

SUPPLEMENTAL MATERIAL

Table S1. ICD-9-CM codes for comorbidities, a frailty index, and endpoint diagnosis.

Outcome	ICD-9-CM Codes
Endpoints	
Stroke	346.6, 414.12, V45.81, V45.82, 430-437, 444
Myocardial infarction	410, 412
Heart Failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.9, 428
Comorbidities	
Hypertension	362.11, 401, 402, 403, 404, 405, 437.2
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Coronary artery disease	410, 411, 412, 413, 414.0, 414.12, 414.2, 414.3, 414.8, 414.9, V45.81, V45.82
Hyperlipidemia	272.0, 272.1, 272.2, 272.3, 272.4
Arthritis	714, 715, 720.0, 721.0, 721.1, 721.2, 721.3, V13.4, 721.90, 721.91
Peripheral artery disease	440.0, 440.2, 440.9, 443.9
Gastrointestinal bleeding	456.20, 530.82, 535.x1, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.85, 455.2, 455.5, 455.8, 456.0, 530.7, 531.0 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 569.3, 578.0, 578.1, 578.9
Cerebral bleeding	430, 431, 432, 852
Other bleeding	423.0, 459.0, 568.81, 593.81, 599.7, 623.8, 626.6, 719.1, 784.7, 784.8, 786.3
Anemia	280-285
Coagulopathy	286, 287.1, 287.3, 287.4, 287.5
Mood disorder	293.83, 296, 311
Cognitive impairment and dementia	290, 293.0, 293.1, 294, 310.0, 310.2, 310.81, 310.89, 310.9, 331, 797
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0, 456.1, 456.2, 572.x, 573.3, 573.4, 573.8, 573.9, V42.7
Alcohol abuse	265.2, 291.1, 291.2, 291.3, 291.5, 291.6, 291.7, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3, V11.3, 980
Asthma	493
Cancer	140.0, 140.1, 140.3-140.9, 141.0-141.6, 141.8, 141.9, 142.0, 142.1, 142.2, 142.8, 142.9, 143.0, 143.1, 143.8, 143.9, 144.0, 144.1, 144.8, 144.9, 145.0-145.6, 145.8, 145.9, 146.x, 147.0-147.3, 147.8, 147.9, 148.0-148.3, 148.8, 148.9, 149.0, 149.1, 149.8, 149.9, 150.0-150.5, 150.8, 150.9, 151.0-151.6, 151.8, 151.9, 152.0-152.3, 152.8, 152.9, 153.x, 154.0-154.3, 154.8, 155.0-155.2, 156.0-156.2, 156.8, 156.9, 157.0-157.4, 157.8, 157.9, 158.0, 158.8, 158.9, 159.0, 159.1, 159.8, 159.9, 160.0-160.5, 160.8, 160.9, 161.0-161.3, 161.8, 161.9, 162.0, 162.2-162.5, 162.8, 162.9, 163.0, 163.1, 163.8., 163.9, 164.0-164.3, 164.8, 164.9, 165.0, 165.8, 165.9, 170.x,

	171.0, 171.2-171.9, 172.x, 173.x, 174.0-174.6, 174.8, 174.9, 175.0, 175.9, 176.0-176.5, 176.8, 176.9, 179, 180.0, 180.1, 180.8, 180.9, 181, 182.0, 182.1, 182.8, 183.0, 183.2-183.5, 183.8, 183.9, 184.0-184.4, 184.8, 184.9, 185, 186.0, 186.9, 187.x, 188.x, 184.0-184.4, 186.0, 186.9, 187.x, 188.x, 189.0-189.4, 189.8, 198.9, 192.0-192.3, 192.8, 192.9, 193, 194.0, 194.1, 194.3-194.6, 194.8, 194.9, 195.0-195.5, 195.8, 196.0-196.3, 196.5, 196.6, 196.8, 196.9, 197.x, 198.x, 199.0-199.2, 203.0, 203.1, 203.8, 204.0-204.2, 204.8, 204.9, 205.0-205.3, 205.8, 205.9, 206.0-206.2, 206.8, 206.9, 207.0-207.2, 207.8, 208.0-208.2, 208.8, 208.9, 230.x, 231.0-231.2, 231.8, 231.9, 232.x, 233.x, 234.0, 234.8, 234.9, 795.0, V10.3, V10.9, V71.1, 173.00-173.02, 173.09, 173.10-173.12, 173.19, 173.20-173.22, 173.29, 173.30-173.32, 173.39, 173.40-173.42, 173.49, 173.50-173.52, 173.59, 173.60-173.62, 173.69, 173.70-173.72, 173.79, 173.80-173.82, 173.89, 173.90-173.92, 173.99, 198.81, 198.82, 198.89, 200.x, 201.x, 202.x, 203.x, 204.x, 205.x, 206.x, 207.x, 208.x, 209.x, 233.3x, 258.02, 258.03, 511.81, 789.51, 795.00-795.04, 795.06, 795.10-795.14, 795.16, 796.70-796.74, 796.76, V10.x
Chronic kidney disease	236.91, 249.40, 249.41, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 753.1x, V45.11, V45.12, V56.31, V56.32, 189.0, 198.9, 223.0, 250.4, 271.4, 440.1, 442.1, 572.4, 753.2, 792.5, 794.4, 016.0, 095.4, V42.0, V45.1, V56.0, V56.1, V56.2, V56.8, 580-588, 591
Chronic pulmonary disease	490, 491, 492, 494, 496
Depression	296.2, 296.3, 296.5x, 296.6, 296.89, 298.0, 300.4, 309.1, 311
Diabetes	249, 250, 357.2, 362.01, 362.02, 366.41, 790.2, 791.5, 791.6, V45.85, V53.91, V65.46
Hepatitis	070, 072.71, 571.4, 573.1, 573.2, 573.3
Osteoporosis	733.0
Schizophrenia	293.81, 293.82, 295, 297, 298
Substance abuse	291, 292, 303, 304, 305.x, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3, 648.3, 655.5, 760.71, 760.72, 760.73, 760.75, 779.5, 965.0, 980.0, V65.42
Frailty Index	
Abnormal gait	781.2
Abnormal weight loss	260-263, 783.2
Arthritis	710-712, 714, 715, 718, 725, 716.5-716.9, 719.0, 719.1, 719.4, 719.5, 719.9
Bladder dysfunction	596.5, 599.6, 788.2, 788.3
Cachexia	799.4
Debility	799.3
Difficulty walking	719.7, 781.2, 781.3, V46.3
Failure to thrive	783.7
Fall	V15.88, E880-E888, E929.3
Malaise/fatigue	780.7
Muscular wasting/disuse atrophy	728.2

Muscle weakness	V49.84, 728.2, 728.3, 728.87, 799.3
Paralysis	342, 344, 438.2-438.5, 781.4
Parkinson's disease	332
Podiatric care	681.1, 700, 703
Pressure ulcers	707.x
Psychiatric illness	29x, 300.0, 310, 311
Rehabilitation care	V57.1, V57.21, V57.3, V57.8, V57.9
Senility, minus psychosis	797
Shock/hypotension	458, 785.5, 958.4, 998.0
Stroke and brain injury	348, 349.82, 430-432, 433.01, 433.11, 433.21, 433.31, 433.91, 436, 434.01, 434.11, 434.91, 852-854

Table S2. Medications prescribed at the time of atrial fibrillation (AF) diagnosis (polypharmacy definition 1) and within the 30-day period after AF diagnosis (polypharmacy definition 2): MarketScan, 2007-2015.

Therapeutic Class	Active at time of AF diagnosis	Prescribed within 30 days after AF diagnosis
Prescriptions, n	1,761,660	1,596,888
Most common prescriptions, n (%)		
Antihyperlipidemic drugs	158,531 (9.0)	94,294 (5.9)
Beta blockers	156,229 (8.9)	139,253 (8.7)
Anticoagulants	108,588 (6.2)	141,680 (8.9)
Calcium channels	92,047 (5.2)	76,395 (4.8)
Angiotensin converting enzyme (ACE) inhibitors	79,726 (4.5)	55,582 (3.5)
Loop diuretics	73,271 (4.2)	69,242 (4.3)
Thyroid hormones	64,211 (3.6)	39,310 (2.5)
Unclassified agents	61,669 (3.5)	38,007 (2.4)
Gastrointestinal drugs	61,138 (3.5)	47,901 (3.0)
Cardiac drugs, not otherwise specified	60,241 (3.4)	34,493 (2.2)
Antidepressants	55,693 (3.2)	40,752 (2.6)
Potassium supplements	42,714 (2.4)	40,837 (2.6)
Cardiac glycosides	40,728 (2.3)	40,355 (2.5)
Antidiabetic agents	35,321 (2.0)	19,923 (1.3)
Antiplatelet agents	34,086 (1.9)	24,464 (1.5)
Hormonal agents (adrenal)	28,059 (1.6)	31,845 (2.0)
Eye/ear/nose/throat	27,933 (1.6)	17,255 (1.1)
Thiazides and related	26,880 (1.5)	15,798 (1.0)
Antiarrhythmic agents	23,983 (1.4)	39,350 (2.5)
Opiate agonists	21,757 (1.2)	51,660 (3.2)

Table S3. Medications prescribed at the time of atrial fibrillation (AF) diagnosis, by polypharmacy category: MarketScan, 2007-2015. Polypharmacy redefined to include substantial polypharmacy category (≥ 10 prescriptions) at the time of AF diagnosis (polypharmacy definition 1).

Therapeutic Class	≤ 5 prescriptions (Polypharmacy = 0)	5 – 9 prescriptions (Polypharmacy = 1)	≥ 10 prescriptions (Polypharmacy = 2)
Prescriptions, n (%)	367,377 (20.9)	896,247 (50.9)	498,036 (28.3)
Most common prescriptions			
Antihyperlipidemic drugs	32,326 (8.8)	86,257 (9.6)	39,948 (8.0)
Beta blockers	38,890 (10.6)	83,399 (9.3)	33,940 (6.8)
Anticoagulants	23,936 (6.5)	58,933 (6.6)	25,719 (5.2)
Calcium channels	21,876 (6.0)	49,219 (5.5)	20,952 (4.2)
Angiotensin converting enzyme (ACE) inhibitors	18,334 (5.0)	43,504 (4.9)	17,888 (3.6)
Loop diuretics	9,617 (2.6)	38,722 (4.3)	24,932 (5.0)
Thyroid hormones	13,675 (3.7)	33,984 (3.8)	16,552 (3.3)
Unclassified agents	12,785 (3.5)	32,374 (3.6)	16,510 (3.3)
Gastrointestinal drugs	10,163 (2.8)	31,977 (3.6)	18,998 (3.8)
Cardiac drugs, not otherwise specified	13,281 (3.6)	32,417 (3.6)	14,543 (2.9)
Antidepressants	8,380 (2.3)	28,294 (3.2)	19,019 (3.8)
Potassium supplements	4,781 (1.3)	22,613 (2.5)	15,320 (3.1)
Cardiac glycosides	8,299 (2.3)	21,620 (2.4)	10,809 (2.2)
Antidiabetic agents	3,996 (1.1)	18,186 (2.0)	13,139 (2.6)
Antiplatelet agents	5,792 (1.6)	18,215 (2.0)	10,079 (2.0)
Hormonal agents (adrenal)	4,347 (1.2)	13,483 (1.5)	10,229 (2.1)
Eye/ear/nose/throat	5,679 (1.6)	14,536 (1.6)	7,718 (1.6)
Thiazides and related	5,782 (1.6)	14,774 (1.7)	6,324 (1.3)
Antiarrhythmic agents	5,148 (0.3)	12,881 (0.7)	5,954 (0.3)
Opiate agonists	3,748 (0.2)	10,485 (0.6)	7,524 (0.4)

Table S4. Characteristics by polypharmacy use among atrial fibrillation (AF) patients \geq 75: MarketScan, 2007-2015. Polypharmacy defined by the 30-day period after AF diagnosis (polypharmacy definition 2).

	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)
N (%)	195,448 (57.7)	143,362 (42.3)
Age, mean (standard deviation)	83.3 (5.4)	82.8 (5.3)
Female, %	49.6	52.7
Comorbidities, %		
Hypertension	70.2	75.0
Congestive heart failure	28.8	39.6
Coronary artery disease	43.2	51.1
Hyperlipidemia	44.6	48.5
Stroke	27.4	29.5
Arthritis	32.1	35.9
Myocardial infarction	9.2	12.5
Peripheral artery disease	18.1	20.6
Gastrointestinal bleeding	9.9	11.1
Cerebral bleeding	2.1	1.7
Other bleeding	11.6	12.7
Anemia	25.7	29.6
Coagulopathy	6.9	7.7
Mood disorder	7.8	9.6
Cognitive impairment	6.4	6.2
Liver disease	3.5	4.2
Alcohol abuse	0.8	0.9
Asthma	6.2	9.3
Cancer	31.6	32.4
Chronic kidney disease	22.3	27.0
Chronic pulmonary disease	22.5	30.0
Dementia	14.2	13.9
Depression	7.9	9.9
Diabetes	27.8	36.1
Hepatitis	0.5	0.7
Osteoporosis	9.8	10.7
Schizophrenia	4.1	4.2
Substance abuse	1.4	1.7
AF treatment during 30 days after AF, %		
Oral anticoagulation	16.3	45.7
Antiarrhythmic drugs	1.2	2.9
Catheter ablation	0.2	0.3
Cardioversion	1.3	1.9
Rate control therapy	26.1	74.9

Table S5. Characteristics by polypharmacy use among atrial fibrillation (AF) patients \geq 75: MarketScan, 2007-2015. Polypharmacy defined by time at AF diagnosis plus the 30-day period after AF diagnosis (polypharmacy definition 3).

	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)
N (%)	74,787 (22.1)	264,023 (77.9)
Age, mean (standard deviation)	83.8 (5.6)	82.9 (5.3)
Female, %	49.8	51.2
Comorbidities, %		
Hypertension	65.8	74.0
Congestive heart failure	29.2	34.5
Coronary artery disease	39.0	48.6
Hyperlipidemia	39.2	48.2
Stroke	28.1	28.3
Arthritis	31.4	34.4
Myocardial infarction	9.4	11.0
Peripheral artery disease	17.9	19.5
Gastrointestinal bleeding	10.5	10.3
Cerebral bleeding	2.7	1.7
Other bleeding	11.3	12.3
Anemia	27.3	27.4
Coagulopathy	6.9	7.3
Mood disorder	8.8	8.5
Cognitive impairment	8.7	5.7
Liver disease	3.6	3.8
Alcohol abuse	1.1	0.8
Asthma	5.4	8.1
Cancer	30.3	32.4
Chronic kidney disease	22.6	24.8
Chronic pulmonary disease	22.5	26.6
Dementia	18.5	12.8
Depression	8.8	8.7
Diabetes	24.2	33.4
Hepatitis	0.6	0.6
Osteoporosis	9.7	10.4
Schizophrenia	5.3	3.8
Substance abuse	1.7	1.5
AF treatment during 30 days after AF, %		
Oral anticoagulation	7.0	34.9
Antiarrhythmic drugs	0.6	2.3
Catheter ablation	0.2	0.3
Cardioversion	0.9	1.7
Rate control therapy	12.8	56.4

Table S6. Characteristics by polypharmacy use among atrial fibrillation (AF) patients ≥ 75 : MarketScan, 2007-2015. Polypharmacy redefined to include substantial polypharmacy category (≥ 10 prescriptions) at the time of AF diagnosis (polypharmacy definition 1).

	≤ 5 prescriptions (Polypharmacy=0)	5 – 9 prescriptions (Polypharmacy=1)	≥ 10 prescriptions (Polypharmacy=2)
N (%)	162,803 (48.1)	135,063 (39.9)	40,944 (12.1)
Age, mean (standard deviation)	83.3 (5.5)	83.0 (5.3)	82.4 (5.1)
Female, %	50.5	51.3	51.0
Comorbidities, %			
Hypertension	64.1	71.8	73.3
Congestive heart failure	26.5	31.0	43.6
Coronary artery disease	38.7	46.5	56.2
Hyperlipidemia	40.8	47.0	47.5
Stroke	25.3	26.3	30.0
Arthritis	30.2	32.2	37.8
Myocardial infarction	9.3	9.7	12.2
Peripheral artery disease	15.8	18.2	22.4
Gastrointestinal bleeding	8.9	9.1	10.6
Cerebral bleeding	1.9	1.5	1.6
Other bleeding	10.3	11.1	11.9
Anemia	23.8	24.3	30.4
Coagulopathy	5.9	6.3	7.1
Mood disorder	6.6	7.4	10.9
Cognitive impairment	6.6	5.1	5.8
Liver disease	3.4	3.3	3.7
Alcohol abuse	0.9	0.7	0.7
Asthma	5.7	7.4	11.2
Cancer	30.2	31.0	30.9
Chronic kidney disease	19.9	22.9	31.9
Chronic pulmonary disease	21.5	24.0	33.2
Dementia	13.1	11.4	14.0
Depression	6.8	7.6	11.1
Diabetes	23.2	32.7	50.1
Hepatitis	0.5	0.5	0.6
Osteoporosis	9.5	9.7	10.1
Schizophrenia	3.7	3.1	4.3
Substance abuse	1.5	1.3	1.6
AF treatment during 30 days after AF, %			
Oral anticoagulation	24.5	32.7	32.7
Antiarrhythmic drugs	1.7	2.2	1.9
Catheter ablation	0.2	0.3	0.3
Cardioversion	1.3	1.7	2.0
Rate control therapy	41.2	51.8	52.2

Table S7. Hazard ratios (HRs) and 95% confidence intervals (CIs)* of the outcomes after 30 days post atrial fibrillation (AF) comparing polypharmacy users with non-polypharmacy users among AF patients ≥ 75 : MarketScan, 2007-2015. Polypharmacy defined by the 30-day period after AF diagnosis (polypharmacy definition 2).

Outcome	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)
N	195,448	143,362
Stroke		
n (%)	5,281 (2.7)	4,161 (2.9)
follow-up, year (SD)	2.0 (1.8)	2.0 (1.8)
Incident rate †	13.8	14.5
HR (95%CI)	1	1.03 (0.98, 1.08)
Major bleeding		
n (%)	8,874 (4.5)	8,305 (5.8)
follow-up, year	1.9 (1.8)	1.9 (1.8)
Incident rate †	23.6	29.7
HR (95%CI)	1	1.12 (1.09, 1.17)
Heart failure		
n (%)	11,195 (5.7)	12,374 (8.6)
follow-up, year	1.9 (1.8)	1.9 (1.8)
Incident rate †	29.9	44.8
HR (95%CI)	1	1.22 (1.18, 1.26)

SD, standard deviation. HR, hazard ratio. CI, confidence interval.

* models adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy).

† Per 1,000 person-years

Table S8. Hazard ratios (HRs) and 95% confidence intervals (CIs)* of the outcomes after 30 days post atrial fibrillation (AF) comparing polypharmacy users with non-polypharmacy users among AF patients ≥ 75 : MarketScan, 2007-2015. Polypharmacy defined by time at AF diagnosis plus within 30 days after AF diagnosis (polypharmacy definition 3).

Outcome	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)
N	74,787	264,023
Stroke		
n (%)	1,932 (2.6)	7,510 (2.8)
follow-up, year (SD)	1.8 (1.8)	2.0 (1.8)
Incident rate †	14.6	14.0
HR (95%CI)	1	0.98 (0.93, 1.03)
Major bleeding		
n (%)	2,819 (3.8)	14,360 (5.4)
follow-up, year	1.7 (1.7)	2.0 (1.8)
Incident rate †	21.6	27.4
HR (95%CI)	1	1.17 (1.12, 1.22)
Heart failure		
n (%)	3,330 (4.5)	20,239 (7.7)
follow-up, year	1.7 (1.7)	2.0 (1.8)
Incident rate †	25.5	38.9
HR (95%CI)	1	1.32 (1.27, 1.37)

SD, standard deviation. HR, hazard ratio. CI, confidence interval.

* models adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy).

† Per 1,000 person-years

Table S9. Hazard ratios (HRs) and 95% confidence intervals (CIs)* of the outcomes after 30 days post atrial fibrillation (AF) comparing polypharmacy users with non-polypharmacy users among AF patients ≥ 75 : MarketScan, 2007-2015. Polypharmacy redefined to include substantial polypharmacy category (≥ 10 prescriptions) at the time of AF diagnosis (polypharmacy definition 1).

	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)	Exposed (Polypharmacy=2)
N (%)	162,803 (48.1)	135,063 (39.9)	40,944 (12.1)
Stroke			
Event, n (%)	4,582 (2.8)	3,747 (2.8)	1,113 (2.7)
Follow-up, year (SD)	2.0 (1.8)	2.1 (1.8)	2.0 (1.8)
Incident rate †	14.0	13.1	13.6
HR (95%CI)	1	0.96 (0.92, 1.00)	0.99 (0.092, 1.06)
Major bleeding			
n (%)	7,212 (4.4)	7,395 (5.5)	2,572 (6.3)
Follow-up, year	2.0 (1.8)	2.1 (1.8)	1.9 (1.7)
Incident rate †	22.3	26.5	32.2
HR (95%CI)	1	1.13 (1.10, 1.17)	1.25 (1.20, 1.32)
Heart failure			
n (%)	8,718 (5.4)	10,397 (7.7)	4,454 (10.9)
Follow-up, year	2.0 (1.8)	2.1 (1.8)	1.9 (1.7)
Incident rate †	27.0	37.5	57.0
HR (95%CI)	1	1.26 (1.22, 1.29)	1.55 (1.50, 1.61)

SD, standard deviation. HR, hazard ratio. CI, confidence interval.

* models adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy).

† Per 1,000 person-years

Table S10. Hazard ratios (HRs) and 95% confidence intervals (CIs)* of the outcomes after 30 days' post atrial fibrillation (AF) comparing different AF treatments by polypharmacy use among AF patients ≥ 75 , MarketScan, 2007-2015. Polypharmacy redefined to include substantial polypharmacy category (≥ 10 prescriptions) at the time of AF diagnosis (polypharmacy definition 1).

Hazard ratios (HRs) and 95% confidence intervals (CIs)* of the outcomes after 30 days post atrial fibrillation (AF) comparing different AF treatments by polypharmacy use among AF patients ≥ 75, MarketScan, 2007-2015									
HR (95% CI)	Stroke			Major bleeding			Heart failure		
	Polypharmacy =0	Polypharmacy =1	Polypharmacy =2	Polypharmacy =0	Polypharmacy =1	Polypharmacy =2	Polypharmacy =0	Polypharmacy =1	Polypharmacy =2
N=338,810	OAC vs No OAC								
No OAC	1	1	1	1	1	1	1	1	1
OAC	0.93 (0.86, 0.99)	0.93 (0.86, 0.99)	0.78 (0.68, 0.89)	1.32 (1.25, 1.39)	1.22 (1.16, 1.28)	1.13 (1.04, 1.23)	1.09 (1.04, 1.15)	1.08 (1.03, 1.12)	1.07 (1.00, 1.14)
			p=0.17			p=0.01			p=0.90
N=97,335	Warfarin vs Dabigatran vs Rivaroxaban vs Apixaban								
Warfarin	1	1	1	1	1	1	1	1	1
Dabigatran	1.16 (0.92, 1.48)	1.08 (0.84, 1.38)	0.97 (0.58, 1.65)	0.87 (0.72, 1.05)	0.98 (0.84, 1.15)	0.88 (0.65, 1.20)	0.68 (0.56, 0.84)	0.85 (0.73, 1.00)	0.94 (0.75, 1.18)
Rivaroxaban	0.79 (0.57, 1.11)	0.93 (0.67, 1.29)	0.81 (0.41, 1.58)	0.95 (0.77, 1.17)	1.03 (0.86, 1.25)	1.21 (0.89, 1.64)	0.87 (0.71, 1.07)	0.84 (0.70, 1.01)	0.74 (0.56, 0.98)
Apixaban	0.65 (0.33, 1.25)	0.56 (0.28, 1.12)	0.57 (0.14, 2.31)	0.65 (0.42, 1.00)	0.81 (0.57, 1.14)	0.61 (0.30, 1.23)	0.79 (0.56, 1.12)	0.89 (0.67, 1.18)	0.65 (0.39, 1.06)
			p=0.76			p=0.85			p=0.33
N=163,506	Rhythm control vs Rate control								
Rate control	1	1	1	1	1	1	1	1	1
Rhythm control	0.78 (0.64, 0.93)	0.84 (0.71, 1.01)	0.64 (0.44, 0.91)	0.85 (0.74, 0.98)	0.93 (0.83, 1.05)	0.92 (0.76, 1.13)	0.87 (0.76, 0.99)	0.99 (0.90, 1.10)	0.95 (0.82, 1.10)
			p=0.64			p=0.26			p=0.06

HR, hazard ratio. CI, confidence interval. OAC, oral anticoagulant.

* models adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy).

Table S11. Hazard ratios (HRs) and 95% confidence intervals (CIs)* of the outcomes after 30 days' post atrial fibrillation (AF) comparing different AF treatments by polypharmacy use among AF patients ≥ 75 , MarketScan, 2007-2015. Polypharmacy defined by the 30-day period after AF diagnosis (polypharmacy definition 2).

HR (95% CI)	Stroke		Major bleeding		Heart failure	
	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)
N=338,810	OAC vs No OAC					
No OAC	1	1	1	1	1	1
OAC	0.94 (0.87, 1.01)	0.86 (0.81, 0.92)	1.15 (1.09, 1.22)	1.25 (1.20, 1.31)	0.98 (0.93, 1.03)	1.08 (1.04, 1.12)
		p=0.07		p=0.01		p=0.0003
N=97,335	Warfarin vs Dabigatran vs Rivaroxaban vs Apixaban					
Warfarin	1	1	1	1	1	1
Dabigatran	1.06 (0.80, 1.41)	1.13 (0.92, 1.38)	0.76 (0.61, 0.94)	1.01 (0.89, 1.15)	0.78 (0.63, 0.97)	0.83 (0.73, 0.94)
Rivaroxaban	1.11 (0.80, 1.54)	0.72 (0.54, 0.97)	1.04 (0.83, 1.30)	1.02 (0.88, 1.19)	0.79 (0.61, 1.01)	0.84 (0.73, 0.97)
Apixaban	0.76 (0.38, 1.53)	0.52 (0.29, 0.95)	0.61 (0.37, 1.00)	0.78 (0.58, 1.04)	0.67 (0.43, 1.06)	0.84 (0.67, 1.05)
		p=0.77		p=0.30		p=0.57
N=163,506	Rhythm control vs Rate control					
Rate control	1	1	1	1	1	1
Rhythm control	0.84 (0.70, 1.01)	0.75 (0.64, 0.89)	0.92 (0.80, 1.05)	0.90 (0.81, 1.00)	0.86 (0.76, 0.98)	0.99 (0.91, 1.07)
		p=0.51		p=0.95		p=0.03

HR, hazard ratio. CI, confidence interval. OAC, oral anticoagulant.

* models adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy).

Table S12. Hazard ratios (HRs) and 95% confidence intervals (CIs)* of the outcomes after 30 days' post atrial fibrillation (AF) comparing different AF treatments by polypharmacy use among AF patients ≥ 75 , MarketScan, 2007-2015. Polypharmacy defined by time at AF diagnosis plus within 30 days after AF diagnosis (polypharmacy definition 3).

HR (95% CI)	Stroke		Major bleeding		Heart failure	
	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)	Control (Polypharmacy=0)	Exposed (Polypharmacy=1)
N=338,810	OAC vs No OAC					
No OAC	1	1	1	1	1	1
OAC	0.98 (0.83, 1.16)	0.90 (0.86, 0.94)	1.13 (0.99, 1.30)	1.23 (1.18, 1.27)	0.85 (0.74, 0.99)	1.07 (1.04, 1.10)
		p=0.19		p=0.11		p=0.001
N=97,335	Warfarin vs Dabigatran vs Rivaroxaban vs Apixaban					
Warfarin	1	1	1	1	1	1
Dabigatran	1.68 (0.93, 3.02)	1.07 (0.90, 1.27)	0.78 (0.43, 1.40)	0.93 (0.83, 1.04)	0.43 (0.19, 0.99)	0.82 (0.74, 0.91)
Rivaroxaban	1.16 (0.53, 2.53)	0.84 (0.66, 1.05)	1.00 (0.54, 1.86)	1.02 (0.90, 1.16)	0.20 (0.05, 0.79)	0.84 (0.74, 0.95)
Apixaban	2.23 (0.69, 7.20)	0.53 (0.32, 0.86)	1.28 (0.47, 3.49)	0.70 (0.54, 0.90)	NA	0.82 (0.67, 1.00)
		p=0.55		p=0.94		p=0.35
N=163,506	Rhythm control vs Rate control					
Rate control	1	1	1	1	1	1
Rhythm control	0.72 (0.47, 1.08)	0.79 (0.70, 0.90)	0.62 (0.42, 0.91)	0.92 (0.85, 1.01)	1.04 (0.77, 1.40)	0.93 (0.87, 1.00)
		p=0.45		p=0.03		p=0.58

HR, hazard ratio. CI, confidence interval. OAC, oral anticoagulant.

* models adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy).

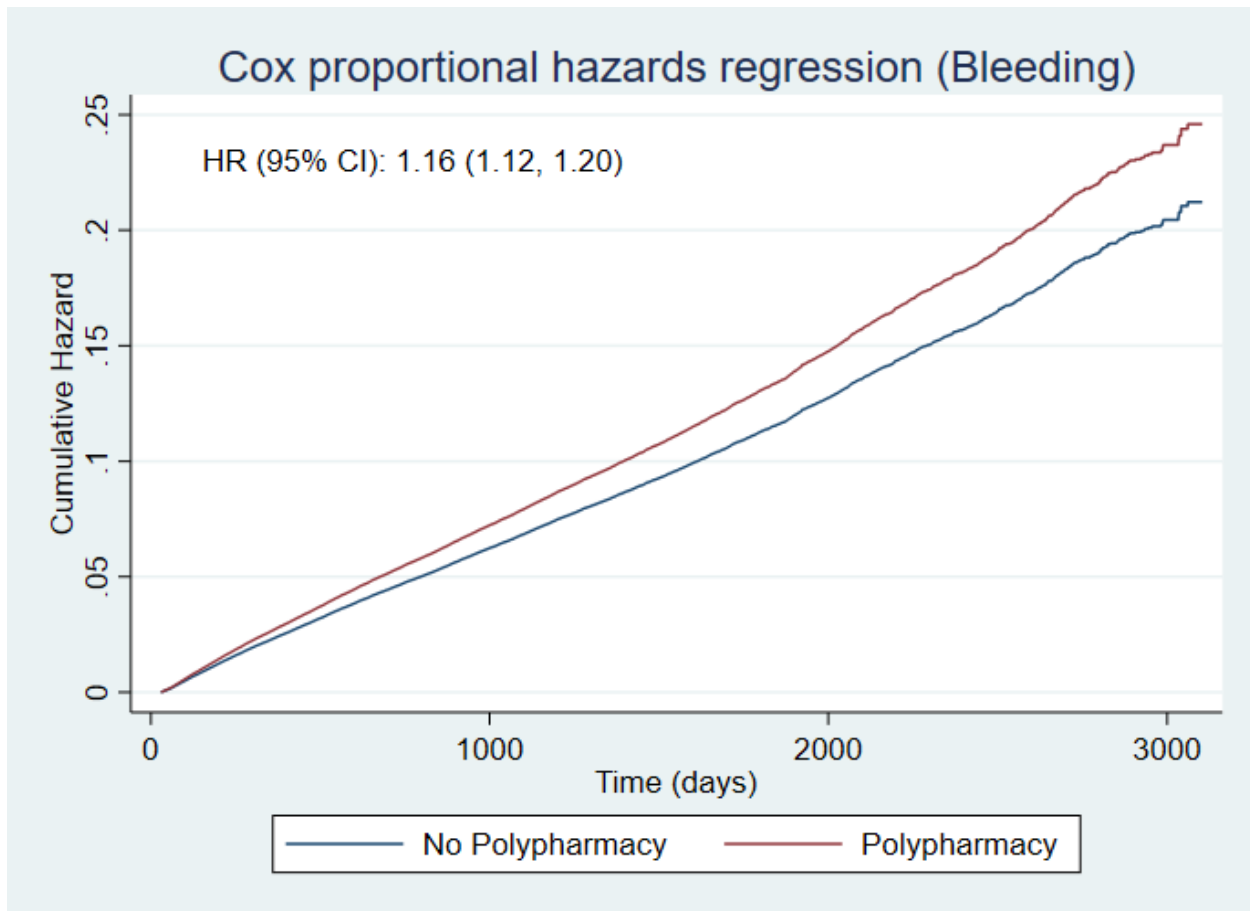


Figure S1. Cumulative hazard of bleeding events by polypharmacy status among atrial fibrillation (AF) patients ≥ 75 , MarketScan, 2007-2015 (polypharmacy definition 1). HR (95% CI) listed is adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy). HR, hazard ratio. CI, confidence interval.

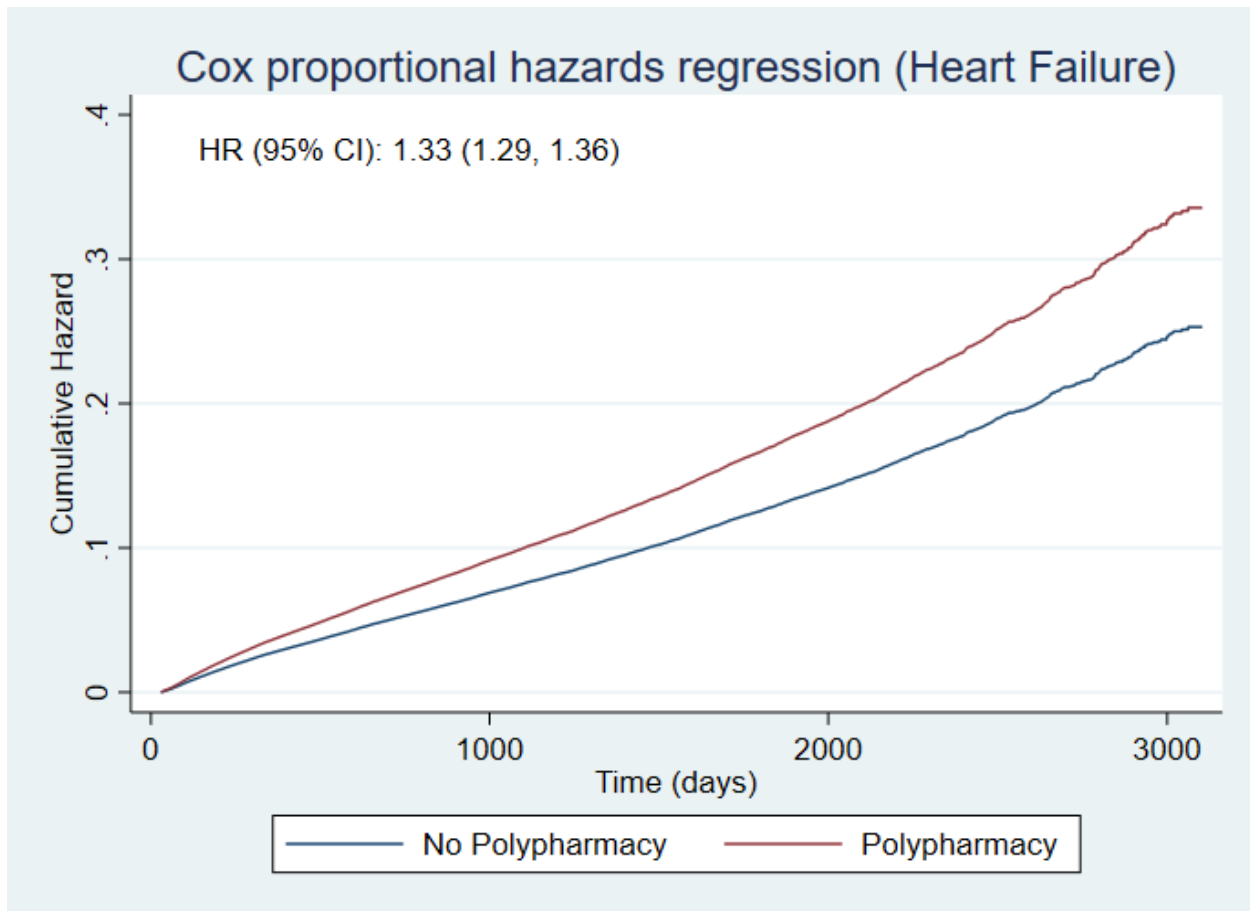


Figure S2. Cumulative hazard of heart failure by polypharmacy status among atrial fibrillation (AF) patients ≥ 75 , MarketScan, 2007-2015 (polypharmacy definition 1). HR (95% CI) listed is adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy). HR, hazard ratio. CI, confidence interval.

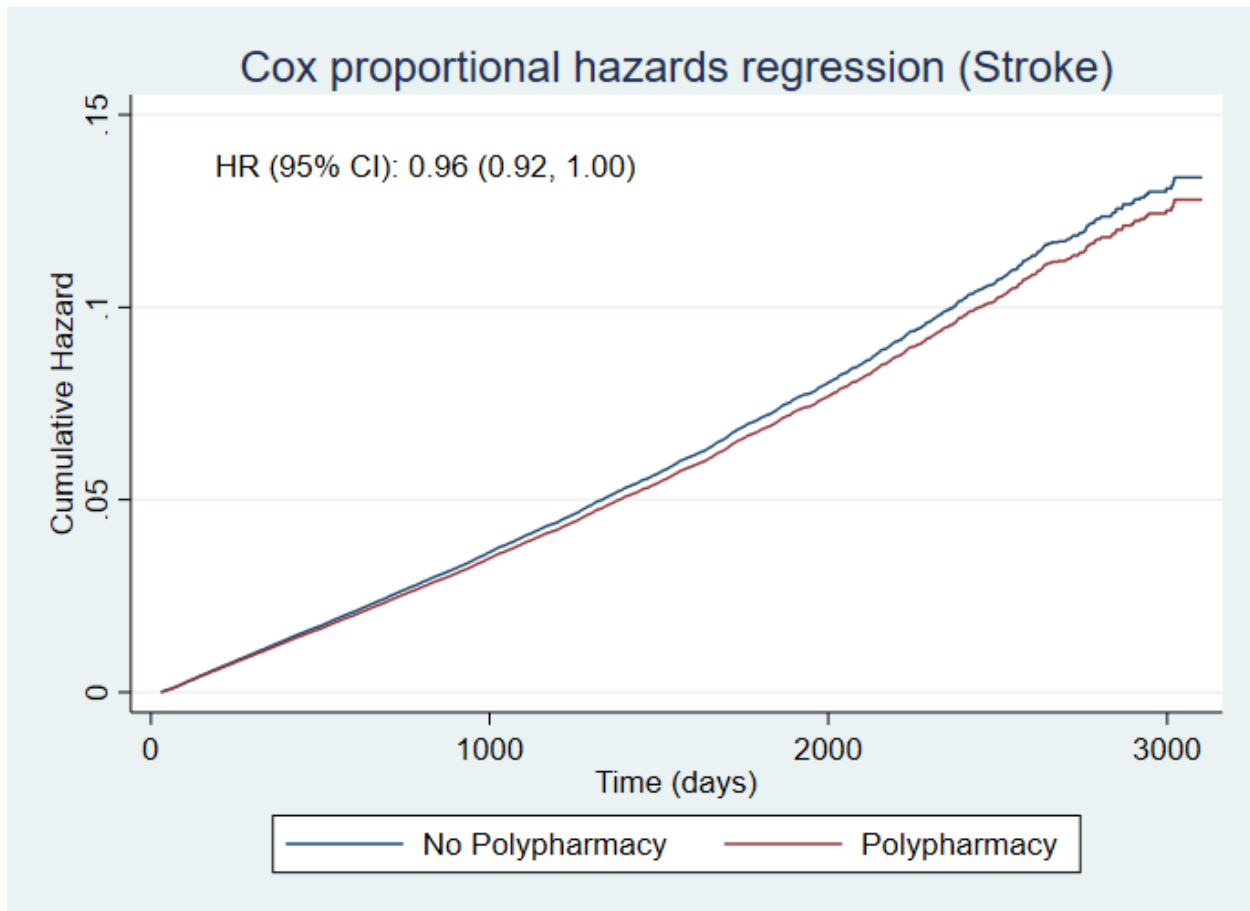


Figure S3. Cumulative hazard of stroke by polypharmacy status among atrial fibrillation (AF) patients ≥ 75 , MarketScan, 2007-2015 (polypharmacy definition 1). HR (95% CI) listed is adjusted for age, sex, frailty index, comorbidities (congestive heart failure, coronary artery disease, hyperlipidemia, stroke, arthritis, myocardial infarction, peripheral artery disease, gastrointestinal bleeding, cerebral bleeding, other bleeding, anemia, coagulopathy, mood disorder, cognitive impairment, liver disease, alcohol abuse, asthma, cancer, chronic kidney disease, chronic pulmonary disease, dementia, depression, diabetes, hepatitis, osteoporosis, schizophrenia, and substance abuse), and AF treatment (oral anticoagulation, antiarrhythmic drugs, catheter ablation, cardioversion, rate control therapy). HR, hazard ratio. CI, confidence interval.