Supplemental Material

ORBIT-AF II Investigators

Sanjiv Sobti, Anthony Alfieri, James Bacon, Noel Bedwell, John Berry, Ravi Bhagwat, Stephen Bloom, Fernando Boccalandro, Leonard Parilak, James Capo, Shaival Kapadia, J. Edwin Morriss, III, Basharat Muneer, Harinder Gogia, William Herzog, David Hotchkiss, John Ip, Naseem Jaffrani, Alan Jones, John Kazmierski, Waqar Khan MPH, G. Larsen Kneller, Ajay Labroo, Brian Jaffe, Mark Lebenthal, Daniel Lee, Homayoun Reza Ahmadian, Paul Maccaro, Nolan Mayer, Paul McLaughlin, Robert Mendelson, Benzy Padanilam, James Poock, Joseph Raffetto, Matthew Sackett, Ricky Schneider, Jeffrey Shanes, Nasser Smiley, Calvin Snipes, Rodolfo Sotolongo, Shawn Speirs, Tahir Tak, Preet Radhawa, S. Luke Kusmirek, Preetham Jetty, Tomas Vasiliauskas, Dennis Spiller, Chakri Yarlagadda, John Griffin, Richard Simons, Terrance Castor, Joseph McGarvey, Roger Guthrie, George Deriso, Craig Vogel, Sabrina Benjamin, Robert Detweiler, John Pappas, Ronald Littlefield, Paul Grena, Seth Goldbarg, Kevin Browne, Steven Forman, Matthew Ebinger, David Rosenbaum, David Williams, Robert Stein, Keith Davis, Odilon Alvarado, Steven Rothman, Hicham Siouty, John Kobayashi, David Scollan, Alexander Adler, Denis Ruiz Serrano, Charles Gottlieb, Charles Gornick, Yogesh Paliwal, Raman Mitra, Shamaila A. Aslam, Larry Allen, Minang Turakhia, Mark Lurie, Albert Sun, Lawrence Rink, Mahmoud Atieh, Andrew Drabick, Eric Harman, Brent Ashcraft, Elvin Rivera-Zayas, Christopher Henes, Steven Schwartz, Hector Malave, Antony Chu, Sandip Mukherjee, Michael Underhill, Kent R. Nilsson, Michael DiGiovanna, Craig McPherson, Thomas R. Bowden, Herbert Pardell, Richard Smith, Emil Hayek, Ram Reddy, Howard Sawyer, Hyeun Park, Mir Varquez, Thomas Pow, Jeffrey Harris, Felix Sogade, C.P. Dunbar, John Dongas, Jose Birriel, Jasbir Sra, James H. French, Victor Farrah, James Cirbus, Emanuel Shaoulian, Jeffrey Whitehill, Thomas S. Backer, Bernard Grunstra, Andrew Muller, Sharan Mahal, Mark Dawson, John Earl, Afolabi O. Sangosanya, Steven Tang, Ahmad Quaddour, Abraham Salacata, Roger Estevez, Barry Troyan, Nan Jiang, Amin Karim, Kannappan Krishnaswamy, Ruben Ayala, Randeep Suneja, Anthony Inzerello, Philip Patel, Austin Kutscher, Thomas Wolf, Shaik Ali, Fernando Mera, Osvaldo Gigliotti, Mirza Baig, Kurt Lesh, Gary Korff, Hector Jimenez, Melissa Kong, Clark Soderlund, John Chin, James Allred, Roddy Canosa, Alex Foxman, Scott Wilson, Nicolas Shammas, Aylmer Tang, Edo Kaluski, J. Thomas Svinarich, John Covalesky, Rohit Sundrani, Dinesh Singal, John Norris, Ramzi Nassif, Joon Ahn, Jonathan Goldberg, Severino Pimentel, Ira Friedlander, Jason Zagrodzky, Craig Cameron, Rubina Husain, Rakesh Shah, Ofsman Quintana, Hitesh Mehta, Ian Weisberg, Vicken Vorperian, Eric Ball, Emily Morawski, Majed Chane, Salman Khan, Mehrdad K Ariani, Chad Bates, Raul Garg, Aveh Bastani, Harpreet Grewal, Kamlesh Dave, Ronald Solbrig, Chaitany Ravi, Raul Torres-Heisecke, Chafik Assal, Daniel R. Frisch, Randall Richwine, Lindsey White, Anand Irimpen, Michael D. Moran, James Kmetzo, Otis Barnum, Narendra Singh, Anna Chang, Kevin Longshaw, Jun Anthony Quion, Henri Marais, Jayson Liu, Rajesh Chawla, Mark Huth, Tyler Barrett, Raed Bargout, Allan Murphy, Naveed Razzaque, David Allen, Son Giep, Kevin Pounds, Craig R. Peterson, Amarnath Vedere, Juma Bharadia, Henry Yee, Krishnan Challappa, David Garcia, Bengt Herweg, Aga Kuliev, Steven Pearlman, Ata T. Salek, Howard Noveck, Jason Fleming, Adeeba Akhtar, Dat Tran, Amir Malik, John L. Cosby, Roberto Lopez, Rajesh Bhakta, Ned Gutman, Jimin Wang, Michael Gabris, Tak W. Kwan, Anil Gehi, Devang Desai, Valerian L. Fernandes, Valeriani Bead, Tariq Salam, Kevin Merkes, Christopher Cole, Jeffrey Banker, Joseph Sacco, Bonifasiyo Ssennyamantono, William J. French, Annette Quick, Viral Mehta, Aron Schlau, Jay Pandhi, Jawad Zar Shaikh, Justin Weiner, Rajesh Kabra, Hector Rodriguez, Alan Tenaglia, Paul LeLorier, Lawrence Blitz, Timothy Logemann, Chris Christodoulou, John Heath, Esperanza Arce-Nunez, Hans Moore, Thor Markwood, Yamirka Duardo Guerra, Michael T. Morris, Luis Ramos, Timothy Shinn, Stephen Welka, Vijay Divakaran, M. Akram Khan, Randy Mintz, Thomas Galski, Jerald Young, Alexander Paraschos, James D. Nelson, Jerrold Grodin, David Harnick, Clayton Bredlau, Anil Chhabra, Ram Dandillaya, Raul Gazmuri, Michael Radin, Ronald D'Agostino, Chibuzo Nwokolo, Vipul Shah, Charles Henrikson, David Navratil, Mark Lieb, Subhash Banerjee, Robert D Chamberlain, Jr, Shawn Howell, Peter Rouvelas, Nikhil Kapoor,

William Eaves, Gauarv Aggarwala, Ibrahim Elgabry, Walid Saber, Rakesh Passi, Syed Ahmed, Mayer Rashtian, Ivan Mendoza,

Table S1. Dosing Criteria

The appropriate NOAC dosing is defined as follows, according to which NOAC agent is prescribed:

- Dabigatran[1]
  - 150 mg twice daily is standard dose.
  - CrCl 30 to 50 mL/min: No dosage adjustment necessary unless patient receiving concomitant dronedarone, then consider reducing dabigatran to 75 mg twice daily.
  - CrCl 15 to 30 mL/min: 75 mg twice daily unless patient receiving concomitant dronedarone, then avoid concurrent use.
  - CrCl <15 mL/min or on dialysis: not recommended.
- Rivaroxaban[2]
  - 20 mg once daily is standard dose.
  - CrCl 15 to 50 mL/min: 15 mg once daily.
  - CrCl <15 mL/min or on dialysis: Avoid use.
- Apixaban[3]
  - 5 mg twice daily unless patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily.
  - On dialysis: 5 mg twice daily; reduce to 2.5 mg twice daily if age ≥80 years or body weight ≤60 kg.
- Edoxaban[4]
  - 60 mg daily is standard dose, used when 50 < CrCl ≤ 95 mL/min
  - CrCl 15-50: 30 mg daily
  - CrCl >95 mL/min: Contraindicated
  - CrCl <15 mL/min: Contraindicated

Table S2. List of covariates for propensity score

Demographics

1. Age, years
2. Race – African American/Hispanic/White/Others
3. Gender – Male/Female
4. Level of Education – Some School/High School Graduate/College Graduate/Post Graduate
5. Payor/Insurance – Medicare or Medicaid/private/Others

Medical History

1. Smoking – Current/Recent or Former/Non-smoker
2. Cancer – Yes/No
3. Hypertension – Yes/No
4. Diabetes – Yes/No
5. Hyperthyroidism – Yes/No
6. Hypothyroidism – Yes/No
7. GI Bleed – Yes/No
8. Obstructive Sleep Apnea – Yes/No
9. Dialysis – Yes/No
10. Hyperlipidemia – Yes/No
11. Anemia – Yes/No
12. Cognitive Impairment/Dementia – Yes/No
13. Frailty – Yes/No
14. Liver Disease – Yes/No
15. COPD – Yes/No
16. Alcohol Abuse – Yes/No
17. Drug Abuse – Yes/No

Cardiovascular History

1. Family History of AF – Yes/No
2. Peripheral Vascular Disease – Yes/No
3. Sinus Node Dysfunction/Sick Sinus Syndrome – Yes/No
4. Stroke or TIA – Yes/No
5. Congestive Heart Failure (CHF) – No CHF/NYHA Class I/NYHA Class II/NYHA Class III or NYHA Class IV
6. Significant Valvular Disease – Yes/No
7. Prior Valve Replacement/Repair – Yes/No

Coronary Artery Disease History

1. History of Coronary Artery Disease – Yes/No
2. Prior MI – Yes/No
3. Prior CABG – Yes/No
4. Any PCI – Yes/No

Vital Signs & AF status

1. Height, cm
2. Weight, kg
3. Heart Rate, bpm
4. Diastolic Blood Pressure, mmHG
5. Systolic Blood Pressure, mmHG

6. Body Mass Index, kg/m^2 (For imputation purpose, we will impute individual components which are weight, height)
7. Most Recent 12 Lead EKG – Sinus Rhythm
8. Most Recent 12 Lead EKG – Atrial Fibrillation
9. Most Recent 12 Lead EKG – Atrial Flutter
10. Most Recent 12 Lead EKG – Paced
11. Most Recent 12 Lead EKG – Other
12. Intraventricular Conduction – RBBB/LBBB/Non-specific IVCD or Unknown-Ventricularly Paced/none
13. QRS Duration, milliseconds

Echocardiographic Assessment (TTE or TEE)

1. LVEF – Normal (≥50%)/Mild dysfunction (>40%, <50%)/Moderate dysfunction (≥30%, ≤40%)/Severe dysfunction (<30%)
2. LAD Type – Normal/Mild enlargement/Moderate enlargement/Severe enlargement

Laboratory Data

1. Hemotocrit, % (fill in from Hemoglobin by Hemoglobin*3 if missing)

Atrial Fibrillation Diagnosis

1. Type of AF – First Detected or New Onset/Paroxysmal AF/Persistent AF /Permanent AF
2. EHRA Score – No symptoms/Mild/Severe/Disabling
3. AF management strategy – Rate Control/Rhythm Control
4. Prior Cardioversions – Yes/No
5. Prior antiarrhythmic drug – Yes/No
6. Catheter Ablation of AF – Yes/No
7. AV Node or HIS Bundle Ablation – Yes/No

Enrolling Physician Specialty

1. PI/Site Specialty – Cardiology/Electrophysiology/Neurology or Internal Medicine

Table S3: Standardized differences between propensity matched subjects (N=1,302)

Variable	*Appropriate-Standard N=651*	*Inappropriate-Reduced N=651*	*Standardized difference*	*P*
NOAC			0.0%	0.9999
Rivaroxaban	278 (42.7)	278 (42.7)		
Apixaban	373 (57.3)	373 (57.3)		
Age, years	77.0 (8.8)	77.4 (8.8)	4.8%	0.3900
Race			11.4%	0.6515
White	561 (86.2)	565 (86.8)		
Black/African American	29 (4.5)	29 (4.5)		
Hispanic	42 (6.5)	39 (6.0)		
American Indian/Alaska Native	2 (0.3)	0 (0.0)		
Asian	9 (1.4)	13 (2.0)		
Native Hawaiian/Pacific Islander	1 (0.2)	0 (0.0)		
Other/Not Reported	7 (1.1)	5 (0.8)		
Female	310 (47.6)	321 (49.3)	3.4%	0.5419
Level of education			4.7%	0.8674
Some school	74 (11.4)	83 (12.7)		
High school graduate	330 (50.7)	320 (49.2)		
College graduate	179 (27.5)	182 (28.0)		
Post graduate	68 (10.4)	66 (10.1)		
Insurance			6.9%	0.8153
Private Health Insurance	285 (43.8)	278 (42.7)		
Medicaid	24 (3.7)	28 (4.3)		
Medicare	319 (49.0)	321 (49.3)		
Other	15 (2.3)	19 (2.9)		
None	8 (1.2)	5 (0.8)		
Smoking status			7.5%	0.6099
Never	344 (52.8)	353 (54.2)		
Current	39 (6.0)	32 (4.9)		
Former	268 (41.2)	265 (40.7)		
Recent	0 (0.0)	1 (0.2)		
Cancer	168 (25.8)	173 (26.6)	1.7%	0.7526
Hypertension	562 (86.3)	557 (85.6)	2.2%	0.6901
Diabetes	226 (34.7)	198 (30.4)	9.2%	0.0977
Hyperthyroidism	14 (2.2)	10 (1.5)	4.6%	0.4099
Hypothyroidism	125 (19.2)	139 (21.4)	5.4%	0.3345
GI bleed	34 (5.2)	37 (5.7)	2.0%	0.7142
Obstructive sleep apnea	83 (12.7)	86 (13.2)	1.4%	0.8046
Dialysis	4 (0.6)	4 (0.6)	0.0%	0.9999
Hyperlipidemia	485 (74.5)	464 (71.3)	7.3%	0.1905
Anemia	85 (13.1)	81 (12.4)	1.8%	0.7396

Variable	*Appropriate-Standard N=651*	*Inappropriate-Reduced N=651*	*Standardized difference*	*P*
Cognitive impairment/Demetia	16 (2.5)	19 (2.9)	2.8%	0.6072
Frailty	32 (4.9)	37 (5.7)	3.4%	0.5362
Liver disease	10 (1.5)	12 (1.8)	2.4%	0.6672
COPD	74 (11.4)	82 (12.6)	3.8%	0.4948
Alcohol abuse	15 (2.3)	16 (2.5)	1.0%	0.8558
Drug abuse	6 (0.9)	7 (1.1)	1.5%	0.7804
Family history of AF	50 (7.7)	46 (7.1)	2.4%	0.6714
Peripheral vascular disease	74 (11.4)	68 (10.4)	3.0%	0.5937
Sinus node dysfunction/Sick sinus syndrome	76 (11.7)	74 (11.4)	1.0%	0.8622
Stroke or TIA	81 (12.4)	93 (14.3)	5.4%	0.3284
CHF/ NYHA class				
No CHF	487 (74.8)	492 (75.6)	6.4%	0.5848
NYHA Class I	48 (7.4)	51 (7.8)		
NYHA Class II	87 (13.4)	82 (12.6)		
NYHA Class III	28 (4.3)	26 (4.0)		
NYHA Class IV	1 (0.2)	0 (0.0)		
Significant valvular disease	110 (16.9)	115 (17.7)	2.0%	0.7140
Prior valve replacement/repair	21 (3.2)	24 (3.7)	2.5%	0.6490
History of coronary artery disease	229 (35.2)	231 (35.5)	0.6%	0.9077
Prior MI	86 (13.2)	93 (14.3)	3.1%	0.5732
Prior CABG	70 (10.8)	80 (12.3)	4.8%	0.3854
Any PCI	122 (18.7)	123 (18.9)	0.4%	0.9435
Height, cm	170 (11.1)	169 (10.7)	4.3%	0.4362
Weight, kg	87.5 (21.8)	86.1 (22.2)	6.1%	0.2677
Heart rate, bpm	73.7 (16.1)	73.8 (15.3)	1.1%	0.8461
Diastolic blood pressure, mmHg	71.6 (10.4)	71.9 (10.9)	3.4%	0.5419
Systolic blood pressure, mmHg	127 (17.5)	127 (17.4)	0.6%	0.9101
BMI, kg/m^2	30.4 (7.0)	30.1 (7.2)	4.2%	0.4536
Most recent 12 lead EKG - Sinus rhythm	230 (35.3)	230 (35.3)	0.0%	0.9999

Variable	*Appropriate-Standard N=651*	*Inappropriate-Reduced N=651*	*Standardized difference*	*P*
Most recent 12 lead EKG - Atrial fibrillation	320 (49.2)	321 (49.3)	0.3%	0.9558
Most recent 12 lead EKG - Atrial flutter	17 (2.6)	14 (2.2)	3.0%	0.5855
Most recent 12 lead EKG - Paced	70 (10.8)	66 (10.1)	2.0%	0.7170
Most recent 12 lead EKG - Other	57 (8.8)	64 (9.8)	3.7%	0.5040
Intraventricular conduction			8.1%	0.7098
LBBB	33 (5.1)	32 (4.9)		
RBBB	69 (10.6)	61 (9.4)		
Non-specific IVCD	17 (2.6)	22 (3.4)		
Ventricularly-paced	54 (8.3)	45 (6.9)		
None	478 (73.4)	491 (75.4)		
QRS duration, milliseconds	105 (28.2)	104 (27.9)	3.1%	0.5772
LVEF			0.6%	0.9997
Normal (≥50%)	537 (82.5)	536 (82.3)		
Mild dysfunction (41-49%)	51 (7.8)	51 (7.8)		
Moderate dysfunction (30-40%)	54 (8.3)	55 (8.4)		
Severe dysfunction (<30%)	9 (1.4)	9 (1.4)		
LAD type			9.1%	0.4424
Normal	191 (29.3)	211 (32.4)		
Mild enlargement	205 (31.5)	196 (30.1)		
Moderate enlargement	168 (25.8)	149 (22.9)		
Severe enlargement	87 (13.4)	95 (14.6)		
Hematocrit (%)	39.2 (5.6)	39.2 (5.4)	0.5%	0.9236
AF type			5.1%	0.8417
First detected/New-onset	241 (37.0)	256 (39.3)		
Paroxysmal	275 (42.2)	264 (40.6)		
Persistent	89 (13.7)	84 (12.9)		
Permanent	46 (7.1)	47 (7.2)		
EHRA score			5.2%	0.8307
No symptoms	226 (34.7)	230 (35.3)		
Mild	309 (47.5)	316 (48.5)		
Severe	108 (16.6)	96 (14.7)		
Disabling	8 (1.2)	9 (1.4)		
AF management strategy (%)	246 (37.8)	229 (35.2)	5.4%	0.3277
Prior cardioversions (%)	140 (21.5)	139 (21.4)	0.4%	0.9462
Prior antiarrhythmic drug (%)	206 (31.6)	194 (29.8)	4.0%	0.4710
Catheter ablation of AF (%)	19 (2.9)	15 (2.3)	3.9%	0.4870
AV node or HIS bundle ablation (%)	4 (0.6)	3 (0.5)	2.1%	0.7047
PI/Site specialty			11.8%	0.2104
Internal medicine/Primary care	60 (9.2)	43 (6.6)		
Cardiology	494 (75.9)	498 (76.5)		

Variable	*Appropriate-Standard N=651*	*Inappropriate-Reduced N=651*	*Standardized difference*	*P*
Electrophysiology	97 (14.9)	109 (16.7)		
Neurology	0 (0.0)	1 (0.2)		

Figure S1. Distribution and appropriateness of dosing re-categorizing patients with borderline CrCl as appropriate for reduced dosing.

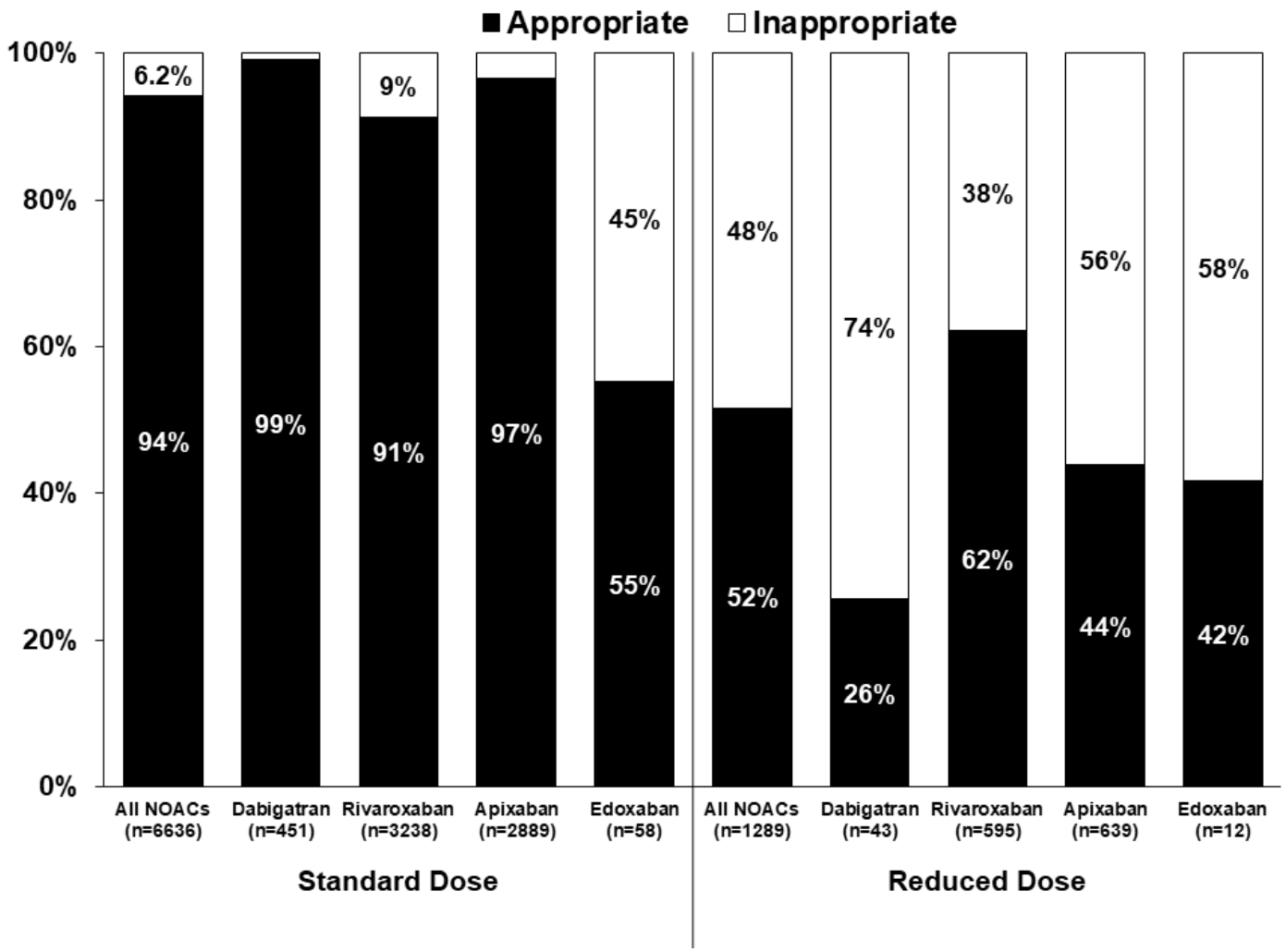

Table S4. Event rates by NOAC dose received (rivaroxaban or apixaban), among patients *recommended* for standard NOAC dosing (n=6,584), and in propensity-matched, adjusted cohort (n=651).

	Overall (n=6,584)	Unadjusted (n=6,584)				Propensity Matched* (n=651)	
	# Events (Rate per 100 patient-year)	Appropriate Standard (n=5895)	Inappropriately-Reduced (n=689)	*HR*† *(95% CI)*	*P*	*HR*† *(95% CI)*	*P*
Thromboembolic Outcomes							
Stroke, non-CNS embolism, or TIA	107 (1.43)	91 (1.35)	16 (2.11)	1.56 (0.92-2.67)	0.10	0.85 (0.41-1.78)	0.7
MI	47 (0.62)	41 (0.60)	6 (0.78)	1.29 (0.62-2.69)	0.5	3.17 (0.65-15.38)	0.2
Death	229 (3.03)	177 (2.60)	52 (6.77)	2.61 (1.86-3.67)	<.0001	1.36 (0.89-2.06)	0.2
MACNE	217 (2.91)	181 (2.70)	36 (4.78)	1.77 (1.28-2.46)	0.0006	1.24 (0.76-2.02)	0.4
Bleeding Outcomes							
Major bleeding	221 (2.98)	189 (2.84)	32 (4.28)	1.49 (1.02-2.18)	0.04	1.16 (0.73-1.84)	0.5
Bleeding hospitalization	186 (2.50)	159 (2.38)	27 (3.60)	1.49 (0.98-2.27)	0.06	1.13 (0.64-1.99)	0.7

†HR for inappropriately reduced dose subjects relative to appropriately standard dose subjects.

*Matched analysis is limited to 651 appropriately standard dosed subjects and 651 inappropriately reduce dosed subjects.

NOAC: non-vitamin K antagonist oral anticoagulant; CI: confidence interval; TIA: transient ischemic attack; MI: myocardial infarction; MACNE: major adverse cardiovascular and neurological events, including a composite of TIA, stroke, non-CNS embolism, MI, or cardiovascular death.

References

1. Boehringer-Ingelheim. Dabigatran Prescribing Information. In; 2010.
2. Pharmaceuticals J. Rivaroxaban Prescribing Information. In; 2011.
3. Squibb B-M. Apixaban Prescribing Information. In; 2012.
4. Daiichi Sankyo I. Edoxaban Prescribing Information. In; 2015.