**Supplementary Table S1** Summary of design of trials from which data were drawn

| Trial | Study population | Study design | Intervention (s) | Control | *N* | Median follow-up |
|---|---|---|---|---|---|---|
| RE-LY | Atrial fibrillation | RCT | Dabigatran 150 mg bid; Dabigatran 110 mg bid | VKA | 18, 113 | 2.0 y |
| AVERROES | Atrial fibrillation | RCT | Apixaban 5 mg bid (2.5 mg bid in certain patients) | ASA 81–324 mg daily | 5,599 | 1.1 y |
| COMPASS | Coronary and peripheral artery disease | RCT | Rivaroxaban 2.5 mg bid and ASA 100 mg daily; Rivaroxaban 5 mg bid | ASA 100 mg daily | 27, 395 | 1.9 y |
| NAVIGATE ESUS | Embolic stroke of undetermined source | RCT | Rivaroxaban 15 mg daily | ASA 100 mg daily | 7,213 | 1.1 y |

Abbreviations: ASA, acetyl salicylic acid; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; NAVIGATE ESUS, New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source; RCT, randomized controlled trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; VKA, vitamin K antagonist.

**Supplementary Table S2** Baseline variables reported in the trials

| Variable | COMPASS | NAVIGATE | RE-LY | AVERROES |
|---|---|---|---|---|
| Demographics | | | | |
| Sex | x | x | x | x |
| Age | x | x | x | x |
| Ethnicity/race (Asian, black/African American, white/Caucasian, other) | x | x | x | x |
| Baseline physical measurements | | | | |
| Systolic blood pressure | x | x | x | x |
| Diastolic blood pressure | x | x | x | x |
| Heart rate | x | x | x | x |
| Weight | x | x | x | x |
| Height | x | x | x | x |
| Hip circumference | x | | x | x |
| Waist circumference | x | | x | x |
| Baseline laboratory tests | | | | |
| Creatinine | x | x | x | x |
| Blood urea nitrogen | | | x | |
| Hemoglobin | x | x | x | x |
| Platelets | x | x | x | x |
| Leukocytes | x | x | x | x |
| Aspartate aminotransferase | x | x | x | X |
| Alanine aminotransferase | | x | x | x |
| Alkaline phosphatase | | x | x | x |
| Total bilirubin | | x | x | x |
| Direct bilirubin | | x | | |
| Sodium | | | x | |
| Potassium | | | x | |
| Chloride | | | x | |
| Phosphorus | | | x | |
| Protein | | | x | |

 

**Supplementary Table S2** (*Continued*)

| Variable | COMPASS | NAVIGATE | RE-LY | AVERROES |
|---|---|---|---|---|
| Albumin | | | x | |
| Lactate dehydrogenase | | | x | |
| Urate | | | x | |
| Total cholesterol | | | x | |
| Triglycerides | | | x | |
| Electrocardiogram | | | x | x |
| Baseline concomitant medications | | | | |
| Aspirin | x | x | x | x |
| Clopidogrel | x | x | x | x |
| Prasugrel | x | x | | |
| Ticagrelor | x | x | | |
| Ticlopidine | x | x | x | x |
| Dipyridamole | x | x | x | x |
| Other antiplatelet | x | x | x | x |
| Parenteral anticoagulant | x | x | x | x |
| Rivaroxaban | x | x | | |
| Apixaban | x | x | | |
| Dabigatran | x | x | | |
| Edoxaban | | x | | |
| Warfarin/vitamin K antagonist | x | x | x | X |
| Other anticoagulant | x | x | | |
| Angiotensin receptor blocker | x | x | x | x |
| ACE inhibitor | x | x | x | x |
| Diuretic | x | x | x | x |
| Alpha blocker or other vasodilator | x | x | x | x |
| Calcium channel blocker | x | x | x | x |
| Beta blocker | x | x | x | x |
| Statin | x | x | x | x |
| Nonstatin lipid-lowering agent | | | x | x |
| COXII inhibitor | | | x | x |
| Other nonsteroidal anti-inflammatory drug | x | x | x | x |
| Insulin | x | x | x | x |
| Oral hypoglycemic | x | x | x | x |
| Proton pump inhibitor | x | x | x | x |
| H2 blocker | | | x | x |
| Digoxin | | | x | x |
| Amiodarone | | | x | x |
| Other antiarrhythmic | | | x | x |
| Selective serotonin reuptake inhibitor | x | | | x |
| Vitamins | | | x | |
| Herbal remedies | | | x | |
| Antibiotics | | | x | |

(*Continued*)

 

**Supplementary Table S2** (*Continued*)

| Variable | COMPASS | NAVIGATE | RE-LY | AVERROES |
|---|---|---|---|---|
| Questionnaires/assessments | | | | |
| International Physical Activity Questionnaire | x | | | |
| Self-Administered Gerocognitive Exam | x | x | | |
| Digit symbol substitution task | x | | | x |
| Montreal cognitive assessment | x | x | | x |
| EuroQol 5D questionnaire | x | x | x | x |
| Trail-making test | | | | x |
| 1-minute semantic fluency (animal naming) | | | | x |
| Medical history | | | | |
| Stroke | x | x | x | x |
| Territory of qualifying stroke | | x | | |
| Treatment of qualifying stroke | | x | | |
| Severity of qualifying stroke (modified Rankin Scale, NIH stroke scale) | | x | | |
| Transient ischemic attack | x | x | x | x |
| Systemic embolism (non-CNS) | | | x | |
| Hypertension | x | x | x | x |
| Diabetes mellitus | x | x | x | x |
| Heart failure | x | x | x | x |
| Coronary artery disease | x | x | x | |
| Myocardial infarction | x | x | x | |
| Angina—stable or unstable | x | | | |
| Coronary atherectomy or percutaneous coronary intervention | x | x | | |
| Coronary artery bypass grafting | x | x | | |
| Carotid endarterectomy or stent | | x | | |
| Other cardiac arrhythmia | | | x | |
| Valvular heart disease | | | x | |
| Peripheral artery disease | x | x | | x |
| Peripheral artery bypass surgery | x | | | |
| Percutaneous angioplasty | x | | | |
| Limb or foot amputation | x | | | |
| Intermittent claudication | x | | | |
| Asymptomatic carotid stenosis >50% or revascularization | x | | | |
| Aortic aneurysm | x | | | |
| Bioprosthetic heart valve present | | x | | |
| Permanent pacemaker or implantable cardiac defibrillator present | | x | x | x |
| Venous thromboembolism | | x | | |
| Hyperlipidemia | | x | | |
| Tobacco use (current, former, and never) | x | x | x | x |
| Alcohol—more than five drinks per week | x | | x | x |
| Cancer and site of primary | x | x | x | x |
| Bleeding requiring transfusion and site | x | x | | |
| Prior vitamin K antagonist use | | | x | x |
| Bleeding while on oral anticoagulation | | | x | x |

 

**Supplementary Table S2** (*Continued*)

| Variable | COMPASS | NAVIGATE | RE-LY | AVERROES |
|---|---|---|---|---|
| Difficulty with INR control | | | x | x |
| Surgical history associated with gastrointestinal disease | x | | | |
| Peptic ulcer | x | | | |
| Diverticulitis | x | | | |
| Inflammatory bowel disease | x | | | |
| *H. pylori* | x | | | |
| Hemorrhoids | x | | | x |
| Daily or occasional nosebleeds | | | | x |
| Liver disease | x | x | | |
| Gilbert syndrome | | | x | x |
| History of fainting, falling, or fractures | | | x | x |
| History of seizures | | | x | |
| Ejection fraction | x | x | x | x |
| Qualifying atrial fibrillation episode | | | x | x |
| Type of atrial fibrillation (permanent, paroxysmal, and persistent) | | | x | x |
| Previous ablation | | | x | x |
| Previous cardioversion | | | x | x |
| Reasons why vitamin K antagonist is unsuitable | | | | x |
| Social factors | | | | |
| Health care costs (paid by self, public insurance, and private insurance) | x | | | |
| Driving status | x | x | | |
| Employment status | | | x | x |
| Live alone | | | | x |
| <12 y formal education | x | x | | x |

Abbreviations: ACE, angiotensin-converting enzyme; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; CNS, central nervous system; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; INR, international normalized ratio; NAVIGATE ESUS, New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source; NIH, National Institutes of Health; RCT, randomized controlled trial; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy.
Note: x indicates variable collected in trial.

**Supplementary Table S3** Number of patients with bleeding events per trial

| First major bleeding event | COMPASS (*N* = 27,359) | | RE-LY (*N* = 17,713) | | NAVIGATE-ESUS (*N* = 7,195) | | AVERROES (*N* = 5,546) | | Total (*N* = 57,813) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | %/y | *N* | %/y | *N* | %/y | *N* | %/y | *N* | %/y |
| Any major bleeding | 688 | 1.3 | 1100 | 3.3 | 83 | 1.2 | 77 | 1.1 | 1,948 | 2.0 |
| Intracranial bleeding | 94 | 0.2 | 128 | 0.4 | 30 | 0.4 | 22 | 0.3 | 274 | 0.3 |
| Major GI bleeding | 272 | 0.5 | 393 | 1.1 | 30 | 0.4 | 22 | 0.3 | 717 | 0.7 |

Abbreviations: AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; ESUS, embolic stroke of undetermined source; GI, gastrointestinal; NAVIGATE ESUS, New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy.

 

**Supplementary Table S4** Univariate analysis: Hazard ratios (95% confidence intervals) of variables for major bleeding, major GI bleeding, intracranial hemorrhage, and non-GI, nonintracranial bleeding

| | Major bleeding | | Major GIB | | ICH | |
|---|---|---|---|---|---|---|
| | Hazard ratio | *p*-Value | Hazard ratio | *p*-Value | Hazard ratio | *p*-Value |
| Treatment arm (vs. aspirin alone) | | | | | | |
| Warfarin | 1.83 (1.30–2.57) | 0.0005 | 0.90 (0.50–1.62) | 0.72 | 5.11 (2.64–9.92) | <0.0001 |
| DOAC, theraupetic dose | 1.55 (1.13–2.13) | 0.007 | 1.17 (0.68–2.02) | 0.57 | 1.60 (0.92–2.81) | 0.1 |
| Rivaroxaban alone | 1.56 (1.27–1.90) | <0.0001 | 1.66 (1.18–2.34) | 0.003 | 1.50 (0.91–2.47) | 0.11 |
| Rivaroxaban + aspirin | 1.78 (1.47–2.17) | <0.0001 | 2.47 (1.79–3.40) | <0.0001 | 1.11 (0.65–1.88) | 0.7 |
| Age (per 10 y increase) | 1.72 (1.62–1.82) | <0.0001 | 1.98 (1.79–2.19) | <0.0001 | 1.66 (1.42–1.93) | <0.0001 |
| Female | 0.94 (0.85–1.03) | 0.19 | 0.92 (0.78–1.09) | 0.33 | 0.88 (0.67–1.14) | 0.33 |
| Race | | | | | | |
| Caucasian | 1.11 (1.00–1.22) | 0.04 | 0.95 (0.81–1.11) | 0.51 | 0.67 (0.53–0.86) | 0.001 |
| Asian | 0.96 (0.85–1.09) | 0.53 | 1.02 (0.83–1.24) | 0.86 | 2.02 (1.56–2.64) | <0.0001 |
| Black | 1.43 (0.97–2.10) | 0.07 | 1.63 (0.90–2.95) | 0.11 | 1.51 (0.56–4.05) | 0.41 |
| Other | 0.85 (0.74–0.97) | 0.01 | 1.02 (0.84–1.25) | 0.81 | 0.75 (0.52–1.08) | 0.12 |
| Weight (per 10 kg increase) | 0.98 (0.95–1.00) | 0.07 | 0.95 (0.92–1.00) | 0.03 | 0.85 (0.79–0.91) | <0.0001 |
| Height (per 10 cm increase) | 0.99 (0.94–1.03) | 0.55 | 0.96 (0.89–1.03) | 0.27 | 0.94 (0.84–1.06) | 0.34 |
| BMI (per 10 units increase) | 0.92 (0.85–1.00) | 0.06 | 0.85 (0.74–0.99) | 0.03 | 0.53 (0.41–0.68) | <0.0001 |
| Baseline diastolic BP (per 10 units increase) | 0.81 (0.78–0.85) | <0.0001 | 0.72 (0.67–0.78) | <0.0001 | 1.06 (0.94–1.18) | 0.35 |
| Baseline systolic BP (per 10 units increase) | 1.00 (0.97–1.02) | 0.87 | 0.97 (0.93–1.01) | 0.2 | 1.04 (0.97–1.11) | 0.3 |
| Pulse pressure (per 10 units increase) | 1.11 (1.07–1.14) | <0.0001 | 1.13 (1.07–1.18) | <0.0001 | 1.02 (0.94–1.11) | 0.56 |
| Heart rate (per 10 units increase) | 0.98 (0.95–1.02) | 0.3 | 0.98 (0.93–1.04) | 0.51 | 0.97 (0.88–1.06) | 0.46 |
| Creatinine (per 10 µmol/L increase) | 1.11 (1.09–1.14) | <0.0001 | 1.13 (1.09–1.17) | <0.0001 | 1.03 (0.96–1.12) | 0.39 |
| GFR (per 10 mL/min/1.73 $m^3$ increase) | 0.86 (0.84–0.88) | <0.0001 | 0.82 (0.79–0.85) | <0.0001 | 0.86 (0.81–0.91) | <0.0001 |
| Medical history | | | | | | |
| Previous PAD | 1.31 (1.14–1.51) | 0.0001 | 1.30 (1.04–1.63) | 0.02 | 0.76 (0.49–1.18) | 0.21 |
| Previous stroke | 1.15 (0.99–1.33) | 0.07 | 0.95 (0.73–1.24) | 0.73 | 2.39 (1.76–3.26) | <0.0001 |
| Previous TIA | 1.16 (0.98–1.37) | 0.09 | 1.18 (0.89–1.56) | 0.26 | 1.06 (0.65–1.72) | 0.81 |
| HTN history | 1.22 (1.09–1.37) | 0.0006 | 1.25 (1.03–1.51) | 0.02 | 1.18 (0.88–1.60) | 0.27 |
| Previous MI | 1.20 (1.07–1.33) | 0.001 | 1.33 (1.12–1.59) | 0.001 | 1.06 (0.78–1.43) | 0.72 |
| Previous HF | 1.02 (0.93–1.13) | 0.65 | 1.21 (1.03–1.42) | 0.02 | 0.86 (0.64–1.15) | 0.32 |
| Coronary artery disease | 1.47 (1.31–1.65) | <0.0001 | 1.63 (1.35–1.97) | <0.0001 | 1.07 (0.77–1.48) | 0.7 |
| Cancer | 1.53 (1.34–1.75) | <0.0001 | 1.35 (1.07–1.70) | 0.01 | 1.35 (0.93–1.96) | 0.12 |

**Supplementary Table S4** (*Continued*)

| | Major bleeding | | Major GIB | | ICH | |
|---|---|---|---|---|---|---|
| | Hazard ratio | *p*-Value | Hazard ratio | *p*-Value | Hazard ratio | *p*-Value |
| Diabetes | 1.18 (1.07–1.30) | 0.001 | 1.16 (0.99–1.37) | 0.06 | 0.96 (0.73–1.26) | 0.76 |
| Prerandomization medications | | | | | | |
| Statin | 1.09 (0.99–1.21) | 0.09 | 1.16 (0.98–1.38) | 0.08 | 0.78 (0.60–1.03) | 0.08 |
| Antiplatelet or aspirin | 1.42 (1.27–1.59) | <0.0001 | 1.39 (1.16–1.68) | 0.0004 | 1.32 (0.97–1.80) | 0.07 |
| Anticoagulant | 1.11 (0.99–1.25) | 0.08 | 1.09 (0.90–1.33) | 0.37 | 1.19 (0.87–1.64) | 0.27 |
| PPI | 1.31 (1.18–1.46) | <0.0001 | 1.31 (1.11–1.56) | 0.002 | 1.26 (0.95–1.68) | 0.11 |
| NSAID | 1.32 (1.11–1.56) | 0.001 | 1.48 (1.14–1.93) | 0.004 | 1.31 (0.83–2.07) | 0.24 |
| ACE or ARB | 1.05 (0.96–1.16) | 0.28 | 1.12 (0.95–1.31) | 0.17 | 0.88 (0.69–1.13) | 0.33 |
| Beta blocker | 0.93 (0.85–1.03) | 0.16 | 0.91 (0.78–1.07) | 0.25 | 0.85 (0.66–1.10) | 0.22 |
| Calcium channel blocker | 1.11 (1.01–1.22) | 0.03 | 1.08 (0.92–1.26) | 0.34 | 1.04 (0.80–1.35) | 0.76 |
| Diuretic | 0.86 (0.84–0.88) | <0.0001 | 0.82 (0.79–0.85) | <0.0001 | 0.87 (0.82–0.92) | <0.0001 |
| > 12 y education | 0.93 (0.81–1.07) | 0.32 | 0.83 (0.66–1.04) | 0.1 | 1.00 (0.72–1.39) | 0.99 |
| Smoking (vs. never smoking) | | | | | | |
| Former | 1.37 (1.25–1.51) | <0.0001 | 1.47 (1.25–1.72) | <0.0001 | 1.18 (0.91–1.52) | 0.21 |
| Current | 1.09 (0.94–1.27) | 0.26 | 1.13 (0.88–1.46) | 0.33 | 1.01 (0.68–1.50) | 0.95 |
| >5 drinks of alcohol/wk | 0.98 (0.89–1.08) | 0.64 | 0.89 (0.76–1.05) | 0.16 | 0.99 (0.76–1.29) | 0.94 |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BMI, body mass index; DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; HF, Heart failure; HTN, hypertension; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drugs; PAD, peripheral artery disease; PPI, proton-pump inhibitors; TIA, transient ischemic attack.
Note: Univariate analysis by univariate Cox models. *p*-Values are from the Wald test used in the Cox models.

**TRIPOD Checklist:** Prediction Model Development

| Section/Topic | Item | Checklist item | Page |
|---|---|---|---|
| Title and abstract | | | |
| Title | 1 | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. | 1 |
| Abstract | 2 | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | 2 |
| Introduction | | | |
| Background and objectives | 3a | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | 4 |
| | 3b | Specify the objectives, including whether the study describes the development or validation of the model or both. | 4 |
| Methods | | | |
| Source of data | 4a | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | 5 |
| | 4b | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | 5 |
| Participants | 5a | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. | S1 |
| | 5b | Describe eligibility criteria for participants. | S1 |
| | 5c | Give details of treatments received, if relevant. | S1 |
| Outcome | 6a | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | 5–7 |
| | 6b | Report any actions to blind assessment of the outcome to be predicted. | 5–6 |
| Predictors | 7a | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured. | 10–11 |
| | 7b | Report any actions to blind assessment of predictors for the outcome and other predictors. | 7-8 |
| Sample size | 8 | Explain how the study size was arrived at. | 5 |
| Missing data | 9 | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | 8 |
| Statistical analysis methods | 10a | Describe how predictors were handled in the analyses. | 7–8 |
| | 10b | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | 7–8 |
| | 10d | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | 8–9 |
| Risk groups | 11 | Provide details on how risk groups were created, if done. | n/a |
| Results | | | |
| Participants | 13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | S1,S9 |
| | 13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | 23–26 |
| Model development | 14a | Specify the number of participants and outcome events in each analysis. | 23 |
| | 14b | If done, report the unadjusted association between each candidate predictor and outcome. | S10–16 |
| Model specification | 15a | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | 27–29 |

**TRIPOD Checklist:** (*Continued*)

| Section/Topic | Item | Checklist item | Page |
|---|---|---|---|
| | 15b | Explain how to the use the prediction model. | n/a |
| Model performance | 16 | Report performance measures (with CIs) for the prediction model. | 11–14 |
| Discussion | | | |
| Limitations | 18 | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). | 17–18 |
| Interpretation | 19b | Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence. | 15–18 |
| Implications | 20 | Discuss the potential clinical use of the model and implications for future research. | 18 |
| Other information | | | |
| Supplementary information | 21 | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | n/a |
| Funding | 22 | Give the source of funding and the role of the funders for the present study. | 19 |

Abbreviation: CI, confidence interval.
Note: We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

 