

Supplementary Online Content

Lin Y-S, Chen Y-L, Chen T-H, et al. Comparison of Clinical Outcomes Among Patients With Atrial Fibrillation or Atrial Flutter Stratified by CHA₂DS₂-VASc Score. *JAMA Netw Open*. 2018;1(4):e180941. doi:10.1001/jamanetworkopen.2018.0941

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Diagnoses Used to Define the Cohorts, Comorbidities, and Outcomes

| Disease | Criteria of Diagnosis | |
|---------------------------------------|---|---|
| Study Cohorts | | |
| Atrial fibrillation | Defined from diagnosis | ICD9-CM: 42731 |
| Atrial flutter | Defined from diagnosis | ICD9-CM: 42732 |
| Excluding Diseases | | |
| Hyperthyroidism | Defined from diagnosis plus treatment | ICD9-CM: 242 and any anti-thyroid drugs |
| Rheumatic heart disease | Defined from diagnosis | ICD9-CM: 394.0, 394.1, 394.2, 395, 398.9 |
| Sepsis | Defined from diagnosis during hospitalization | ICD9-CM: 038, 790.7 |
| Comorbidities | | |
| Hypertension | Defined from diagnosis plus treatment | 401, 402, 403, 404, 405 and any anti-hypertension drugs |
| Diabetes mellitus | Defined from diagnosis plus treatment | 250 and any oral hypoglycemic drugs and insulin |
| Ischemic heart disease | Defined from diagnosis | 410 ~414 |
| Heart failure | Defined from diagnosis | 428 |
| Dyslipidemia | Defined from diagnosis plus treatment | 272 and any lipid-lowering agents |
| Gout | Defined from diagnosis | 274 |
| Chronic obstructive pulmonary disease | Defined from diagnosis | 491, 492, 496 |
| Peripheral arterial disease | Defined from diagnosis | 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8 and 447.9 |
| Chronic kidney disease | Defined from diagnosis | 580 ~589, 403 ~404 016.0, 095.4, 236.9 250.4, 274.1, 442.1, 447.3, 440.1, 572.4, 642.1, 646.2 753.1 |

| | | |
|--------------------------|--|---|
| | | 283.11, 403.01, and 404.02, 446.21 |
| Dialysis | Defined from diagnosis in catastrophic registry data | 585 |
| Abnormal liver function | Defined from diagnosis | 070 , 456.0–456.2, 570, 571, 572.2–572.8, 573, V42.7 |
| Malignancy | Defined from diagnosis in catastrophic registry data | 140 ~208 |
| History of Events | | |
| Systemic thromboembolism | Defined from diagnosis in hospitalization | 444.22, 444.81, 444.21, 557.0, 557.9, 557.1 362.30, 362.34, 593.81, 444.89, 433.8, 444.9 |
| Myocardial infarction | Defined from diagnosis in hospitalization | 410 , 412 |
| Ischemic stroke | Defined from diagnosis in hospitalization | 433 ~437 |
| Outcomes | | |
| Ischemic stroke | Defined from principle diagnosis of hospitalization | 433 ~437 |
| Heart failure | Defined from principle diagnosis of hospitalization | 428 |

eTable 2. Anatomical Therapeutic Chemical (ATC) Codes of the Study Medications

| Medication ^a | ATC code | Medication ^a | ATC Code |
|---|----------|-----------------------------------|------------------|
| Angiotensin converting enzyme inhibitors/angiotensin II receptor blockers | C09 | Dipeptidyl peptidase 4 inhibitors | A10BH |
| β-blockers | C07 | Biguanides | A10BA |
| Calcium channel blockers | C08 | Glinides | A10BX02, A10BX03 |
| Diuretics | C03 | Alpha-glucosidase inhibitors | A10BF |
| Statins | C10AA | Sulfonylurea | A10BB |
| Antiplatelet agents | B01AC | Thiazolidinedione | A10BG02, A10BG03 |
| Warfarin | B01AA | Insulin | A10A |
| Digoxin | C01AA05 | | |

^aThe usage of these medications was defined as being prescribed with the medication for at least 3 months.

eTable 3. Medications Among the Atrial Fibrillation, Atrial Flutter and Matched Control Groups

| Medications (No. (%)) | Matched control (n = 24,484) | AFL (n = 6,121) | AF (n = 188,811) |
|---|---------------------------------|---------------------------|------------------------------|
| Angiotensin converting enzyme inhibitors / angiotensin II receptor blockers | 4,568 (18.7) | 1,867 (30.5) ^a | 68,671 (36.4) ^{a b} |
| Calcium channel blockers | 4,888 (20.0) | 1,344 (22.0) ^a | 46,407 (24.6) ^{a b} |
| β-blockers | 3,560 (14.5) | 1,959 (32.0) ^a | 54,890 (29.1) ^{a b} |
| Digoxin | 221 (.9) | 624 (10.2) ^a | 33,498 (17.7) ^{a b} |
| Diuretics | 972 (4.0) | 995 (16.3) ^a | 39,530 (20.9) ^{a b} |
| Spirolactone | 180 (0.7) | 269 (4.4) ^a | 10,519 (5.6) ^{a b} |
| Dipeptidyl peptidase 4 inhibitors | 162 (0.7) | 86 (1.4) ^a | 2,523 (1.3) ^a |
| Statins | 1,729 (7.1) | 631 (10.3) ^a | 18,172 (9.6) ^a |
| Biguanides | 2,053 (8.4) | 586 (9.6) ^a | 17,457 (9.2) ^a |
| Sulfonylurea | 2,279 (9.3) | 649 (10.6) ^a | 19,518 (10.3) ^a |
| Thiazolidinedione | 382 (1.6) | 101 (1.7) | 2,595 (1.4) |
| Insulin | 333 (1.4) | 225 (3.7) ^a | 6,509 (3.4) ^a |
| Anti-arrhythmic drugs | | | |
| Amiodarone/Dronedarone | 73 (0.3) | 815 (13.3) ^a | 28,497 (15.1) ^{a b} |
| Propafenone | 0 (0.0) | 287 (4.7) ^a | 9,385 (5.0) ^a |
| Sotalol | 0 (0.0) | 13 (0.2) ^a | 199 (0.1) ^{a b} |
| Flecainide | 0 (0.0) | 9 (0.15) ^a | 116 (0.06) ^{a b} |
| Antiplatelet | 3,449 (14.1) | 1,940 (31.7) ^a | 80,518 (42.6) ^{a b} |

Data are presented as mean ± SD or number (percentage);

Abbreviations: AF: atrial fibrillation; AFL: atrial flutter;

The character “^a” and “^b” denotes a significant *post hoc* comparison versus control and AFL respectively.

eTable 4. Detailed Information Of Ischemic Stroke In The AF, AFL And Control Groups Stratified By CHA2DS2-VASc

| CHA2DS2-VASc | Incidence density (95% CI) | | | AF vs. AFL | | AFL vs. Control | | AF vs. Control | |
|--------------|----------------------------------|--------------------|---------------------|-------------------|---------|-------------------|---------|-------------------|---------|
| | Matched controls (n = 24,484) | AFL (n = 6,121) | AF (n = 188,811) | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| 0 | 0.19 (0.13–0.25) | 0.39 (0.13–0.64) | 0.65 (0.57–0.72) | 1.64 (0.85, 3.19) | .14 | 1.98 (0.96, 4.07) | .064 | 3.25 (2.34, 4.51) | <.001 |
| 1 | 0.44 (0.36–0.52) | 0.40 (0.21–0.59) | 1.14 (1.06–1.22) | 2.84 (1.76, 4.60) | <.001 | 0.87 (0.53, 1.45) | .60 | 2.49 (2.06, 3.00) | <.001 |
| 2 | 1.02 (0.90–1.14) | 1.02 (0.69–1.34) | 2.30 (2.20–2.40) | 2.22 (1.60, 3.07) | <.001 | 0.94 (0.67, 1.33) | .73 | 2.08 (1.83, 2.37) | <.001 |
| 3 | 1.23 (1.07–1.38) | 1.37 (0.97–1.77) | 3.17 (3.06–3.28) | 2.26 (1.69, 3.02) | <.001 | 1.05 (0.77, 1.44) | .76 | 2.37 (2.09, 2.70) | <.001 |
| 4 | 1.78 (1.54–2.02) | 2.30 (1.72–2.88) | 3.82 (3.69–3.95) | 1.63 (1.27, 2.10) | <.001 | 1.20 (0.90, 1.60) | .21 | 1.96 (1.71, 2.25) | <.001 |
| 5-9 | 2.83 (2.48–3.18) | 3.99 (3.22–4.76) | 5.38 (5.24–5.52) | 1.34 (1.10, 1.62) | .004 | 1.29 (1.02, 1.62) | .033 | 1.72 (1.51, 1.95) | <.001 |

Abbreviations: AF: atrial fibrillation; AFL: atrial flutter; HR: hazard ratio; CI: confidence interval.

eTable 5. Baseline Characteristics and Ischemic Stroke Event of Population with Anticoagulation Therapy After Index Date

| Variables | Total (n = 46,000) | AFL (n = 703) | AF (n = 45,297) |
|---|-------------------------------|--------------------------|----------------------------|
| Age (years; mean ± SD) * | 70.5±11.9 | 67.0±13.8 | 70.5±11.8 |
| Age group (No. (%))* | | | |
| < 65 years | 13,275 (28.9) | 279 (39.7) | 12,996 (28.7) |
| 65~74 years | 14,141 (30.7) | 202 (28.7) | 13,939 (30.8) |
| ≥ 75 years | 18,584 (40.4) | 222 (31.6) | 18,362 (40.5) |
| Gender (No. (%))* | | | |
| Male | 26,124 (56.8) | 466 (66.3) | 25,658 (56.6) |
| Female | 19,876 (43.2) | 237 (33.7) | 19,639 (43.4) |
| Comorbidities (No. (%)) | | | |
| Hypertension | 29,008 (63.1) | 426 (60.6) | 28,582 (63.1) |
| Ischemic heart disease | 18,045 (39.2) | 294 (41.8) | 17,751 (39.2) |
| Diabetes mellitus* | 8,655 (18.8) | 168 (23.9) | 8,487 (18.7) |
| Chronic obstructive pulmonary disease | 6,756 (14.7) | 92 (13.1) | 6,664 (14.7) |
| Dyslipidemia* | 6,233 (13.6) | 114 (16.2) | 6,119 (13.5) |
| Heart failure* | 5,561 (12.1) | 103 (14.7) | 5,458 (12.0) |
| Gout | 5,549 (12.1) | 91 (12.9) | 5,458 (12.0) |
| Peripheral arterial disease | 1,363 (3.0) | 25 (3.6) | 1,338 (3.0) |
| Renal status* | | | |
| Non-chronic kidney disease | 40,986 (89.1) | 584 (83.1) | 40,402 (89.2) |
| Chronic kidney disease without dialysis | 4,198 (9.1) | 90 (12.8) | 4,108 (9.1) |
| Chronic kidney disease with dialysis | 816 (1.8) | 29 (4.1) | 787 (1.7) |
| Immune disease* | 719 (1.6) | 18 (2.6) | 701 (1.5) |

| | | | |
|---|---------------|---------------|---------------|
| Abnormal liver function | 4,578 (10.0) | 72 (10.2) | 4,506 (9.9) |
| Malignancy | 2,411 (5.2) | 41 (5.8) | 2,370 (5.2) |
| History of disease (No. (%)) | | | |
| Prior stroke or systemic thromboembolism | 8,137 (17.7) | 126 (17.9) | 8,011 (17.7) |
| Prior stroke | 6,736 (14.6) | 90 (12.8) | 6,646 (14.7) |
| Old myocardial infarction* | 1,871 (4.1) | 57 (8.1) | 1,814 (4.0) |
| CHA ₂ DS ₂ -VASc score (mean ± SD) * | 3.3±1.8 | 3.0±1.9 | 3.3±1.8 |
| CHA ₂ DS ₂ -VASc group* | | | |
| 0 | 2,889 (6.3) | 53 (7.5) | 2,836 (6.3) |
| 1 | 5,563 (12.1) | 114 (16.2) | 5,449 (12.0) |
| 2 | 7,836 (17.0) | 129 (18.3) | 7,707 (17.0) |
| 3 | 9,702 (21.1) | 135 (19.2) | 9,567 (21.1) |
| 4 | 8,805 (19.1) | 116 (16.5) | 8,689 (19.2) |
| 5~9 | 11,205(24.4) | 156(22.2) | 11,049(24.4) |
| Events of ischemic stroke after index date | | | |
| Event rate | 9,645 (20.97) | 63 (8.96) | 9,582 (21.15) |
| Incidence density | 6.1 (6.0–6.2) | 2.7 (2.0–3.3) | 6.2 (6.0–6.3) |

Data are presented as mean ± SD or number (percentage);

*indicates $P < 0.05$ between the two groups;

Abbreviations: AF: atrial fibrillation; AFL: atrial flutter.

eTable 6. Baseline Characteristics of Patients Who Were Prescribed Anticoagulants After Event of Ischemic Stroke After Index Date

| Variables | Total (n = 5,080) | AFL (n = 33) | AF (n = 5,047) |
|---|------------------------------|-------------------------|---------------------------|
| Age (years; mean ± SD) | 71.1±10.3 | 67.6±12.3 | 71.1±10.3 |
| Age group (No. (%)) | | | |
| < 65 years | 1,272 (25.0) | 13 (39.4) | 1,259 (24.9) |
| 65~74 years | 1,791 (35.3) | 10 (30.3) | 1,781 (35.3) |
| ≥ 75 years | 2,017 (39.7) | 10 (30.3) | 2,007 (39.8) |
| Gender (No. (%)) | | | |
| Male | 2,696 (53.1) | 23 (69.7) | 2,673 (53.0) |
| Female | 2,384 (46.9) | 10 (30.3) | 2,374 (47.0) |
| Comorbidities (No. (%)) | | | |
| Hypertension | 3,237 (63.7) | 24 (72.7) | 3,213 (63.7) |
| Ischemic heart disease | 2,057 (40.5) | 14 (42.4) | 2,043 (40.5) |
| Diabetes mellitus | 987 (19.4) | 10 (30.3) | 977 (19.4) |
| Dyslipidemia | 679 (13.4) | 5 (15.2) | 674 (13.4) |
| Gout* | 623 (12.3) | 8 (24.2) | 615 (12.2) |
| Chronic obstructive pulmonary disease | 659 (13.0) | 3 (9.1) | 656 (13.0) |
| Heart failure | 434 (8.5) | 4 (12.1) | 430 (8.5) |
| Peripheral arterial disease | 128 (2.5) | 2 (6.1) | 126 (2.5) |
| Renal status | | | |
| Non-chronic kidney disease | 4,616 (90.9) | 28 (84.8) | 4,588 (90.9) |
| Chronic kidney disease without dialysis | 412 (8.1) | 4 (12.1) | 408 (8.1) |
| Chronic kidney disease with dialysis | 52 (1.0) | 1 (3.0) | 51 (1.0) |

| | | | |
|---|--------------|----------|--------------|
| Immune disease | 66 (1.3) | 0 (0.0) | 66 (1.3) |
| Abnormal liver function | 444 (8.7) | 4 (12.1) | 440 (8.7) |
| Malignancy | 185 (3.6) | 1 (3.0) | 184 (3.6) |
| History of disease (No. (%)) | | | |
| Prior stroke or systemic thromboembolism | 823 (16.2) | 8 (24.2) | 815 (16.1) |
| Prior stroke | 765 (15.1) | 8 (24.2) | 757 (15.0) |
| Old myocardial infarction* | 176 (3.5) | 5 (15.2) | 171 (3.4) |
| CHA ₂ DS ₂ -VASc score (mean ± SD) | 3.3±1.7 | 3.3±1.8 | 3.3±1.7 |
| CHA ₂ DS ₂ -VASc group | | | |
| 0 | 278 (5.5) | 2 (6.1) | 276 (5.5) |
| 1 | 539 (10.6) | 4 (12.1) | 535 (10.6) |
| 2 | 894 (17.6) | 4 (12.1) | 890 (17.6) |
| 3 | 1,126 (22.2) | 9 (27.3) | 1,117 (22.1) |
| 4 | 1,044 (20.6) | 5 (15.2) | 1,039 (20.6) |
| 5~9 | 1,199(23.6) | 9(23.3) | 1,190(23.6) |

Data are presented as mean ± SD or number (percentage);

*indicates $P < 0.05$ between the two groups;

Abbreviations: AF: atrial fibrillation; AFL: atrial flutter.

eTable 7. Sensitivity Analysis For Those Who Did Not Receive Any Antiarrhythmic Drugs After The Index Date

| Outcome / CHA2DS2-VASc | Incidence density (95% CI) | | | AF vs. AFL | | AFL vs. Matched controls | | AF vs. Matched controls | |
|--------------------------------------|-------------------------------------|--------------------|---------------------|-----------------------|------------|-----------------------------|------------|----------------------------|------------|
| | Matched controls (n = 24,411) | AFL (n = 5,021) | AF (n = 151,640) | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Ischemic stroke | | | | | | | | | |
| 0 | 0.19 (0.13– 0.25) | 0.47 (0.16–0.77) | 0.66 (0.58–0.75) | 1.40 (0.72, 2.73) | .32 | 2.37 (1.15, 4.88) | .019 | 3.33 (2.39, 4.64) | <.001 |
| 1 | 0.44 (0.36– 0.52) | 0.41 (0.20–0.61) | 1.19 (1.09–1.28) | 2.88 (1.73, 4.80) | <.001 | 0.90 (0.53, 1.54) | .70 | 2.59 (2.14, 3.13) | <.001 |
| 2 | 1.02 (0.90– 1.15) | 1.11 (0.73–1.50) | 2.52 (2.40–2.64) | 2.21 (1.56, 3.14) | <.001 | 1.02 (0.71, 1.48) | .90 | 2.26 (1.99, 2.58) | <.001 |
| 3 | 1.23 (1.08– 1.38) | 1.30 (0.86–1.74) | 3.42 (3.29–3.54) | 2.55 (1.81, 3.57) | <.001 | 1.002 (0.70, 1.43) | .99 | 2.55 (2.24, 2.90) | <.001 |
| 4 | 1.78 (1.54– 2.02) | 2.29 (1.65–2.93) | 4.04 (3.89–4.19) | 1.72 (1.30, 2.29) | <.001 | 1.20 (0.88, 1.63) | .26 | 2.06 (1.79, 2.37) | <.001 |
| 5-9 | 2.85 (2.49– 3.20) | 4.17 (3.30–5.04) | 5.66 (5.50–5.83) | 1.33 (1.08, 1.65) | .008 | 1.34 (1.05, 1.71) | .019 | 1.78 (1.57, 2.02) | <.001 |
| Hospitalization for heart failure | | | | | | | | | |
| 0 | 0.02 (0.00– 0.04) | 0.47 (0.16–0.77) | 0.59 (0.51–0.67) | 1.22 (0.62, 2.37) | .56 | 19.39 (6.50, 57.85) | <.001 | 23.60 (9.72, 57.31) | <.001 |
| 1 | 0.07 (0.04– 0.10) | 0.19 (0.05–0.33) | 0.95 (0.87–1.03) | 4.94 (2.34, 10.41) | <.001 | 2.48 (1.06, 5.84) | .037 | 12.25 (7.92, 18.95) | <.001 |

| | | | | | | | | | |
|---------------------|---------------------|---------------------|---------------------|-------------------|-------|-------------------|-------|--------------------|-------|
| 2 | 0.20 (0.15–0.26) | 1.01 (0.64–1.38) | 1.90 (1.79–2.00) | 1.82 (1.26, 2.63) | .001 | 4.59 (2.92, 7.23) | <.001 | 8.36 (6.34, 11.04) | <.001 |
| 3 | 0.41 (0.32–0.50) | 1.19 (0.77–1.61) | 3.23 (3.11–3.36) | 2.61 (1.83, 3.71) | <.001 | 2.65 (1.76, 3.99) | <.001 | 6.90 (5.57, 8.54) | <.001 |
| 4 | 0.71 (0.57–0.86) | 2.21 (1.58–2.83) | 4.38 (4.23–4.54) | 1.92 (1.45, 2.56) | <.001 | 2.82 (1.98, 4.01) | <.001 | 5.42 (4.38, 6.70) | <.001 |
| 5-9 | 1.33 (1.09–1.56) | 4.75 (3.82–5.67) | 6.95 (6.77–7.13) | 1.42 (1.17, 1.72) | <.001 | 3.11 (2.39, 4.05) | <.001 | 4.41 (3.69, 5.28) | <.001 |
| All-cause mortality | | | | | | | | | |
| 0 | 0.63 (0.53–0.74) | 4.75 (3.79–5.72) | 4.82 (4.59–5.04) | 0.98 (0.79, 1.21) | .84 | 7.21 (5.54, 9.38) | <.001 | 7.06 (5.93, 8.40) | <.001 |
| 1 | 1.40 (1.27–1.54) | | 6.72 (6.51–6.93) | 1.43 (1.23, 1.66) | <.001 | 3.13 (2.62, 3.74) | <.001 | 4.47 (4.04, 4.95) | <.001 |
| 2 | 4.94 (4.67–5.21) | 12.44 (11.16–13.72) | 15.85 (15.57–16.14) | 1.25 (1.12, 1.38) | <.001 | 2.30 (2.05, 2.59) | <.001 | 2.87 (2.71, 3.04) | <.001 |
| 3 | 6.15 (5.82–6.48) | 16.69 (15.15–18.24) | 20.70 (20.39–21.00) | 1.20 (1.09, 1.32) | <.001 | 2.47 (2.22, 2.76) | <.001 | 2.97 (2.81, 3.14) | <.001 |
| 4 | 7.38 (6.90–7.86) | 21.87 (19.94–23.81) | 23.52 (23.17–23.87) | 1.05 (0.96, 1.15) | .26 | 2.71 (2.42, 3.02) | <.001 | 2.85 (2.66, 3.04) | <.001 |
| 5-9 | 10.89 (10.22–11.55) | 31.78 (29.46–34.09) | 32.91 (32.53–33.28) | 1.02 (0.95, 1.10) | .62 | 2.61 (2.37, 2.87) | <.001 | 2.65 (2.49, 2.82) | <.001 |

Abbreviations: AF: atrial fibrillation; AFL: atrial flutter; HR: hazard ratio; CI: confidence interval.

eTable 8. Analysis Of Falsification End-Point Using Hepatocellular Carcinoma As Outcome

| CHA2DS2-VASc | Incidence density (95% CI) | | AF vs. AFL | |
|--------------|----------------------------|-----------------------------|--------------------|----------------|
| | AFL (<i>n</i> = 6,121) | AF (<i>n</i> = 188,811) | HR (95% CI) | <i>P</i> value |
| 0 | 0.04 (-0.04–0.13) | 0.23 (0.19–0.28) | 5.41 (0.75, 38.74) | .09 |
| 1 | 0.18 (0.06–0.31) | 0.30 (0.26–0.34) | 1.60 (0.79, 3.24) | .19 |
| 2 | 0.22 (0.07–0.37) | 0.36 (0.32–0.40) | 1.62 (0.81, 3.27) | .18 |
| 3 | 0.44 (0.22–0.66) | 0.37 (0.34–0.41) | 0.83 (0.50, 1.39) | .48 |
| 4 | 0.32 (0.11–0.53) | 0.40 (0.36–0.44) | 1.21 (0.63, 2.35) | .57 |
| 5-9 | 0.43 (0.19–0.68) | 0.32 (0.29–0.35) | 0.74 (0.42, 1.31) | .30 |

Abbreviations: AF: atrial fibrillation; AFL: atrial flutter; HR: hazard ratio; CI: confidence interval.