Supplemental materials

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eTable 1: Search strategy

The following search terms were used in Medline:

Patient	“Atrial Fibrillation"[Mesh] OR "Atrial Fibrillation"[TIAB]
Intervention and **C**ontrol	“Apixaban"[TIAB] OR "Apixaban"[Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "Rivaroxaban"[TIAB] OR "Edoxaban"[TIAB] OR “Edoxaban"[Supplementary Concept] OR "Dabigatran"[Mesh] OR "Dabigatran"[TIAB] OR "Antithrombins"[Mesh] OR "Factor Xa Inhibitors"[Mesh] OR "New oral anticoagulants"[TIAB] OR "NOAC"[TIAB] OR "Direct oral anticoagulants"[TIAB] OR "DOAC"[TIAB] OR "Non-vitamin K antagonist oral anticoagulants"[TIAB]
Outcome	"Thromboembolism"[Mesh] OR "Thromboembolism"[TIAB] OR "Thrombosis"[TIAB] OR "Stroke"[TIAB] OR "Hemorrhage"[TIAB] OR "Hemorrhage"[Mesh] OR "Bleeding"[TIAB]
Filter	English

The following search terms were used in Embase:

Patient	('atrial fibrillation':ab,ti OR 'atrial fibrillation'/exp) AND ('cha2ds2-vasc score':ab,ti OR 'cha2ds2-vasc score'/exp OR 'stroke risk factor':ab,ti OR 'chads2 score':ab,ti OR 'chads2 score'/exp)
Intervention and **C**ontrol	apixaban:ab,ti OR 'apixaban'/exp OR rivaroxaban:ab,ti OR 'rivaroxaban'/exp OR edoxaban:ab,ti OR 'edoxaban'/exp OR dabigatran:ab,ti OR 'dabigatran'/exp OR 'new oral anticoagulant':ab,ti OR 'new oral anticoagulant'/exp OR NOAC:ab,ti OR DOAC:ab,ti OR 'direct oral anticoagulant':ab,ti OR 'direct oral anticoagulant'/exp OR 'non vitamin k antagonist oral anticoagulant':ab,ti OR 'non-vitamin k antagonist oral anticoagulant':ab,ti OR 'non vitamin k antagonist oral anticoagulant'/exp OR 'non vitamin k oral anticoagulant':ab,ti OR 'non-vitamin k oral anticoagulant':ab,ti
Outcome	thromboembolism:ab,ti OR 'thromboembolism'/exp OR thrombosis:ab,ti OR 'thrombosis'/exp OR stroke:ab,ti OR 'stroke'/exp OR hemorrhage:ab,ti OR haemorrhage:ab,ti OR bleeding:ab,ti OR 'bleeding'/exp

eTable 1: Search strategy.

eTable 2: Impact of a single non-sex-related stroke risk factor

Author	Study design	Study cohort	n	Mean/median age (years +/- SD; [IQR])	Mean/median follow-up (+/- SD; [IQR])	Thromboembolism (Event rate [95% CI] and/or HR [95% CI])		
Olesen et al. 2011[1]	Observational retrospective nationwide study (Denmark)	Hospital-discharged non-anticoagulated AF patients in Denmark (1997-2006), using the national patient registry. Impact of individual CHA_2DS_2-VASc score risk factors on the risk of thromboembolism (stroke/SE and/or pulmonary embolism; in supplemental materials risk estimates on stroke/SE risk).	73 538 overall, 6369 with CHA_2DS_2-VASc score 0, 8203 with CHA_2DS_2-VASc score 1	**<65 years old:** 15 130 (20.5%) **65-74 years old:** 14 544 (19.8%) **≥75 years old:** 43 864 (59.7%) (mean/median age NR)	Up to 10 years of follow-up (maximum duration, no mean/median follow-up reported)	**After 1y follow-up:** ***Stroke/SE/pulmonary embolism:*** **CHA_2DS_2-VASc score 0:** Event rate: 0.78 per 100 PY [0.58-1.04] **CHA_2DS_2-VASc score 1:** *Overall:* 2.01 per 100 PY [1.70-2.36] *Heart failure:* 1.50 per 100 PY [0.37-5.98] *Hypertension:* 2.14 per 100 PY [1.46-3.15] *Diabetes:* 3.47 per 100 PY [1.65-7.27] *Vascular disease:* 0.75 per 100 PY [0.24-2.33] *Age 65-74y:* 2.88 per 100 PY [2.29-3.62] *Female sex:* 1.24 per 100 PY [0.89-1.73] ***Stroke/SE (supplemental materials):*** **CHA_2DS_2-VASc score 0:** HR 1.00 (reference) **CHA_2DS_2-VASc score 1:** *Heart failure:* HR 2.40 [0.58-9.98] *Hypertension: HR 2.92 [1.72-4.96]* *Age 65-74 years: HR 3.54 [2.33-5.38]* *Diabetes mellitus: HR 4.77 [2.01-11.31]* *Vascular disease:* HR 1.21 [0.37-3.93] *Female sex:* HR 1.47 [0.88-2.44]	**After 5y follow-up:** ***Stroke/SE/pulmonary embolism:*** **CHA_2DS_2-VASc score 0:** Event rate: 0.69 per 100 PY [0.59-0.81] **CHA_2DS_2-VASc score 1:** *Overall:* 1.51 per 100 PY [1.37-1.67] ***Stroke/SE:*** **CHA_2DS_2-VASc score 0:** HR 1.00 (reference) **CHA_2DS_2-VASc score 1:** *Heart failure: HR 3.52 [1.85-6.69]* *Hypertension: HR 2.33 [1.73-3.15]* *Age 65-74 years: HR 2.95 [2.34-3.72]* *Diabetes mellitus: HR 3.54 [2.11-5.94]* *Vascular disease: HR 2.10 [1.30-3.40]* *Female sex:* HR 1.18 [0.88-1.57]	**After 10y follow-up:** ***Stroke/SE/pulmonary embolism:*** **CHA_2DS_2-VASc score 0:** Event rate: 0.66 per 100 PY [0.57-0.76] **CHA_2DS_2-VASc score 1:** *Overall:* 1.45 per 100 PY [1.32-1.58] ***Stroke/SE:*** **CHA_2DS_2-VASc score 0:** HR 1.00 (reference) **CHA_2DS_2-VASc score 1:** *Heart failure: HR 2.75 [1.45-5.20]* *Hypertension: HR 2.17 [1.65-2.85]* *Age 65-74 years: HR 3.02 [2.46-3.71]* *Diabetes mellitus: HR 3.04 [1.85-5.01]* *Vascular disease: HR 2.21 [1.45-3.37]* *Female sex:* HR 1.16 [0.90-1.50]
Chao et al. 2015[2]	Observational retrospective nationwide study (Taiwan)	Non-anticoagulated AF patients with a single non-sex-related stroke risk factor, using the National Health Insurance Research Database in Taiwan from 1996-2011. Male AF patients with one risk factor: 38.3% age 65-74y, 31.5% hypertension, 15.6%	**AF males with CHA_2DS_2-VASc score 1:** 12 935; **AF females with score 2:** 7900	**AF males with CHA_2DS_2-VASc score 1:** 59.1y +/- 11.3 **AF females with score 2:** 59.1y +/- 10.2	5.2 years +/- 4.3	***Ischemic stroke:*** **AF males:** **CHA_2DS_2-VASc score 0:** HR 1.00 (reference) **CHA_2DS_2-VASc score 1:** *Overall*: Event rate 2.75 per 100 PY [2.62-2.87]; *HR 2.39 [2.18-2.60]* *Heart failure:* Event rate 2.37 per 100 PY [2.10-2.67]; *HR 2.06 [1.79-2.37]* *Hypertension:* Event rate 2.18 per 100 PY [1.99-2.38]; *HR 1.95 [1.73-2.19]* *Age 65-74 years:* Event rate 3.50 per 100 PY [3.27-3.74]; *HR 3.09 [2.79-3.41]* *Diabetes mellitus:* Event rate 2.96 per 100 PY [2.52-3.47]; *HR 2.66 [2.23-3.16]* *Vascular disease:* Event rate 1.96 per 100 PY [1.56-2.42]; *HR 1.68 [1.33-2.12]*		

		heart failure, 8.5% diabetes, 6.1% vascular disease; female AF patients with one risk factor: 34.9% hypertension, 33.4% age 65-74y, 17.0% heart failure, 8.9% diabetes, 5.8% vascular disease.				**AF females:** **CHA_2DS_2-VASc score 1:** HR 1.00 (reference) **CHA_2DS_2-VASc score 2:** *Overall*: Event rate 2.55 per 100 PY [2.41-2.70]; *HR 2.25 [2.02-2.50]* *Heart failure:* Event rate 2.22 per 100 PY [1.91-2.57]; *HR 1.98 [1.67-2.35]* *Hypertension:* Event rate 1.91 per 100 PY [1.70-2.14]; *HR 1.71 [1.48-1.98]* *Age 65-74 years:* Event rate 3.34 per 100 PY [3.06-3.64]; *HR 3.03 [2.68-3.43]* *Diabetes mellitus:* Event rate 2.88 per 100 PY [2.37-3.47]; *HR 2.66 [2.16-3.27]* *Vascular disease:* Event rate 2.25 per 100 PY [1.72-2.91]; *HR 2.15 [1.64-2.82]*
Hung et al. 2016[3]	Observational retrospective nationwide study (Taiwan)	Non-anticoagulated AF patients with a single non-sex-related stroke risk factor, using the National Health Insurance Research Database in Taiwan from 1996-2003, stratified into 3 age groups: 20-49, 50-64 and 65-74 years old.	**Age 20-49y:** 3674 no risk factors, 1852 one risk factor (766 heart failure, 705 hypertension, 224 diabetes, 157 vascular disease) **Age 50-64y:** 4301 no risk factors, 4561 one risk factor (1350 heart failure, 2230 hypertension, 679 diabetes, 302 vascular disease) **Age 65-74y:** 5422 one risk factor (age)	NR	**Age 20-49y:** 36 942.2 PY in patients with no risk factors, 15 838.9 PY in patients with one risk factor **Age 50-64y:** 37 265.0 PY in patients with no risk factors, 9535.9 PY in patients with one risk factor **Age 65-74y:** 33 727.0 PY	***Ischemic stroke:*** **20-49 years:** **CHA_2DS_2-VASc score 0 (male) or 1 (female):** Event rate 0.63 per 100 PY; HR 1.00 (reference) **CHA_2DS_2-VASc score 1 (male) or 2 (female):** *Overall*: Event rate 1.33 per 100 PY; *HR 2.12 [1.76-2.55]* *Heart failure:* Event rate 1.69 per 100 PY; *HR 2.67 [2.11-3.38]* *Hypertension:* Event rate 1.00 per 100 PY; *HR 1.59 [1.21-2.09]* *Diabetes mellitus:* Event rate 1.59 per 100 PY; *HR 2.53 [1.73-3.70]* *Vascular disease:* Event rate 1.07 per 100 PY; *HR 1.72 [1.03-2.85]* **50-64 years:** **CHA_2DS_2-VASc score 0 (male) or 1 (female):** Event rate 1.96 per 100 PY; HR 1.00 (reference) **CHA_2DS_2-VASc score 1 (male) or 2 (female):** *Overall*: Event rate 2.90 per 100 PY, *HR 1.51 [1.37-1.66]* *Heart failure:* Event rate 2.81 per 100 PY; *HR 1.46 [1.27-1.68]* *Hypertension:* Event rate 2.81 per 100 PY; *HR 1.46 [1.31-1.64]* *Diabetes mellitus:* Event rate 4.12 per 100 PY; *HR 2.17 [1.84-2.56]* *Vascular disease:* Event rate 1.94 per 100 PY; HR 1.02 [0.77-1.35] **65-74 years:** **CHA_2DS_2-VASc score 1 (male) or 2 (female):** *Age 65-74 years:* Event rate 3.60 per 100 PY; *HR 1.90 [1.73-2.08]* compared to age 50-64y; *HR 5.87 [5.10-6.76]* compared to age 20-49y
Joundi et al. 2016[4]	Meta-analysis	Meta-analysis of 10 studies, reporting the risk of ischemic stroke for non-anticoagulated AF patients with a CHA_2DS_2-VASc score or 0, 1 or 2.	**CHA_2DS_2-VASc score 0:** 109 197 PY; **Score 1:** 166 017 PY; **Score 2:** 133 298 PY	NR	**Score 0:** 109 197 PY; **Score 1:** 166 017 PY; **Score 2:** 133 298 PY	***Ischemic stroke:*** **CHA_2DS_2-VASc score 0:** Event rate 0.68 per 100 PY [0.12-1.23] **CHA_2DS_2-VASc score 1:** Event rate 1.61 per 100 PY [0.00-3.23] **CHA_2DS_2-VASc score 2:** Event rate 2.49 per 100 PY [1.16-3.83]

eTable 2: Overview of included studies investigating the impact of a single non-sex-related stroke risk factor on thromboembolic outcomes in atrial fibrillation.

Italic: significantly higher risk.

AF: atrial fibrillation; CI: confidence interval; HR hazard ratio; IQR: interquartile range; NR: not reported; PY: person-years; SD: standard deviation; Stroke/SE: stroke/systemic embolism; y: year.

eTable 3: Role of anticoagulation therapy versus no anticoagulation in case of a single non-sex-related stroke risk factor

Author	Study design	Study cohort	n	Mean/median age (years +/- SD; [IQR])	Mean/median follow-up (+/- SD; [IQR])	Thromboembolism (Event rate [95% CI] and/or HR [95% CI])	Major bleeding (Event rate)	Intracranial bleeding (Event rate)	All-cause mortality (Event rate)	Other
Olesen et al. 2011[1]	Observational retrospective nationwide study (Denmark)	Hospital-discharged AF patients in Denmark (1997-2006), using the national patient registry. Risk of thromboembolism using VKAs versus no OAC in patients with CHA2DS2-VASc score of 0 or 1.	73 538 overall, 6369 with CHA_2DS_2-VASc score 0, 8203 with CHA_2DS_2-VASc score 1	**<65 years old:** 15 130 (20.5%); **65-74 years old:** 14 544 (19.8%); **≥75 years old:** 43 864 (59.7%) (mean/median age NR)	Up to 10 years of follow-up (maximum duration, no mean/median follow-up reported)	***Stroke/SE/pulmonary embolism:*** **CHA_2DS_2-VASc score 0:** *No OAC:* 0.78 per 100 PY [0.58-1.04] *VKA:* 0.81 per 100 PY [0.56-1.17] **CHA_2DS_2-VASc score 1:** *No OAC:* 2.01 per 100 PY [1.70-2.36] *VKA:* **1.23 per 100 PY [0.98-1.56]** (event rates, risk estimates NR)	NR	NR	NR	NR
Lip et al. 2015[5]	Observational retrospective nationwide study (Denmark)	AF patients with no or one non-sex-related stroke risk factor using the national patient registry, net clinical benefit (based on stroke, major extracranial bleeding, intracranial bleeding and myocardial infarction, weighted for the risk of death following an event) of VKA versus no OAC.	**No risk factor:** 23 219 no OAC, 1563 warf; **Single risk factor:** 20 103 no OAC, 2262 warf	60y [52-66] no OAC, 62y [57-68] warf	5.77y +/- 4.47 no OAC, 4.72y +/- 4.51 warf	***Ischemic stroke:*** **No stroke risk factors:** ***After 1y of follow-up:*** *No OAC:* 0.75 per 100 PY *Warf:* 0.53 per 100 PY ***After 5y of follow-up:*** *No OAC:* 0.55 per 100 PY *Warf:* 0.54 per 100 PY **One non-sex-related stroke risk factor:** ***After 1y of follow-up:*** *No OAC:* 1.78 per 100 PY *Warf:* 1.15 per 100 PY ***After 5y of follow-up:*** *No OAC:* 1.34 per 100 PY *Warf:* 0.96 per 100 PY (event rates, risk estimates NR)	***Extracranial bleeding:*** **No risk factors:** ***After 1y:*** *No OAC:* 1.22 per 100 PY *Warf:* 1.41 per 100 PY ***After 5y:*** *No OAC:* 1.02 per 100 PY *Warf:* 1.05 per 100 PY **One risk factor:** ***After 1y:*** *No OAC:* 2.51 per 100 PY *Warf:* 1.91 per 100 PY ***After 5y:*** *No OAC:* 1.92 per 100 PY *Warf:* 1.90 per 100 PY	**No risk factors:** ***After 1y:*** *No OAC:* 0.27 per 100 PY *Warf:* 0.09 per 100 PY ***After 5y:*** *No OAC:* 0.15 per 100 PY *Warf:* 0.19 per 100 PY **One risk factor:** ***After 1y:*** *No OAC:* 0.48 per 100 PY *Warf:* 0.57 per 100 PY ***After 5y:*** *No OAC:* 0.35 per 100 PY *Warf:* 0.40 per 100 PY	**No risk factors:** ***After 1y:*** *No OAC:* 4.21 per 100 PY *Warf:* 1.93 per 100 PY ***After 5y:*** *No OAC:* 2.18 per 100 PY *Warf:* 1.26 per 100 PY **One risk factor:** ***After 1y:*** *No OAC:* 9.67 per 100 PY *Warf:* 4.40 per 100 PY ***After 5y:*** *No OAC:* 5.76 per 100 PY *Warf:* 3.15 per 100 PY	***Net clinical benefit*:*** **No risk factors:** ***After 1y:*** Warf vs no OAC: 0.59 [-0.19; 1.38] ***After 5y:*** Warf vs no OAC: -0.11 [-0.54; 0.32] **One risk factor:** ***After 1y:*** Warf vs no OAC: **1.68 [0.63; 2.74]** ***After 5y:*** Warf vs no OAC: **0.59 [0.11; 1.08]**

Friberg et al. 2012[6]	Observational retrospective nationwide study (Sweden)	AF patients (53% male) included from the Swedish Hospital Discharge Register, stratified according to the CHA_2DS_2-VASc score. Net clinical benefit (based on ischemic stroke versus intracranial bleeding) and adjusted composite risk of ischemic stroke, intracranial bleeding and death, of warfarin versus no OAC.	**Overall:** 68 306 warf, 90 706 no OAC (NR for no versus single stroke risk factor)	**Overall:** 78.4y +/- 12.6 no OAC; 73.8y +/- 10.2 warf (NR for no versus single stroke risk factor)	1.5 y +/- 1.1 (260 000 PY)	***Ischemic stroke/intracranial bleeding/death:*** **CHA_2DS_2-VASc score 0:** Warf vs no OAC: **HR 0.74 [0.58-0.93]** **CHA_2DS_2-VASc score 1:** Warf vs no OAC: **HR 0.50 [0.43-0.57]**	NR	NR	NR	***Net clinical benefit**:*** **CHA_2DS_2-VASc score 0:** Warf vs no OAC: 0.0 [-0.1, 0.1] **CHA_2DS_2-VASc score 1:** Warf vs no OAC: **0.3 [0.1-0.4]**
Fauchier et al. 2016[7]	Observational prospective cohort study (France)	AF patients (30% female) with no or one non-sex-related stroke risk factor included in the Loire Valley AF Project. Risk of stroke/SE/death using VKAs versus no OAC, adjusted for age and sex.	**No risk factor:** 1078 (453 VKA use (42%)) **Single risk factor:** 1099 (600 VKA use (55%))	55y +/- 14 overall; 50y +/- 15 no OAC; 58y +/- 11 VKA (NR for no versus single stroke risk factor)	979 days +/- 1158	***Stroke/SE/death:*** **No stroke risk factors:** VKA vs no OAC: HR 0.68 [0.35-1.31] **One non-sex-related stroke risk factor:** VKA vs no OAC: **HR 0.59 [0.40-0.86]**	NR	NR	NR	NR
Eckman et al. 2011[8]	Markov state transition decision model	Ischemic stroke rates derived from the ATRIA cohort and RE-LY trial (dabi)	NR	NR	NR	NR	NR	NR	NR	***Treatment threshold:*** *Warf:* Ischemic stroke rate >1.7%/y *NOAC:* ischemic stroke rate >0.9%/y

eTable 3: Overview of included studies investigating the role of anticoagulation versus no anticoagulation in case of a single non-sex-related stroke risk factor.

Bold: significantly lower risk.

* Net clinical benefit (NCB)[5]: Calculated as the weighted sum of differences in outcome rates between non-anticoagulated AF patients and VKA-treated AF patients. Outcomes of interest were ischemic stroke, major extracranial bleeding, intracranial bleeding and myocardial infarction. Weights were estimated based on the adjusted risk for death after occurrence of these outcomes during five years of follow-up. A positive NCB represents an advantage for treatment.

** Net clinical benefit (NCB)[6]: The risk for ischemic stroke without warfarin use minus the risk of intracranial bleeding with warfarin use.

AF: atrial fibrillation; Api: apixaban; CI: confidence interval; Dabi: dabigatran; HR hazard ratio; IQR: interquartile range; NCB: net clinical benefit; NOAC: non-vitamin K antagonist oral anticoagulant; NR: not reported; OAC: oral anticoagulant; PY: person-years; RCT: randomized controlled trial; Riva: rivaroxaban; SD: standard deviation; Stroke/SE: stroke/systemic embolism; VKA: vitamin K antagonist; Warf: warfarin; y: year.

eTable 4: Effectiveness and safety of NOACs as compared to VKAs in case of a single non-sex-related stroke risk factor

Author	Study design	Study cohort	n	Mean/median age (years +/- SD; [IQR])	Mean/median follow-up (+/- SD; [IQR])	Stroke/SE (HR [95% CI])	Major bleeding (HR [95% CI])	Intracranial bleeding (HR [95% CI])	All-cause mortality (HR [95% CI])
Oldgren et al. 2011[9]	Phase III RCT (worldwide)	AF patients included in the RE-LY trial (dabi vs warf), categorized according to **$CHADS_2$ score 0-1**, 2 and 3-6. $CHADS_2$ score 0-1 driven by hypertension in 58.8%, age ≥75 years in 18.1%, heart failure in 12.5% and diabetes mellitus in 2.8%. Industry-sponsored.	**$CHADS_2$ 0:** 452; **$CHADS_2$ 1:** 5323;	**$CHADS_2$ 0-1:** 69.5y +/- 7.4;	2 years (overall, NR for $CHADS_2$ 0-1 group)	**$CHADS_2$ 0-1:** Dabi 150 vs warf: **0.61 [0.37-0.99]** Dabi 110 vs warf: 0.98 [0.63-1.51]	**$CHADS_2$ 0-1:** Dabi 150 vs warf: **0.74 [0.56-0.99]** Dabi 110 vs warf: **0.65 [0.49-0.88]**	**$CHADS_2$ 0-1:** Dabi 150 vs warf: **0.37 [0.16-0.84]** Dabi 110 vs warf: **0.37 [0.16-0.83]**	**$CHADS_2$ 0-1:** Dabi 150 vs warf: **0.73 [0.54-0.98]** Dabi 110 vs warf: 0.88 [0.66-1.16]
Lopes et al. 2012[10]	Phase III RCT (worldwide)	AF patients included in the ARISTOTLE trial (api vs warf), categorized according to **$CHADS_2$ or CHA_2DS_2-VASc score 1**, 2 or ≥3. $CHADS_2$ score 1 driven by hypertension in 77.3%, heart failure in 16.1%, age ≥75 years in 9.3% and diabetes in 3.2%. CHA_2DS_2-VASc score 1 also included female sex as single stroke risk factor. Industry-sponsored.	**$CHADS_2$ 1**: 6183 overall (3100 api, 3083 warf); **CHA_2DS_2-VASc 1**: 1604 overall	**$CHADS_2$ 1**: 67.0y [60-71] (overall, no separate results in CHA_2DS_2-VASc or HAS-BLED score groups)	1.8 years [1.4-2.3] (overall, no separate results in $CHADS_2$ score groups)	**$CHADS_2$ 1**: Api vs warf: 0.85 [0.57-1.27] **CHA_2DS_2-VASc score 1:** Api vs warf: 1.18 [0.46-2.89]	**$CHADS_2$ 1**: Api vs warf: **0.59 [0.44-0.78]** **CHA_2DS_2-VASc score 1**: Api vs warf: 0.65 [0.31-1.37]	**$CHADS_2$ 1**: Api vs warf: **0.45 [0.24-0.82]** **CHA_2DS_2-VASc score 1**: Api vs warf: 0.55 [0.13-2.29]	**$CHADS_2$ 1**: Api vs warf: 0.96 [0.76-1.22] **CHA_2DS_2-VASc score 1**: Api vs warf: 0.82 [0.50-1.35]
Lega et al. 2014[11]	Meta-analysis	Pooling of results in AF patients with a $CHADS_2$ score of 0-1 from the RE-LY and ARISTOTLE trial. NOAC (dabi 150, dabi 110, api) vs warfarin.	**$CHADS_2$ 0-1:** 11 958 overall	NR	NR	**$CHADS_2$ 0-1:** NOAC vs warf: RR 0.83 [0.64, 1.07]	**$CHADS_2$ 0-1:** NOAC vs warf: **RR 0.67 [0.57-0.79]**	NR	NR
Coleman et al. 2019[12]	Observational retrospective nationwide study (U.S.A.)	AF patients with a single non-sex-related stroke risk factor from administrative claims database, OAC-naïve patients initiating rivaroxaban 20 mg or warfarin (1:1 PSM). Hypertension in 68.3% of patients, age 65-74 years in 19.1%, diabetes in 6.1% and heart failure in 5.1%. Industry-sponsored.	**CHA_2DS_2-VASc score 1 (men) or 2 (women):** 3319 riva, 3319 warf (1:1 PSM)	**CHA_2DS_2-VASc score 1 (men) or 2 (women):** 60y [55-64] riva, 60y [56-64] warf	1.6 years [0.7-2.0]	**CHA_2DS_2-VASc score 1 (men) or 2 (women):** ***After 1y of follow-up:*** Riva vs warf: **0.41 [0.17-0.98]** ***After 2y:*** Riva vs warf: **0.46 [0.23-0.92]**	**Score 1 (men) or 2 (women):** ***After 1y:*** Riva vs warf: 0.74 [0.44-1.26] ***After 2y:*** Riva vs warf: 0.65 [0.42-1.02]	**Score 1 (men) or 2 (women):** ***After 1y:*** Riva vs warf: 0.33 [0.03-3.17] ***After 2y:*** Riva vs warf: 0.14 [0.02-1.11]	NR
Lip et al. 2017[13]	Observational retrospective nationwide study	AF patients with a single non-sex-related stroke risk factor using the national patient registry, OAC-naïve, standard dose NOACs	**CHA_2DS_2-VASc score 1 (men) or 2 (women):**	**CHA_2DS_2-VASc score 1 (men) or 2 (women):**	2.6 years +/- 1.6 overall,	**CHA_2DS_2-VASc score 1 (men) or 2 (women):** ***After 1y follow-up:*** Dabi 150 vs warf:	**Score 1 (men) or 2 (women):** ***After 1y:*** Dabi 150 vs warf:	NR	**Score 1 (men) or 2 (women):** ***After 1y:*** Dabi 150 vs warf:

	(Denmark)	(dabi 150 mg, riva 20 mg and api 5 mg) vs warf. Age 65-74 years in 59.3% of patients, hypertension in 31.7%, diabetes in 3.2%, vascular disease in 3.1% and heart failure in 2.6%.	14 020 overall: 3272 dabi, 1604 riva, 1470 api, 7674 warf	66.2y [61.3-69.8] dabi, 67.2y [62.4-70.7] riva, 67.4y [62.5-70.9] api, 66.2y [60.5-70.4] warf	1.1 years +/- 0.7 api, otherwise NR	0.81 [0.49-1.34] Riva 20 vs warf: 1.46 [0.79-2.70] Api 5 vs warf: 1.01 [0.51-2.01] ***After 2.5y:*** Dabi 150 vs warf: 0.84 [0.58-1.21] Riva 20 vs warf: 1.08 [0.63-1.87] Api 5 vs warf: 1.09 [0.60-1.99]	**0.48 [0.30-0.77]** Riva 20 vs warf: 0.84 [0.49-1.44] Api 5 vs warf: **0.35 [0.17-0.72]** ***After 2.5y:*** Dabi 150 vs warf: **0.49 [0.35-0.69]** Riva 20 vs warf: 0.75 [0.47-1.20] Api 5 vs warf: **0.37 [0.20-0.69]**		**0.59 [0.43-0.81]** Riva vs warf: **0.52 [0.34-0.79]** Api vs warf: **0.47 [0.29-0.76]** ***After 2.5y:*** Dabi 150 vs warf: **0.60 [0.47-0.76]** Riva vs warf: 0.80 [0.58-1.10] Api vs warf: **0.45 [0.29-0.70]**

eTable 4: Overview of included studies investigating the effectiveness and safety of NOACs as compared to VKAs in case of a single non-sex-related stroke risk factor

Bold: significantly lower risk.

AF: atrial fibrillation; Api: apixaban; Api 5: apixaban 5 mg (standard dose); CI: confidence interval; Dabi: dabigatran; Dabi 110: dabigatran 110 mg (reduced dose); Dabi 150: dabigatran 150 mg (standard dose); HR hazard ratio; IQR: interquartile range; NOAC: non-vitamin K antagonist oral anticoagulant; NR: not reported; OAC: oral anticoagulant; PSM: propensity score matching; RCT: randomized controlled trial; Riva: rivaroxaban; Riva 20: rivaroxaban 20 mg (standard dose); SD: standard deviation; Stroke/SE: stroke/systemic embolism; U.S.A.: United States of America; VKA: vitamin K antagonist; Warf: warfarin; y: year.

eTable 5: Assessment of bias within studies on the impact of a single stroke risk factor

A)

Reference: Olesen et al. 2011[1]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (prospective observational study with baseline characteristics reported for included non-anticoagulated AF cohort, but not specifically compared in subgroup with CHA_2DS_2-VASc score 0, 1 or 2)		
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (only adjusted for antiplatelet use; due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 19/22 (86.4%)					

B)

Reference: Chao et al. 2015[2]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (only description of mean age, sex and baseline prevalence of CHA_2DS_2-VASc risk factor components in male and female non-anticoagulated AF cohort)		
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (only adjusted for sex; due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 19/22 (86.4%)					

C)

Reference: Hung et al. 2016[3]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (only description of baseline prevalence of CHA_2DS_2-VASc risk factor components in non-anticoagulated AF cohort, stratified according to age 20-49, 50-64 and 65-74 years old)		
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (only stratified according to age; due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 19/22 (86.4%)					

eTable 5: Assessment of bias within studies included in the first meta-analysis regarding the impact of a single non-sex-related stroke risk factor on ischemic stroke risk in non-anticoagulated atrial fibrillation patients (**A-C:** 3 longitudinal observational cohort studies), using the quality assessment tool 'QUALSYST' from the "Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields" was used.[14] With this tool, 14 items of each quantitative study, were scored on the study and outcome levels depending on the degree to which the specific criteria were met or reported ("yes" = 2, "partial" = 1, "no" = 0). Items not applicable to a particular study design were marked "n/a" and were excluded from the calculation of the summary score. A percentage was calculated for each paper by dividing the total sum score obtained across rated items by the total possible score.

AF: atrial fibrillation; ICD: International Classification of Diseases.

eTable 6: Assessment of bias within studies on the effectiveness and safety of NOACs versus VKAs in patients with a single stroke risk factor

A)

Reference: Lopes et al. 2012[10]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (randomized study with description of baseline characteristics for NOAC- and VKA-treated cohort according to $CHADS_2$ score 1, 2 or ≥3, but not specifically compared between NOAC and VKA, nor according to CHA_2DS_2-VASc score 0, 1 or 2)		
5	If interventional and random allocation was possible, was it reported?	2			
6	If interventional and blinding of investigators was possible, was it reported?	2			
7	If interventional and blinding of subjects was possible, was it reported?	2			
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	2			
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?	2			
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 27/28 (96.4%)					

B)

Reference: Coleman et al. 2019[12]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (adequately adjusted for predefined set of covariates using propensity score matching, but due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 20/22 (90.9%)					

C)

Reference: Lip et al. 2017[13]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				N/A
6	If interventional and blinding of investigators was possible, was it reported?				N/A
7	If interventional and blinding of subjects was possible, was it reported?				N/A
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (outcome measures retrospectively assessed in administrative healthcare claims database using ICD-codes, which are prone to misclassification bias)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?		1 (adequately adjusted for predefined set of covariates using inverse probability of treatment weighted analysis, but due to retrospective use of administrative healthcare claims database, unmeasured confounders and biases (such as confounding by indication) may still be present)		
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 20/22 (90.9%)					

eTable 6: Assessment of bias within studies included in the second meta-analysis regarding the effectiveness and safety of NOACs versus VKAs in atrial fibrillation patients with a single stroke risk factor (**A:** 1 post hoc analysis of randomized controlled trial; **B-C:** 2 longitudinal observational cohort studies), using the quality assessment tool 'QUALSYST' from the "Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields" was used.[14]

AF: atrial fibrillation; ICD: International Classification of Diseases.

eTable 7: PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eTable 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

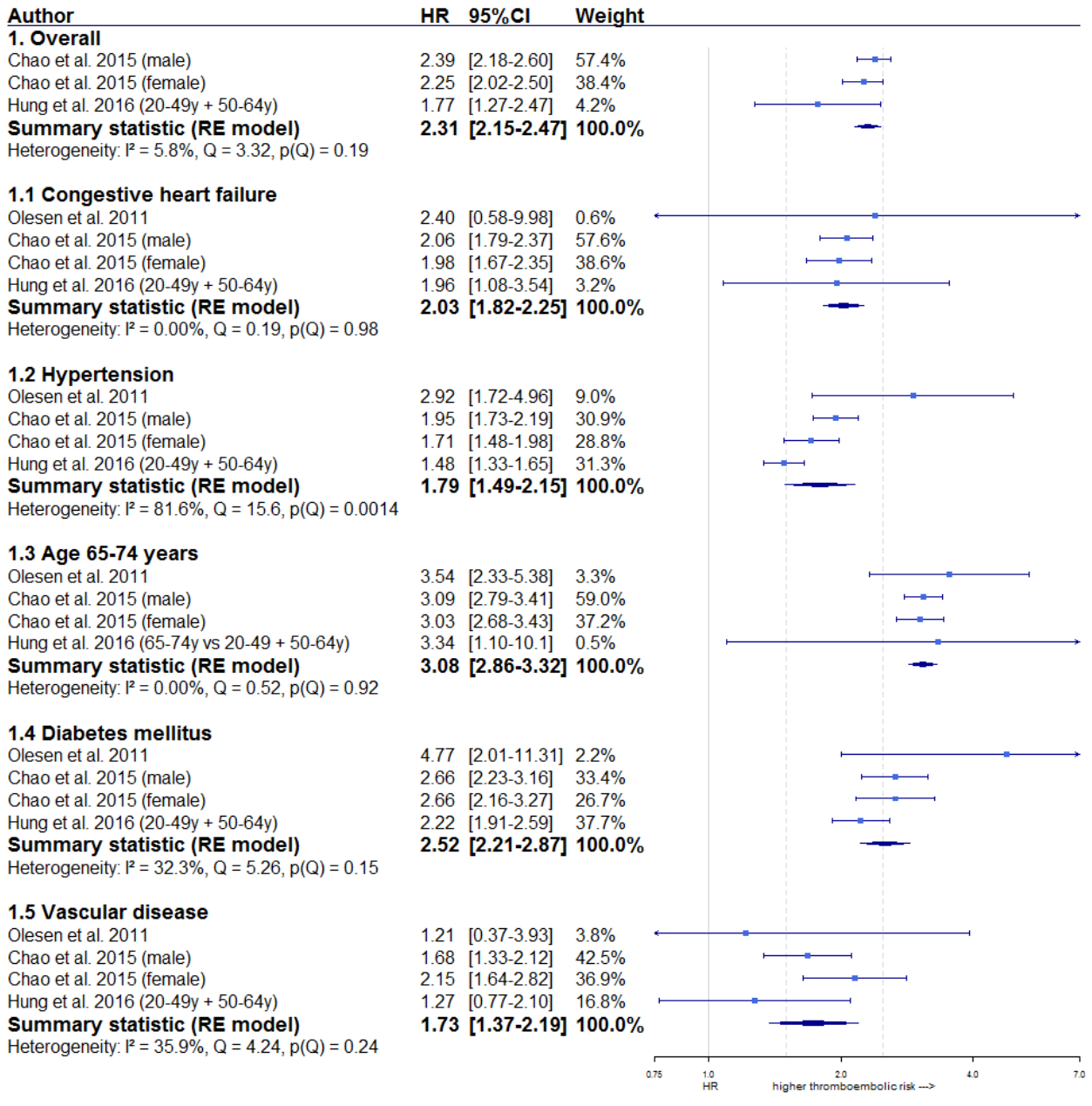
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5 + Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	eTable 2-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	eTable 5-6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	eTable 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8, 10 + Figure 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, 10 + eFigure 3-4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8 + eFigure 1
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplemental figures

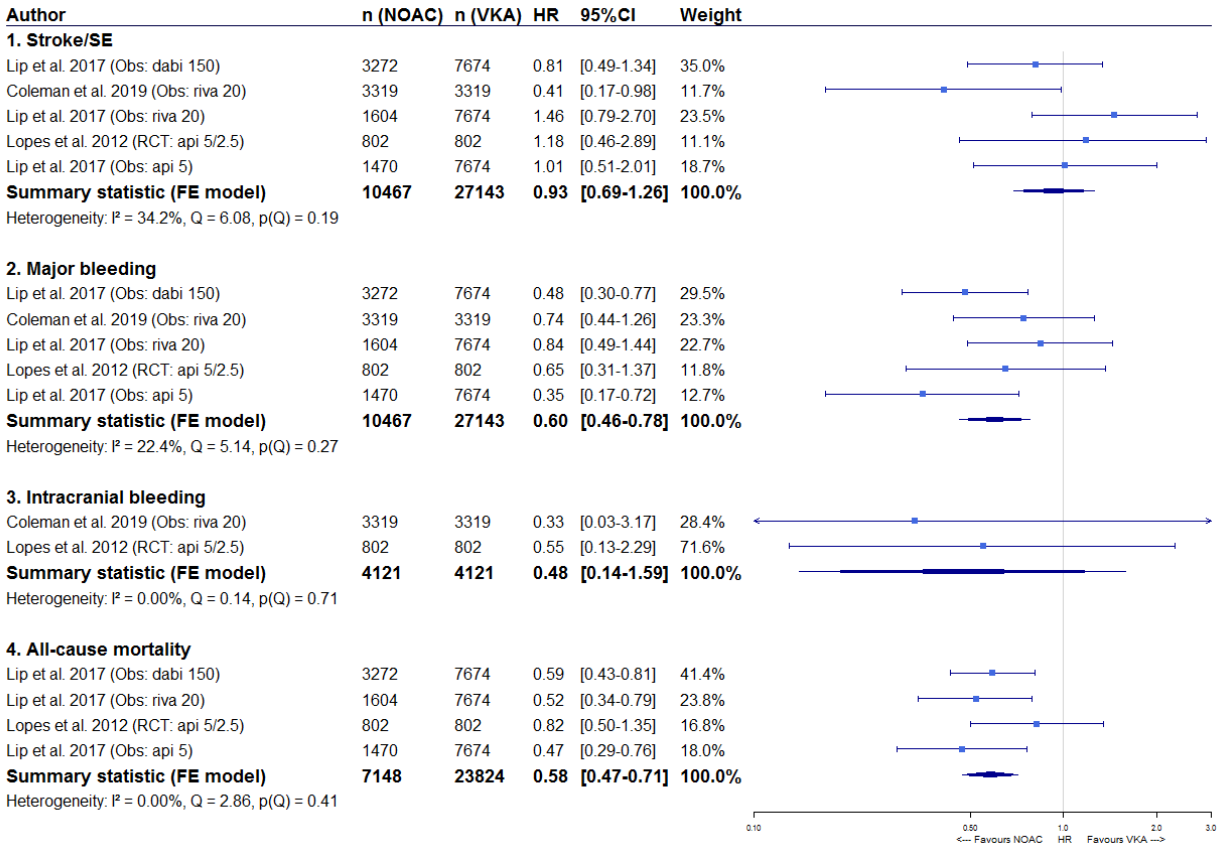
eFigure 1: Sensitivity analysis on the impact of a single non-sex-related stroke risk factor after first pooling the results of the study by Hung et al.



eFigure 1: Sensitivity analysis on the impact of a single non-sex-related stroke risk factor on the ischemic stroke risk in non-anticoagulated atrial fibrillation patients (CHA_2DS_2-VASc score of 1 in men or 2 in women), represented by hazard ratios as compared to AF patients without stroke risk factors (CHA_2DS_2-VASc score 0 in men or 1 in women) (reference group), after first pooling the risk estimates of 20-49 and 50-64 year old patients included in the study of Hung et al., and then subsequently pooling with the results of the other two included studies.

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio; RE model: random effects model; y: year.

eFigure 2: The effectiveness and safety of NOACs versus warfarin in AF patients with a single stroke risk factor, using a fixed effects model

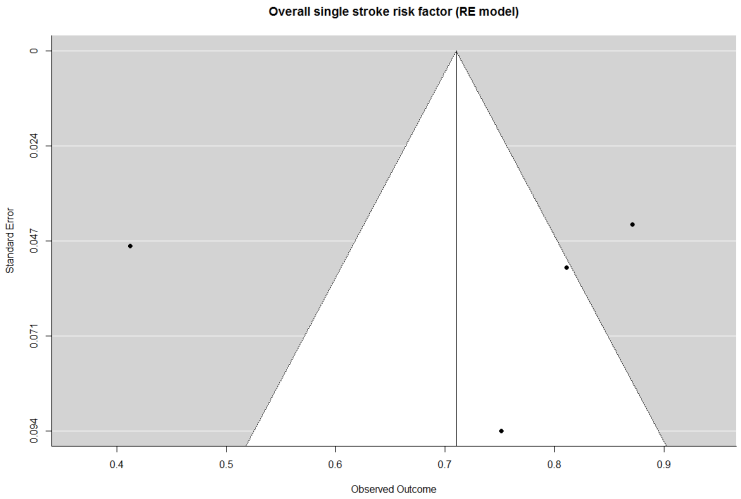


eFigure 2: The risk of stroke/systemic embolism, major bleeding, intracranial bleeding and all-cause mortality of NOACs as compared to warfarin in atrial fibrillation patients with a single stroke risk factor (CHA_2DS_2-VASc score of 1 in men or 2 in women), using a fixed effects model (instead of random effects model)

Api 5/2.5: apixaban 5 mg (standard dose) or 2.5 mg (reduced dose); Api 5: apixaban 5 mg (standard dose); CI: confidence interval; Dabi 150: dabigatran 150 mg (standard dose); FE model: fixed effects model; HR: hazard ratio; NOAC: non-vitamin K antagonist oral anticoagulant; Obs: longitudinal observational cohort study; RCT: randomized controlled trial (post hoc analysis); Riva 20: rivaroxaban 20 mg (standard dose); Stroke/SE: stroke/systemic embolism

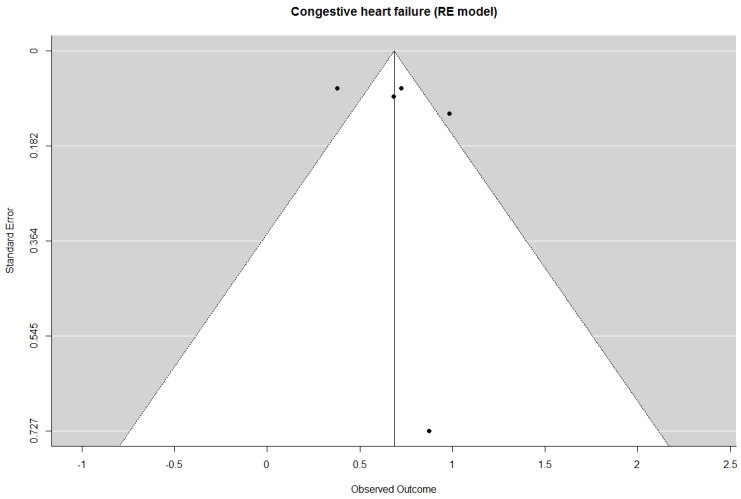
eFigure 3: Assessment of publication bias in studies on the impact of a single stroke risk factor

A)



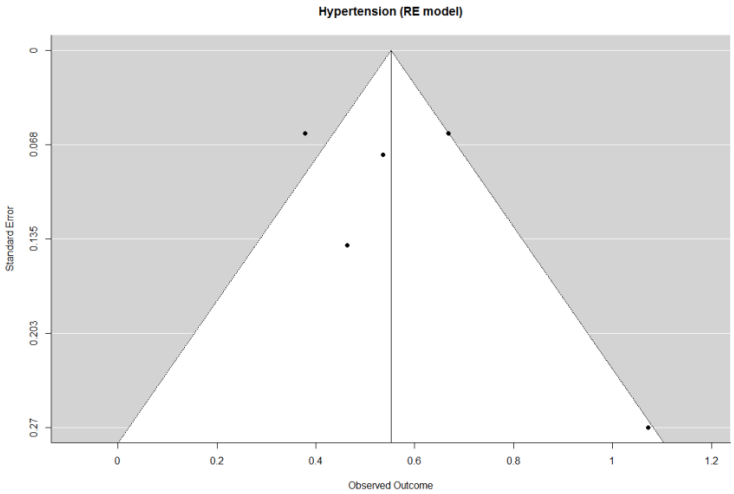
Egger's test: test for funnel plot asymmetry: z = 0.14, p = 0.89

B)



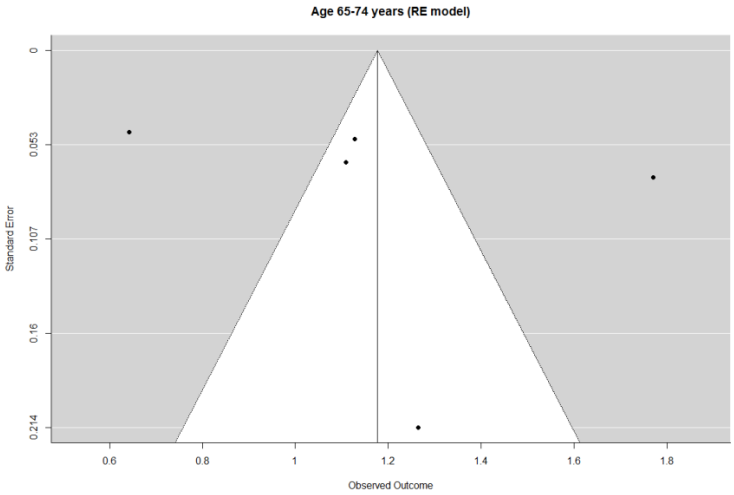
Egger's test: test for funnel plot asymmetry: z = 0.54, p = 0.59

C)



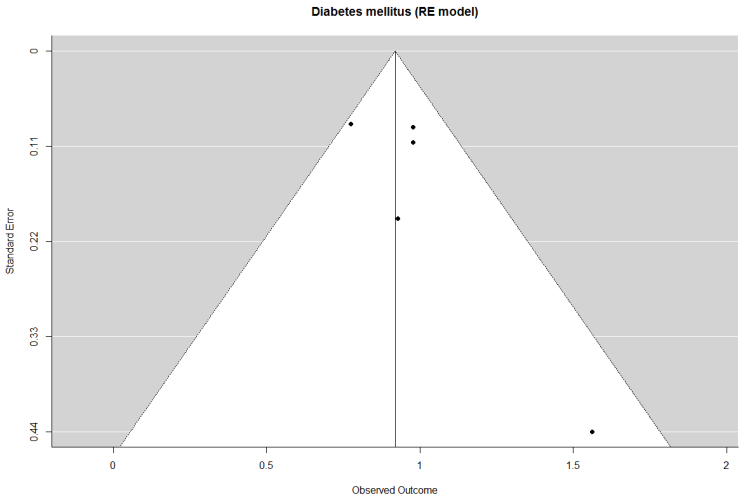
Egger's test: test for funnel plot asymmetry: z = 1.39, p = 0.17

D)



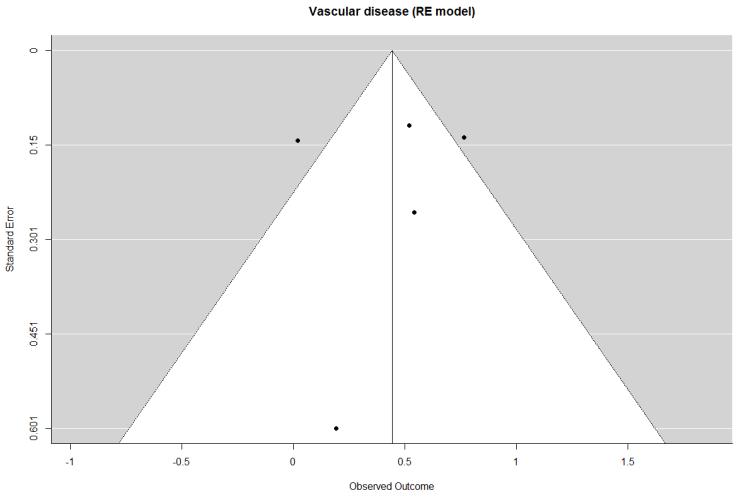
Egger's test: test for funnel plot asymmetry: z = 0.44, p = 0.66

E)



Egger's test: test for funnel plot asymmetry: z = 1.43, p = 0.15

F)

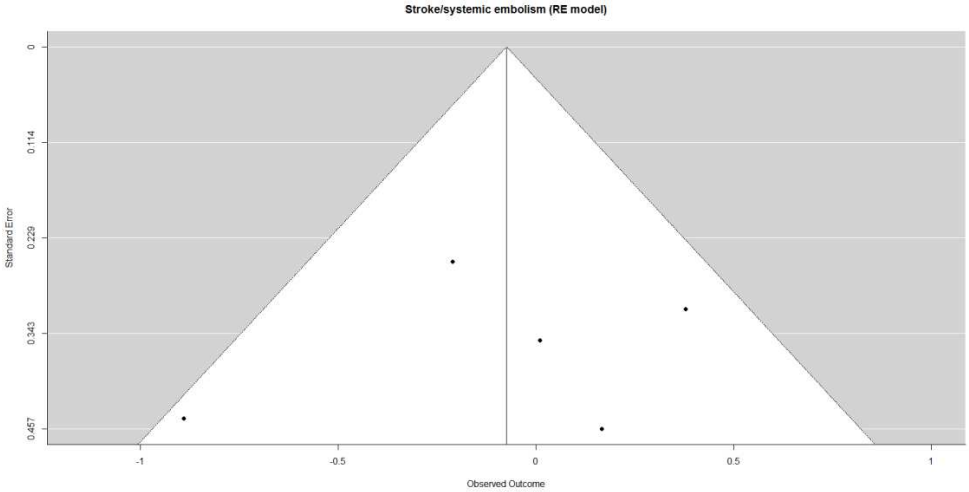


Egger's test: test for funnel plot asymmetry: z = -0.30, p = 0.76

eFigure 3: Funnel plot and Egger's test for assessment of potential publication bias for studies on the impact of **A)** any single non-sex-related stroke risk factor, **B)** congestive heart failure, **C)** hypertension, **D)** age 65-74 years old, **E)** diabetes mellitus, and **F)** vascular disease, in non-anticoagulated atrial fibrillation patients as compared to atrial fibrillation patients without stroke risk factors (CHA_2DS_2-VASc score 0 in men, 1 in women).
RE model: random effects model.

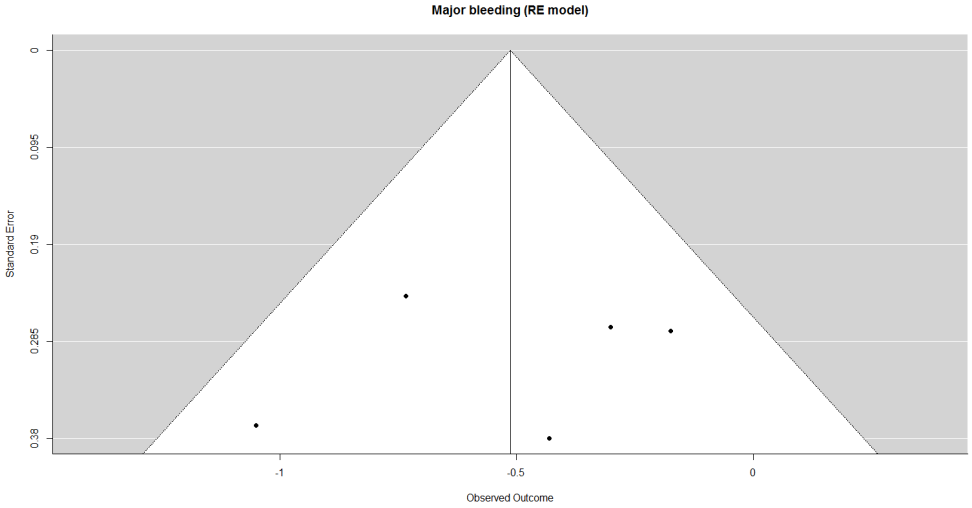
eFigure 4: Assessment of publication bias in studies on the effectiveness and safety of NOACs versus VKAs in patients with a single stroke risk factor

A)



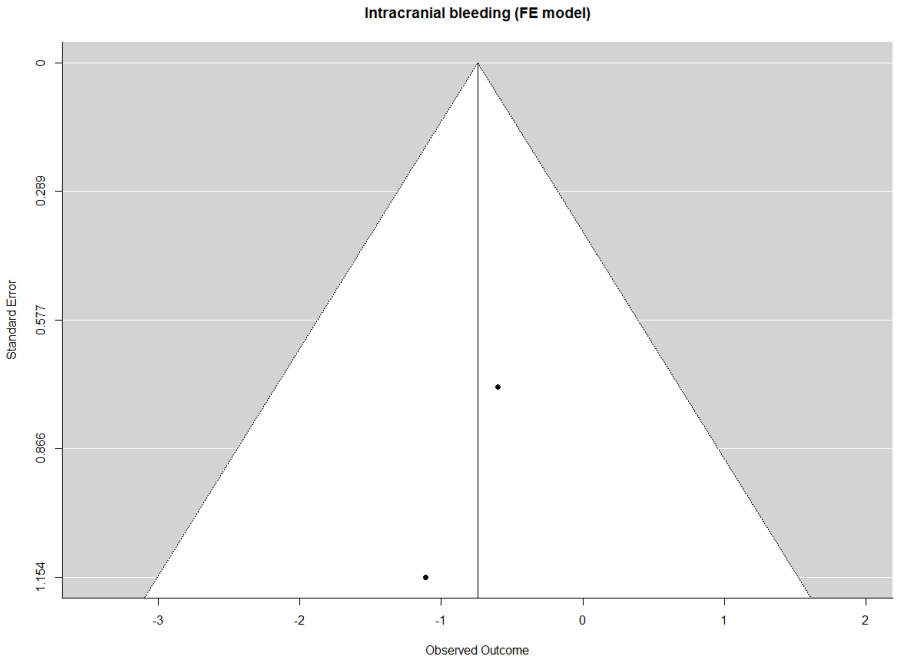
Egger's test: test for funnel plot asymmetry: z = -0.51, p = 0.61

B)



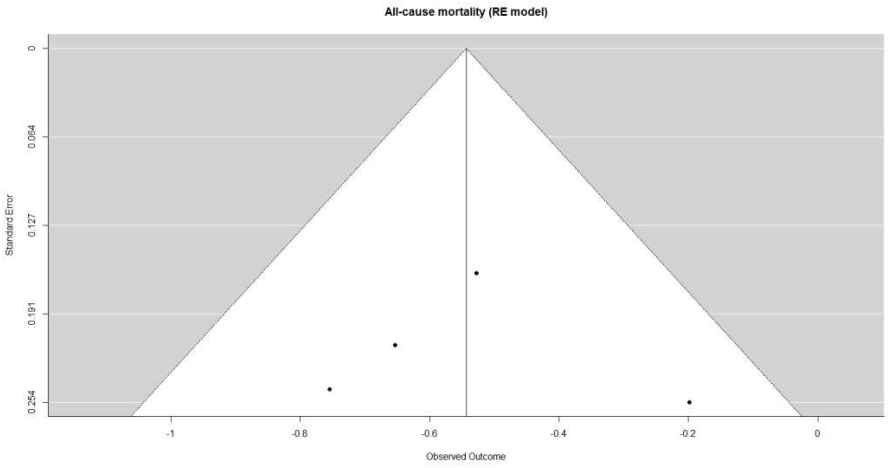
Egger's test: test for funnel plot asymmetry: z = -0.50, p = 0.62

C)



Egger's test: test for funnel plot asymmetry (fixed effects model): z = -0.37, p = 0.71

D)



Egger's test: test for funnel plot asymmetry: z = 0.22, p = 0.83

eFigure 4: Funnel plot and Egger's test for assessment of potential publication bias for studies on the risk of **A)** stroke/systemic embolism, **B)** major bleeding, **C)** intracranial bleeding, and **D)** all-cause mortality of NOACs as compared to warfarin in atrial fibrillation patients with a single stroke risk factor, based on a CHA_2DS_2-VASc score of 1 in men or 2 in women.

FE model: fixed effects model; RE model: random effects model.

References

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