

Article Title: Comparative Outcomes Between Direct Oral Anticoagulants, Warfarin, and Antiplatelet Monotherapy Among Chinese Patients With Atrial Fibrillation: A Population-Based Cohort Study

Running title: Use of Antithrombotic Treatments in Atrial Fibrillation

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Authors: Xue Li (PhD)^{1,4}, Swathi Pathadka (PharmD)¹, Kenneth KC Man (PhD)^{1,4,5}, Vanessa WS Ng(BPharm)¹, Chung Wah Siu (MD)⁶, Ian CK Wong (PhD)^{1,4,5}, Esther W Chan (PhD)^{1,4}, Wallis CY Lau (PhD)^{1,4,5}

Affiliation:

1 Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, University of Hong Kong

2 Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, University of Hong Kong

3 Department of Social Work and Social Administration, Faculty of Social Science, University of Hong Kong

4 The University of Hong Kong-Shenzhen Hospital, Shenzhen, Guangdong, China

5 Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom

6 Department of Medicine, LKS Faculty of Medicine, University of Hong Kong

Addresses for correspondence:

Dr Wallis CY Lau, Research Department of Practice and Policy, UCL School of Pharmacy,
Mezzanine Floor, BMA House, Tavistock Square, London WC1H 9JP, United Kingdom
(email: wallis.lau@ucl.ac.uk; tel: +44 (0) 20 7874 1271)

Supplemental Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study.

ICD-9-CM codes	Descriptions
Atrial fibrillation	
427.3	Atrial fibrillation and flutter
Valvular heart diseases/replacement or hyperthyroidism	
242	Thyrotoxicosis with or without goitre
394.0	Mitral stenosis
Procedure codes	
35.20	Open and other replacement of unspecified heart valve
35.22	Open and other replacement of aortic valve
35.24	Open and other replacement of mitral valve
35.26	Open and other replacement of pulmonary valve
35.28	Open and other replacement of tricuspid valve
Transient atrial fibrillation	
Cardiac surgery (procedure codes)	
00.5	Other cardiovascular procedures
35	Operations on valves and septa of heart
36	Operations on vessels of heart
37	Other operations on heart and pericardium
Pericarditis	
391	Rheumatic fever with heart involvement
393	Chronic rheumatic pericarditis
420	Acute pericarditis
423.2	Constrictive pericarditis
036.41	Meningococcal pericarditis
074.21	Coxsackie pericarditis
093.81	Syphilitic pericarditis
098.83	Gonococcal pericarditis
Myocarditis	
130.3	
391.2	Acute rheumatic myocarditis
398.0	Rheumatic myocarditis
422	Acute myocarditis
429.0	Myocarditis, unspecified
032.82	Diphtheritic myocarditis
036.43	Meningococcal myocarditis
074.23	Coxsackie myocarditis
093.82	Syphilitic myocarditis
Pulmonary embolism	
415.1	Pulmonary embolism and infarction

Supplemental Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
CHADS₂ and CHA₂DS₂-VASc scores	
Congestive Heart Failure	
398.91	Rheumatic heart failure (congestive)
402.01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure
404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and chronic kidney disease Stage I through Stage IV, or unspecified
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and chronic kidney disease Stage V or End Stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage I through Stage IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease Stage V or End Stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease Stage I through Stage IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease Stage V or End Stage renal disease
428	Heart failure
Hypertension	
401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
405	Secondary hypertension
437.2	Hypertensive encephalopathy
Diabetes	
250	Diabetes mellitus
Ischemic stroke	
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434	Occlusion of cerebral arteries
436	Acute, but ill-defined, cerebrovascular disease
437.0	Cerebral atherosclerosis
437.1	Other generalized ischemic cerebrovascular disease

Supplemental Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Transient ischemic attack	
435	Transient cerebral ischemia
Systemic embolism	
444	Arterial embolism and thrombosis
445	Atheroembolism
Vascular disease	
410-414	Ischemic heart disease
443.8	Other specified peripheral vascular diseases
443.9	Peripheral vascular disease, unspecified
Myocardial infarction	
410	Acute myocardial infarction
Intracranial hemorrhage	
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432	Other and unspecified intracranial hemorrhage
Gastrointestinal bleeding	
531.0	Acute gastric ulcer with hemorrhage
531.2	Acute gastric ulcer with hemorrhage and perforation, without mention of obstruction
531.4	Chronic or unspecified gastric ulcer with hemorrhage
531.6	Chronic or unspecified gastric ulcer with hemorrhage and perforation
532.0	Acute duodenal ulcer with hemorrhage
532.2	Acute duodenal ulcer with hemorrhage and perforation
532.4	Chronic or unspecified duodenal ulcer with hemorrhage
532.6	Chronic or unspecified duodenal ulcer with hemorrhage and perforation
533.0	Acute peptic ulcer of unspecified site with hemorrhage
533.2	Acute peptic ulcer of unspecified site with hemorrhage and perforation
533.4	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage
533.6	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and perforation
534.0	Acute gastrojejunal ulcer with hemorrhage
534.2	Acute gastrojejunal ulcer with hemorrhage and perforation, without mention of obstruction
534.4	Chronic or unspecified gastrojejunal ulcer with hemorrhage
534.6	Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation
535.01	Acute gastritis, with hemorrhage
535.11	Atrophic gastritis, with hemorrhage
535.21	Gastric mucosal hypertrophy, with hemorrhage
535.31	Alcoholic gastritis, with hemorrhage

Supplemental Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Gastrointestinal bleeding [continued]	
535.41	Other specified gastritis, with hemorrhage
535.51	Unspecified gastritis and gastroduodenitis, with hemorrhage
535.61	Duodenitis, with hemorrhage
535.71	Eosinophilic gastritis, with hemorrhage
562.02	Diverticulosis of small intestine with hemorrhage
562.03	Diverticulitis of small intestine with hemorrhage
562.12	Diverticulosis of colon with hemorrhage
562.13	Diverticulitis of colon with hemorrhage
569.3	Hemorrhage of rectum and anus
569.85	Angiodysplasia of intestine with hemorrhage
569.86	Dieulafoy lesion (hemorrhagic) of intestine
578.0	Hematemesis
578.1	Melena
578.9	Hemorrhage of gastrointestinal tract, unspecified
Other bleeding	
423.0	Hemopericardium
459.0	Hemorrhage NOS
593.81	Vascular disorders of kidney
599.7	Hematuria
623.8	Other specified noninflammatory disorders of vagina
626.2	Excessive menstruation
626.6	Metrorrhagia
719.1	Hemarthrosis
784.7	Epistaxis
784.8	Hemorrhage from throat
786.3	Hemoptysis
Renal disease	
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
580	Acute glomerulonephritis
581	Nephrotic syndrome
582	Chronic glomerulonephritis
583	Nephritis and nephropathy not specified as acute or chronic
584	Acute kidney failure
585	Chronic kidney disease (ckd)
586	Renal failure unspecified
590.0	Chronic pyelonephritis
753.1	Cystic kidney disease

Supplemental Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Charlson Comorbidity Index	
Myocardial infarction	
410	Acute myocardial infarction
Congestive Heart Failure	
398.91	Rheumatic heart failure (congestive)
402.01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure
404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
428	Heart failure
Peripheral vascular disease	
441	Aortic aneurysm and dissection
443.9	Peripheral vascular disease, unspecified
785.4	Gangrene
V43.4	Blood vessel replaced by other means
Cerebrovascular disease	
430-438	Cerebrovascular disease
Chronic obstructive pulmonary disease	
490-496	Chronic Obstructive Pulmonary Disease and Allied Conditions
500	Coal workers' pneumoconiosis
501	Asbestosis
502	Pneumoconiosis due to other silica or silicates
503	Pneumoconiosis due to other inorganic dust
504	Pneumonopathy due to inhalation of other dust
505	Pneumoconiosis, unspecified
506.4	Respiratory conditions due to chemical fumes and vapors
Dementia	
290	Dementias

Supplemental Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Charlson Comorbidity Index [continued]	
Paralysis	
342	Hemiplegia and hemiparesis
344.1	Paraplegia
Diabetes without chronic complication	
250.0	Diabetes mellitus without mention of complication
250.1	Diabetes with ketoacidosis
250.2	Diabetes with hyperosmolarity
250.3	Diabetes with other coma
250.7	Diabetes with peripheral circulatory disorders
Diabetes with chronic complication	
250.4	Diabetes with renal manifestations
250.5	Diabetes with ophthalmic manifestations
250.6	Diabetes with neurological manifestations
Chronic renal failure	
582	Chronic glomerulonephritis
583.0	Nephritis and nephropathy, not specified as acute or chronic, with lesion of proliferative glomerulonephritis
583.1	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranous glomerulonephritis
583.2	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranoproliferative glomerulonephritis
583.4	Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
583.6	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal cortical necrosis
583.7	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal medullary necrosis
585	Chronic kidney disease (ckd)
586	Renal failure, unspecified
588	Disorders resulting from impaired renal function
Various cirrhodites	
571.2	Alcoholic cirrhosis of liver
571.4	Chronic hepatitis
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
Moderate-severe liver disease	
456.0	Esophageal varices with bleeding
456.1	Esophageal varices without bleeding
456.2	Esophageal varices in diseases classified elsewhere

Supplemental Table I. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study [continued].

ICD-9-CM codes	Descriptions
Charlson Comorbidity Index [continued]	
Moderate-severe liver disease [continued]	
572.2	Hepatic encephalopathy
572.3	Portal hypertension
572.4	Hepatorenal syndrome
572.8	Other sequelae of chronic liver disease
Ulcers	
531	Gastric ulcer
532	Duodenal ulcer
533	Peptic ulcer site unspecified
534	Gastrojejunal ulcer
Rheumatoid arthritis and other inflammatory polyarthropathies	
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.4	Polymyositis
714.0	Rheumatoid arthritis
714.1	Felty's syndrome
714.2	Other rheumatoid arthritis with visceral or systemic involvement
714.81	Rheumatoid lung
725	Polymyalgia rheumatica
Acquired Immune Deficiency Syndrome	
042	Human immunodeficiency virus [HIV] disease
Malignancy	
140-149	Malignant neoplasm of lip, oral cavity, and pharynx
150-159	Malignant neoplasm of digestive organs and peritoneum
160-165	Malignant neoplasm of respiratory and intrathoracic organs
170-172, 174-176	Malignant neoplasm of bone, connective tissue, and breast
179-189	Malignant neoplasm of genitourinary organs
190-195	Malignant neoplasm of other sites
200-208	Malignant neoplasm of lymphatic and hematopoietic tissue
Metastatic solid tumour	
196	Secondary and unspecified malignant neoplasm of lymph nodes
197	Secondary malignant neoplasm of respiratory and digestive systems
198	Secondary malignant neoplasm of other specified sites
199	Malignant neoplasm without specification of site

Supplemental Table 2. Comparison of antiplatelet monotherapy, warfarin, and direct oral anticoagulant outcomes before propensity score matching.

	Antiplatelet monotherapy (N=18 878)	Warfarin (N=3803)	DOACs (N=4933)	Warfarin vs Antiplatelet monotherapy	DOACs vs Antiplatelet monotherapy	DOACs vs Warfarin
Outcomes	No. of events (Incidence per 100 py)	No. of events (Incidence per 100 py)	No. of events (Incidence per 100 py)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Ischemic stroke	1646 (3.7)	179 (1.6)	146 (1.5)	0.42 (0.36-0.50)*	0.42 (0.35-0.50)*	1.00 (0.80-1.26)
Intracranial hemorrhage	382 (0.9)	131 (1.2)	61 (0.6)	1.36 (1.12-1.66)*	0.72 (0.55-0.94)*	0.57 (0.42-0.78)*
Gastrointestinal bleeding	1039 (2.3)	235 (2.1)	204 (2.1)	0.90 (0.78-1.03)	0.89 (0.77-1.04)	1.04 (0.86-1.27)
All-cause mortality	5428 (12.2)	475 (4.2)	345 (3.6)	0.35 (0.32-0.39)*	0.28 (0.25-0.31)*	0.88 (0.76-1.01)

Abbreviations: CI=confidence interval; DOACs=direct oral anticoagulants; HR=hazard ratio; py=person-years. *p<0.05.

Supplemental Table 3. Comparison of antiplatelet monotherapy, warfarin, and direct oral anticoagulant outcomes using inverse probability of treatment weighting.

	Antiplatelet monotherapy (N=18 878)	Warfarin (N=3803)	DOACs (N=4933)	Warfarin vs Antiplatelet monotherapy	DOACs vs Antiplatelet monotherapy	DOACs vs Warfarin
Outcomes	No. of events (Weighted incidence per 100 py)	No. of events (Weighted incidence per 100 py)	No. of events (Weighted incidence per 100 py)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Ischemic stroke	1646 (3.5)	179 (1.7)	146 (2.2)	0.49 (0.41-0.58)*	0.63 (0.41-0.97)*	1.30 (0.82-2.06)
Intracranial hemorrhage	382 (0.8)	131 (1.3)	61 (0.6)	1.58 (1.26-1.98)*	0.68 (0.44-1.07)	0.43 (0.27-0.70)*
Gastrointestinal bleeding	1039 (2.2)	235 (2.3)	204 (2.3)	1.06 (0.90-1.26)	1.04 (0.80-1.36)	0.98 (0.72-1.33)
All-cause mortality	5428 (10.9)	475 (5.3)	345 (4.4)	0.48 (0.43-0.54)*	0.40 (0.33-0.49)*	0.83 (0.66-1.04)

Abbreviations: CI=confidence interval; DOACs=direct oral anticoagulants; HR=hazard ratio; py=person-years. *p<0.05.

Supplemental Table 4. Comparison of antiplatelet monotherapy, warfarin, and direct oral anticoagulant outcomes using Fine-Grey Cox regression model.

	Warfarin vs Antiplatelet monotherapy	DOACs vs Antiplatelet monotherapy	DOACs vs Warfarin
Outcomes	HR (95% CI)	HR (95% CI)	HR (95% CI)
Ischemic stroke	0.51 (0.39-0.65)*	0.69 (0.55-0.86)*	1.18 (0.92-1.51)
Intracranial hemorrhage	1.69 (1.19-2.41)*	0.89 (0.61-1.31)	0.53 (0.38-0.74)*
Gastrointestinal bleeding	0.80 (0.64-1.01)	0.80 (0.62-1.03)	0.95 (0.76-1.19)

Abbreviations: CI=confidence interval; DOACs=direct oral anticoagulants; HR=hazard ratio; *p<0.05.

Supplemental Table 5. Comparison of antiplatelet monotherapy, warfarin, and direct oral anticoagulant outcomes, stratified by quality of international normalized control of warfarin users before propensity score matching.

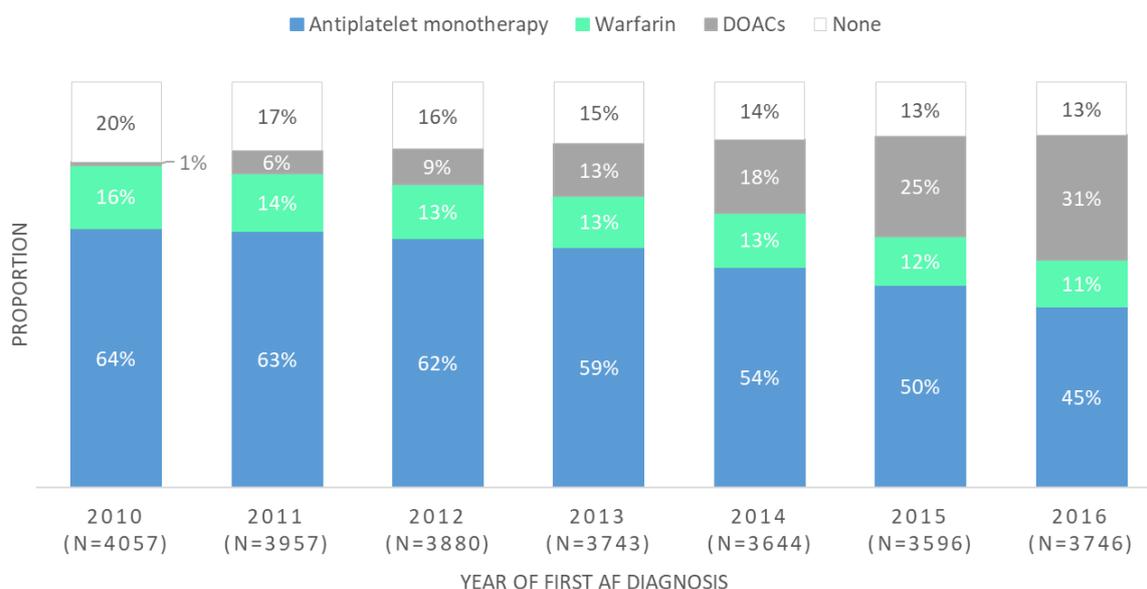
	Good INR control (N=1340)	Poor INR control (N=2463)	DOACs (N=4933)	DOACs vs Good INR control	DOACs vs Poor INR control	
Outcomes	No. of events (Incidence per 100 py)	No. of events (Incidence per 100 py)	No. of events (Incidence per 100 py)	HR (95% CI)	HR (95% CI)	p for interaction
Ischemic stroke	55 (1.3)	124 (1.8)	146 (1.5)	1.22 (0.89-1.68)	0.88 (0.69-1.13)	0.11
Intracranial hemorrhage	45 (1.0)	86 (1.2)	61 (0.6)	0.61 (0.41-0.91)*	0.54 (0.39-0.76)*	0.65
Gastrointestinal bleeding	90 (2.1)	145 (2.1)	204 (2.1)	1.05 (0.81-1.36)	1.04 (0.84-1.30)	0.96
All-cause mortality	147 (3.4)	328 (4.7)	345 (3.6)	1.10 (0.90-1.34)	0.78 (0.67-0.91)*	0.01

	Good INR control (N=1340)	Poor INR control (N=2463)	APT (N=18 878)	Good INR control vs APT	Poor INR control vs APT	
Outcomes	No. of events (Incidence per 100 py)	No. of events (Incidence per 100 py)	No. of events (Incidence per 100 py)	HR (95% CI)	HR (95% CI)	p for interaction
Ischemic stroke	55 (1.3)	124 (1.8)	1646 (3.7)	0.34 (0.26-0.44)*	0.48 (0.40-0.57)*	0.04
Intracranial hemorrhage	45 (1.0)	86 (1.2)	382 (0.9)	1.24 (0.91-1.68)	1.45 (1.14-1.83)*	0.43
Gastrointestinal bleeding	90 (2.1)	145 (2.1)	1039 (2.3)	0.90 (0.73-1.12)	0.90 (0.75-1.07)	0.97
All-cause mortality	147 (3.4)	328 (4.7)	5428 (12.2)	0.29 (0.25-0.34)*	0.39 (0.35-0.44)*	0.002

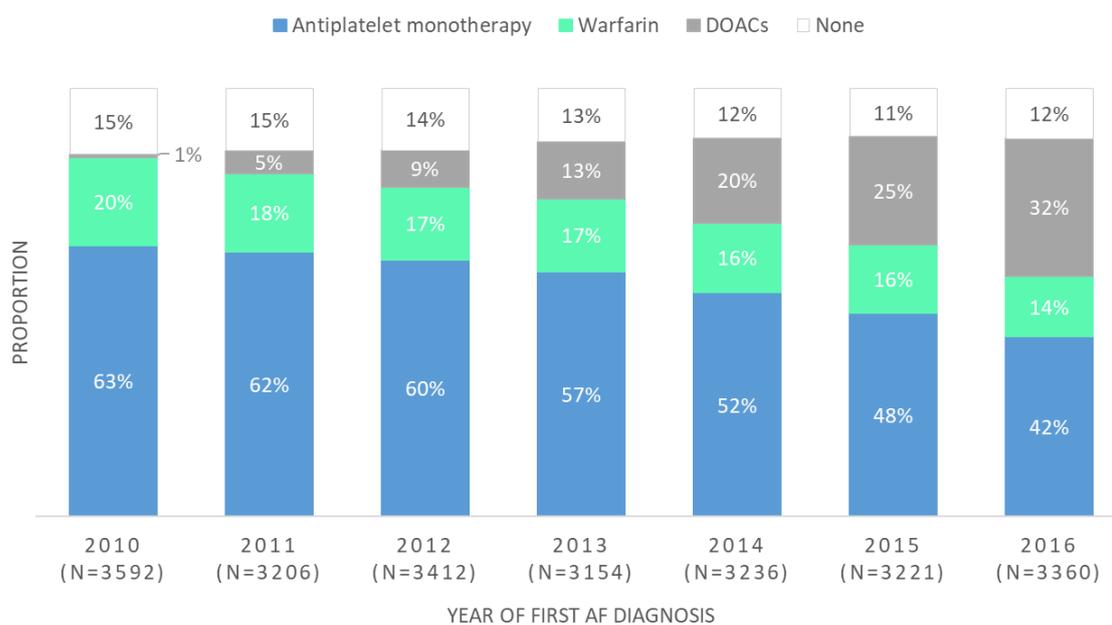
	Good INR control (N=1340)	Poor INR control (N=2463)	Good vs Poor INR control
Outcomes	No. of events (Incidence per 100 py)	No. of events (Incidence per 100 py)	HR (95% CI)
Ischemic stroke	55 (1.3)	124 (1.8)	0.70 (0.51-0.96)*
Intracranial hemorrhage	45 (1.0)	86 (1.2)	0.83 (0.58-1.19)
Gastrointestinal bleeding	90 (2.1)	145 (2.1)	0.99 (0.76-1.29)
All-cause mortality	147 (3.4)	328 (4.7)	0.71 (0.59-0.87)*

Abbreviations: APT= antiplatelet monotherapy; CI= confidence interval; DOACs= direct oral anticoagulants; HR= hazard ratio; INR= international normalized ratio; py= person-year. *p<0.05.

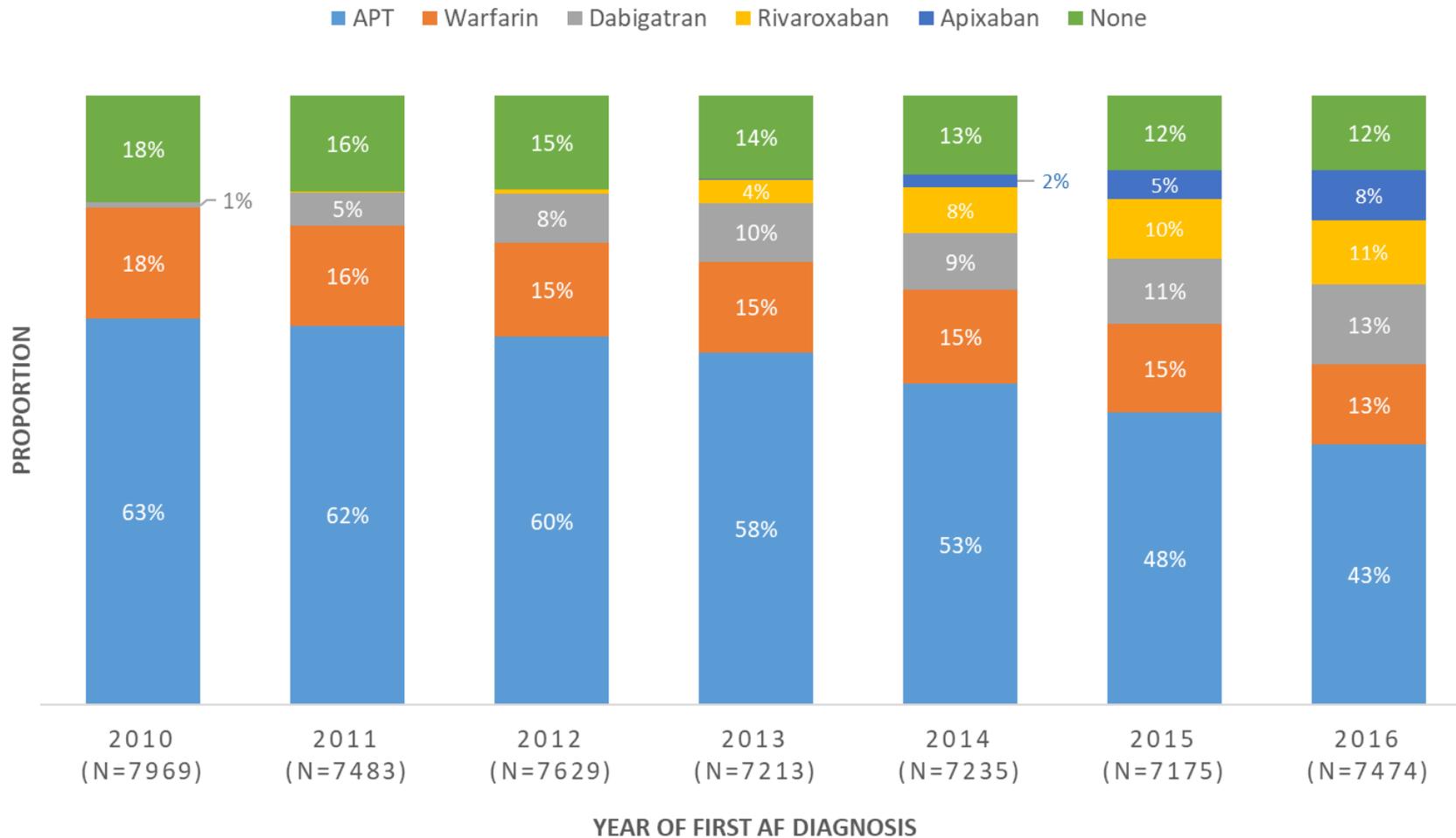
A) Women with CHA₂DS₂-VASc ≥ 3



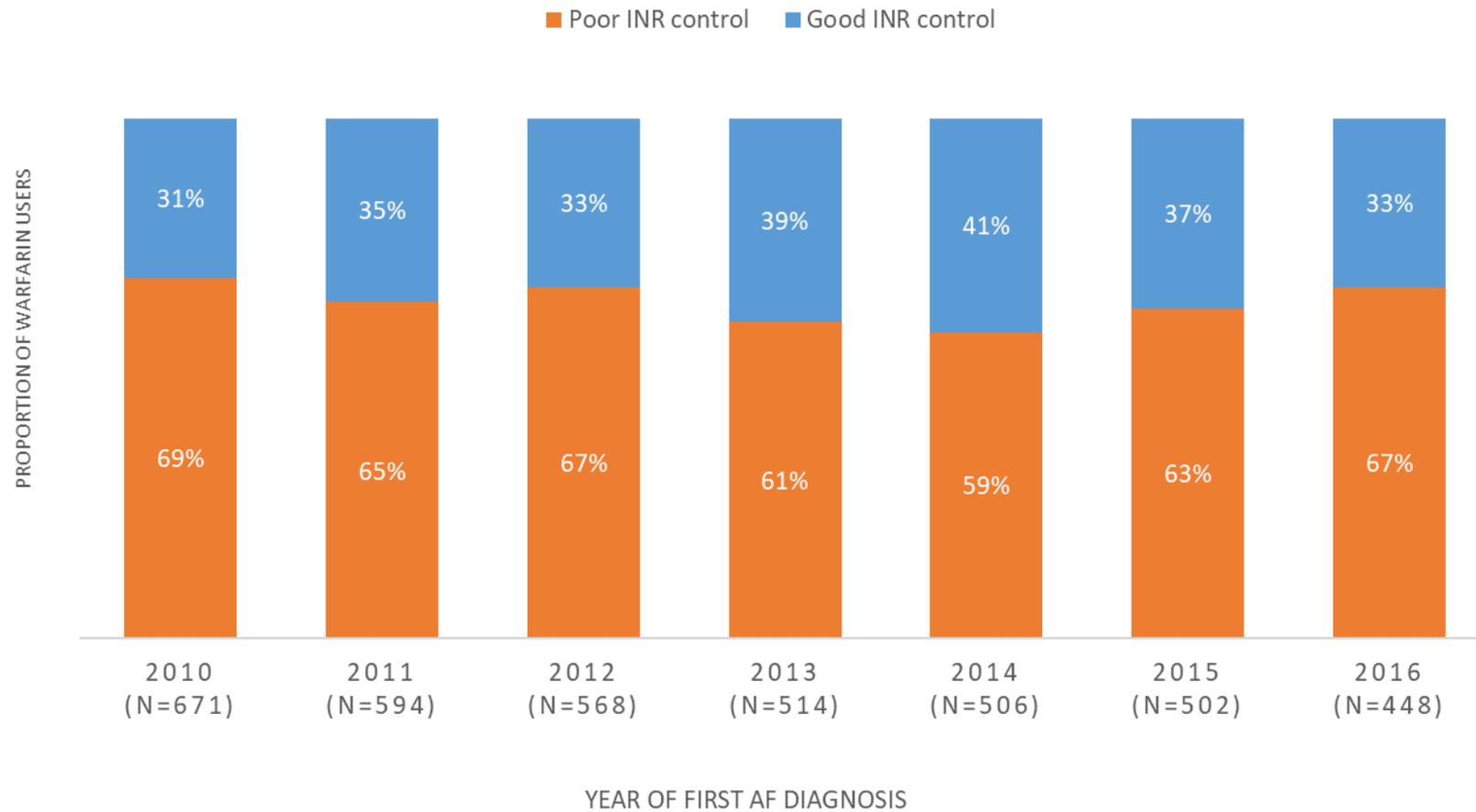
B) Men with CHA₂DS₂-VASc ≥ 2



Supplemental Figure 1. Antithrombotic treatment in patients with atrial fibrillation by cohort year among A) Women with CHA₂DS₂-VASc ≥ 2; B) Men with CHA₂DS₂-VASc ≥ 3. (CHA₂DS₂-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack/systemic embolism, Vascular disease, Age 65 to 74 years, Sex category [female]; Abbreviation: AF=atrial fibrillation)



Supplemental Figure 2. Antithrombotic treatment in patients with atrial fibrillation and CHA₂DS₂-VASc ≥ 2 by cohort year, with details of individual direct oral anticoagulants. (CHA₂DS₂-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke/transient ischemic attack/systemic embolism, Vascular disease, Age 65 to 74 years, Sex category [female]; Abbreviation: AF=atrial fibrillation)



Supplemental Figure 3. Proportion of warfarin users with good and poor international normalized ratio control by cohort year (poor control was defined as time-in-therapeutic range < 60%).

Abbreviations: AF=atrial fibrillation; INR= international normalized ratio