**Appendix GRADE summary of findings Table 1.** Rivaroxaban vs warfarin for stroke prevention in subgroups of adults with nonvalvular atrial fibrillation

**Population:** Adults with nonvalvular atrial fibrillation

**Settings:** Outpatient

**Intervention:** Rivaroxaban (10-20 mg/day)

**Comparator:** Warfarin

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **Risk with intervention per 1000** | **Risk with comparator per 1000** | **Relative risk (95% CI)** | **Number of participants (studies)** | **Comments** |
| **Stroke or systemic embolism, Age ≥75** | **NR** | **NR** | **HR 0.78 (0.62;0.98)** | **6660 (2 RCTs)54,73** | **Favors rivaroxaban\*\*** |
| Stroke or systemic embolism, Age <75 | NR | NR | HR 0.82 (0.45;1.49) | 8785 (2 RCTs)54,73 | No difference\*\* |
| Hemorrhagic stroke, Age ≥75 | NR | NR | HR 0.73 (0.42;1.25) | 6660 (2 RCTs)54,73 | No difference\*\* |
| **Hemorrhagic stroke, Age <75** | **NR** | **NR** | **HR 0.47 (0.25;0.89)** | **8007 (1 RCT)54** | **Favors rivaroxaban\*** |
| Ischemic stroke, Age ≥75 | NR | NR | HR 0.77 (0.43;1.35) | 6660 (2 RCTs)54,73 | No difference\*\* |
| Ischemic stroke, Age <75 | NR | NR | HR 0.78 (0.29;2.10) | 8785 (2 RCTs)54,73 | No difference\* |
| Major bleeding, Age ≥75 | NR | NR | HR 1.22 (0.96;1.56) | 6711 (2 RCTs)54,73 | No difference\*\* |
| Major bleeding, Age <75 | NR | NR | HR 0.96 (0.78;1.18) | 8799 (2 RCTs)54,73 | No difference\*\* |
| Major and nonmajor clinically relevant bleeding,  Age ≥75 | NR | NR | HR 1.22 (0.96;1.56) | 6711 (2 RCTs)54,73 | No difference\*\* |
| Major and nonmajor clinically relevant bleeding,  Age <75 | NR | NR | HR 0.93 (0.84;1.03) | 8799 (2 RCTs)54,73 | No difference\*\* |
| **Fatal bleeding, Age ≥75** | **NR** | **NR** | **HR 0.47 (0.25;0.90)** | **6711 (2 RCTs)54,73** | **Favors rivaroxaban\*\*** |
| Fatal bleeding, Age <75 | NR | NR | HR 0.55 (0.29;1.05) | 8021 (1 RCT)54 | No difference\* |
| **Hemoglobin drop ≥2 g/dL, Age ≥75** | **NR** | **NR** | **HR 1.30 (1.04;1.62)** | **6711 (2 RCTs)54,73** | **Favors warfarin\*\*** |
| Major and nonmajor clinically relevant bleeding,  Japanese, Age >75 years, CrCl 30-49 mL/min | 294 | 232 | RR 1.27 (0.81;1.99) | 214 (1 RCT)73 | No difference\* |
| **Major and nonmajor clinically relevant bleeding,  Japanese adults >75 years, CrCl >50 mL/min** | **253** | **149** | **RR 1.70 (1.04;2.77)** | **284 (1 RCT)73** | **Favors warfarin\*** |
| Major bleeding, Japanese, Age >75 years, CrCl 30-49 mL/min | 78 | 54 | RR 1.46 (0.53;4.08) | 214 (1 RCT)73 | No difference\* |
| Major bleeding, Japanese, Age >75 years, CrCl >50mL/min | 53 | 30 | RR 1.79 (0.55;5.80) | 284 (1 RCT)73 | No difference\* |
| Stroke or systemic embolism, Sex: male | 33 | 38 | RR 0.87 (0.70;1.09) | 8566 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, Sex: female | 45 | 51 | RR 0.89 (0.70;1.12) | 5605 (1 RCT)53 | No difference\* |
| Major bleeding, Sex: male | 60 | 59 | RR 1.03 (0.87;1.22) | 8601 (1 RCT)43 | No difference\*\* |
| Major bleeding, Sex: female | 48 | 48 | RR 1.00 (0.79;1.26) | 5663 (1 RCT)43 | No difference\* |
| Stroke or systemic embolism, Race: White | 37 | 42 | RR 0.90 (0.75;1.08) | 11,786 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, Race: Black | 53 | 70 | RR 0.76 (0.24;2.41) | 180 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, Race: Asian | 40 | 56 | RR 0.71 (0.47;1.08) | 1786 (1 RCT)53 | No difference\* |
| Major bleeding, Race: White | 57 | 51 | RR 1.11 (0.95;1.29) | 11,786 (1 RCT)43 | No difference, **Significant interaction\*\*** |
| Major bleeding, Race: Black | 64 | 35 | RR 1.83 (0.47;7.09) | 180 (1 RCT)43 | No difference, **Significant interaction\*** |
| **Major bleeding, Race: Asian** | **49** | **79 Attributable avoided events per 1000 treated 30 (7; 52)** | **HR 0.61 (0.42;0.89) NNTp 34 (19; 142)** | **1786 (1 RCT)43** | **Favors rivaroxaban, Significant interaction\*** |
| Stroke or systemic embolism, Region: North America | 34 | 37 | RR 0.91 (0.61;1.34) | 2731 (1 RCT)53 | No difference**\*** |
| Stroke or systemic embolism, Region: Latin America | 39 | 48 | RR 0.82 (0.54;1.26) | 1878 (1 RCT)53 | No difference**\*** |
| Stroke or systemic embolism, Region: Western Europe | 38 | 41 | RR 0.93 (0.61;1.42) | 2096 (1 RCT)53 | No difference**\*** |
| Stroke or systemic embolism, Region: Eastern Europe | 37 | 42 | RR 0.88 (0.68;1.14) | 5407 (1 RCT)53 | No difference**\*** |
| Stroke or systemic embolism, Region: Asian Pacific | 43 | 51 | RR 0.83 (0.57;1.23) | 2109 (1 RCT)53 | No difference**\*** |
| **Major bleeding, Region: North America** | **111** | **83 Attributable events per 1000 treated 29 (6;51)** | **HR 1.43 (1.12;1.82) NNTp 35 (20;162)** | **2681 (1 RCT)43** | **Favors warfarin,**  **Significant interaction\*** |
| Major bleeding, Region: Latin America | 49 | 44 | RR 1.12 (0.74;1.69) | 1878 (1 RCT)43 | No difference,  Significant interaction\* |
| Major bleeding, Region: Western Europe | 47 | 66 | RR 0.71 (0.50;1.02) | 2096 (1 RCT)43 | No difference,  Significant interaction\* |
| Major bleeding, Region: Eastern Europe | 33 | 31 | RR 1.05 (0.78;1.41) | 5407 (1 RCT)43 | No difference,  Significant interaction\* |
| Major bleeding, Region: Asian Pacific | 60 | 77 | RR 0.78 (0.57;1.07) | 2109 (1 RCT)43 | No difference,  Significant interaction\* |
| **Major or nonmajor clinical GI bleeding, North America** | **117** | **67 Attributable events per 1000 treated 49 (28;71)** | **HR 1.89 (1.45;2.45) NNT 20 (14;36)** | **2681 (1 RCT)60** | **Favors warfarin, Significant interaction**\* |
| Major or nonmajor clinical GI bleeding, Rest of world | 41 | 35 | RR 1.19 (0.99;1.43) | 11,583 (1 RCT)60 | No difference,  Significant interaction\* |
| **Intracranial hemorrhage, East Asian** | **9** | **37 Attributable avoided events per 1000 treated 28 (9; 47)** | **HR 0.23 (0.08;0.69) NNTp 36 (21; 110)** | **932 (1 RCT)65** | **Favors rivaroxaban Significant interaction**\* |
| Intracranial hemorrhage, Non–East Asian | 8 | 10 | RR 0.76 (0.53;1.10) | 13,239 (1 RCT)65 | No difference,  Significant interaction\* |
| Stroke or systemic embolism, East Asian | 45 | 58 | RR 0.77 (0.44;1.34) | 932 (1 RCT)65 | No difference\* |
| Stroke or systemic embolism, Non–East Asian | 38 | 42 | RR 0.89 (0.75;1.05) | 13,239 (1 RCT)65 | No difference\* |
| **All-cause mortality, Stable renal function** | **NR** | **NR** | **HR 0.75 (0.59;0.96)** | **9292 (1 RCT)52** | **Favors rivaroxaban**\* |
| All-cause mortality, Worsening renal function | NR | NR | HR 0.83 (0.50;1.39) | 3320 (1 RCT)52 | No difference\* |
| Stroke and non-CNS systemic embolism,  Moderate renal impairment | NR | NR | HR 0.84 (0.58;1.21) | 4230 (2 RCTs)62,66 | No difference\*\* |
| Stroke and non-CNS systemic embolism,  Renal normal | NR | NR | HR 0.61 (0.30;1.24) | 12,557 (2 RCTs)62,66 | No difference\* |
| Stroke or systemic embolism, CrCl <50 | 52 | 59 | RR 0.88 (0.65;1.18) | 2949 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, CrCl 50-80 | 38 | 44 | RR 0.86 (0.68;1.08) | 6698 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, CrCl >80 | 28 | 31 | RR 0.93 (0.66;1.30) | 4507 (1 RCT)53 | No difference\* |
| Ischemic stroke, Moderate renal impairment | NR | NR | HR 1.07 (0.70;1.64) | 4230 (2 RCTs)62,66 | No difference\*\* |
| Ischemic stroke, Renal normal | NR | NR | HR 0.60 (0.21;1.69) | 12,557 (2 RCTs)62,66 | No difference\* |
| Major and nonmajor clinically relevant bleeding,  Moderate renal impairment | NR | NR | HR 1.00 (0.87;1.16) | 4230 (2 RCTs)62,66 | No difference\*\* |
| Major and nonmajor clinically relevant bleeding,  Renal normal | NR | NR | HR 1.04 (0.96;1.13) | 12,557 (2 RCTs)62,66 | No difference\*\* |
| Major bleeding, Moderate renal impairment | NR | NR | HR 0.95 (0.72;1.23) | 4230 (2 RCTs)62,66 | No difference\*\* |
| Major bleeding, Renal normal | NR | NR | HR 1.05 (0.90;1.23) | 12,557 (2 RCTs)62,66 | No difference\*\* |
| **Epistaxis, Moderate renal impairment** | **110** | **85** | **RR 1.30 (1.04;1.63)** | **3234 (2 RCTs)62,66** | **Favors warfarin**\*\* |
| Epistaxis, Renal normal | 106 | 87 | RR 1.38 (0.94;2.02) | 12,271 (2 RCTs)62,66 | No difference\*\*\* |
| **Urinary tract infection, Moderate renal impairment** | **52** | **74** | **RR 0.70 (0.54;0.92)** | **3234 (2 RCTs)62,66** | **Favors rivaroxaban**\*\* |
| Urinary tract infection, Renal normal | 43 | 45 | RR 0.91 (0.67;1.23) | 12,271 (2 RCTs)62,66 | No difference\* |
| **Hematuria, CrCl ≥50 mL/min** | **44** | **32 Attributable events per 1000 treated 12 (5;19)** | **HR 1.36 (1.13;1.64) NNT 85 (53;215)** | **11,277 (1 RCT)62** | **Favors warfarin**\* |
| Hematuria, CrCl 30-49 mL/min | 32 | 39 | RR 0.81 (0.56;1.18) | 2950 (1 RCT)62 | No difference\* |
| **Gingival bleeding, Japanese patients with preserved renal function, CrCl ≥50 mL/min** | **90** | **52** | **RR 1.72 (1.08;2.75)** | **994 (1 RCT)66** | **Favors warfarin**\* |
| Gingival bleeding, Japanese patients with moderate renal impairment, CrCl 30-49 mL/min | 64 | 35 | RR 1.83 (0.63;5.31) | 284 (1 RCT)66 | No difference\* |
| Stroke and non-CNS systemic embolism,  CHADS2 = 2 | NR | NR | HR 0.89 (0.40;1.97) | 2498 (2 RCTs)42,69 | No difference\*\* |
| Stroke and non-CNS systemic embolism,  CHADS2 ≥3 | NR | NR | HR 0.76 (0.44;1.30) | 18,168 (2 RCTs)42,69 | No difference\* |
| Stroke or systemic embolism, CHADS =3 | 27 | 35 | RR 0.77 (0.58;1.02) | 6169 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, CHADS =4 | 50 | 53 | RR 0.95 (0.73;1.23) | 4067 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, CHADS= 5 | 47 | 54 | RR 0.87 (0.58;1.31) | 1797 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, CHADS =6 | 90 | 58 | RR 1.56 (0.67;3.65) | 278 (1 RCT)53 | No difference\* |
| Major bleeding, CHADS2 =2 | NR | NR | HR 1.14 (0.70;1.87) | 3137 (2 RCTs)43,69 | No difference\*\*\* |
| Major bleeding, CHADS2 =3 | NR | NR | HR 1.01 (0.82;1.24) | 7494 (2 RCTs)43,69 | No difference\*\*\* |
| Major bleeding, CHADS2 =4 | NR | NR | HR 1.00 (0.78;1.29) | 5369 (2 RCTs)43,69 | No difference\*\*\* |
| Major bleeding, CHADS2 =5 | NR | NR | HR 0.88 (0.59;1.31) | 3091 (2 RCTs)43,69 | No difference\*\*\* |
| **Major and nonmajor clinically relevant bleeding,  CHADS2 = 2** | **NR** | **NR** | **HR 1.40 (1.01;1.93)** | **2498 (2 RCTs)42,69** | **Favors warfarin**\*\* |
| **Major and nonmajor clinically relevant bleeding,  CHADS2 = 3** | **NR** | **NR** | **HR 1.16 (1.00;1.34)** | **18,168 (2 RCTs)42,69** | **Favors warfarin**\*\* |
| Major and nonmajor clinically relevant bleeding,  CHADS2 ≥5 | NR | NR | HR 1.02 (0.91;1.14) | 13,078 (2 RCTs)42,69 | No difference\*\* |
| All-cause mortality, History of major bleed | 200 | 257 | HR 0.69 (0.46;1.04) | 840 (1 RCT)56 | No difference\* |
| Stroke, BMI 18.50-24.99 kg/m2 | NR | NR | HR 0.76 (0.55;1.04) | 3289 (1 RCT)45 | No difference\* |
| Stroke, BMI 25.00-29.99 kg/m2 | NR | NR | HR 0.93 (0.71;1.21) | 5535 (1 RCT)45 | No difference\* |
| Stroke, BMI >30.0 kg/m2 | NR | NR | HR 1.06 (0.78;1.45) | 5206 (1 RCT)45 | No difference\* |
| Stroke and non-CNS systemic embolism,  BMI 18.50-24.99 kg/m2 | NR | NR | HR 0.76 (0.56;1.03) | 3289 (1 RCT)45 | No difference\* |
| Stroke and non-CNS systemic embolism,  BMI 25.00-29.99 kg/m2 | NR | NR | HR 0.89 (0.69;1.16) | 5535 (1 RCT)45 | No difference\* |
| Stroke and non-CNS systemic embolism,  BMI >30.0 kg/m2 | NR | NR | HR 1.02 (0.76;1.36) | 5535 (1 RCT)45 | No difference\* |
| Intracranial hemorrhage, BMI 18.50-24.99 kg/m2 | NR | NR | HR 0.47 (0.19;1.14) | 3289 (1 RCT)45 | No difference\* |
| Intracranial hemorrhage, BMI 25.00-29.99 kg/m2 | NR | NR | HR 1.03 (0.53;2.03) | 5535 (1 RCT)45 | No difference\* |
| **Intracranial hemorrhage, BMI >30.0 kg/m2** | **NR** | **NR** | **HR 0.29 (0.11;0.77)** | **5206 (1 RCT)45** | **Favors rivaroxaban**\* |
| Ischemic stroke, BMI 18.50-24.99 kg/m2 | NR | NR | HR 0.84 (0.59;1.20) | 3289 (1 RCT)45 | No difference\* |
| Ischemic stroke, BMI 25.00-29.99 kg/m2 | NR | NR | HR 0.90 (0.66;1.23) | 5535 (1 RCT)45 | No difference\* |
| Ischemic stroke, BMI >30.0 kg/m2 | NR | NR | HR 1.37 (0.96;1.96) | 5206 (1 RCT)45 | No difference\* |
| Major and nonmajor clinically relevant bleeding,  BMI 18.50-24.99 kg/m2 | NR | NR | HR 0.97 (0.84;1.13) | 3289 (1 RCT)45 | No difference, Significant interaction\* |
| **Major and nonmajor clinically relevant bleeding,  BMI 25.00-29.99 kg/m2** | **NR** | **NR** | **HR 1.18 (1.05;1.33)** | **5535 (1 RCT)45** | **Favors warfarin, Significant interaction\*** |
| Major and nonmajor clinically relevant bleeding,  BMI >30.0 kg/m2 | NR | NR | HR 0.93 (0.82;1.04) | 5206 (1 RCT)45 | No difference, Significant interaction\* |
| Major bleeding, BMI 18.50-24.99 kg/m2 | NR | NR | HR 0.92 (0.69;1.24) | 3289 (1 RCT)45 | No difference\* |
| Major bleeding, BMI 25.00-29.99 kg/m2 | NR | NR | HR 1.05 (0.84;1.31) | 5535 (1 RCT)45 | No difference\* |
| Major bleeding, BMI >30.0 kg/m2 | NR | NR | HR 1.15 (0.91;1.45) | 5206 (1 RCT)45 | No difference\* |
| Stroke or systemic embolism, Prior stroke TIA: Yes | 48 | 49 | RR 0.98 (0.80;1.19) | 7767 (1 RCT)53 | No difference\* |
| **Stroke or systemic embolism, Prior stroke TIA: no** | **26** | **36** | **RR 0.71 (0.54;0.94)** | **6404 (1 RCT)53** | **Favors rivaroxaban**\* |
| **Stroke, No prior stroke** | **22** | **31 Attributable avoided events per 1000 treated 9 (2; 16)** | **HR 0.75 (0.56;0.99) NNTp 111 (63; 500)** | **7433 (2 RCTs)68,76** | **Favors rivaroxaban**\*\* |
| Stroke, Prior stroke | 43 | 48 | HR 0.77 (0.40;1.49) | 8105 (2 RCTs)68,76 | No difference\* |
| **Fatal stroke (MRS 6), No prior stroke** | **6** | **11 Attributable avoided events per 1000 treated 5 (1; 10)** | **HR 0.54 (0.32;0.93) NNTp 193 (104;1334)** | **6796 (1 RCT)76** | **Favors rivaroxaban**\* |
| Fatal stroke (MRS 6), Prior stroke: Yes | 12 | 13 | HR 0.97 (0.64;1.45) | 7468 (1 RCT)76 | No difference\* |
| **Intracerebral hemorrhage,**  **No prior stroke** | **4** | **8 Attributable avoided events per 1000 treated 5 (1; 8)** | **HR 0.46 (0.24;0.89) NNTp 216 (120;1092)** | **6796 (1 RCT)76** | **Favors rivaroxaban**\* |
| Intracerebral hemorrhage, Prior stroke: Yes | 7 | 8 | HR 0.84 (0.50;1.41) | 7468 (1 RCT)76 | No difference\* |
| **Intracranial hemorrhage, No prior stroke** | **6** | **11** | **HR 0.57 (0.34;0.97)** | **6796 (1 RCT)76** | **Favors rivaroxaban**\* |
| Intracranial hemorrhage, Prior stroke: Yes | 9 | 13 | HR 0.74 (0.47;1.15) | 7468 (1 RCT)76 | No difference\* |
| Ischemic stroke, Prior stroke | 38 | 40 | HR 0.78 (0.36;1.68) | 8105 (2 RCTs)68,76 | No difference\* |
| Ischemic stroke, No prior stroke | 38 | 40 | HR 0.72 (0.29;1.80) | 7433 (2 RCTs)68,76 | No difference\*\* |
| **Hemorrhagic stroke, No prior stroke** | **3** | **8 Attributable avoided events per 1000 treated 4 (1;8)** | **HR 0.43 (0.22;0.86) NNTp 250 (125;1000)** | **7433 (2 RCTs)68,76** | **Favors rivaroxaban**\* |
| Hemorrhagic stroke, Prior stroke | 6 | 8 | HR 0.72 (0.43;1.22) | 8105 (2 RCTs)68,76 | No difference\*\* |
| Major and nonmajor clinically relevant bleeding,  No prior stroke | NR | NR | HR 1.19 (0.92;1.54) | 7261 (2 RCTs)68,76 | No difference\*\* |
| Major and nonmajor clinically relevant bleeding,  Prior stroke | NR | NR | HR 0.96 (0.87;1.06) | 8281 (2 RCTs)68,76 | No difference\*\* |
| Major bleeding, No prior stroke | NR | NR | HR 1.12 (0.93;1.34) | 7261 (2 RCTs)68,76 | No difference\*\* |
| Major bleeding, Prior stroke | NR | NR | HR 0.90 (0.67;1.23) | 8281 (2 RCTs)68,76 | No difference\*\* |
| Nonmajor clinically relevant bleeding, No prior stroke | NR | NR | HR 1.17 (0.92;1.49) | 7261 (2 RCTs)68,76 | No difference\*\* |
| Nonmajor clinically relevant bleeding, Prior stroke | NR | NR | HR 1.00 (0.90;1.11) | 8281 (2 RCTs)68,76 | No difference\*\* |
| **Fatal bleeding, No prior stroke** | **4** | **8 Attributable avoided events per 1000 treated 4 (1; 8)** | **HR 0.46 (0.23;0.90) NNTp 230 (126;1313)** | **6796 (1 RCT)76** | **Favors rivaroxaban**\* |
| Fatal bleeding, Prior stroke | NR | NR | HR 0.56 (0.30;1.02) | 8281 (2 RCTs)68,76 | No difference\*\* |
| Epistaxis, Japanese patients, Primary stroke prevention | 169 | 115 | RR 1.46 (0.93;2.31) | 465 (1 RCT)68 | No difference\* |
| **Epistaxis, Japanese patients, Secondary stroke prevention (previous stroke/TIA/non-CNS systemic embolism)** | **159** | **81** | **RR 1.96 (1.32;2.90)** | **813 (1 RCT)68** | **Favors warfarin**\* |
| Stroke, VKA-naive | 37 | 45 | RR 0.83 (0.65;1.05) | 6315 (1 RCT)58 | No difference\* |
| Stroke, VKA-experienced | 34 | 35 | RR 0.98 (0.77;1.23) | 7856 (1 RCT)58 | No difference\* |
| Stroke or systemic embolism, VKA-naive | 39 | 48 | RR 0.81 (0.64;1.03) | 6315 (1 RCT)58 | No difference\* |
| Stroke or systemic embolism, VKA-experienced | 37 | 39 | RR 0.95 (0.76;1.18) | 7856 (1 RCT)58 | No difference\* |
| Major and nonmajor clinically relevant bleeding: After the 30th day, VKA-naive | 140 | 156 | RR 0.90 (0.80;1.01) | 6350 (1 RCT)58 | No difference, Significant interaction\*\* |
| Major and nonmajor clinically relevant bleeding: After the 30th day, VKA-experienced | 200 | 201 | RR 0.99 (0.91;1.09) | 7886 (1 RCT)58 | No difference, Significant interaction\*\* |
| **Major and nonmajor clinically relevant bleeding: Before the 7th day, VKA-naive** | **13** | **3 Attributable events per 1000 treated 10 (6;14)** | **HR 5.83 (3.25;10.44) NNT 99 (69;170)** | **6350 (1 RCT)58** | **Favors warfarin\*** |
| **Major and nonmajor clinically relevant bleeding: Before the 7th day, VKA-experienced** | **15** | **2 Attributable events per 1000 treated 13 (9;17)** | **HR 6.66 (3.83;11.58) NNT 76 (58;110)** | **7886 (1 RCT)58** | **Favors warfarin\*** |
| Major and nonmajor clinically relevant bleeding: Between the 7th and 30th, VKA-naive | 19 | 26 | HR 0.98 (0.72;1.34) | 6350 (1 RCT)58 | No difference**\*** |
| Major and nonmajor clinically relevant bleeding: Between the 7th and 30th, VKA-experienced | 21 | 15 | RR 1.35 (0.97;1.87) | 7886 (1 RCT)58 | No difference**\*** |
| Major bleeding, VKA-naive | 46 | 53 | RR 0.87 (0.70;1.07) | 6350 (1 RCT)58 | No difference, Significant interaction\* |
| Major bleeding, VKA-experienced | 63 | 55 | RR 1.15 (0.96;1.37) | 7886 (1 RCT)58 | No difference, Significant interaction\* |
| **Nonmajor clinically relevant bleeding: Before the 7th day, VKA-naive** | **12** | **3 Attributable events per 1000 treated 10 (5;14)** | **HR 7.04 (3.74;13.27) NNT 105 (73;188)** | **6350 (1 RCT)58** | **Favors warfarin\*** |
| **Nonmajor clinically relevant bleeding: Before the 7th day, VKA-experienced** | **14** | **1 Attributable events per 1000 treated 13 (9;17)** | **HR 7.44 (4.06;13.64) NNT 77 (60;110)** | **7886 (1 RCT)58** | **Favors warfarin\*** |
| **Bleeding, extracerebral, VKA-naive** | **2** | **6** | **HR 0.39 (0.16;0.93)** | **6350 (1 RCT)58** | **Favors rivaroxaban\*** |
| Bleeding, extracerebral, VKA-experienced | 3 | 5 | RR 0.68 (0.34;1.38) | 7886 (1 RCT)58 | No difference**\*** |
| **Fatal bleeding, VKA-naive** | **4** | **10 Attributable avoided events per 1000 treated 6 (2; 10)** | **HR 0.42 (0.22;0.80) NNTp 178 (103; 647)** | **6350 (1 RCT)58** | **Favors rivaroxaban\*** |
| Fatal bleeding, VKA-experienced | 4 | 6 | RR 0.58 (0.30;1.12) | 7886 (1 RCT)58 | No difference**\*** |
| Transfusion, VKA-naive | 17 | 19 | RR 0.94 (0.65;1.35) | 6350 (1 RCT)58 | No difference**\*** |
| **Transfusion, VKA-experienced** | **32** | **23 Attributable events per 1000 treated 10 (2;17)** | **HR 1.46 (1.12;1.92) NNT 105 (60;428)** | **7886 (1 RCT)58** | **Favors warfarin\*** |
| **Hemoglobin drop ≥2 g/dL, Peripheral artery disease** | **75** | **37 Attributable events per 1000 treated 38 (7;69)** | **HR 2.29 (1.25;4.21) NNT 26 (14;141)** | **839 (1 RCT)55** | **Favors warfarin,** Significant interaction**\*** |
| Hemoglobin drop ≥2 g/dL, No peripheral artery disease | 41 | 36 | RR 1.15 (0.97;1.36) | 13,425 (1 RCT)55 | No difference, Significant interaction\*\* |
| Hemorrhagic stroke, Peripheral artery disease | 0 | 2 | RR 0.36 (0.01;8.91) | 839 (1 RCT)55 | No difference\* |
| **Hemorrhagic stroke, No peripheral artery disease** | **4** | **7** | **HR 0.60 (0.38;0.96)** | **13,425 (1 RCT)55** | **Favors rivaroxaban**\* |
| Stroke or systemic embolism, Diabetes: Yes | 33 | 41 | RR 0.82 (0.63;1.07) | 5647 (1 RCT)53 | No difference\* |
| Stroke or systemic embolism, Diabetes: No | 41 | 45 | RR 0.92 (0.75;1.12) | 8524 (1 RCT)53 | No difference\* |
| **Vascular death, Diabetes** | **53** | **68 Attributable avoided events per 1000 treated 15 (3; 28)** | **HR 0.80 (0.64;0.99) NNTp 65 (36;338)** | **5695 (1 RCT)59** | **Favors rivaroxaban, Significant interaction**\* |
| Vascular death, No diabetes | 52 | 48 | RR 1.08 (0.90;1.30) | 8569 (1 RCT)59 | No difference, Significant interaction\* |
| All-cause hospitalization, Pre-digoxin | 144 | 144 | RR 1.00 (0.92;1.08) | 14,171 (1 RCT)61 | No difference\* |
| All-cause hospitalization, Post-digoxin in patients event-free at digoxin start | 144 | 149 | RR 0.96 (0.87;1.07) | 8932 (1 RCT)61 | No difference\* |
| All-cause mortality, Pre-digoxin | 46 | 45 | RR 1.03 (0.89;1.20) | 14,171 (1 RCT)61 | No difference\* |
| **All-cause mortality, Post-digoxin in patients event-free at digoxin start** | **57** | **71 Attributable avoided events per 1000 treated 13 (3; 24)** | **RR 0.81 (0.69;0.95) NNTp 74 (42; 300)** | **8932 (1 RCT)61** | **Favors rivaroxaban**\*\* |
| **Fatal bleeding, Concomitant 0-4 medications** | **1** | **7 Attributable avoided events per 1000 treated 7 (3;10)** | **RR 0.11 (0.02;0.46) NNTp 150 (98; 318)** | **5073 (1 RCT)51** | **Favors rivaroxaban**\* |
| Fatal bleeding, Concomitant 5-9 medications | 5 | 8 | RR 0.63 (0.36;1.12) | 7298 (1 RCT)**51** | No difference\* |
| Fatal bleeding, Concomitant ≥10 medications | 6 | 6 | RR 0.99 (0.32;3.06) | 1865 (1 RCT)**51** | No difference\* |
| **Intracranial hemorrhage, Concomitant 0-4 medications** | **4** | **10 Attributable avoided events per 1000 treated 6 (2; 11)** | **RR 0.39 (0.19;0.81) NNTp 161 (92; 618)** | **5073 (1 RCT)51** | **Favors rivaroxaban**\* |
| Intracranial hemorrhage, Concomitant 5-9 medications | 10 | 13 | RR 0.76 (0.49;1.18) | 7298 (1 RCT)**51** | No difference\* |
| Intracranial hemorrhage, Concomitant ≥10 medications | 11 | 13 | RR 0.83 (0.36;1.90) | 1865 (1 RCT)**51** | No difference\* |
| Major and nonmajor clinically relevant bleeding,  Concomitant 0-4 medications | 167 | 164 | RR 1.02 (0.90;1.15) | 5073 (1 RCT)**51** | No difference\* |
| Major and nonmajor clinically relevant bleeding,  Concomitant 5-9 medications | 208 | 204 | RR 1.02 (0.93;1.12) | 7298 (1 RCT)51 | No difference\*\* |
| Major and nonmajor clinically relevant bleeding,  Concomitant ≥10 medications | 313 | 309 | RR 1.01 (0.88;1.16) | 1865 (1 RCT)51 | No difference\*\* |
| **Major bleeding, Concomitant 0-4 medications** | **29** | **42 Attributable avoided events per 1000 treated 14 (4; 24)** | **HR 0.71 (0.52;0.95) NNTp 73 (42; 278)** | **5073 (1 RCT)51** | **Favors rivaroxaban, Significant interaction**\* |
| Major bleeding, Concomitant 5-9 medications | 62 | 52 | RR 1.21 (1.00;1.46) | 7298 (1 RCT)51 | No difference, Significant interaction\* |
| Major bleeding, Concomitant ≥10 medications | 101 | 97 | RR 1.05 (0.80;1.37) | 1865 (1 RCT)51 | No difference, Significant interaction\* |

Abbreviations: BMI, body mass index; CI, confidence interval; CNS, central nervous system; CrCl, creatinine clearance; GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; MRS, modified Rankin scale; NNT, number needed to treat; NNTp, number needed to treat to prevent an outcome in one patient; NR, not reported; RCT, randomized controlled trial; RR, relative risk; TIA, transient ischemic attack; VKA, vitamin K antagonist.

\* Very low quality of evidence. \*\* Low quality of evidence. \*\*\* Moderate quality of evidence.