Supplementary Online Content

Lutsey PL, Norby FL, Ensrud KE, et al. Association of anticoagulant therapy with risk of fracture among patients with atrial fibrillation. *JAMA Intern Med.* Published online November 25, 2019. doi:10.1001/jamainternmed.2019.5679

eFigure 1. Exclusions Flowchart

eFigure 2. Adjusted Hazard Ratios (95% Confidence Intervals) of Incident Fracture, According to Initial Oral Anticoagulant Therapy for the Treatment of Patients With Atrial Fibrillation, Stratified by Subgroups of Interest

eTable 1. *ICD-9-CM* Codes Used to Define Comorbidities

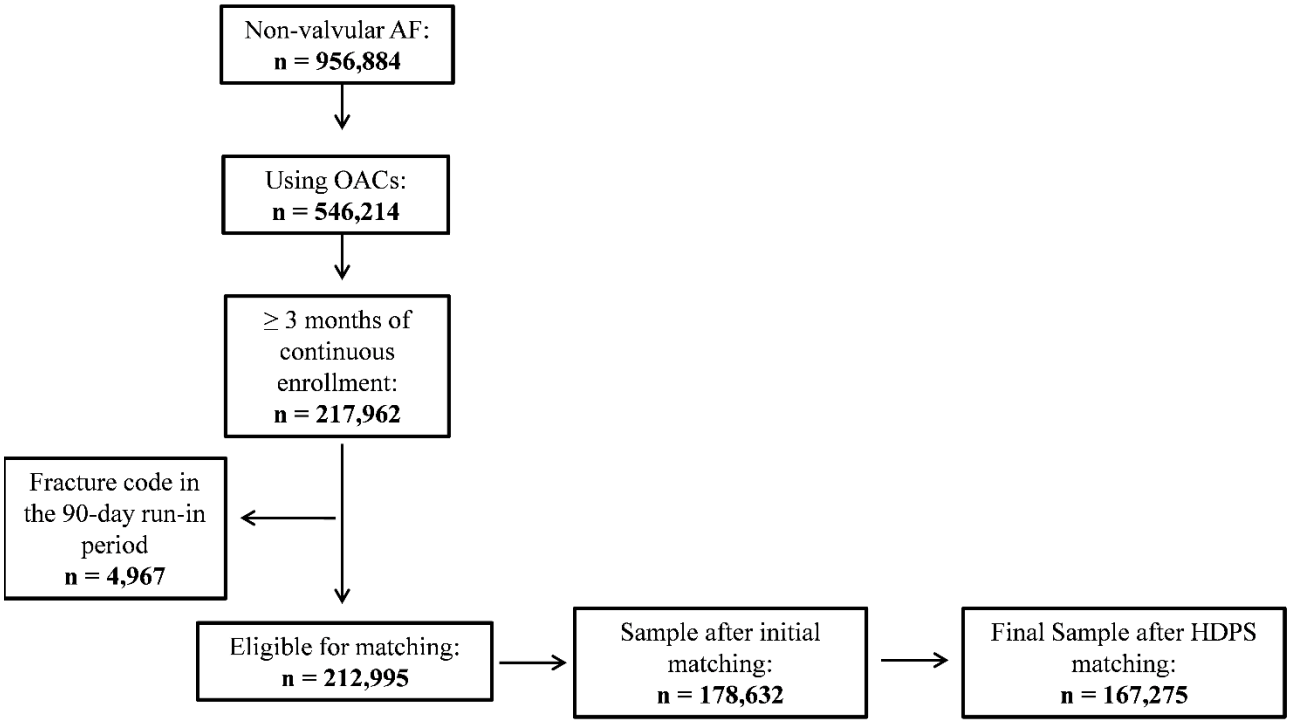
eTable 2. Sensitivity Analyses Evaluating the Association Between DOACs vs Warfarin on Risk of Hip and Inpatient Fractures Among Patients With Atrial Fibrillation

eTable 3. Adjusted Hazard Ratios (95% Confidence Intervals) for Incident Fracture Comparing New Users of Oral Anticoagulants Among Patients With Nonvalvular AF

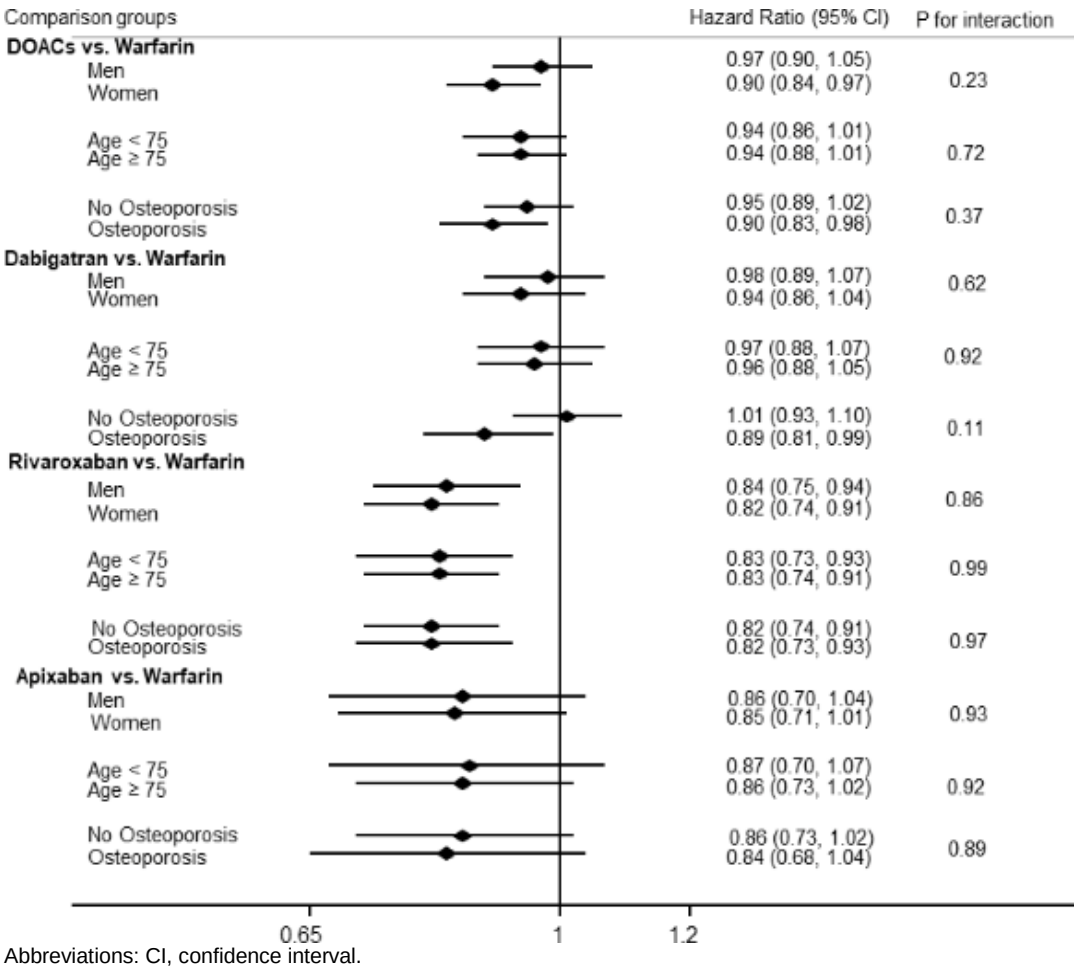
eTable 4. Adjusted Hazard Ratios (95% Confidence Intervals) for Incident Fracture Comparing New Users of Oral Anticoagulants by Dose of Direct Oral Anticoagulant to Warfarin, Among Patients With Nonvalvular AF

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

eFigure 1. Exclusions Flowchart



eFigure 2. Adjusted Hazard Ratios (95% Confidence Intervals) of Incident Fracture, According to Initial Oral Anticoagulant Therapy for the Treatment of Patients With Atrial Fibrillation, Stratified by Subgroups of Interest



Abbreviations: CI, confidence interval.

[a]OAC users matched, and models adjusted for age, sex, CHA_2DS_2-VASc score, high-dimensional propensity score, and frailty.

MarketScan 2010-2015.

eTable 1. *ICD-9-CM* Codes Used to Define Comorbidities

Condition	ICD-9-CM codes
Alcoholism	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, 980, V11.3
Chronic pulmonary disease	416.8, 416.9, 506.4, 508.1, 508.8, 490-505
Dementia	290.x, 294.1, 331.2
Depression	296.2, 296.3, 296.5, 300.4, 309, 311
Diabetes	250
Frailty	260.xx, 261.xx, 262.xx, 263.xx, 272, 290.x-299.x, 300.0, 310.x, 311.x, 332.x, 342.xx, 344.xx, 348.xx, 349.82, 386, 432.xx, 433.01, 433.11, 433.21, 433.31, 433.91, 434.01, 434.11, 434.91, 436.xx, 438.2-438.5, 438.85, 458.x, 596.5, 599.6, 681.1, 700, 703.x, 707.0, 707.1, 707.2, 707.8, 707.9, 710.xx-712.xx, 714.xx, 715.xx, 716.5, 716.6, 716.8, 716.9, 718.xx, 719.0, 719.1, 719.4, 719.5, 719.7, 719.9, 725.xx, 728.2, 780.4, 780.7, 781.2, 781.3, 781.4, 783.2, 783.7, 785.5, 788.3, 797, 799.4, 799.3, 852.xx-854xx, 958.4, 998.0, E880-E888, E929.3, V46.3, V15.88 V571, V573, V578, V579, V572.1
Malignancy	140-172, 174-195, 200-208, 238.6
Metastatic cancer	196-199
Gastrointestinal bleeding	455.2, 455.5, 455.8, 456.0, 456.20, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.9, 428
Hemorrhagic stroke	430, 431, 432
Hematological disorders	280-286, 287.1, 287.3, 287.4, 287.5
Hypertension	401, 402, 403, 404, 405
Ischemic stroke	433, 434, 435, 436, 437, 438
Kidney disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0, 583.1, 583.2, 583.3, 583.4, 583.5, 583.6, 583.7, 585, 586, 588.0, V42.0, V45.1, V56
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0, 456.1, 456.2, 570, 571, 572.2, 572.3, 572.4, 572.5, 572.6, 572.7, 572.8, 573.3, 573.4, 573.8, 573.9, V42.7
Myocardial infarction	410, 412
Osteoporosis	715, 733
Other bleeding	423.0, 459.0, 568.81, 593.81, 599.7, 623.8, 626.6, 719.1, 784.7, 784.8, 786.3
Peripheral artery disease	440.0, 440.2, 440.9, 443.9

eTable 2. Sensitivity Analyses Evaluating the Association Between DOACs vs Warfarin on Risk of Hip and Inpatient Fractures Among Patients With Atrial Fibrillation[a]

Dabigatran vs. Warfarin		**Hazard Ratio (95% CI)[a]**	**p-value**
Hip fractures, 1st position			
	Original model from Table 2	0.98 (0.80, 1.20)	0.86
	Model + adjust for prevalent fracture[b]	0.98 (0.80, 1.21)	0.87
	Model + adjust for osteoporosis	0.98 (0.80, 1.21)	0.88
	Excluding those with prevalent fracture (original model)	0.98 (0.79, 1.22)	0.88
	Requiring 6 month run-in (original model)	0.97 (0.78, 1.21)	0.79
Inpatient fractures, 1st position			
	Original model from Table 2	0.88 (0.78, 1.00)	0.06
	Model + adjust for prevalent fracture[b]	0.88 (0.78, 1.00)	0.06
	Model + adjust for osteoporosis	0.88 (0.78, 1.00)	0.05
	Excluding those with prevalent fracture (original model)	0.88 (0.77, 1.00)	0.05
	Requiring 6 month run-in (original model)	0.89 (0.78, 1.02)	0.09
Rivaroxaban vs. Warfarin			
Hip fractures, 1st position			
	Original model from Table 2	0.89 (0.71, 1.12)	0.33
	Model + adjust for prevalent fracture[b]	0.89 (0.71, 1.13)	0.34
	Model + adjust for osteoporosis	0.89 (0.71, 1.12)	0.33
	Excluding those with prevalent fracture (original model)	0.95 (0.75, 1.21)	0.66
	Requiring 6 month run-in (original model)	0.81 (0.62, 1.06)	0.12
Inpatient fractures, 1st position			
	Original model from Table 2	0.80 (0.69, 0.93)	0.003
	Model + adjust for prevalent fracture[b]	0.80 (0.69, 0.93)	0.003
	Model + adjust for osteoporosis	0.80 (0.69, 0.93)	0.003
	Excluding those with prevalent fracture (original model)	0.82 (0.70, 0.95)	0.008
	Requiring 6 month run-in (original model)	0.79 (0.67, 0.94)	0.008
Apixaban vs. Warfarin			
Hip fractures, 1st position			
	Original model from Table 2	0.67 (0.45, 0.98)	0.04
	Model + adjust for prevalent fracture[b]	0.66 (0.45, 0.98)	0.04
	Model + adjust for osteoporosis	0.66 (0.45, 0.98)	0.04
	Excluding those with prevalent fracture (original model)	0.58 (0.38, 0.88)	0.01
	Requiring 6 month run-in (original model)	0.65 (0.42, 1.02)	0.06
Inpatient fractures, 1st position			
	Original model from Table 2	0.60 (0.47, 0.78)	<0.0001
	Model + adjust for prevalent fracture[b]	0.60 (0.46, 0.77)	<0.0001
	Model + adjust for osteoporosis	0.60 (0.47, 0.78)	<0.0001
	Excluding those with prevalent fracture (original model)	0.58 (0.44, 0.76)	<0.0001
	Requiring 6 month run-in (original model)	0.63 (0.47, 0.84)	0.002
DOACs vs. Warfarin			
Hip fractures, 1st position			
	Original model from Table 2	0.91 (0.78, 1.07)	0.27
	Model + adjust for prevalent fracture[b]	0.91 (0.78, 1.07)	0.27
	Model + adjust for osteoporosis	0.92 (0.78, 1.07)	0.28
	Excluding those with prevalent fracture (original model)	0.90 (0.76, 1.07)	0.23
	Requiring 6 month run-in (original model)	0.91 (0.76, 1.08)	0.27
Inpatient fractures, 1st position			
	Original model from Table 2	0.87 (0.79-0.96)	0.007
	Model + adjust for prevalent fracture[b]	0.87 (0.79-0.96)	0.007
	Model + adjust for osteoporosis	0.87 (0.79-0.96)	0.007
	Excluding those with prevalent fracture (original model)	0.87 (0.78-0.97)	0.01

	Requiring 6 month run-in (original model)	0.87 (0.78-0.97)	0.01

[a]Matched 1-1 on high-dimensional propensity score and adjusted for age, sex, CHA_2DS_2-VASc score, high-dimensional propensity score and frailty. MarketScan 2010-2015.
[b]Claims indicating fracture prior to the 90 day run-in period

eTable 3. Adjusted Hazard Ratios (95% Confidence Intervals) for Incident Fracture Comparing New Users of Oral Anticoagulants Among Patients With Nonvalvular AF

DOACS vs. warfarin	Group	Hazard Ratio (95% CI)[a]	p-value for interaction
Hip fractures, 1st position			
	Men	0.97 (0.76, 1.25)	0.53
	Women	0.88 (0.71, 1.10)	
	Age <75	0.88 (0.60, 1.31)	0.67
	Age>= 75	0.94 (0.79, 1.12)	
	No Osteoporosis	1.06 (0.86, 1.30)	0.03
	Osteoporosis	0.74 (0.58, 0.96)	
Inpatient fractures, 1st position			
	Men	0.97 (0.82, 1.13)	0.12
	Women	0.81 (0.71, 0.93)	
	Age <75	0.79 (0.65, 0.97)	0.10
	Age>= 75	0.92 (0.82, 1.03)	
	No Osteoporosis	0.97 (0.85, 1.11)	0.01
	Osteoporosis	0.75 (0.64, 0.88)	
All fractures, 1st position			
	Men	0.97 (0.90, 1.05)	0.23
	Women	0.90 (0.84, 0.97)	
	Age <75	0.94 (0.86, 1.01)	0.72
	Age>= 75	0.94 (0.88, 1.01)	
	No Osteoporosis	0.95 (0.89, 1.02)	0.37
	Osteoporosis	0.90 (0.83, 0.98)	
Dabigatran vs. Warfarin			
Hip fractures, 1st position			
	Men	1.08 (0.79, 1.48)	0.46
	Women	0.92 (0.70, 1.21)	
	Age <75	0.74 (0.45, 1.22)	0.14
	Age>= 75	1.06 (0.85, 1.33)	
	No Osteoporosis	1.16 (0.89, 1.50)	0.06
	Osteoporosis	0.76 (0.54, 1.07)	
Inpatient fractures, 1st position			
	Men	1.06 (0.87, 1.29)	0.02
	Women	0.78 (0.66, 0.92)	
	Age <75	0.75 (0.59, 0.96)	0.03
	Age>= 75	0.99 (0.83, 1.12)	
	No Osteoporosis	1.00 (0.85, 1.20)	0.02
	Osteoporosis	0.74 (0.61, 0.90)	
All fractures, 1st position			
	Men	0.98 (0.89, 1.07)	0.62
	Women	0.94 (0.86, 1.04)	
	Age <75	0.97 (0.88, 1.07)	0.92
	Age>= 75	0.96 (0.88, 1.05)	
	No Osteoporosis	1.01 (0.93, 1.10)	0.11
	Osteoporosis	0.89 (0.81, 0.99)	
Rivaroxaban vs. Warfarin			
Hip fractures, 1st position			
	Men	0.98 (0.67, 1.44)	0.52
	Women	0.85 (0.64, 1.13)	
	Age <75	0.98 (0.56, 1.71)	0.93
	Age>= 75	0.88 (0.68, 1.13)	
	No Osteoporosis	0.94 (0.69, 1.27)	0.67

	Osteoporosis	0.83 (0.58, 1.18)	
Inpatient fractures, 1st position			
	Men	0.94 (0.74, 1.20)	0.13
	Women	0.74 (0.62, 0.89)	
	Age <75	0.91 (0.68, 1.24)	0.54
	Age>= 75	0.78 (0.66, 0.92)	
	No Osteoporosis	0.88 (0.72, 1.07)	0.17
	Osteoporosis	0.72 (0.58, 0.89)	
All fractures, 1st position			
	Men	0.84 (0.75, 0.94)	0.86
	Women	0.82 (0.74, 0.91)	
	Age <75	0.83 (0.73, 0.93)	0.99
	Age>= 75	0.83 (0.74, 0.91)	
	No Osteoporosis	0.82 (0.74, 0.91)	0.97
	Osteoporosis	0.82 (0.73, 0.93)	
Apixaban vs. warfarin			
Hip fractures, 1st position			
	Men	0.57 (0.30, 1.05)	0.50
	Women	0.74 (0.45, 1.21)	
	Age <75	1.06 (0.43, 2.62)	0.34
	Age>= 75	0.61 (0.40, 0.94)	
	No Osteoporosis	0.70 (0.41, 1.17)	0.83
	Osteoporosis	0.65 (0.36, 1.15)	
Inpatient fractures, 1st position			
	Men	0.77 (0.52, 1.12)	0.14
	Women	0.51 (0.36,0.71)	
	Age <75	0.89 (0.54, 1.46)	0.20
	Age>= 75	0.55 (0.41, 0.73)	
	No Osteoporosis	0.58 (0.42, 0.81)	0.69
	Osteoporosis	0.64 (0.42, 0.95)	
All fractures, 1st position			
	Men	0.86 (0.70, 1.04)	0.93
	Women	0.85 (0.71, 1.01)	
	Age <75	0.87 (0.70, 1.07)	0.92
	Age>= 75	0.86 (0.73, 1.02)	
	No Osteoporosis	0.86 (0.73, 1.02)	0.89
	Osteoporosis	0.84 (0.68, 1.04)	

[a]Adjusted for age, sex, CHA_2DS_2-VASc score, high-dimensional propensity score, and frailty where appropriate. MarketScan, 2010-2015.
Osteoporosis defined by ICD-9 codes and medications. Codes make up most of the diagnosis.

eTable 4. Adjusted Hazard Ratios (95% Confidence Intervals) for Incident Fracture Comparing New Users of Oral Anticoagulants by Dose of Direct Oral Anticoagulant to Warfarin, Among Patients With Nonvalvular AF

	Warfarin	**Dabigatran**		
		Reduced dose (75 mg)	Standard dose (150 mg)	
Hip fractures, 1st position	186	39	143	
HR (95% CI)	1.00 (ref)	0.98 (0.69, 1.40)	0.98 (0.79, 1.22)	
# Inpatient fractures, 1st position	510	80	367	
HR (95% CI)	1.00 (ref)	0.87 (0.68, 1.10)	0.89 (0.77, 1.02)	
# All fractures, 1st position	1803	245	1519	
HR (95% CI)	1.00 (ref)	1.01 (0.88, 1.16)	0.95 (0.89, 1.02)	
	Warfarin	**Rivaroxaban**		
		Reduced dose (10mg)	Reduced dose (15 mg)	Standard dose (20 mg)
Hip fractures, 1st position	170	14	51	63
HR (95% CI)	1.00 (ref)	1.05 (0.61, 1.82)	1.02 (0.74, 1.40)	0.78 (0.58, 1.05)
# Inpatient fractures, 1st position	445	27	110	170
HR (95% CI)	1.00 (ref)	0.78 (0.53, 1.16)	0.90 (0.73, 1.12)	0.75 (0.63, 0.90)
# All fractures, 1st position	1493	114	286	724
HR (95% CI)	1.00 (ref)	1.05 (0.87, 1.27)	0.86 (0.76, 0.98)	0.78 (0.72, 0.86)
	Warfarin	**Apixaban**		
	Any dose	Reduced dose (2.5 mg)	Standard dose (5 mg)	
Hip fractures, 1st position	70	17	24	
HR (95% CI)	1.00 (ref)	0.73 (0.42, 1.25)	0.63 (0.39, 1.01)	
# Inpatient fractures, 1st position	174	36	56	
HR (95% CI)	1.00 (ref)	0.69 (0.48, 0.99)	0.56 (0.41, 0.76)	
# All fractures, 1st position	521	120	276	
HR (95% CI)	1.00 (ref)	1.02 (0.83, 1.26)	0.80 (0.69, 0.92)	

[a]Adjusted for age, sex, CHA_2DS_2-VASc score, high-dimensional propensity score, and frailty. MarketScan, 2010-2015.