**Apixaban versus Warfarin in Atrial Fibrillation Patients with Chronic Kidney Disease**

**Supplemental materials**

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Supplemental Table 1. Codes for clinical condition and medication used in this study

|  |  |
| --- | --- |
| **Condition** | **Coding system /Code** |
| Atrial fibrillation/atrial flutter | ≥ 2 visits in outpatient/emergency department within 365 days and apart ≥ 28 days or ≥ 1 hospitalization for the disease defined by International Classification of Diseases (ICD)-9/10 codes:ICD-9-CM: 427.31, 427.32; ICD10-CM: I48 |
| Oral anticoagulant treatment  | New user was identified by Anatomical Therapeutic Chemical Classification system (ATC) code for warfarin or apixaban initiation: warfarin: B01AA03; dabigatran: B01AE07; rivaroxaban:B01AF01; apixaban B01AF02; edoxaban:B01AF03 |
| **Outcome** | **≥1 hospitalizations for the disease after the index date** |
| **Stroke/systemic embolism (SE)** | 　 |
| Ischemic or uncertain stroke | ICD-9-CM: 433.x-437.xICD10-CM: I63, I65, I66, I67.2, I67.5-I67.82, I67.841-I67.848, I67.89-I67.9, I68, G45.0-G45.2, G45.4-G45.9, G46, Z86.73 |
| SE, pulmonary embolism | ICD-9-CM: 453.x, 415.xICD10-CM: I82.2-I82.9, I82.A, I82.B, I82.C, Z86.71,I26.02, I26.09, I26,9, I27.82 |
| **Major bleeding [1-5]** | 　 |
| Intracranial | ICD-9-CM: 430, 431, 432.0, 432.1, 432.9, 852.0, 852.2, 852.4, 853.0ICD10-CM: I60, I61, I62, S06.340A-S06.349A, S06.350A-S06.359A, S06.360A-06.369A, S06.4X0A-S06.4X9A, S06.5X0A-S06.5X9A, S06.6X0A-S06.6X9A |
|  Ocular | ICD-9-CM: 360.43, 362.81, 363.6, 364.4, 377.42, 379.23, 376.32, 372.72ICD10-CM: H44.8, H35.6, H31.3, H21.0, H47.02, H43.1, H05.23, H11.3 |
|  Gastrointestinal | ICD-9-CM: 530.7, 531, 531.2, 531.4, 531.6, 532, 532.2, 532.4, 532.6, 533, 533.2, 533.4, 533.6, 534, 534.2, 534.4, 534.6, 569.3, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 569.85, 578ICD10-CM: K22.6, K25-K28, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K52.81, K55.21, K56.60, K56.60, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.81, K57.91, K57.93, K62.5, K92.0, K92.1, K92.2 |
|  Intra-abdominal | ICD-9-CM: 568.81, 866.01, 866.02, 866.11, 866.12ICD10-CM: K66.1, S37.011A, S31.001A |
|  Hematuria | ICD-9-CM: 599.7ICD10-CM: R31, N30.01, N30.21, N30.31, N30.81, N30.91 |
|  Other sites | ICD-9-CM: 336.1(spinal hemorrhage), 363.6, 372.72, 376.32, 377.42, 379.23 (Ocular bleeding), 593.81(renal artery hemorrhage), 866.01, 866.11(kidney hematoma), 866.02, 866.12(kidney laceration), 719.1, 729.92 (intra-articular hemorrhage), 423.0(pericardial hemorrhage), 772.5(Adrenal gland bleeding)ICD10-CM: G95.11, G95.19(spinal hemorrhage), H05.23, H11.3, H31.3, H43.1, H47.02(Ocular bleeding), I31.2 (pericardial hemorrhage), M25.0(intra-articular hemorrhage), N28.0 (kidney hematoma), S31.001A, S37.011A, S37.012A, S37.019A, S37.021A, S37.022A, S37.029A, S37.031A, S37.032A, S37.039A, S37.041A, S37.042A, S37.049A, S37.051A, S37.052A, S37.059A (Injury of kidney), P54.4 (Adrenal bleeding). |
| Pneumonia | ICD-9-CM: 480-488/ ICD10-CM: J09X1, J10.0, J11.0, J12-J16, J18 |
| Hip fracture | ICD-9-CM: 820-821/ ICD10-CM: S72 |
| **Baseline comorbidity**  | **≥2 visits in the outpatient/emergency department within 365 days prior to the index date and ≥28 days apart or ≥1 hospitalization for the disease**  |
| Charlson Comorbidity Index | 1.Acute myocardial infarction =ICD-9:410,412/ICD-10:I21,I22, I252; 2.Congestive heart failure=ICD-9:428/ICD-10:I50; 3.Peripheral vascular disease=ICD-9: 441, 443.9, 785.4, V434/ICD-10:I71,I790, R02, Z958, Z959; 4.Cerebral vascular accident=ICD-9:430-438/ICD-10: I60, I61, I62, I63, I65, I66,G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69; 5.Dementia=ICD-9:290/ICD-10: F00, F01, F02, F051; 6.Pulmonary disease=ICD-9: 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505/ICD-10: J40, J41, J42, J44, J43, J45, J46, J47, J67, J44, J60, J61, J62, J63, J66, J64, J65; 7.Connective tissue disorder=ICD-9: 7100, 7101, 7104, 7140, 7141, 7142, 71481/ 5171, 725/ICD-10: M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353; 8.Peptic ulcer=ICD-9: 531, 532, 533, 534/ICD-10: K25, K26, K27, K28; 9.Liver disease=ICD-9: 5712, 5714, 5715, 5716/ICD-10: K702, K703, K73, K717, K740, K742, K746, K743, K744, K745; 10. Diabetes=ICD-9: 2500, 2501, 2502, 2503, 2507/ICD-10: E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145; 11. Diabetes complications=ICD-9: 2504, 2505, 2506/ICD-10: E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144; 12. Paraplegia=ICD9:342, 3441/ICD-10: G81 G041, G820, G821, G822; 13.Renal disease=ICD9: 582, 5830, 5831, 5832, 5833, 5835, 5836, 5837, 5834, 585, 586,588/ICD-10: N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25; 14. Cancer=ICD-9: 14-16, 18, 170-172, 174-176, 179, 190-194, 195.0-195.55, 195.8, 200-208/ICD-10: C0-C3, C40,C41, C43, C45-C49, C5, C6, C70-C76, C80-C85, C883, C887, C889, C900, C901, C91, C92, C93, C940-C943, C9451, C947, C95, C96; 15. Metastatic cancer=ICD-9: 196-198, 1990, 1991/ICD-10: C77-C80; 16. Severe liver disease=ICD-9: 5722, 5723, 5724, 5728/ICD-10:K729, K766, K767, K721; 17. HIV=ICD-9:042,043,044/ICD-10: B20, B21, B22, B23, B24. |
| CHA2DS2-VASc score  | score=[(Congestive heart failure+ Hypertension+Age 65-74years+Dabetes mellitus+Vascular disease+Sex\_female)x1]+[(Age ≥75+Stroke)\*2] C=ICD-9:428 or ICD10: I11.0, I50, I97.1; D=ICD-9:250 or ICD-10: E10, E11, E12, E13, E14;V=ICD-9:443 or ICD-10: I21, I22, I25.2, I70.0, I70.1, I70.2, I70.8, I70; S/TIA/TE=ICD-9: 433, 434, 435, 453, 415 or ICD-10:I63, I64,G45.  |
| HASBLED score | score=[Hypertension+abnormal renal/liver function(0, 1 or 2)+stroke+ bleeding history or predisposition+labile INR (international normalized ratio>3)+age >65 years+concomitant use of NSAIDs or alcohol (0,1 or 2); whenever data for the disease, medication use and INR were available]Renal=ICD-9: ICD9: 403, 404, 580 -589; or ICD-10:N280; Liver=ICD-9:570-573 or ICD-10: B15-B19, C22, C64-C65, D684C, E102, E112, E132, E142, I12-I13, I15, I982B, K70-K77, N1, N25-N26, N289, Q61, Z940, Z944, Z992; Stroke (inpatient)=ICD-9:433, 434 or ICD-10: G458, G459, I63, I64, I74; Bleeding (inpatient)= ICD9: 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 456.0, 456.20, 530.7, 530.82, 578.0, 455.2, 455.5, 455.8, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.1, 578.9, 593.81, 599.7, 623.8, 626.2, 626.6, 430, 431, 432, 432.0, 432.1, 432.9, 852.0, 852.2, 852.4, 853.0, 423.0, 459.0, 568.81, 719.1x, 784.7, 784.8, 786.3 or critical site bleeding (ICD-9: 430, 431, 432, 852.0, 852.2, 852.4, 853.0, 336.1, 363.6, 372.72, 376.32, 377.42, 379.23, 719.1, 729.92, 729.97, 423.0, 593.81, 772.5, 866.01, 866.02, 866.11, 866.12) or ICD-10: I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R04, R31, S064-S066; Use of NSAID or anti-platelet: M01A or ATCB01AC; Alcohol=ICD-9: 291.0-291.9; 303.x; 305.0; 357.5; 425.5;571.0-571.3 or ICD-10: F1, K70, E52, T51, K860, E244, G312, I426, O354, Z714, Z721, G312, G621, G721, K292, L278A.  |
| Hypertension in CHA2DS2-VASc and HASBLED score | (1) medication use duration>=90 days in outpatient setting; ATC: C02A-C02D, C02L, C03A, C03B, C03D, C03E, C03X, C04, C05, C07-C09. (2) or ICD-9: 401-405; ICD-10: I10, I11, I12, I13, I15. |
| **Prior medication use** | **≥28 days of supply within 365 days prior to the index date for the medication use defined by ATC code** |
| Lipid-lowering agent | C10AA,C10BA, C10AB, C10AC, C10AD,C10AX, C10BX |
| Antidiabetic agent | A10A, A10B |
| Anti-hypertension  | C09A, C09B, C09C, C09D, C09X, C03, C07, C08 |
| Anti-platelet agent | B01AC06, B01AC04, B01AC24, B01AC07, B01AC22, B01AC30, B01AC91 |
| Amiodarone | C01BD01, C01BD07 |
| Digoxin | C01AA05  |
| Non-steroidal anti-inflammatory drugs | M01AA, M01AX, M01AB, M01AC, M01AE, M01AG, M01AH |
| Gastric antacids | A02BA, A02BC |

The major bleeding was defined as hospitalization with any diagnosis of ICD-9/10-CM codes for bleeding events in order to comparable with the International Society of Thrombosis and Haemostasis major bleeding definitions.

References

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3. Yu HT., et al., Clinical Significance of Hematuria in Atrial Fibrillation With Oral Anticoagulation Therapy. Circ J, 2017. 81(2):158-164.

4. Limdi NA et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol, 2009. 20(4): 912-21.

Supplemental Table 2. Cox proportional hazards regression model for ischemic stroke or systemic embolism

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 　 | 　 | **No ofpatient** | **No ofevent** | **Main analysis** | 　 | **Apixaban subgroup analysis** |
| **Variable** | **aHR** | **95% CI** | *p-value* | 　 | **aHR** | **95% CI** | *p-value* |
| **Treatment**  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Warfarin | 1625 | 175 | 1.00  |  |  |  | - | - |  | - | - |
|  | Apixaban  | 1625 | 115 | 0.74  | (0.57 |  | 0.97) | 0.0296  |  | - | - |  | - | - |
| **Treatment**  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Warfarin | 1625 | 175 | - | - |  | - | - |  | 1.00  |  |  |
|  | **Apixaban (reduced dose 2.5-5 mg/day)** | **915** | **69** | **-** | **-** |  | **-** | **-** |  | **0.77**  | **(0.57** |  | **1.05)** | **0.0955**  |
|  | **Apixaban (standard dose 10 mg/day)**  | **710** | **46** | **-** | **-** |  | **-** | **-** |  | **0.71**  | **(0.50** |  | **1.01)** | **0.0575**  |
| **Age, years** |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | <40 | 23 | 1 | 1.00  |  |  |  | 1.00  |  |  |
|  | 40-64  | 502 | 36 | 1.50  | (0.21 |  | 11.03) | 0.6887  |  | 1.50  | (0.20 |  | 10.98) | 0.6915  |
|  | 65-74  | 1007 | 73 | 1.47  | (0.20 |  | 10.69) | 0.7027  |  | 1.46  | (0.20 |  | 10.61) | 0.7081  |
|  | ≥75  | 1718 | 180 | 2.15  | (0.30 |  | 15.52) | 0.4476  |  | 2.12  | (0.29 |  | 15.31) | 0.4570  |
| **Sex** |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Male | 1864 | 156 | 0.88  | (0.69 |  | 1.11) | 0.2766  |  | 0.88  | (0.69 |  | 1.12) | 0.2811  |
|  | Female | 1386 | 134 | 1.00  |  |  |  | 1.00  |  |  |
| **Baseline estimated glomerular filtration rate (eGFR), ml/min/1.73 m2** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | ≧60 | 1915 | 179 | 1.00  |  |  |  | 1.00  |  |  |
|  | 30-59.9  | 1085 | 90 | 0.75  | (0.56 |  | 1.01) | 0.0555  |  | 0.75  | (0.56 |  | 1.00) | 0.0518  |
|  | <30 | 250 | 21 | 0.63  | (0.37 |  | 1.08) | 0.0943  |  | 0.63  | (0.37 |  | 1.07) | 0.0891  |
| **Baseline international normalized ratio**  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | <1.5 | 2080 | 181 | 1.00  |  |  |  | 1.00  |  |  |
|  | 1.5-2  | 324 | 31 | 0.86  | (0.58 |  | 1.29) | 0.4721  |  | 0.86  | (0.58 |  | 1.29) | 0.4706  |
|  | >2  | 390 | 49 | 1.08  | (0.76 |  | 1.53) | 0.6672  |  | 1.08  | (0.76 |  | 1.53) | 0.6690  |
|  | Missing | 456 | 29 | 0.96  | (0.64 |  | 1.44) | 0.8526  |  | 0.97  | (0.65 |  | 1.45) | 0.8653  |
| **Baseline comorbid condition** |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Ischemic stroke/systemic embolism | 1014 | 153 | 2.40  | (1.87 |  | 3.08) | <.0001 |  | 2.40  | (1.87 |  | 3.09) | <.0001 |
|  | Major bleeding | 963 | 108 | 1.25  | (0.96 |  | 1.61) | 0.0972  |  | 1.25  | (0.96 |  | 1.62) | 0.0936  |
|  | Hypertension | 2363 | 212 | 0.82  | (0.62 |  | 1.09) | 0.1619  |  | 0.82  | (0.62 |  | 1.08) | 0.1594  |
|  | Renal disease | 627 | 70 | 1.79  | (1.28 |  | 2.51) | 0.0007  |  | 1.79  | (1.28 |  | 2.51) | 0.0007  |
|  | Liver diseases/Severe liver diseases | 236 | 22 | 0.97  | (0.62 |  | 1.51) | 0.8969  |  | 0.97  | (0.62 |  | 1.51) | 0.8857  |
|  | Diabetes mellitus | 1030 | 95 | 1.18  | (0.83 |  | 1.66) | 0.3573  |  | 1.18  | (0.83 |  | 1.66) | 0.3528  |
|  | Heart failure | 1064 | 85 | 1.03  | (0.79 |  | 1.34) | 0.8330  |  | 1.03  | (0.79 |  | 1.34) | 0.8346  |
|  | Peripheral vascular disease  | 111 | 14 | 1.45  | (0.83 |  | 2.53) | 0.1918  |  | 1.44  | (0.82 |  | 2.51) | 0.2018  |
| **Prior medications uses**  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Lipid-lowering agent  | 817 | 66 | 0.80  | (0.60 |  | 1.08) | 0.1421  |  | 0.80  | (0.60 |  | 1.08) | 0.1437  |
|  | Glucose-lowering agent | 682 | 59 | 0.83  | (0.55 |  | 1.25) | 0.3715  |  | 0.83  | (0.55 |  | 1.25) | 0.3715  |
|  | Anti-hypertension  | 2508 | 217 | 0.97  | (0.71 |  | 1.32) | 0.8529  |  | 0.97  | (0.71 |  | 1.32) | 0.8498  |
|  | Anti-platelet agent | 1398 | 120 | 0.81  | (0.62 |  | 1.05) | 0.1084  |  | 0.81  | (0.62 |  | 1.05) | 0.1071  |
|  | Amiodarone | 603 | 47 | 0.92  | (0.67 |  | 1.27) | 0.6107  |  | 0.92  | (0.66 |  | 1.27) | 0.5997  |
|  | Digoxin | 295 | 14 | 0.52  | (0.30 |  | 0.90) | 0.0196  |  | 0.52  | (0.30 |  | 0.90) | 0.0193  |
|  | Non-steroidal anti-inflammatory drugs | 374 | 47 | 1.35  | (0.98 |  | 1.87) | 0.0652  |  | 1.35  | (0.98 |  | 1.87) | 0.0652  |
| 　 | Gastric antacids | 844 | 87 | 1.21  | (0.92 | 　 | 1.59) | 0.1744  | 　 | 1.20  | (0.92 | 　 | 1.58) | 0.1822  |

aHR=adjusted hazard ratio, CI=confidence interval

Supplemental Table 3. Cox proportional hazards regression model for major bleeding

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 　 | 　 | **No of patient** | **No of event** | **Main analysis** | 　 | **Apixaban subgroup analysis** |
| **Variable** | **aHR** | **95% CI** | *p-value* | 　 | **aHR** | **95% CI** | *p-value* |
| **Treatment**  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Warfarin | 1625 | 183 | 1.00 |  |  |  | - | - |  | - | - |
|  | Apixaban  | 1625 | 122 | 0.78 | (0.60 |  | 1.00) | 0.0503 |  | - | - |  | - | - |
| **Treatment**  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Warfarin | 1625 | 183 | - | - |  | - | - |  | 1.00 |  |  |
|  | Apixaban (reduced dose 2.5-5 mg/day) | 915 | 85 | - | - |  | - | - |  | 0.84 | (0.63 |  | 1.12) | 0.2286 |
|  | Apixaban (standard dose 10 mg/day)  | 710 | 37 | - | - |  | - | - |  | 0.66 | (0.45 |  | 0.96) | 0.0287 |
| **Age, years** |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | <40 | 23 | 1 | 1.00 |  |  |  | 1.00 |  |  |
|  | 40-64  | 502 | 22 | 1.03 | (0.14 |  | 7.65) | 0.9796 |  | 1.02 | (0.14 |  | 7.58) | 0.9869 |
|  | 65-74  | 1007 | 82 | 1.80 | (0.25 |  | 13.02) | 0.5616 |  | 1.76 | (0.24 |  | 12.77) | 0.5751 |
|  | ≥75 | 1718 | 200 | 2.40 | (0.33 |  | 17.28) | 0.3857 |  | 2.30 | (0.32 |  | 16.57) | 0.4097 |
| **Sex** |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Male | 1864 | 169 | 1.08 | (0.86 |  | 1.37) | 0.5030 |  | 1.09 | (0.86 |  | 1.37) | 0.4924 |
|  | Female | 1386 | 136 | 1.00 |  |  |  | 1.00 |  |  |
| **Baseline estimated glomerular filtration rate, ml/min/1.73 m2** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | ≧60 | 1915 | 136 |  |  |  |  |  |  |  |
|  | 30-59.9  | 1085 | 125 | 1.40 | (1.07 |  | 1.83) | 0.0139 |  | 1.38 | (1.05 |  | 1.80) | 0.0195 |
|  | <30 | 250 | 44 | 2.21 | (1.44 |  | 3.38) | 0.0003 |  | 2.16 | (1.41 |  | 3.31) | 0.0004 |
| **Baseline international normalized ratio** |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | <1.5 | 2080 | 203 | 1.00  |  |  |  | 1.00  |  |  |
|  | 1.5-2  | 324 | 29 | 0.79  | (0.52 |  | 1.18) | 0.2494  |  | 0.79  | (0.52 |  | 1.18) | 0.2475  |
|  | >2  | 390 | 47 | 1.00  | (0.71 |  | 1.41) | 0.9887  |  | 0.99  | (0.70 |  | 1.41) | 0.9723  |
|  | Missing | 456 | 26 | 0.72  | (0.47 |  | 1.09) | 0.1154  |  | 0.72  | (0.48 |  | 1.10) | 0.1279  |
| **Baseline comorbid condition** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Ischemic stroke/systemic embolism | 1014 | 106 | 1.06  | (0.83 |  | 1.37) | 0.6437  |  | 1.07  | (0.83 |  | 1.37) | 0.6244  |
|  | Major bleeding | 963 | 138 | 1.77  | (1.37 |  | 2.27) | <.0001 |  | 1.78  | (1.38 |  | 2.29) | <.0001 |
|  | Hypertension | 2363 | 239 | 1.13  | (0.84 |  | 1.52) | 0.4077  |  | 1.13  | (0.84 |  | 1.51) | 0.4187  |
|  | Renal disease | 627 | 81 | 1.08  | (0.78 |  | 1.48) | 0.6581  |  | 1.07 | (0.78 |  | 1.47) | 0.6753  |
|  | Liver diseases/severe liver diseases | 236 | 28 | 1.16  | (0.78 |  | 1.73) | 0.4564  |  | 1.15 | (0.77 |  | 1.72) | 0.4899  |
|  | Diabetes mellitus | 1030 | 115 | 1.18  | (0.85 |  | 1.65) | 0.3314  |  | 1.18 | (0.85 |  | 1.65) | 0.3215  |
|  | Heart failure | 1064 | 116 | 1.27  | (0.99 |  | 1.62) | 0.0578  |  | 1.27 | (0.99 |  | 1.62) | 0.0605  |
|  | Peripheral vascular disease  | 111 | 14 | 1.23  | (0.71 |  | 2.13) | 0.4607  |  | 1.22 | (0.70 |  | 2.11) | 0.4807  |
| **Prior medication use**  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Lipid-lowering agent  | 817 | 76 | 0.94  | (0.71 |  | 1.25) | 0.6782  |  | 0.94 | (0.71 |  | 1.25) | 0.6874  |
|  | Glucose-lowering agent | 682 | 77 | 1.00 | (0.68 |  | 1.47) | 0.9966 |  | 1.00 | (0.68 |  | 1.47) | 0.9946 |
|  | Anti-hypertension  | 2508 | 236 | 0.80 | (0.58 |  | 1.09) | 0.1508 |  | 0.80 | (0.58 |  | 1.09) | 0.1518 |
|  | Anti-platelet agent | 1398 | 122 | 0.68 | (0.53 |  | 0.88) | 0.0031 |  | 0.68 | (0.52 |  | 0.87) | 0.0028 |
|  | Amiodarone | 603 | 51 | 0.83 | (0.61 |  | 1.13) | 0.2442 |  | 0.83 | (0.61 |  | 1.12) | 0.2230 |
|  | Digoxin | 295 | 26 | 0.88 | (0.58 |  | 1.34) | 0.5424 |  | 0.87 | (0.57 |  | 1.33) | 0.5290 |
|  | Non-steroidal anti-inflammatory drug | 374 | 41 | 1.05 | (0.75 |  | 1.46) | 0.7962 |  | 1.05 | (0.75 |  | 1.47) | 0.7861 |
| 　 | Gastric antacids | 844 | 119 | 1.55 | (1.19 |  | 2.00) | 0.0009 |  | 1.53 | (1.18 |  | 1.99) | 0.0012 |

aHR=adjusted hazard ratio, CI=confidence interval

Supplemental Table 4. Cox proportional hazards regression model for pneumonia and hip fracture

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Outcome: pneumonia** | 　 | **Outcome: hip fracture** |
| **aHR** | **95% CI** | ***p-value*** |  | **aHR** | **95% CI** | ***p-value*** |
| **Treatment** |  |  |  |  |  |  |  |  |  |  |  |
|  | Warfarin | 1.00  |  |  |  | 1.00  |  |  |
|  | Apixaban  | **0.99**  | **(0.76** |  | **1.28)** | **0.9110**  |  | **0.71**  | **(0.29** |  | **1.70)** | **0.4363**  |
| **Mean age (years)** | 1.07  | (1.05 |  | 1.09) | <.0001 |  | 1.08  | (1.02 |  | 1.14) | 0.0081  |
| **Sex** |  |  |  |  |  |  |  |  |  |  |  |
|  | Male | 1.10  | (0.87 |  | 1.40) | 0.4156  |  | 0.29  | (0.12 |  | 0.75) | 0.0104  |
|  | Female | 1.00  |  |  |  | 1.00  |  |  |
| **Baseline estimated glomerular filtration rate (ml/min/1.73 m2)** |  |  |  |  |  |  |  |  |  |  |
|  | ≧60 | 1.00  |  |  |  | 1.00  |  |  |
|  | 30-59.9  | 0.90  | (0.68 |  | 1.18) | 0.4353  |  | 1.13  | (0.46 |  | 2.82) | 0.7860  |
|  | <30 | 0.95  | (0.60 |  | 1.50) | 0.8358  |  | 2.46  | (0.56 |  | 10.70) | 0.2312  |
| **Baseline international normalized ratio**  |  |  |  |  |  |  |  |  |  |  |  |
|  | <1.5 | 1.00  |  |  |  | 1.00  |  |  |
|  | 1.5-2 | 1.39  | (0.98 |  | 1.98) | 0.0660  |  | 0.56  | (0.12 |  | 2.58) | 0.4556  |
|  | >2  | 1.18  | (0.82 |  | 1.68) | 0.3765  |  | 0.39  | (0.09 |  | 1.81) | 0.2316  |
|  | Missing | 0.72  | (0.47 |  | 1.11) | 0.1361  |  | 0.26  | (0.03 |  | 1.94) | 0.1870  |
| **Baseline comorbid condition** |  |  |  |  |  |  |  |  |  |  |
|  | Ischemic stroke/systemic embolism | 1.28  | (1.00 |  | 1.65) | 0.0519  |  | 1.69  | (0.72 |  | 3.99) | 0.2295  |
|  | Major bleeding | 1.32  | (1.02 |  | 1.70) | 0.0351  |  | 0.67  | (0.26 |  | 1.76) | 0.4211  |
|  | Hypertension | 0.84  | (0.63 |  | 1.13) | 0.2480  |  | 0.69  | (0.25 |  | 1.90) | 0.4710  |
|  | Renal disease | 1.72  | (1.26 |  | 2.36) | 0.0007  |  | 0.82  | (0.26 |  | 2.60) | 0.7308  |
|  | Liver diseases/severe liver diseases | 1.29  | (0.87 |  | 1.90) | 0.2114  |  | 0.56  | (0.07 |  | 4.35) | 0.5815  |
|  | Diabetes mellitus | 1.62  | (1.18 |  | 2.23) | 0.0029  |  | 1.83  | (0.56 |  | 5.93) | 0.3150  |
|  | Heart failure | 1.41  | (1.10 |  | 1.80) | 0.0060  |  | 1.18  | (0.48 |  | 2.93) | 0.7145  |
|  | Peripheral vascular disease  | 1.73  | (1.09 |  | 2.77) | 0.0213  |  | 0.00  | (0.00 |  | . | 0.9863  |
| **Prior medication use** |  |  |  |  |  |  |  |  |  |  |  |
|  | Lipid-lowering agent  | 0.80  | (0.60 |  | 1.07) | 0.1270  |  | 0.54  | (0.20 |  | 1.45) | 0.2200  |
|  | Antidiabetic agents | 0.98  | (0.68 |  | 1.41) | 0.9042  |  | 0.93  | (0.25 |  | 3.40) | 0.9108  |
|  | Anti-hypertension | 0.80  | (0.59 |  | 1.10) | 0.1720  |  | 1.35  | (0.36 |  | 5.08) | 0.6554  |
|  | Anti-platelet agent | 0.73  | (0.57 |  | 0.95) | 0.0187  |  | 1.48  | (0.64 |  | 3.42) | 0.3618  |
|  | Amiodarone | 0.93  | (0.68 |  | 1.27) | 0.6605  |  | 1.60  | (0.66 |  | 3.85) | 0.2972  |
|  | Digoxin | 0.86  | (0.57 |  | 1.31) | 0.4829  |  | 0.97  | (0.26 |  | 3.70) | 0.9665  |
|  | Non-steroidal anti-inflammatory drugs | 1.07  | (0.77 |  | 1.50) | 0.6774  |  | 4.60  | (2.03 |  | 10.43) | 0.0003  |
| 　 | Gastric antacids | 1.49  | (1.15 | 　 | 1.94) | 0.0028  | 　 | 1.50  | (0.63 | 　 | 3.56) | 0.3617  |

aHR=adjusted hazard ratio, CI=confidence interval

Supplemental Table 5. Patient characteristics by apixaban dose

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 　　 | 　　 | 　　 | **No. of patients** | **Reduced dose\*, n=915** |  | **Standard dose\*, n=710** | ***p-value*** |
|  |
| **Age (years), n (%)** |  |  |  |  |  |  | <.0001 |
|  | <40 | 12 | 2 | (0.22) |  | 10 | (1.41) |  |
|  | 40-64  | 245 | 69 | (7.54) |  | 176 | (24.79) |  |
|  | 65-74  | 504 | 217 | (23.72) |  | 287 | (40.42) |  |
|  | ≥75  | 864 | 627 | (68.52) |  | 237 | (33.38) |  |
| **Sex, n (%)** |  |  |  |  |  |  | <.0001 |
|  | Male |  | 938 | 484 | (52.90) |  | 454 | (63.94) |  |
|  | Female | 687 | 431 | (47.10) |  | 256 | (36.06) |  |
| **Baseline estimated glomerular filtration rate (ml/min/1.73m2), n (%)** |  |  |  |  |  |  | <.0001 |
|  | ≥90  | 277 | 120 | (13.11) |  | 157 | (22.11) |  |
|  | 60-89.9  | 674 | 302 | (33.01) |  | 372 | (52.39) |  |
|  | 45-59.9  | 357 | 224 | (24.48) |  | 133 | (18.73) |  |
|  | 30-44.9  | 198 | 162 | (17.70) |  | 36 | (5.07) |  |
|  | 15-29.9  | 103 | 93 | (10.16) |  | 10 | (1.41) |  |
|  | <15  | 16 | 14 | (1.53) |  | 2 | (0.28) |  |
| **Baseline international normalized ratio, n (%)** |  |  |  |  |  |  | 0.0085  |
|  |  | <1.5  | 1291 | 744 | (81.31) |  | 547 | (77.04) |  |
|  |  | 1.5-2  | 37 | 23 | (2.51) |  | 14 | (1.97) |  |
|  |  | >2  | 17 | 13 | (1.42) |  | 4 | (0.56) |  |
|  |  | Missing | 280 | 135 | (14.75) |  | 145 | (20.42) |  |
| **Mean (SD) value** |  |  |  |  |  |  |  |
|  | Age at the index date, year | 1625 | 78.51 | (9.52) |  | 69.80 | (10.34) | <.0001 |
|  | Baseline eGFR, ml/min/1.73m2  | 1625 | 60.60  | (26.44) |  | 74.68  | (23.26) | <.0001 |
|  | Low-density lipoprotein, mg/dl | 1625 | 93.70  | (37.47) |  | 100.34  | (42.51) | 0.0032  |
|  | Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke, Vascular disease, Age 65-74 years, Sex score | 1625 | 4.18  | (1.62) |  | 3.39  | (1.66) | <.0001 |
|  | Hypertension, Abnormal liver/renal, Bleeding, Labile INRs, Elderly (>65 years), Drugs (aspirin or NSAIDs) or alcohol score | 1625 | 3.13  | (1.32) |  | 2.66  | (1.33) | <.0001 |

\*Standard dose of apixaban: 10 mg/day; reduced dose: 2.5-5 mg/day

Supplemental Figure 1. The mean international normalized ratios in patients treated with warfarin who developed systemic embolism (n=70)



|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Time (month) | Number of patient-test | Mean INR | SD |  | Time (month) | Number of patient-test | Mean INR | SD |
| 0 | 85 | 2.54 | (1.52) |  | 13 | 4 | 3.14 | (1.67) |
| 1 | 90 | 2.05 | (1.11) |  | 14 | 9 | 1.43 | (0.51) |
| 2 | 54 | 2.22 | (1.13) |  | 15 | 7 | 1.91 | (0.60) |
| 3 | 36 | 2.01 | (0.90) |  | 16 | 16 | 2.64 | (2.00) |
| 4 | 40 | 2.44 | (1.15) |  | 17 | 3 | 1.90 | (1.14) |
| 5 | 44 | 2.52 | (1.51) |  | 18 | 12 | 2.14 | (0.78) |
| 6 | 22 | 1.86 | (0.59) |  | 19 | 3 | 1.74 | (0.79) |
| 7 | 14 | 1.75 | (0.59) |  | 20 | 1 | 1.05 | . |
| 8 | 29 | 1.72 | (0.72) |  | 21 | 1 | 2.15 | . |
| 9 | 20 | 1.73 | (0.76) |  | 22 | 1 | 1.00 | . |
| 10 | 16 | 1.97 | (0.85) |  | 23 | 1 | 2.45 | . |
| 11 | 5 | 2.36 | (1.31) |  | 24 | 1 | 0.98 | . |
| 12 | 8 | 2.29 | (1.26) |  |  |  |  |  |

Among the number of patient-tests for INR per month in the warfarin group, a high frequency of INR testing was within the first 5 months and most INR results were within the range of 2.0 and 2.5. Less frequent INR testing and great fluctuations (mean INR ranged, 1.72–3.14) occurred after the initial 5 months.

INR=international normalized ratio, TTR= time in therapeutic range (INR= 2.0-3.0)