Appendix 3: Supplementary figures [posted as supplied by author]

Fig A: Flowchart of the study population

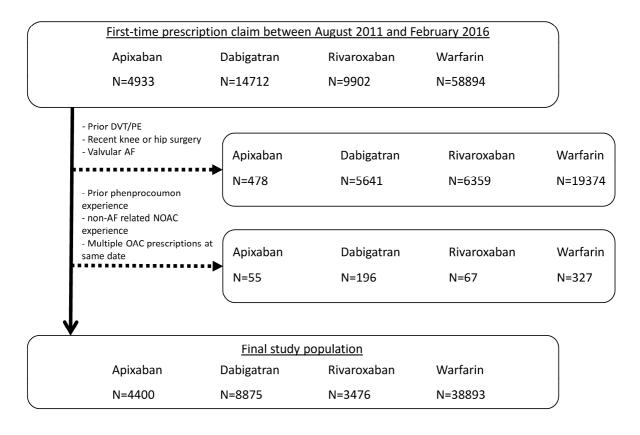


Fig B: Forest plot of effectiveness outcomes; 2.5 years follow-up

Strata / Treatment		Ischemic stroke/SE Hazard ratio (95% CI)		Ischemic stroke Hazard ratio (95% CI)		Death Hazard ratio (95% CI)	
Entire cohort (IPTW analysis)							
Apixaban	1.22 (1.00-1.50)	├	1.23 (1.00–1.52)	 	1.55 (1.39–1.74)	├	
Dabigatran	1.03 (0.92–1.16)	H - 1	1.05 (0.93–1.18)	H +1	1.05 (0.99–1.12)	+1	
Rivaroxaban	0.92 (0.73-1.15)		0.95 (0.75–1.19)		1.47 (1.34–1.62)	H-1	
Reduced dose indication (addition	onal analysis)						
Apixaban	1.29 (1.05–1.58)	⊢• -I	1.31 (1.07–1.61)	⊢	1.23 (1.13–1.35)	H	
Dabigatran	0.99 (0.86–1.13)	1	0.97 (0.84–1.12)	1-1	0.94 (0.88–1.01)	 -	
Rivaroxaban	0.69 (0.54-0.89)	⊢	0.71 (0.54–0.92)	⊢ •−	1.37 (1.25–1.51)	H	
Entire cohort (adjusted analysis)						
Apixaban	1.08 (0.93-1.25)	H - -I	1.09 (0.94–1.27)	H 1	1.34 (1.25–1.44)	H	
Dabigatran	1.02 (0.92–1.14)	H+1	1.01 (0.91–1.12)	1+1	1.05 (0.99–1.11)	 -	
Rivaroxaban	0.81 (0.67-0.97)	├	0.82 (0.68-0.99)	├	1.34 (1.24–1.45)	H	
Age >80 years (sensitivity analys	sis)						
Apixaban	1.14 (0.95–1.37)	H1	1.17 (0.98–1.41)	 - -	1.52 (1.40–1.66)	+	
Dabigatran	1.03 (0.90–1.19)	 	1.00 (0.87–1.15)	+-1	1.01 (0.94–1.08)	1+1	
Rivaroxaban	0.75 (0.59-0.97)		0.75 (0.58-0.97)	⊢ •−	1.54 (1.40–1.70)	H	
Cohort with hospital diagnosed	AF (sensitivity analysi	s)					
Apixaban	1.15 (0.90–1.47)	 	1.14 (0.89–1.46)	 - 	1.61 (1.43–1.82)	 - 	
Dabigatran	1.07 (0.93-1.23)	H • 1	1.07 (0.92–1.23)	H -1	1.05 (0.98–1.13)	 +	
Rivaroxaban	0.99 (0.76–1.30)	<u> </u>	1.02 (0.77–1.34)		1.43 (1.27–1.61)	 +-	
							
		0.2 0.5 1.0 2.0 Favours Favours Alternative Warfarin		0.5 1.0 2.0 Favours Favours Alternative Warfarin		0.5 1.0 2.0 avours Favours ernative Warfarir	

Fig C: Forest plot of safety outcomes; 2.5 years follow-up

Strata / Treatment	Any bleeding Hazard ratio (95% CI)		Major bleeding Hazard ratio (95% CI)		Haemorrhagic stroke Hazard ratio (95% CI)	
Entire cohort (IPTW analysis)						
Apixaban	1.02 (0.80-1.29)	 	1.10 (0.84–1.44)	 	0.69 (0.40-1.19)	
Dabigatran	0.84 (0.75-0.93)	+	0.89 (0.80-1.01)	⊢ •-	0.59 (0.44-0.80)	⊢
Rivaroxaban	1.11 (0.94–1.31)	 - 	1.19 (0.99–1.43)	├	1.09 (0.66–1.80)	⊢ •
Reduced dose indication (addition	onal analysis)					
Apixaban	0.82 (0.66–1.02)	⊢	0.79 (0.62-1.00)		0.84 (0.50-1.40)	
Dabigatran	0.81 (0.72-0.91)	 - 	0.85 (0.74-0.97)	⊢	0.67 (0.47-0.96)	├
Rivaroxaban	1.10 (0.92–1.32)	H - -I	1.20 (0.98–1.47)	├	0.95 (0.56–1.61)	—
Entire cohort (adjusted analysis)					
Apixaban	0.79 (0.69-0.92)	⊢	0.84 (0.71-0.99)	H-	0.79 (0.53-1.20)	⊢
Dabigatran	0.83 (0.76-0.91)	+	0.89 (0.80-0.98)	+-	0.64 (0.49-0.83)	⊢
Rivaroxaban	1.08 (0.94–1.24)	 ←	1.17 (1.00–1.36)	 1	0.96 (0.64-1.44)	
Age >80 years (sensitivity analys	sis)					
Apixaban	0.79 (0.66-0.96)	⊢• -	0.85 (0.68-1.05)	⊢	0.86 (0.52-1.42)	⊢
Dabigatran	0.86 (0.76-0.97)	├ •-	0.92 (0.80-1.06)	⊢• -	0.68 (0.48-0.97)	⊢
Rivaroxaban	1.16 (0.97–1.39)	 • 	1.26 (1.02–1.54)	├	1.05 (0.61-1.80)	
Cohort with hospital diagnosed	AF (sensitivity analysis	s)				
Apixaban	0.98 (0.74-1.29)	+	1.02 (0.74–1.41)	-	0.76 (0.40-1.42)	⊢
Dabigatran	0.87 (0.76-0.99)	I ••	0.93 (0.80-1.08)	⊢	0.60 (0.42-0.84)	⊢ •
Rivaroxaban	1.11 (0.90–1.38)	 	1.18 (0.93–1.50)	 	1.25 (0.67–2.36)	—
		0.2 0.5 1.0 2.0 Favours Favours	0.2	0.5 1.0 2.0 Favours Favours	0.2	0.5 1.0 2.0 Favours Favours
		Alternative Warfarin		Iternative Warfarin		Alternative Warfarin

Fig D: Time profile of new-starters of reduced dose NOACs or warfarin according to treatment regimen in AF patients age \geq 80 and/or impaired renal function

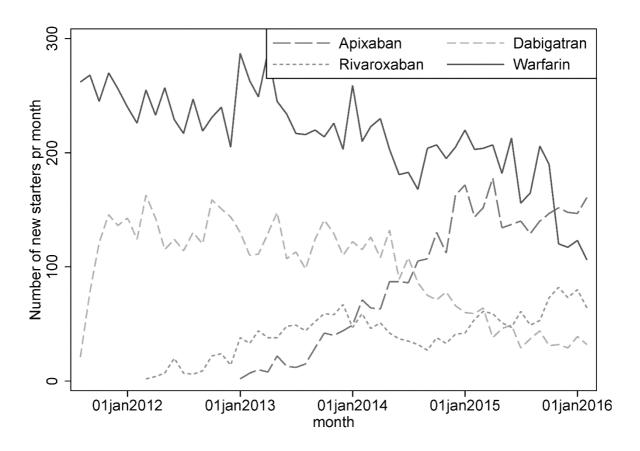


Fig E: Forest plot of effectiveness and safety outcomes for 'reduced dose indication' and outcomes within each strata; one year follow-up.

Strata / Treatment	Ischemic str Hazard ratio		Any bleeding Hazard ratio (95% CI)				
Age ≥80 years or renal impairme	nt						
Apixaban	1.24 (1.00-1.55)		0.78 (0.61-0.99)				
Dabigatran	0.93 (0.79-1.10)		0.81 (0.69-0.94)	⊢			
Rivaroxaban	0.63 (0.47-0.85)		1.00 (0.81-1.24)	—			
Renal impairment							
Apixaban	1.42 (0.85-2.39)	 	0.61 (0.34-1.07)				
Dabigatran	0.89 (0.49-1.64)	—	0.64 (0.41-0.99)				
Rivaroxaban	0.59 (0.25-1.39)	· · · · · · · · · · · · · · · · · · ·	0.63 (0.38-1.05)	<u> </u>			
Age ≥80 years							
Apixaban	1.15 (0.94-1.41)	+	0.78 (0.63-0.96)				
Dabigatran	0.98 (0.82-1.17)	⊢	0.89 (0.76-1.04)	⊢			
Rivaroxaban	0.71 (0.52-0.95)		1.13 (0.91-1.40)	 - 			
	0.2	0.5 1.0 2.0 Favours Favours Alternative Warfarin	0.2	0.5 1.0 2.0 Favours Favours Alternative Warfarin			