Quando iniziare la terapia anticoagulante nella fase acuta dell'ictus ischemico cardioembolico associato a fibrillazione atriale

## Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation

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## Background

- About 13–26% of all acute ischemic strokes are related to non-valvular atrial fibrillation (AF), the most common cardiac arrhythmia globally.
- Deciding when to initiate oral anticoagulation in patients with nonvalvular AF is a longstanding, common, and unresolved clinical challenge.
- Although the risk of early recurrent ischemic stroke is high in this population, early oral anticoagulation is suspected to increase the risk of potentially harmful intracranial hemorrhage, including hemorrhagic transformation of the infarct.
- This assumption, and current treatment guidelines, are based on historical, mostly observational data from patients with ischemic stroke and AF treated with heparins, heparinoids, or vitamin K antagonists (VKAs) to prevent recurrent ischemic stroke.

## Background

- Randomised controlled trials have subsequently shown that direct oral anticoagulants (DOACs) are at least as effective as VKAs in primary and secondary prevention of atrial fibrillation-related ischemic stroke, with around half the risk of intracranial hemorrhage.
- However, none of these DOAC trials included patients who had experienced ischemic stroke recently (within the first few weeks).

## Journal of Stroke wso

#### Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials

George Ntaios<sup>1</sup>, Vasileios Papavasileiou<sup>2</sup>, Hans-Chris Diener<sup>3</sup>, Konstantinos Makaritsis<sup>1</sup> and Patrik Michel<sup>4</sup>

### Stroke and/or Systemic embolism RRR 13.7% RRA 0.78% NNT 127

Figure 2. Forest plot of the effects of non-VKAs versus warfarin on efficacy outcomes (panel A: stroke or systemic embolism/pane B: stroke/panel C: ischemic or unknown stroke/panel D: disabling or fatal stroke) in patients with atrial fibrillation and previous stroke or transient ischemic attack. VKA: Vitamin K antagonist.

	non-V	KΔ	Warfarin		Doto Odds Ratio	Peto Odds Ratio			
Study or Subaroup	Events	Total	tal Events Total Weight		Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl			
ARISTOTI E	73	1694	98	1742	18.6%	0.76 (0.56, 1.03)			
ENGAGE AF-TIMI 48 (60mm)	125	1976	145	1991	28.8%	0.86 [0.67, 1.10]			
RELY (150mg)	51	1233	65	1195	12 7%	0.75 [0.52 1.09]			
ROCKET.AF	179	3754	197	3714	30.0%	0.04 [0.77 1.17]			
	115	51.54	101	5114	33.370	0.04 [0.11] 1.11]	_		
Total (95% CI)		8657		8642	100.0%	0.86 [0.75, 0.98]	•		
Total events	428		495						
Heterogeneity: Chi <sup>2</sup> = 1.93, df =	= 3 (P = 0.	59); l² =	: 0%						
Test for overall effect: Z = 2.28	(P = 0.02)						U.5 U.7 1 1.5 2		
							Pavours non-vica Pavours wananin		
	non-V	KA	Warfa	rin		Peto Odds Ratio	Peto Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl		
ARISTOTLE	67	1694	96	1742	18.9%	0.71 [0.52, 0.97]			
ENGAGE AF-TIMI 48 (60mg)	118	1976	136	1991	28.9%	0.87 [0.67, 1.12]			
RELY (150mg)	47	1233	59	1195	12.3%	0.76 [0.52, 1.13]			
ROCKET-AF	171	3754	172	3714	39.8%	0.98 [0.79, 1.22]			
Total (95% CI)		8657		8642	100.0%	0.86 [0.75, 0.99]	•		
Total events	403		463						
Heterogeneity: Chi <sup>2</sup> = 3.27, df =	= 3 (P = 0.	35); l² =	: 8%						
Test for overall effect: Z = 2.10	(P = 0.04)						Favours non-VKA Favours warfarin		
	non.V	KΔ	Warfa	rin		Peto Odds Ratio	Peto Odds Ratio		
			Vvalidilli Evente Tetal Weight		i oto o duo mano				
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CL	Peto, Fixed, 95% Cl		
Study or Subgroup	Events 57	Total 1694	Events 68	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl		
Study or Subgroup ARISTOTLE ENGAGE AE-TIMI 48 (60mm)	Events 57 105	Total 1694 1976	Events 68	Total 1742 1001	Weight 17.5% 29.5%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 (0.74, 1.28]	Peto, Fixed, 95% Cl		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELV (150mg)	Events 57 105	Total 1694 1976	Events 68 109	Total 1742 1991 1105	Weight 17.5% 29.5% 11.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.57]	Peto, Fixed, 95% Cl		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) POCKET AF	Events 57 105 43 151	Total 1694 1976 1233 2754	Events 68 109 41	Total 1742 1991 1195 2714	Weight 17.5% 29.5% 11.8% 41.2%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.67] 1.04 [0.92, 1.21]	Peto, Fixed, 95% Cl		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) ROCKET-AF	Events 57 105 43 151	Total 1694 1976 1233 3754	Events 68 109 41 144	Total 1742 1991 1195 3714	Weight 17.5% 29.5% 11.8% 41.2%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.67] 1.04 [0.82, 1.31]	Peto, Fixed, 95% Cl		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) ROCKET-AF Total (95% CI)	Events 57 105 43 151	Total 1694 1976 1233 3754 8657	Events 68 109 41 144	Total 1742 1991 1195 3714 8642	Weight 17.5% 29.5% 11.8% 41.2% 100.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.67] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14]	Peto, Fixed, 95% Cl		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) ROCKET-AF Total (95% CI) Total events	Events 57 105 43 151 356	Total 1694 1976 1233 3754 8657	Events 68 109 41 144 362	Total 1742 1991 1195 3714 8642	Weight 17.5% 29.5% 11.8% 41.2% 100.0%	Peto, Fixed, 95% CI 0.86 [0.80, 1.23] 0.97 [0.74, 1.28] 1.02 [0.86, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14]	Peto, Fixed, 95% Cl		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) ROCKET-AF Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.81, df=	Events 57 105 43 151 356 3 (P = 0.	Total 1694 1976 1233 3754 8657 85); I <sup>2</sup> =	Events 68 109 41 144 362 : 0%	Total 1742 1991 1195 3714 8642	Weight 17.5% 29.5% 11.8% 41.2% 100.0%	Peto, Fixed, 95% CI 0.86 [0.80, 1.23] 0.97 [0.74, 1.28] 1.02 [0.86, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14]	Peto, Fixed, 95% CI		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) ROCKET-AF Total (95% CI) Total events Heterogeneity. Chi <sup>2</sup> = 0.81, df = Test for overall effect: Z = 0.24	Events 57 105 43 151 356 3 (P = 0. (P = 0.81)	Total 1694 1976 1233 3754 8657 85); I <sup>2</sup> =	Events 68 109 41 144 362 : 0%	Total 1742 1991 1195 3714 8642	Weight 17.5% 29.5% 11.8% 41.2% 100.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14]	Peto, Fixed, 95% CI		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) ROCKET-AF Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 0.81, df= Test for overall effect: Z = 0.24	Events 57 105 43 151 356 : 3 (P = 0. (P = 0.81) pon-V	Total 1694 1976 1233 3754 8657 85); I <sup>2</sup> =	Events 68 109 41 144 362 0% Warfa	Total 1742 1991 1195 3714 8642	Weight 17.5% 29.5% 11.8% 41.2% 100.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.67] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio	Peto, Fixed, 95% CI		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) ROCKET-AF Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.81, df= Test for overall effect: Z = 0.24 Study or Subgroup	Events 57 105 43 151 356 : 3 (P = 0. (P = 0.81) non-V Events	Total 1694 1976 1233 3754 8657 855; I <sup>2</sup> =	Events 68 109 41 144 362 0% Warfa Events	Total 1742 1991 1195 3714 8642 rin Total	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.67] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
Study or Subgroup ARISTOTLE ENGAGE AF-TIMI 48 (60mg) RELY (150mg) ROCKET-AF Total (95% CI) Total events Heterogeneity: ChiP = 0.81, df= Test for overall effect: Z = 0.24 Study or Subgroup APISTOTLE	Events 57 105 43 151 356 356 30(P = 0. (P = 0.81) non-V Events 30	Total 1694 1976 1233 3754 8657 85); I <sup>2</sup> = KA Total 1694	Events 68 109 41 144 362 0% Warfa Events 46	Total 1742 1991 1195 3714 8642 rin Total 1742	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight 18.4%	Peto, Fixed, 95% CI 0.86 [0.80, 1.23] 0.97 [0.74, 1.28] 1.02 [0.86, 1.57] 1.04 [0.32, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI 0.87 [0.57, 1.34]	Peto, Fixed, 95% CI		
Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total events   Heterogeneity: ChiP = 0.81, df=   Test for overall effect: Z = 0.24   Study or Subgroup   ARISTOTLE   ROGE AE-TIMI 48 (60mm)	Events 57 105 43 151 356 3 (P = 0. (P = 0.81) non-V Events 39 51	Total 1694 1976 1233 3754 8657 85); I <sup>2</sup> = KA Total 1694 1976	Events 68 109 41 144 362 0% Warfa Events 46 61	Total 1742 1991 1195 3714 8642 rin Total 1742 1991	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight 18.4% 24.1%	Peto, Fixed, 95% CI 0.86 [0.80, 1.23] 0.97 [0.74, 1.28] 1.02 [0.86, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI 0.87 [0.57, 1.34] 0.84 [0.58, 1.23]	Peto, Fixed, 95% CI		
Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total events   Heterogeneity: Chill = 0.81, df=   Test for overall effect: Z = 0.24   Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   PELY (15mmt)	Events 57 105 43 151 356 3 (P = 0. (P = 0.81) non-V Events 39 51 23	Total 1694 1976 1233 3754 8657 85); I <sup>2</sup> = KA Total 1694 1976 1222	Events 68 109 41 144 362 0% Warfa Events 46 61	Total 1742 1991 1195 3714 8642 rin Total 1742 1991 1195	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight 18.4% 24.1% 16.5%	Peto, Fixed, 95% CI 0.86 [0.80, 1.23] 0.97 [0.74, 1.28] 1.02 [0.86, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI 0.87 [0.57, 1.34] 0.84 [0.58, 1.22] 0.70 [0.45, 1.12]	Peto, Fixed, 95% CI		
Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total events   Heterogeneity: Chi² = 0.81, df=   Test for overall effect: Z = 0.24   Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   RELY (150mg)	Events 57 105 43 151 356 3(P = 0. (P = 0.81) non-V/ Events 39 51 33 02 20 20 20 20 20 20 20 20 20	Total 1694 1976 1233 3754 8657 85); P=	Events 68 109 41 144 362 0% Warfa Events 46 61 44 90	Total 1742 1991 1195 3714 8642 rin Total 1742 1991 1195 2714	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight 18.4% 24.1% 16.5% 41.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI 0.87 [0.57, 1.34] 0.84 [0.58, 1.23] 0.72 [0.46, 1.23] 0.72 [0.46, 1.23]	Peto, Fixed, 95% CI		
Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total events   Heterogeneity: ChiP = 0.81, df=   Test for overall effect: Z = 0.24   Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF	Events 57 105 43 151 356 36 37 (P = 0. (P = 0.81) non-V/ Events 39 51 33 92	Total 1694 1976 1233 3754 8657 855; I <sup>2</sup> = 855; I <sup>2</sup> = 855; I <sup>2</sup> = 1694 1976 1233 3754	Events 68 109 41 144 362 0% Warfa Events 46 61 44 98	Total 1742 1991 1195 3714 8642 rin Total 1742 1991 1195 3714	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight 18.4% 24.1% 16.5% 41.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI 0.87 [0.57, 1.34] 0.84 [0.58, 1.22] 0.72 [0.46, 1.13] 0.93 [0.69, 1.24]	Peto, Fixed, 95% Cl		
Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total events   Heterogeneity: Chill = 0.81, df =   Test for overall effect: Z = 0.24   Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)	Events   67   105   43   151   356   3 (P = 0.   (P = 0.81)   non-V   Events   39   51   33   92	Total 1694 1976 1233 3754 8657 855; I <sup>2</sup> = KA Total 1694 1976 1233 3754 8657	Events 68 109 41 144 362 0% Warfa Events 46 61 44 98	Total 1742 1991 1195 3714 8642 rin Total 1742 1991 1195 3714 8642	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight 18.4% 24.1% 16.5% 41.0% 100.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.57] 1.04 [0.32, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI 0.87 [0.57, 1.34] 0.84 [0.58, 1.22] 0.72 [0.46, 1.13] 0.93 [0.69, 1.24] 0.86 [0.71, 1.03]	Peto, Fixed, 95% Cl		
Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total events   Heterogeneity: ChiP = 0.81, df=   Test for overall effect: Z = 0.24   Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total (95% CI)   Total events	Events   57   105   43   151   356   3 (P = 0.   (P = 0.81)   non-V   Events   39   51   33   92   215	Total 1694 1976 1233 3754 8657 8657 KA Total 1694 1976 1233 3754 8657 8657	Events 68 109 41 144 362 20% Warfa Events 46 61 44 98 249	Total 1742 1991 1195 3714 8642 rin Total 1742 1991 1195 3714 8642	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight 18.4% 24.1% 16.5% 41.0% 100.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI 0.87 [0.57, 1.34] 0.84 [0.58, 1.22] 0.72 [0.46, 1.13] 0.93 [0.69, 1.24] 0.86 [0.71, 1.03]	Peto, Fixed, 95% Cl		
Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total events   Heterogeneity: Chi² = 0.81, df=   Test for overall effect: Z = 0.24   Study or Subgroup   ARISTOTLE   ENGAGE AF-TIMI 48 (60mg)   RELY (150mg)   ROCKET-AF   Total (95% CI)   Total events   Heterogeneity: Chi² = 0.86, df=	Events 57 105 43 151 356 3 (P = 0. (P = 0.81) non-V Events 39 51 33 92 215 3 (P = 0.	Total 1694 1976 1233 3754 8657 8657 8657 1694 1976 1233 3754 8657 8657 8657 8657 8657	Events 68 109 41 144 362 0% Warfa Events 46 61 44 98 249 0%	Total 1742 1991 1195 3714 8642 1742 1991 1195 3714 8642 8642	Weight 17.5% 29.5% 11.8% 41.2% 100.0% Weight 18.4% 24.1% 16.5% 41.0% 100.0%	Peto, Fixed, 95% CI 0.86 [0.60, 1.23] 0.97 [0.74, 1.28] 1.02 [0.66, 1.57] 1.04 [0.82, 1.31] 0.98 [0.85, 1.14] Peto Odds Ratio Peto, Fixed, 95% CI 0.87 [0.57, 1.34] 0.84 [0.58, 1.22] 0.72 [0.46, 1.13] 0.93 [0.69, 1.24] 0.86 [0.71, 1.03]	Peto, Fixed, 95% CI		

#### Systematic Review

## Journal of Stroke wso

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#### Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials

George Ntaios<sup>1</sup>, Vasileios Papavasileiou<sup>2</sup>, Hans-Chris Diener<sup>3</sup>, Konstantinos Makaritsis<sup>1</sup> and Patrik Michel<sup>4</sup>

Intracranial bleeding RRR 46% RRA 0.88% NNT 113 **Figure 4.** Forest plot of the effects of non-VKAs versus warfarin on safety outcomes (upper panel: major bleeding/middle panel: intracranial bleeding/lower panel: major gastrointestinal bleeding) in patients with atrial fibrillation and previous stroke or transient ischemic attack. VKA: Vitamin K antagonist.

	non-VKA Warfarin		Peto Odds Ratio		Peto Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
ARISTOTLE	77	1694	106	1742	17.7%	0.74 [0.55, 0.99]	
ENGAGE AF-TIMI 48 (60mg)	138	1976	167	1991	28.7%	0.82 [0.65, 1.04]	
RELY (150mg)	102	1233	97	1195	18.6%	1.02 [0.76, 1.36]	
ROCKET-AF	178	3754	183	3714	35.0%	0.96 [0.78, 1.19]	
Total (95% CI)		8657		8642	100.0%	0.89 [0.78, 1.00]	•
Total events	495		553				
Heterogeneity: Chi <sup>2</sup> = 3.36, df = 3 (P = 0.34); I <sup>2</sup> = 11%							
Test for overall effect: Z = 1.89					Favours non-VKA Favours warfarin		

	non-VKA		Warfarin			Peto Odds Ratio	Peto Odds Ratio		
tudy or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI		
RISTOTLE	15	1694	41	1742	22.0%	0.40 [0.24, 0.68]			
NGAGE AF-TIMI 48 (60mg)	27	1976	48	1991	29.4%	0.57 [0.36, 0.90]			
ELY (150mg)	13	1233	30	1195	16.9%	0.43 [0.24, 0.79]			
OCKET-AF	34	3754	46	3714	31.6%	0.73 [0.47, 1.13]	-	•	
otal (95% CI)		8657		8642	100.0%	0.54 [0.42, 0.70]	•		
otal events	89		165						
leterogeneity: Chi <sup>2</sup> = 3.60, df =	: 3 (P = 0.	31); l² =	17%					<u> </u>	
est for overall effect: Z = 4.81					Favours non-VKA	Favours warfarin			

	non-VKA		Warfarin			Peto Odds Ratio	Peto Od	lds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixe	d, 95% Cl	
ARISTOTLE	18	1694	22	1742	31.3%	0.84 [0.45, 1.57]			
ENGAGE AF-TIMI 48 (60mg)	0	0	0	0		Not estimable			
RELY (150mg)	57	1233	33	1195	68.7%	1.68 [1.11, 2.57]			
ROCKET-AF	0	0	0	0		Not estimable			
Total (95% CI)		2927		2937	100.0%	1.35 [0.96, 1.92]	-	•	
Total events	75		55						
Heterogeneity: Chi <sup>2</sup> = 3.28, df =	= 1 (P = 0	07); l² :	= 70%					15 2	
Test for overall effect: Z = 1.70	(P = 0.09	)					Favours non-VKA	Favours warfarin	

RCT	Exclusion criteria
RE-LY	-Stroke with severe disability (mRS 4-5) in the previous 6 months -Stroke in the previous 2 weeks
<b>ROCKET-AF</b>	-Stroke with severe disability (mRS 4-5) in the previous 3 months -Stroke in the previous 2 weeks -TIA in the previous 3 days
ARISTOTLE	-Stroke in the previous week
ENGAGE-AF	-Stroke in the previous 30 days

#### Search strategy and selection criteria

We identified references for this Rapid Review by searches of PubMed between Jan 1, 2016, and July 20, 2018, using the search terms "ischaemic stroke" OR "ischemic stroke" AND "atrial fibrillation" OR "non-valvular atrial fibrillation" OR "AF" AND "oral anticoagulation" OR "direct oral anticoagulants" OR "new oral anticoagulants" OR "novel oral anticoagulants" OR "DOAC" OR "NOAC" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban". Only papers published in English were considered. Additionally, we searched our personal records and abstracts from international conferences in the past five years (2013–18; eq, the European Stroke Organisation Conference 2018 and others) for relevant publications or data. For the section on early anticoagulation, we selected publications presenting original data and published in English. In addition, we searched PubMed, personal records, and an internet search engine (ie, Google) using the search terms "quidelines", "secondary prevention", "stroke", "atrial fibrillation", and "oral anticoagulation" OR "DOAC" OR "direct oral anticoaquiants" to identify guidelines from relevant organisations (national or international expert committees).

## **Recent developments**

- Prospective observational studies and two small randomised trials have investigated the risks and benefits of early DOAC administration initiation (most with a median delay of 3–5 days) in mild-to-moderate AF-associated ischemic stroke.
- These studies reported that early DOAC treatment was associated with a low frequency of clinically symptomatic intracranial hemorrhage or surrogate hemorrhagic lesions on MRI scans, whereas later DOAC-administration initiation (i.e., >7 days or >14 days after index stroke) was associated with an increased frequency of recurrent ischemic stroke.

### Summary of studies on early initiation of anticoagulant treatment in patients with recent AF-related ischemic stroke

Lancet Neurol 2018

	Study population	Patients' median age, median stroke severity, and infarct size*	Median timing of anticoagulation administration initiation	Follow-up period	Recurrent ischaemic stroke†	Intracranial haemorrhage†					
Observational studies with clinical follow-up of ≥3 months											
Seiffge et al <sup>44</sup> (NOACISP)	204 (155 DOAC treated)	79 years; NIHSS score 4; no information on infarct size	5 days (£7 days for 65% [n=100] of DOAC-treated patients)	At least 3 months	7.7% peryear (5.1% peryear for DOAC administration ≤7 days vs 9-3% peryear for DOAC administration >7 days, p=0.53)	1-3% peryear					
Arihiro et al <sup>45</sup> (SAMURA I-NVAF)	1192 (466 DOAC treated)	78 years; NIHSS score 3; 24% small, 48% medium, and 28% large infarcts	5 days for DOAC	3 months	8-5% per year (VKA) and 10-1% per year (DOAC, p= 0.05)	1-2% peryear (VKA) vs 0-8% peryear (DOAC)					
Paciaroni et al <sup>46</sup> (RAF-NOAC)	1127 (all DOAC treated)	76 years; NIHSS score 8; 41% small, 33% medium, and 22% large infarcts	No overall median reported (8 days for dabigatran and rivaroxaban, 7 days for apixaban)	3 months	7.8% peryear	6-4% peryear					
Wilson et al <sup>51</sup>	1355 (475 DOAC)	76 years; NIHSS score 4; 18% large infarcts	11 days (≤4 days for 26% [n=358] of patients)	90 days	57% per year (combined DOAC and VKA)	0.6% peryear (combined DOAC and VKA)					
Observational stu	dies with clinical fo	llow-up within 3 months or with s	urrogate outcome imaging mark	ers							
Macha et a <sup>k7</sup>	243 (all DOAC treated)	78 years; NIHSS score 5; 17% small infarct or TIA, 70% medium, and 13% large infarcts	From 1-7 days for small infarct or TIA to 6-7 days for large infarcts (\$7 days for 89-7% [n=218] of DOAC-treated patients)	In hospital	Not reported	1 case of symptomatic and 2 cases of asymptomatic intracranial haemorrhage					
Cappellari et al <sup>ø</sup>	147 (all DOAC treated)	79 years; NIHSS score 8; 54% small, 22% medium, and 24% large infarcts	3-3 days (≤3 days for 66% [n=97] of patients; ≤7 days for all patients)	CT scan at 7 days	No case observed	8 cases of asymptomatic intracranial haemorrhage (7 new, 1 before DOAC treatment)					
Gioia et al <sup>eg</sup>	60 (all rivaroxaban treated)	74 years; NIHSS score 2; median DWI lesion volume 7·9 mL	3 days	MRI scan at 7 days	1 case	No cases of symptomatic intracranial haemorrhage, 8 cases of asymptomatic petechial haemorrhage					
Deguchi et al <sup>50</sup>	300 (186 DOAC treated)	77 years; NIHSS score 7; no information on infarct size	3 days for DOAC, 7 days for VKA	In hospital	No case observed	2 cases of intracranial haemorrhage, 1 case of extracranial haemorrhage					
Observational stu	dies with a majority	y of patients receiving VKAs or hep	arins								
Abdul-Rahim et al <sup>®</sup>	1300 (no DOAC-treated patients)	73 years; NIHSS score 14; no information on infarct size	2 days	90 days	8-2% of patients (107 events in 1300 patients)	2-3% of patients had symptomatic intracranial haemorrhage (30 events in 1300 patients)					
Paciaroni et al <sup>29</sup>	1029 (93 DOAC treated)	77 years; NIHSS score 9; 37% small, 36% medium, and 27% large infarct	8-5 days for DOAC, 12-1 days for VKA	3 months	77 events (including TIA and systemic embolism)	37 events (including major extracranial haemorrhages)					
Randomised contr	olled trials with pa	tients receiving DOACs									
Hong et al <sup>41</sup>	195 (95 rivaroxaban treated)	70 years; NIHSS score 2; median DWI lesion volume 2-6 mL	2 days	MRI scan at 4 weeks	1 case	30 new haemorrhagic lesions (all asymptomatic)					

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Effect of Anticoagulation and Its Timing: The RAF Study



International multicenter prospective observational study on **1029** patients with acute ischemic stroke and AF

Paciaroni et al., Stroke 2015

Heart sociation Stroke



*Green, anticoagulation between 4 and 14 days from stroke onset Blue, other treated patients (treatment before 4 or after 14 days)* 

Starting anticoagulation for secondary **between 4 and 14 days** from stroke onset seems to be associated with the best efficacy/safety profile.

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Effect of Anticoagulation and Its Timing: The RAF Study



Paciaroni et al., Stroke 2015

At multivariate analysis:

- High CHA<sub>2</sub>DS<sub>2</sub>-VASc score
- High NIHSS
- Large ischemic lesions
- Type of anticoagulant administered (LMWH vs oral anticoagulants alone)

each independently led to a greater risk of recurrence and bleedings.

Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin-K Oral Anticoagulants (RAF-NOACs) Study



Paciaroni et al., J Am Heart Assoc 2017

International multicenter prospective observational study on **1127** patients with acute ischemic stroke and AF treated with NOACs

- Treatment with NOACs was associated with a combined 5.2% rate of ischemic embolic recurrence (2.8%) and severe bleeding (2.4%) within 90 days.
- 80% of the patients received NOACs within 15 days of the index stroke.



Risk of combined outcome events based upon the day of initiating NOAC

Risk of ischemic (blue) and hemorrhagic (red) events based upon the day of initiating NOAC

### Risk of recurrent ischemic stroke and intracranial hemorrhage in patients with AF and a recent ischemic stroke



FSC

Steffel et al., Eur Heart J 2018

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

### (Re-) initiation of anticoagulation after TIA/stroke



## Where next?

- Adequately powered randomised controlled trials comparing early to later oral anticoagulation with DOACs in ischemic stroke associated with AF are justified to confirm the acceptable safety and efficacy of this strategy.
- Four such randomised controlled trials (collectively planned to include around 9000 participants) are underway, either using single cutoff timepoints for early versus late DOACadministration initiation, or selecting DOAC-administration timing according to the severity and imaging features of the ischemic stroke.
- The results of these trials should help to establish the optimal timing to initiate DOAC administration after recent ischemic stroke and whether the timing should differ according to stroke severity. Results of these trials are expected from 2021.

### Summary of ongoing randomised controlled trials investigating early versus late initiation of direct oral anticoagulant treatment in patients with recent AF-related ischemic stroke

	Planned sample size	Intervention (early initiation of anticoagulant treatment)	Control (late initiation of anticoagulant treatment)	Follow-up period	Primary outcome	Patients with haemorrhagic transformation included	NIHSS exclusion criteria	Estimated end of study
ELAN (NCT03148457)	2000	<48 h after symptom onset (minor and moderate stroke) or at day 6 (±1 day) after symptom onset (major stroke)*	Current recommendations (ie, minor stroke after day 3 [±1 day], moderate stroke after day 6 [±1 day] and major stroke after day 12 [±2 days])*	30 days (secondary outcomes after 90 days)	Composite outcome (major bleeding, recurrent ischaemic stroke, systemic embolism, or vascular death, or a combination of these outcomes)	Yes	No exclusion criteria	October 2021
OPTIMAS (EudraCT, 2018- 003859-38)	3474	≤4 days after acute ischaemic stroke	7–14 days after acute ischaemic stroke	90 days	Composite outcome at 90 days (combined incidence of recurrent symptomatic ischaemic stroke, symptomatic intracranial haemorrhage [including extradural, subdural, subarachnoid and intracerebral haemorrhage, and haemorrhagic transformation of the qualifying infarct], and systemic embolism)	Yes	No exclusion criteria	2021-22
TIMING (NCT02961348)	3000	≤4 days after acute ischaemic stroke	5-10 days after acute ischaemic stroke	90 days	Composite outcome (recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality, or a combination of these outcomes)	Yes	No exclusion criteria	December 2020
START (NCT03021928)	1500 (1000 patients with mild or moderate stroke, 500 with severe stroke)t	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke†	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke†	30 days (secondary outcomes after 90 days)	Composite of any CNS haemorrhagic or other major haemorrhagic events and the ischaemic events of stroke or systemic embolism within 30 days of the index stroke	Yes	Score >3 and score <23	August 2021

# **Current suggested strategy**

- Enrolment of eligible patients with ischemic stroke and AF in ongoing randomised controlled trials is suggested on the basis of current guidelines and evidence from observational studies and clinical trials.
- If enrolment in a trial is not possible, clinicians will need to use the data to weigh potential risks and benefits of early DOAC administration although evidence is currently scarce to make strong recommendations.

### Timing for initiation of direct oral anticoagulant administration

