SUPPLEMENTAL MATERIAL

Supplement Table 1. COMBINE AF Investigators.

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Supplement Table 2. Number (%) of patients who remained at risk (i.e. remained alive and active in a given trial) for 71,683 patients at 6-month intervals by individual trial.

	0 months		6 months		12 months		18 months		24 months		30 months		36 months		42 months		48 months	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
RE-LY N=18113	18113	100.0	17764	98.1	17379	95.9	14063	77.6	8950	49.4	4212	23.3	97	0.5	0	0.0	0	0.0
ROCKET AF N=14264	14264	100.0	13734	96.3	13130	92.0	9603	67.3	5843	41.0	2472	17.3	208	1.5	0	0.0	0	0.0
ARISTOTLE N=18201	18201	100.0	17474	96.0	16943	93.1	12216	67.1	7002	38.5	3596	19.8	1203	6.6	245	1.3	5	0.0
ENGAGE AF-TIMI 48 N=21105	21105	100.0	20666	97.9	20254	96.0	19827	93.9	19342	91.6	14348	68.0	7384	35.0	1688	8.0	95	0.5
The exact point (in months) at which each trial dropped below 10% of patients at risk is as follows: 32.2 months for RE-LY, 31.9 months for ROCKET AF, 34.2 months for ARISTOTLE, 41.5 months for ENGAGE AF-TIMI 48.																		

Supplement Table 3. Hazard ratios comparing standard-dose DOAC versus lower-dose DOAC strategies for efficacy and safety outcomes as well as the net clinical benefit. A hazard ratio > 1 favors lower-dose DOAC over standard-dose DOAC, whereas a hazard ratio < 1 favors standard-dose DOAC over lower-dose DOAC.

	Standard-dose DOAC versus lower-dose DOAC
Efficacy Outcomes	Hazard Ratio (95% Confidence Interval)
Stroke or systemic embolism	0.76 (0.68-0.86)
All-cause death	1.02 (0.95-1.11)
Cardiovascular death	0.99 (0.90-1.10)
Any stroke	0.77 (0.68-0.87)
Ischemic stroke	0.71 (0.62-0.81)
Systemic embolism	0.68 (0.44-1.05)
Efficacy composite	0.89 (0.82-0.96)
Safety Outcomes	
Major bleeding	1.37 (0.95-1.96)
Fatal bleeding	1.44 (0.97-2.15)
Major or NMCR bleeding	1.25 (1.00-1.55)
Any bleeding	1.18 (0.98-1.43)
Intracranial bleeding	1.64 (1.17-2.30)
Hemorrhagic stroke	1.51 (1.04-2.18)
Gastrointestinal bleeding	1.53 (1.07-2.17)
Net Clinical Benefit	
Stroke, SE, death, MB	1.07 (0.94-1.23)
Stroke, SE, death, intracranial bleeding	0.88 (0.81-0.97)

MB = major bleeding, NMCR = non-major clinical relevant, DOAC = direct oral anticoagulant, SE = systemic embolism

The efficacy composite outcome consists of ischemic stroke, systemic embolism, or cardiovascular death.

Supplement Table 4. Hazard ratios and the associated standard errors (s.e.) comparing standard-dose DOAC versus warfarin and lower-dose DOAC versus warfarin for efficacy and safety outcomes as well as the net clinical benefit under fixed effect and random effects stratified Cox models. Estimated between-study heterogeneity measures ($\hat{\tau}$) under the random effects models are reported. A hazard ratio > 1 favors lower-dose DOAC over standard-dose DOAC, whereas a hazard ratio < 1 favors standard-dose DOAC over lower-dose DOAC.

	Standard-dose DOAC versus warfarin			**Lower-dose DOAC versus warfarin**		
	Fixed effect Cox model	**Random effects Cox model**		**Fixed effect model**	**Random effect model**	
	HR (s.e.)	**HR (s.e.)**	$\hat{\tau}$	**HR (s.e.)**	**HR (s.e.)**	$\hat{\tau}$
Efficacy Outcomes						
Stroke or systemic embolism	0.81 (0.04)	0.81 (0.04)	0.00	1.06 (0.06)	1.06 (0.06)	0.00
All-cause death	0.92 (0.03)	0.92 (0.03)	0.00	0.90 (0.04)	0.90 (0.04)	0.00
Cardiovascular death	0.89 (0.03)	0.89 (0.03)	0.00	0.90 (0.04)	0.90 (0.04)	0.00
Any stroke	0.82 (0.04)	0.82 (0.04)	0.01	1.07 (0.06)	1.07 (0.06)	0.00
Ischemic stroke	0.95 (0.05)	0.95 (0.05)	0.00	1.35 (0.09)	1.35 (0.09)	0.00
Systemic embolism	0.71 (0.12)	0.71 (0.12)	0.01	1.06 (0.22)	1.05 (0.22)	0.05
Efficacy composite	0.90 (0.03)	0.90 (0.03)	0.00	1.02 (0.04)	1.02 (0.04)	0.00
Safety Outcomes						
Major bleeding	0.86 (0.03)	0.86 (0.07)	0.14	0.62 (0.03)	0.63 (0.11)	0.23
Fatal bleeding	0.60 (0.08)	0.60 (0.08)	0.00	0.42 (0.08)	0.42 (0.08)	0.01
Major or NMCR bleeding	0.89 (0.02)	0.87 (0.07)	0.15	0.66 (0.02)	0.70 (0.06)	0.10
Any bleeding	0.88 (0.01)	0.86 (0.07)	0.15	0.73 (0.02)	0.73 (0.04)	0.08
Intracranial bleeding	0.45 (0.04)	0.45 (0.05)	0.12	0.28 (0.04)	0.28 (0.04)	0.01
Hemorrhagic stroke	0.49 (0.05)	0.49 (0.05)	0.01	0.33 (0.06)	0.33 (0.06)	0.00
Gastrointestinal bleeding	1.33 (0.07)	1.31 (0.12)	0.15	0.85 (0.07)	0.85 (0.14)	0.20
Net Clinical Benefit						
Stroke, SE, death, MB	0.89 (0.02)	0.89 (0.03)	0.03	0.83 (0.03)	0.83 (0.05)	0.08
Stroke, SE, death, intracranial bleeding	0.82 (0.03)	0.82 (0.03)	0.00	0.92 (0.04)	0.92 (0.04)	0.00

DOAC = non-vitamin K antagonist oral anticoagulant, MB = major bleeding, NMCR = non-major clinical relevant, SE = systemic embolism

The efficacy composite outcome consists of ischemic stroke, systemic embolism, or cardiovascular death.

Supplement Table 5. Hazard ratios with 95% confidence intervals for the primary efficacy and primary safety endpoints from each individual trial, for standard-dose DOAC vs warfarin.

	RELY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Stroke/Systemic embolism	0.64 (0.52-0.80) P<0.001	0.87 (0.74-1.02) P=0.09	0.79 (0.66-0.95) P=0.01	0.87 (0.74-1.03) P=0.11
Major bleeding	0.98 (0.85-1.13) P=0.81	1.04 (0.90-1.20) P=0.61	0.69 (0.59-0.79) P<0.001	0.80 (0.70-0.91) P<0.001

Supplement Table 6. Hazard ratios (95% confidence intervals) and interaction p-values for the primary efficacy outcome (stroke or systemic embolism) comparing lower-dose DOAC versus warfarin by categorical baseline covariates. A hazard ratio > 1 favors warfarin over DOAC, whereas a hazard ratio < 1 favors DOAC over warfarin.

		Lower-dose DOAC versus warfarin	
Categorical Baseline Covariate		**HR (95% CI)**	**P-int**
Sex	Female	1.05 (0.89-1.24)	0.87
	Male	1.07 (0.92-1.23)	
Diabetes	Yes	1.03 (0.84-1.26)	0.74
	No	1.07 (0.94-1.23)	
Prior stroke/TIA	Yes	1.03 (0.86-1.23)	0.70
	No	1.08 (0.93-1.24)	
Prior VKA use	Yes	1.18 (1.03-1.34)	0.01
	No	0.86 (0.71-1.04)	
Antiplatelet use	Yes	0.95 (0.79-1.13)	0.11
	No	1.13 (0.98-1.30)	
$CHADS_2$ Score	≥3	0.98 (0.85-1.14)	0.23
	2	1.19 (0.98-1.44)	
	0, 1	1.18 (0.81-1.72)	
Paroxysmal AF	Yes	0.97 (0.77-1.22)	0.36
	No	1.09 (0.96-1.24)	
Coronary artery disease	Yes	1.12 (0.93-1.35)	0.47
	No	1.03 (0.90-1.18)	
Heart failure	Yes	1.11 (0.94-1.31)	0.43
	No	1.02 (0.87-1.19)	
Prior GI bleeding	Yes	1.83 (1.03-3.28)	0.09
	No	1.10 (0.95-1.27)	
Age (years)	>75	1.04 (0.89-1.22)	0.03
	65-75	0.95 (0.79-1.14)	
	<65	1.41 (1.10-1.81)	
Weight (kg)	>120	1.08 (0.56-2.07)	0.90
	60-120	1.07 (0.95-1.22)	
	<60	1.00 (0.76-1.32)	
CrCl (mL/min)	>80	1.15 (0.93-1.42)	0.64
	51-80	1.01 (0.87-1.19)	
	≤50	1.07 (0.88-1.31)	

AF = atrial fibrillation, CrCl = creatinine clearance, GI = gastrointestinal, TIA = transient ischemic attack

Supplement Table 7. Sample size and event rates (% per year) by categorical baseline body weight.

Stroke/Systemic Embolism				
		Event rates (%/yr)		
	# of patients	Standard-dose DOAC	Lower-dose DOAC	Warfarin
Weight <60kg	6693	2.64	3.20	3.25
Weight 60-120kg	61349	1.47	1.79	1.81
Weight >120kg	3473	0.73	0.89	0.90
Major Bleeding				
		Event rates (%/yr)		
	# of patients	Standard-dose DOAC	Lower-dose DOAC	Warfarin
Weight <60kg	6672	3.51	2.71	4.08
Weight 60-120kg	61234	2.94	2.27	3.42
Weight >120kg	3465	2.67	2.06	3.10

DOAC = Direct Oral Anticoagulant

Supplement Table 8. Sample size and event rates (% per year) by categorical baseline creatinine clearance.

Stroke/Systemic Embolism				
		Event rates (%/yr)		
	# of patients	Standard-dose DOAC	Lower-dose DOAC	Warfarin
CrCl ≤50mL/min	13978	2.34	2.83	2.90
CrCl 51-80mL/min	31814	1.60	1.94	1.98
CrCl >80mL/min	25679	1.05	1.27	1.29
Major Bleeding				
		Event rates (%/yr)		
	# of patients	Standard-dose DOAC	Lower-dose DOAC	Warfarin
CrCl ≤50mL/min	13954	4.67	3.60	5.44
CrCl 51-80mL/min	31748	3.17	2.44	3.69
CrCl >80mL/min	25630	1.96	1.51	2.28

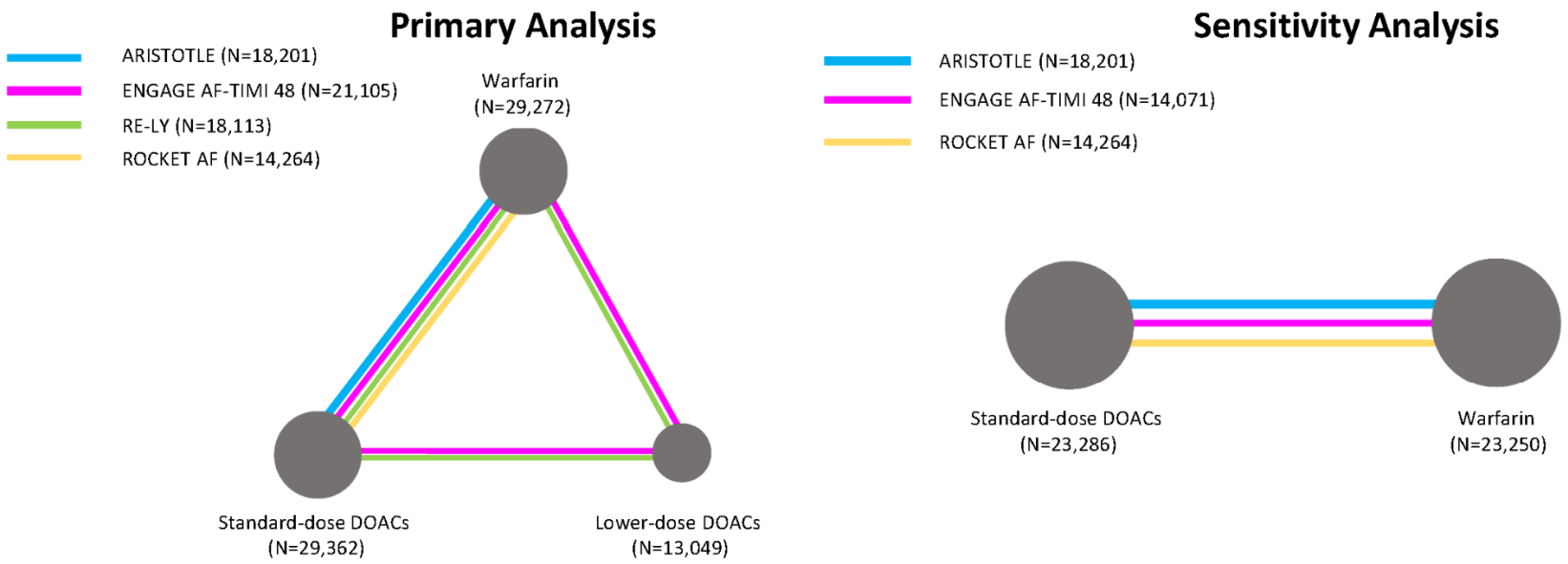
CrCl = Creatinine Clearance; DOAC = Direct Oral Anticoagulant

Supplement Table 9. Hazard ratios (95% confidence intervals) and interaction p-values for the primary safety outcome (major bleeding) comparing lower-dose DOAC versus warfarin by categorical baseline covariates. A hazard ratio > 1 favors warfarin over DOAC, whereas a hazard ratio < 1 favors DOAC over warfarin.

		Lower-dose DOAC versus warfarin	
Categorical Baseline Covariate		**HR (95% CI)**	**P-int**
Sex	Female	0.60 (0.42-0.85)	0.43
	Male	0.65 (0.46-0.91)	
Diabetes	Yes	0.64 (0.45-0.91)	0.89
	No	0.63 (0.45-0.88)	
Prior stroke/TIA	Yes	0.56 (0.39-0.81)	0.17
	No	0.66 (0.48-0.91)	
Prior VKA use	Yes	0.62 (0.45-0.87)	0.66
	No	0.65 (0.46-0.94)	
Antiplatelet use	Yes	0.65 (0.46-0.92)	0.56
	No	0.62 (0.44-0.86)	
$CHADS_2$ Score	≥3	0.64 (0.44-0.92)	0.58
	2	0.65 (0.45-0.94)	
	0, 1	0.55 (0.35-0.85)	
Paroxysmal AF	Yes	0.63 (0.43-0.90)	0.90
	No	0.64 (0.45-0.89)	
Coronary artery disease	Yes	0.75 (0.53-1.06)	0.01
	No	0.57 (0.41-0.80)	
Heart failure	Yes	0.69 (0.48-1.01)	0.09
	No	0.59 (0.40-0.85)	
Prior GI bleeding	Yes	0.69 (0.42-1.13)	0.18
	No	0.49 (0.42-0.57)	
Age (years)	>75	0.70 (0.49-0.98)	0.04
	65-75	0.60 (0.42-0.86)	
	<65	0.46 (0.29-0.71)	
Weight (kg)	>120	0.72 (0.41-1.25)	0.42
	60-120	0.64 (0.46-0.90)	
	<60	0.53 (0.34-0.82)	
CrCl (mL/min)	>80	0.56 (0.39-0.82)	0.40
	51-80	0.67 (0.48-0.94)	
	≤50	0.62 (0.43-0.89)	

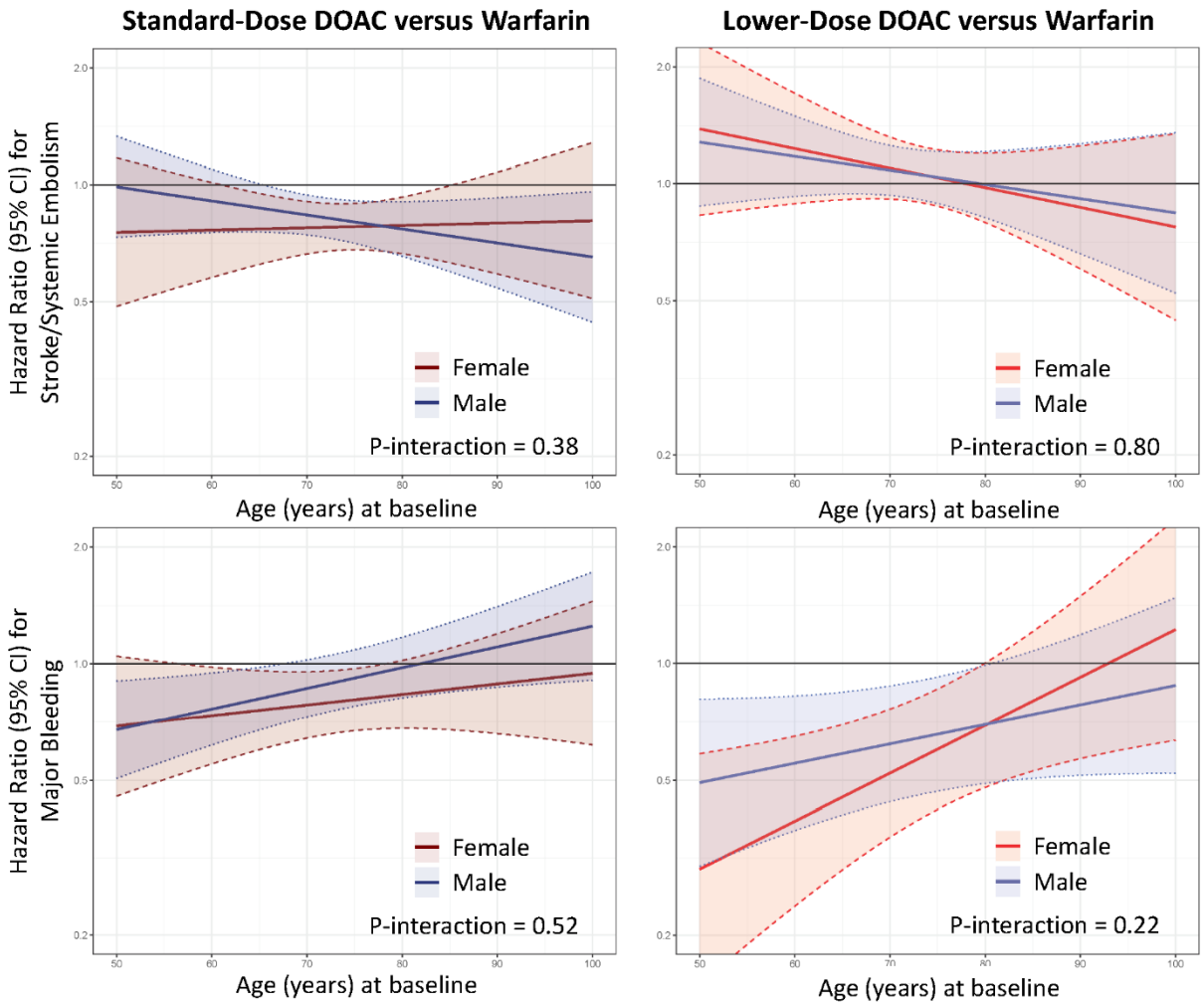
AF = atrial fibrillation, CrCl = creatinine clearance, GI = gastrointestinal, TIA = transient ischemic attack

Supplement Figure 1. Network graph for the primary analyses and the sensitivity analyses.



Footnote: Nodes represent anticoagulation treatment strategies and edges represent trials used for comparison of treatment strategies. Node size is proportional to the number of patients randomized to each treatment strategy. Edge thickness is proportional to the sample size from each individual trial.

Supplement Figure 2. Hazard ratios for the primary efficacy (top) and safety (bottom) outcomes plotted over the range of baseline age with stratification by sex. Hazard ratio > 1 favors warfarin over DOAC, whereas a hazard ratio < 1 favors DOAC over warfarin.



Footnote: X-axis truncated to include 5th and 95th percentiles.

Supplement Figure 3. Forest plots showing hazard ratios and interaction p-vales for the sensitivity analyses (including factor Xa inhibitors only in the standard-dose DOAC treatment strategy groups), with efficacy outcomes (left) and safety outcomes (right).