

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

SUPPLEMENTAL MATERIAL

Title: Risks and Benefits of Direct Oral Anticoagulants across the Spectrum of Glomerular Filtration Rate among Incident and Prevalent Patients with Atrial Fibrillation

Jung-Im Shin, MD, PhD (1); Alex Secora, MPH (1); G. Caleb Alexander, MD, MS (1,2); Lesley A. Inker, MD, MS (4); Josef Coresh, MD, PhD (1,2); Alex R. Chang, MD, MS (3); Morgan E. Grams, MD, PhD (1,2)

(1) Department of Epidemiology, Johns Hopkins University, MD, USA

(2) Department of Medicine, Johns Hopkins University, Baltimore, MD, USA

(3) Kidney Health Research Institute, Geisinger, Danville, PA, USA

(4) Division of Nephrology, Tufts Medical Center, Boston, MA, USA

Supplemental Table 1. International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM) used to define study outcomes and comorbid conditions

Outcome	ICD-9-CM codes
All bleeding events	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
Ischemic stroke	433.x1, 434.x1, 436
Comorbid conditions	
Hypertension	Starting with 401-405
Diabetes	Starting with 250
Congestive heart failure	Starting with 428
Valvular heart disease	Starting with 394-396 or equal to 424
Prosthetic heart valve	V43.3, 35.21, 35.22, 35.23, 35.24
Myocardial infarction	Starting with 410 or equal to 412
Coronary artery disease	Starting with 414.0, 410, 36.1 or equal to 414.8, 414.9, 412
Peripheral artery disease	443.9, 440.2, 440.3, 443.9, 38.18, 39.50, 39.25, 39.29, 785.4 or starting with 84.1, 440.2, 440.4, 707.1
Deep vein thrombosis	451.1x 451.2 451.81 451.83 451.84 451.89 451.9, 453.2, 453.4x, 453.5x, 453.7, 453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79, 453.8, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9, V12.51
Pulmonary embolism	415.13, 415.19, 416.2, V12.55

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

Supplemental Table 2. Test for proportional hazard assumption using Schoenfeld residuals

	P-value	
	Bleeding	Ischemic stroke
As-treated-analyses	0.69	0.32
Intention-to-treat analyses	0.94	0.77
Time-varying analyses	0.91	0.63

Supplemental Table 3. Baseline characteristics of patients initiating direct oral anticoagulants for treatment of atrial fibrillation from October 2010 to February 2017 in the Geisinger Health System

Variable	All	Dabigatran	Rivaroxaban	Apixaban
N (%)	3,647 (100)	880 (24)	1,560 (43)	1,207 (33)
Age (years, mean(SD))	70 (12)	70 (12)	69 (12)	72 (12)
Female (%)	45	42	43	49
White (%)	97	98	98	97
eGFR (ml/min/1.73m ² , mean(SD))	70 (22)	72 (21)	73 (21)	67 (23)
eGFR category (%)				
≥60 ml/min/1.73m ²	68	71	71	62
30-59 ml/min/1.73m ²	28	26	26	33
<30 ml/min/1.73m ²	4	3	3	5
Year (%)				
2010-2012	19	65	8	0
2013-2014	32	22	45	24
2015-2017	49	13	47	76
History of previous warfarin use (%)	34	39	35	30
Duration of previous anticoagulation (years, median (IQR)) [†]	3 (1-6)	3(1-5)	3 (1-6)	4 (1-6)
CHA ₂ DS ₂ -VASc score (mean (SD))	4 (12)	3 (2)	3 (2)	4 (2)
HAS-BLED score (mean (SD))	2 (1)	2 (1)	2 (1)	2 (1)
Number of prior hospitalizations (%)				
None	33	40	32	28
1-3	37	35	36	38
4-7	18	17	18	20
≥8	12	8	14	14
Comorbidities (%)				
Hypertension	82	79	81	86
Diabetes	33	31	32	36
Congestive heart failure	29	27	27	35
Valvular heart disease	23	24	21	25
Non-valvular atrial fibrillation [‡]	4	4	3	3
Myocardial infarction	14	11	13	17
Coronary artery disease	39	39	36	44
Peripheral artery disease	15	13	15	18
Deep vein thrombosis	9	6	11	8
Pulmonary embolism	4	1	7	4
Bleeding	34	30	34	37
Anemia	34	28	34	39
Transient ischemic attack	13	13	11	14
Ischemic stroke	8	7	7	11
End-stage kidney disease	0.4	0	0	1
Medication use (%)				
NSAIDs	24	26	25	23
Anti-platelet agents	23	23	22	23
Statins	30	33	28	31
RAS blockers	30	33	28	31

[†]Only among patients with previous warfarin use. [‡]Valvular atrial fibrillation was defined as atrial fibrillation with rheumatic mitral stenosis or prosthetic heart valve.

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

Abbreviations: SD, standard deviation; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; RAS blockers, renin-angiotensin system blockers

Supplemental Table 4. Baseline characteristics of patients initiating direct oral anticoagulants (with or without previous warfarin use) among patients with atrial fibrillation from October 2010 to February 2017 in the Geisinger Health System

Variable	Previous warfarin (n=1,253)	Warfarin naïve (n=2,394)
Age (years, mean(SD))	71 (12)	70 (12)
Female (%)	45	45
White (%)	97	98
eGFR (ml/min/1.73m ² , mean(SD))	69 (22)	71 (21)
eGFR category (%)		
≥60 ml/min/1.73m ²	65	70
30-59 ml/min/1.73m ²	30	27
<30 ml/min/1.73m ²	5	3
Year (%)		
2010-2012	25	16
2013-2014	30	34
2015-2017	45	50
Type of direct oral anticoagulants (%)		
Dabigatran	27	22
Rivaroxaban	44	42
Apixaban	29	36
Duration of prior anticoagulation (years, median (IQR))*	3 (1-6)	-
CHA ₂ DS ₂ -VASc score (mean (SD))	4.0 (1.9)	3.3 (1.8)
HAS-BLED score (mean (SD))	1.8 (1.0)	1.6 (1.0)
Number of prior hospitalizations (%)		
None	20	40
1-3	34	38
4-7	25	15
≥8	21	7
Comorbidities (%)		
Hypertension	87	80
Diabetes	38	30
Congestive heart failure	39	24
Valvular heart disease	30	19
Valvular atrial fibrillation [†]	7	2
Myocardial infarction	18	13
Coronary artery disease	47	35
Peripheral artery disease	20	13
Deep vein thrombosis	18	4
Pulmonary embolism	9	2
Bleeding	45	28
Anemia	49	26
Transient ischemic attack	18	10
Ischemic stroke	12	6
End-stage kidney disease	0.6	0.3
Medication use (%)		
NSAIDs	18	28
Anti-platelet agents	16	26
Statins	26	32
RAS blockers	27	32

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

*Only among patients with previous warfarin use. [†]Valvular atrial fibrillation was defined as atrial fibrillation with rheumatic mitral stenosis or prosthetic heart valve.

Abbreviations: SD, standard deviation; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; RAS blockers, renin-angiotensin system blockers

Supplemental Table 5. Baseline characteristics in propensity-score matched patients with atrial fibrillation using dabigatran or warfarin

Variable	Dabigatran (n=904)	Warfarin (n=904)	Standardized mean difference
Age (years)	70 (12)	70 (12)	0.01
Female (%)	42	41	0.02
White (%)	98	98	0.000
eGFR (ml/min/1.73m ²)	72 (21)	71 (21)	0.03
eGFR category (%)			
≥60 ml/min/1.73m ²	71	71	0.03
30-59 ml/min/1.73m ²	26	26	0.03
<30 ml/min/1.73m ²	3	3	0.03
Year (%)			
2010-2012	63	63	0.03
2013-2014	23	23	0.03
2015-2017	14	14	0.03
History of prior anticoagulation (%)	41	39	0.04
Duration of prior anticoagulation (years, median (IQR))*	3 (1-5)	3 (1-4)	0.04
CHA ₂ DS ₂ -VASc score	4 (2)	4 (2)	0.01
HAS-BLED score	2 (1)	2 (1)	0.01
Number of prior hospitalizations (%)			
None	40	42	0.03
1-3	35	35	0.03
4-7	17	15	0.03
≥8	8	8	0.03
Comorbidities (%)			
Hypertension	79	79	0.01
Diabetes	31	31	0.002
Congestive heart failure	27	27	0.01
Valvular heart disease	24	24	0.01
Valvular atrial fibrillation [†]	4	4	0.03
Myocardial infarction	12	12	0.01
Coronary artery disease	39	38	0.02
Peripheral artery disease	13	16	0.07
Deep vein thrombosis	6	5	0.02
Pulmonary embolism	1	1	0.01
Bleeding	31	32	0.02
Anemia	28	30	0.03
Transient ischemic attack	13	13	0.003
Ischemic stroke	11	11	0.02
Medication use (%)			
NSAIDs	26	25	0.02
Anti-platelet agents	24	23	0.01
Statins	33	33	0.02
RAS blockers	32	32	0.01

Values are mean (s.d.), unless indicated otherwise. *Only among those with a history of prior anticoagulation.

[†]Valvular atrial fibrillation was defined as atrial fibrillation with rheumatic mitral stenosis or prosthetic heart valve.

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drug; RAS blockers, renin-angiotensin system blockers
All P-values are >0.05 .

Supplemental Table 6. Baseline characteristics in propensity-score matched patients with atrial fibrillation using rivaroxaban or warfarin

Variable	Rivaroxaban (n=1,656)	Warfarin (n=1,656)	Standardized mean difference
Age (years)	70 (11)	70 (12)	0.01
Female (%)	44	43	0.02
White (%)	98	98	0.000
eGFR (ml/min/1.73m ²)	72 (20)	71 (21)	0.03
eGFR category (%)			
≥60 ml/min/1.73m ²	70	69	0.02
30-59 ml/min/1.73m ²	28	28	0.01
<30 ml/min/1.73m ²	2	3	0.02
Year (%)			
2012-2013	30	32	0.05
2014-2015	47	47	0.01
2016-2017	23	21	0.04
History of prior anticoagulation (%)	41	39	0.05
Duration of prior anticoagulation (years, median (IQR))*	3 (1-5)	3 (1-5)	0.02
CHA ₂ DS ₂ -VASc score	4 (2)	4 (2)	0.02
HAS-BLED score	2 (1)	2 (1)	0.02
Number of prior hospitalizations (%)			
None	31	34	0.07
1-3	37	36	0.03
4-7	18	17	0.03
≥8	14	13	0.03
Comorbidities (%)			
Hypertension	82	82	0.005
Diabetes	33	32	0.03
Congestive heart failure	28	28	0.01
Valvular heart disease	22	24	0.06
Valvular atrial fibrillation	4	5	0.06
Myocardial infarction	14	14	0.01
Coronary artery disease	38	39	0.03
Peripheral artery disease	15	15	0.01
Deep vein thrombosis	11	11	0.02
Pulmonary embolism	7	6	0.03
Bleeding	35	35	0.000
Anemia	35	35	0.01
Transient ischemic attack	12	12	0.01
Ischemic stroke	11	11	0.03
Medication use (%)			
NSAIDs	24	26	0.03
Anti-platelet agents	22	23	0.03
Statins	28	30	0.03
RAS blockers	28	29	0.03

Values are mean (s.d.), unless indicated otherwise. *Only among those with a history of prior anticoagulation

†Valvular atrial fibrillation was defined as atrial fibrillation with rheumatic mitral stenosis or prosthetic heart valve.

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; RAS blockers, renin-angiotensin system blockers
All P-values are >0.05.

Supplemental Table 7. Baseline characteristics in propensity-score matched patients with atrial fibrillation using apixaban or warfarin

Variable	Apixaban (n=1,312)	Warfarin (n=1,312)	Standardized mean difference
Age (years)	73 (12)	73 (12)	0.02
Female (%)	49	48	0.02
White (%)	97	98	0.06
eGFR (ml/min/1.73m ²)	66 (22)	65 (22)	0.05
eGFR category (%)			
≥60 ml/min/1.73m ²	61	60	0.02
30-59 ml/min/1.73m ²	34	34	0.002
<30 ml/min/1.73m ²	5	6	0.04
Year (%)			
2013-2014	24	26	0.04
2015	29	29	0.003
2016-2017	47	45	0.04
History of prior anticoagulation (%)	39	36	0.06
Duration of prior anticoagulation (years, median (IQR))*	3 (1-6)	3 (1-6)	0.04
CHA ₂ DS ₂ -VASc score	4 (2)	4 (2)	0.03
HAS-BLED score	2 (1)	2 (1)	0.002
Number of prior hospitalizations (%)			
None	27	28	0.01
1-3	37	37	0.01
4-7	21	19	0.04
≥8	15	16	0.03
Comorbidities (%)			
Hypertension	86	85	0.03
Diabetes	36	35	0.01
Congestive heart failure	36	35	0.01
Valvular heart disease	26	30	0.10
Valvular atrial fibrillation	4	4	0.02
Myocardial infarction	17	18	0.01
Coronary artery disease	45	44	0.02
Peripheral artery disease	18	18	0.01
Deep vein thrombosis	9	8	0.03
Pulmonary embolism	4	5	0.01
Bleeding	39	39	0.02
Anemia	41	40	0.01
Transient ischemic attack	15	14	0.03
Ischemic stroke	13	14	0.01
End-stage kidney disease	1	1	0.01
Medication use (%)			
NSAIDs	22	22	0.01
Anti-platelet agents	21	22	0.02
Statins	31	31	0.000
RAS blockers	31	31	0.01

Values are mean (s.d.), unless indicated otherwise. *Only among those with a history of prior anticoagulation.

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

atrial
was
atrial
with
mitral
prosthetic
valve.

Valvular
fibrillation
defined as
fibrillation
rheumatic
stenosis or
heart

	HR (95% CI)	p-value	p-interaction
Bleeding			
As-treated analyses			
Overall (events=1,171)	1.09 (0.97-1.22)	0.15	
eGFR \geq 60 (events=740)	1.01 (0.88-1.17)	0.87	0.09
eGFR<60 (events=431)	1.24 (1.03-1.50)	0.02	
Intention-to-treat analyses			
Overall (events=1,654)	1.09 (0.99-1.20)	0.07	
eGFR \geq 60 (events=1,057)	1.03 (0.91-1.16)	0.62	0.10
eGFR<60 (events=597)	1.22 (1.04-1.44)	0.01	
Time-varying analyses			
Overall (events=1,304)	1.18 (1.05-1.31)	0.004	
eGFR \geq 60 (events=825)	1.11 (0.96-1.27)	0.16	0.09
eGFR<60 (events=479)	1.33 (1.11-1.59)	0.002	
Ischemic stroke			
As-treated analyses			
Overall (events=462)	0.97 (0.91-1.17)	0.76	
eGFR \geq 60 (events=288)	0.94 (0.74-1.18)	0.58	0.65
eGFR<60 (events=174)	1.03 (0.77-1.39)	0.83	
Intention-to-treat analyses			
Overall (events=601)	1.01 (0.86-1.18)	0.93	
eGFR \geq 60 (events=384)	0.97 (0.79-1.18)	0.74	0.49
eGFR<60 (events=217)	1.09 (0.83-1.42)	0.54	
Time-varying analyses			
Overall (events=500)	0.94 (0.79-1.12)	0.51	
eGFR \geq 60 (events=316)	0.88 (0.71-1.11)	0.30	0.45
eGFR<60 (events=184)	1.03 (0.78-1.39)	0.79	

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; RAS blockers, renin-angiotensin system blockers All P-values are >0.05.

Supplemental Table 8. Sensitivity analyses excluding those on dialysis at baseline (n=28) and censoring at dialysis initiation

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

Supplemental Table 9. Sensitivity analyses exploring the potential effects of misclassification of baseline eGFR

	HR (95% CI)	p-value	p-interaction
Analyses excluding those with AKI^a	Bleeding		
Overall	1.09 (0.98-1.23)	0.13	
eGFR \geq 60	1.02 (0.89-1.18)	0.78	0.11
eGFR<60	1.23 (1.03-1.49)	0.03	
	Ischemic stroke		
Overall	0.98 (0.82-1.18)	0.83	
eGFR \geq 60	0.94 (0.75-1.19)	0.61	0.61
eGFR<60	1.05 (0.78-1.41)	0.76	
Analyses using an average eGFR^b	Bleeding		
Overall	1.08 (0.97-1.22)	0.16	
eGFR \geq 60	1.01 (0.88-1.16)	0.91	0.06
eGFR<60	1.28 (1.05-1.56)	0.02	
	Ischemic stroke		
Overall	0.97 (0.81-1.16)	0.72	
eGFR \geq 60	0.97 (0.77-1.21)	0.76	0.98
eGFR<60	0.97 (0.71-1.33)	0.87	

^a As-treated analyses excluding those with an acute kidney injury (AKI) diagnostic code

^b As-treated analyses using an average eGFR during 1 year prior to the baseline prescription date or 90 days after baseline

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

Supplemental Table 10. Sensitivity analyses using an alternative gap (30 days) for defining

	HR (95% CI)	p-value	p-interaction
	Bleeding		
As-treated analyses			
Overall (events=1,054)	1.13 (1.00-1.28)	0.04	
eGFR \geq 60 (events=653)	1.08 (0.92-1.25)	0.78	0.24
eGFR<60 (events=401)	1.24 (1.02-1.51)	0.03	
Time-varying analyses			
Overall (events=1,236)	1.13 (0.99-1.25)	0.06	
eGFR \geq 60 (events=768)	1.08 (0.93-1.24)	0.35	0.31
eGFR<60 (events=468)	1.20 (1.00-1.44)	0.04	
	Ischemic stroke		
As-treated analyses			
Overall (events=446)	0.97 (0.81-1.17)	0.78	
eGFR \geq 60 (events=277)	0.97 (0.77-1.23)	0.83	0.98
eGFR<60 (events=169)	0.97 (0.72-1.32)	0.86	
Time-varying analyses			
Overall (events=483)	0.98 (0.82-1.17)	0.84	
eGFR \geq 60 (events=303)	0.98 (0.78-1.23)	0.84	0.99
eGFR<60 (events=180)	0.99 (0.74-1.33)	0.95	

medication discontinuation

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

Supplemental Table 11. Sensitivity analyses excluding those with valvular atrial fibrillation

	HR (95% CI)	p-value	p-interaction
As-treated analyses	Bleeding		
Overall	1.09 (0.97-1.23)	0.14	
eGFR \geq 60	1.02 (0.88-1.19)	0.77	0.13
eGFR $<$ 60	1.23 (1.02-1.49)	0.03	
	Ischemic stroke		
Overall	0.95 (0.79-1.14)	0.59	
eGFR \geq 60	0.93 (0.73-1.17)	0.52	0.74
eGFR $<$ 60	0.99 (0.73-1.35)	0.97	

276 (4%) out of 3,206 patients were diagnosed with valvular atrial fibrillation.

Supplemental Table 12. Stratified analyses by prior anticoagulation history

	HR (95% CI)	p-value	p-inter
	Bleeding		
Analyses using incident users			
Overall (N=4,056)	1.12 (0.99-1.27)	0.07	
eGFR \geq 60 (N=2,649)	1.11 (0.95-1.30)	0.20	0.63
eGFR<60 (N=1,407)	1.12 (0.91-1.37)	0.29	
Analyses using prevalent users			
Overall (N=2,356)	0.97 (0.82-1.15)		
eGFR \geq 60 (N=1,520)	0.88 (0.71-1.09)	0.25	0.30
eGFR<60 (N=836)	1.15 (0.86-1.54)	0.33	
	Ischemic stroke		
Analyses using incident users			
Overall (N=4,056)	0.99 (0.77-1.26)	0.91	
eGFR \geq 60 (N=2,649)	1.10 (0.79-1.53)	0.59	0.32
eGFR<60 (N=1,407)	0.89 (0.59-1.32)	0.56	
Analyses using prevalent users			
Overall (N=2,356)	0.81 (0.58-1.12)	0.21	
eGFR \geq 60 (N=1,520)	0.79 (0.52-1.19)	0.25	0.77
eGFR<60 (N=836)	0.83 (0.45-1.53)	0.55	

Incident users: those without prior anticoagulation history

Prevalent users: those with anticoagulation history