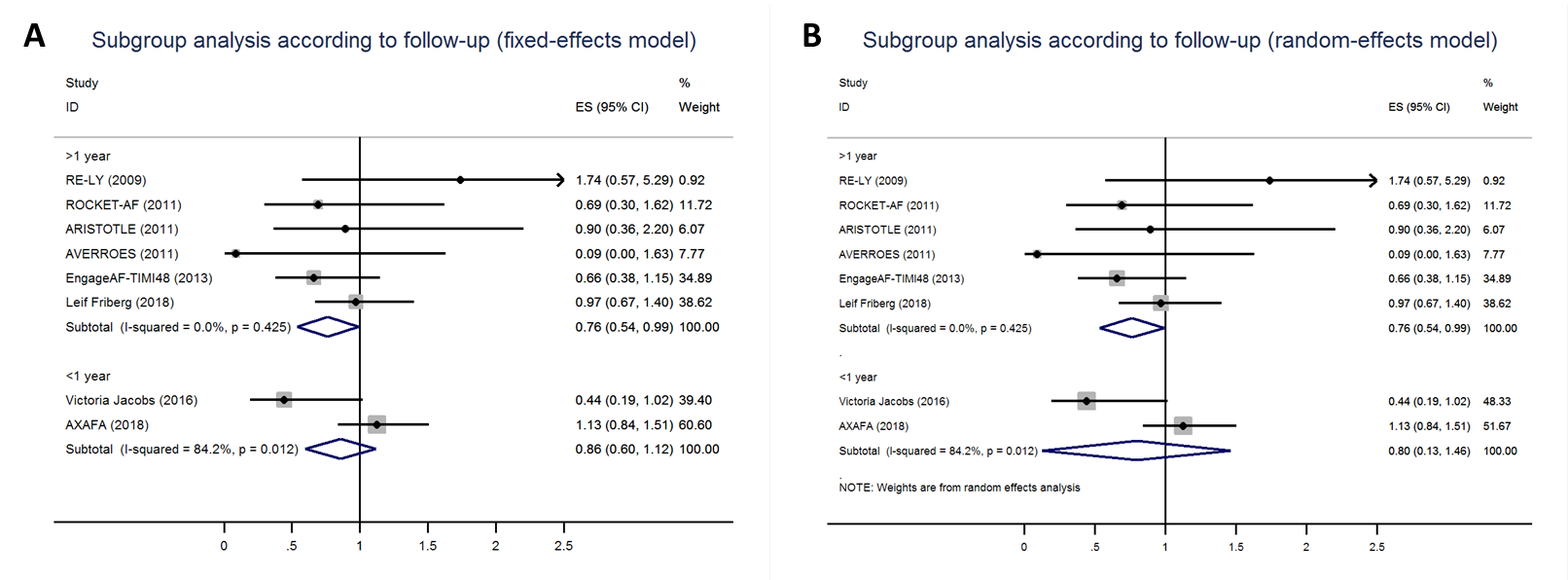
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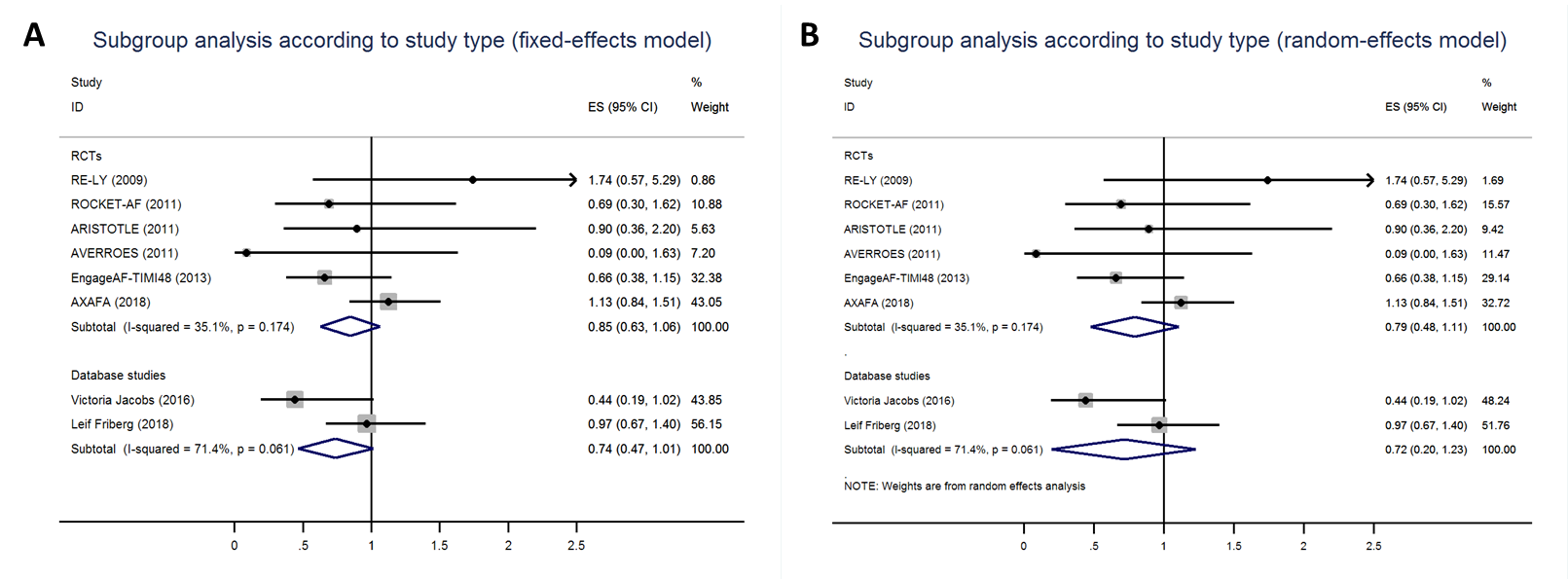
**FigureS1. Flow diagram for the selection of eligible Studies.**

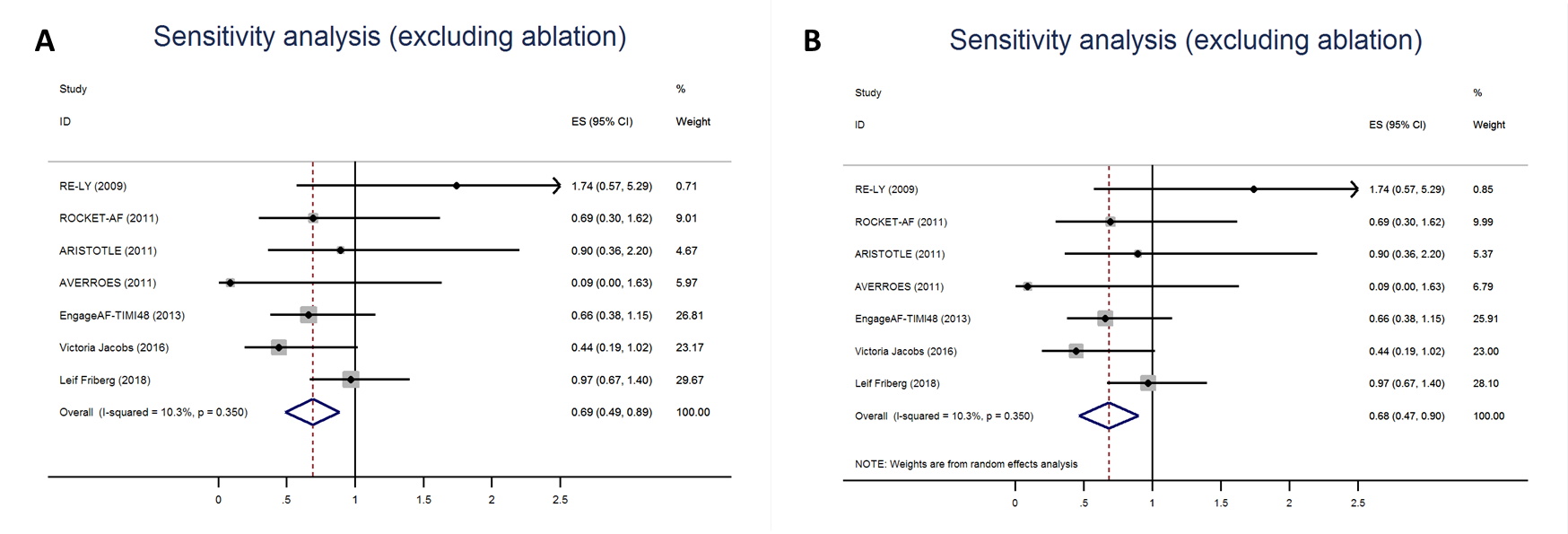
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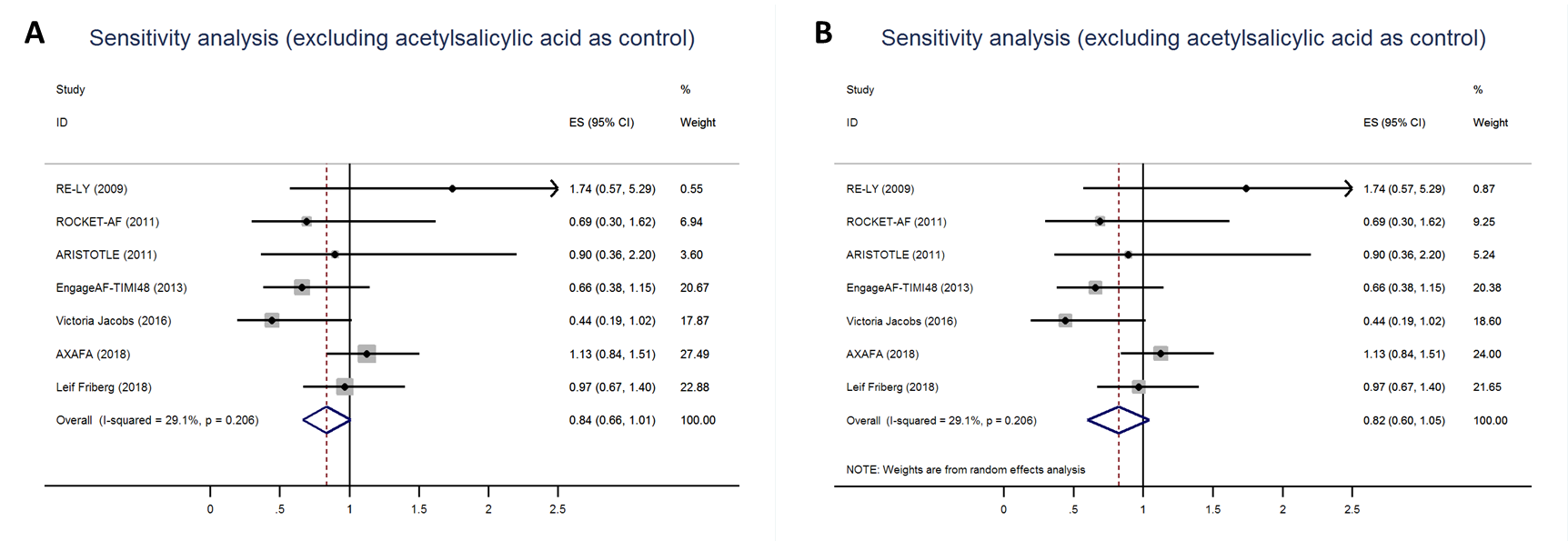
**Figure S2.** Narrow definition of cognitive impairment using fixed-effect model (A) and random-effect model (B)

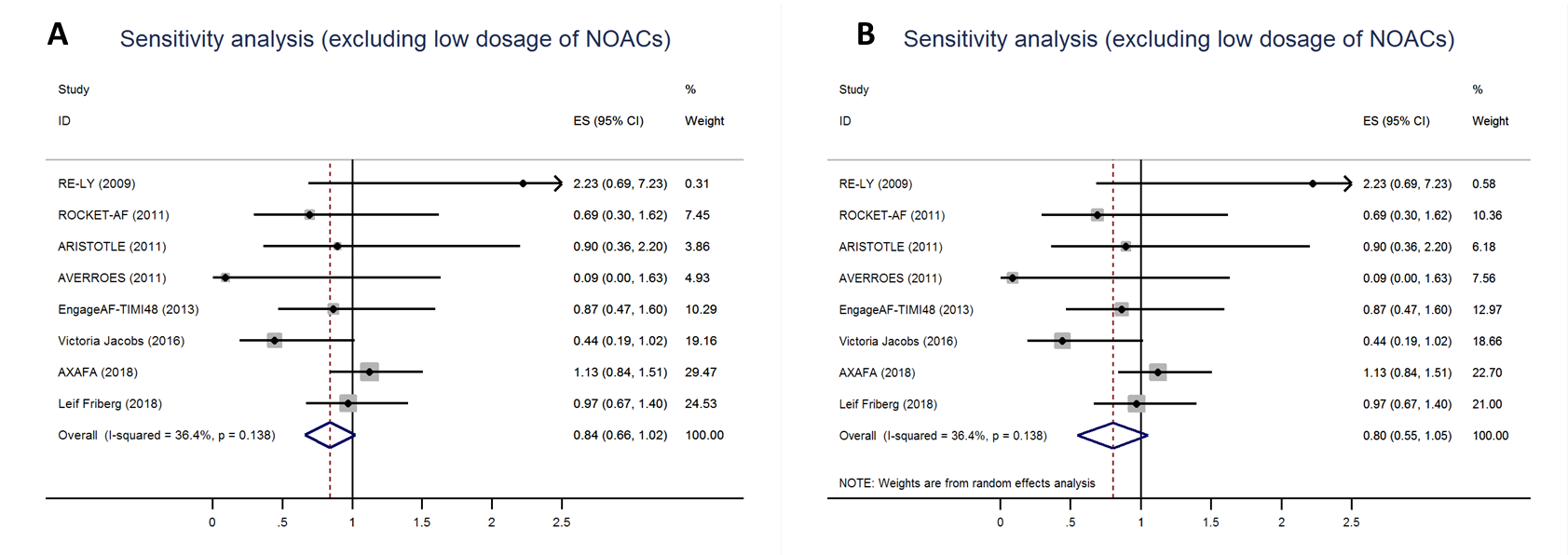
**Figure S3.** Subgroup analysis according to individual NOACs using fixed-effect model (A) and random-effect model (B).

**Figure S4.** Subgroup analysis according to follow-up using fixed-effect model (A) and random-effect model (B).

**Figure S5.** Subgroup analysis according to study type using fixed-effect model (A) and random-effect model (B).

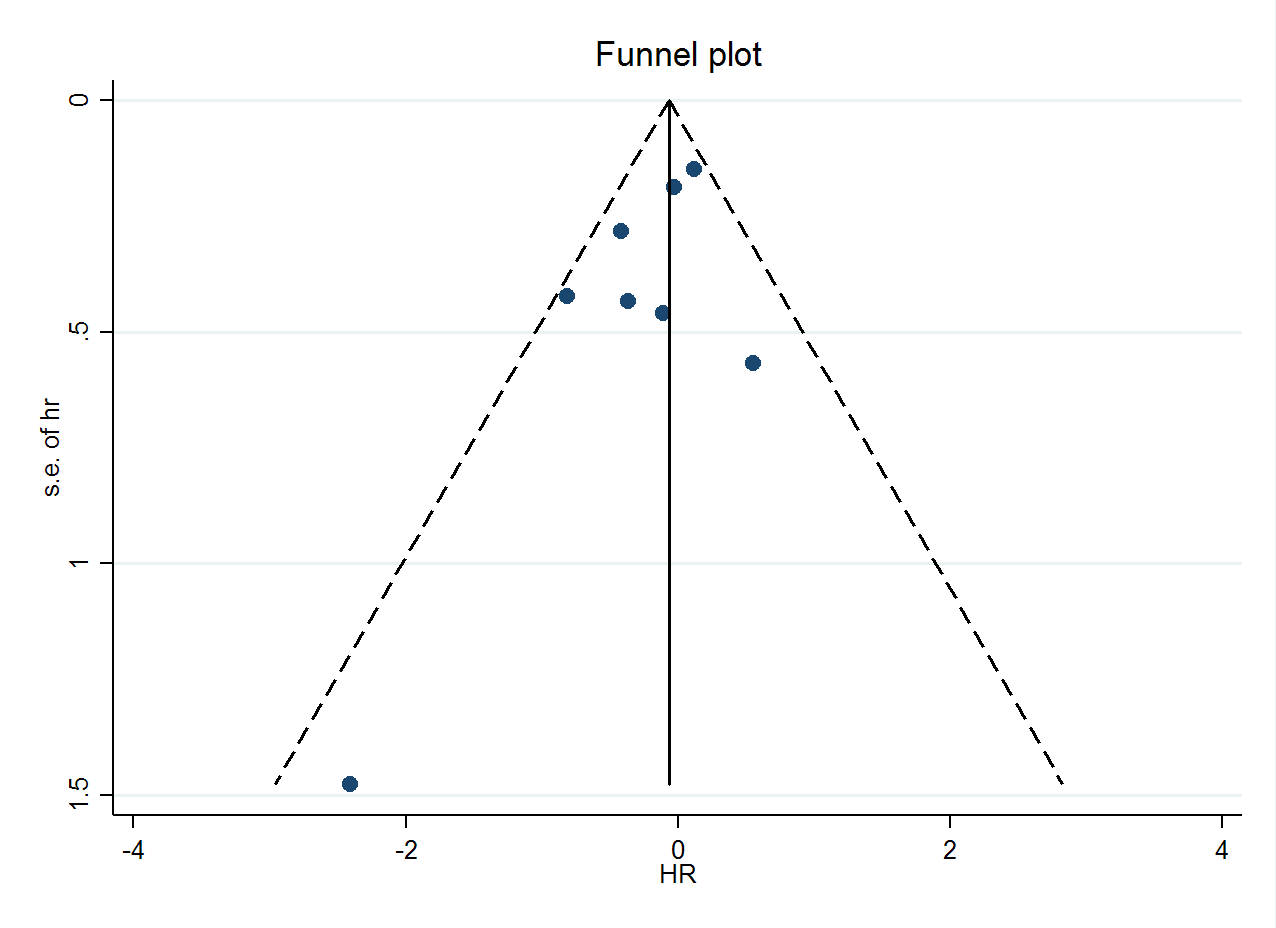
**Figure S6.** Sensitivity analysis by excluding catheter ablation study using fixed-effect model (A) and random-effect model (B).

**Figure S7.** Sensitivity analysis by excluding study involved acetylsalicylic acid as control using fixed-effect model (A) and random-effect model (B).

**Figure S8.** Sensitivity analysis by excluding low dosage arms of NOACs using fixed-effect model (A) and random-effect model (B).



**Figure S9.** Sensitivity analysis by adding the data of magnetic resonance imaging (MRI) sub-study in AXAFA trial using fixed-effect model (A) and random-effect model (B).

**Figure S10. Funnel plot**

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