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Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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Fibrillation auriculaire ↗ risque de l'AVC ischémique 4-5 fois:

- **15% tout age confondu**
- **30% si age >of 80 ans.**

warfarin ↘ ce risque mais necessite un monitorage et ajustement fréquent

Background

- **Rivaroxaban: nouvelle molecule orale anti-Xa in, pourrait remplacer la warfarine.**
- **D'autres publications réalisées dans la prévention de la maladie thrombo-embolique démontre la supériorité et l'efficacité par rapport à l'enoxaparin chez des patients chirurgie orthopédique**

Objective

- **compare once-daily oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular Atrial fibrillation (AF) who were at moderate-to-high risk for stroke**

Methods

- **1178 participating sites in 45 countries**
- **The study was supported by Johnson & Johnson Pharmaceutical**
- **CHADS2 score ≥ 2**
- **20 mg daily or 15 mg daily in patients with a creatinine clearance of 30 to 49 ml per minute)**
- **or adjusted-dose warfarin (target international**
- **normalized ratio [INR], 2.0 to 3.0)**

Outcomes

- **The primary efficacy end point was the composite of stroke (ischemic or hemorrhagic) and systemic embolism**
- **Secondary efficacy end points included a composite of stroke, systemic embolism, or death from cardiovascular causes; a composite of stroke, systemic embolism, death from cardiovascular causes, or myocardial infarction**
- **The principal safety end point was a composite of major and nonmajor clinically relevant bleeding events.**

Outcomes

- **From December 18, 2006, through June 17, 2009, a total of 14,264 patients underwent randomization**
- **the median follow-up period was 707 days**
- **Only 32 patients were lost to followup**

Table 1. Characteristics of the Intention-to-Treat Population at Baseline.

Characteristic	Rivaroxaban (N=7131)	Warfarin (N=7133)
Age — yr		
Median	73	73
Interquartile range	65–78	65–78
Female sex — no. (%)	2831 (39.7)	2832 (39.7)
Body-mass index*		
Median	28.3	28.1
Interquartile range	25.2–32.1	25.1–31.8
Blood pressure — mm Hg		
Systolic		
Median	130	130
Interquartile range	120–140	120–140
Diastolic		
Median	80	80
Interquartile range	70–85	70–85
Type of atrial fibrillation — no. (%)		
Persistent	5786 (81.1)	5762 (80.8)
Paroxysmal	1245 (17.5)	1269 (17.8)
Newly diagnosed or new onset	100 (1.4)	102 (1.4)
Previous medication use — no. (%)		
Aspirin	2586 (36.3)	2619 (36.7)
Vitamin K antagonist	4443 (62.3)	4461 (62.5)

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$CHADS_2$ risk of stroke†		
Mean score (±SD)	3.48±0.94	3.46±0.95
Score — no. (%)		
2	925 (13.0)	934 (13.1)
3	3058 (42.9)	3158 (44.3)
4	2092 (29.3)	1999 (28.0)
5	932 (13.1)	881 (12.4)
6‡	123 (1.7)	159 (2.2)
Coexisting condition — no. (%)		
Previous stroke, systemic embolism, or transient ischemic attack	3916 (54.9)	3895 (54.6)
Congestive heart failure	4467 (62.6)	4441 (62.3)
Hypertension	6436 (90.3)	6474 (90.8)
Diabetes mellitus	2878 (40.4)	2817 (39.5)
Previous myocardial infarction‡	1182 (16.6)	1286 (18.0)
Peripheral vascular disease	401 (5.6)	438 (6.1)
Chronic obstructive pulmonary disease	754 (10.6)	743 (10.4)
Creatinine clearance — ml/min§		
Median	67	67
Interquartile range	52–88	52–86

Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate	No. of Patients	No. of Events	Event Rate		Noninferiority	Superiority
			no./100 patient-yr			*no./100 patient-yr*			
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

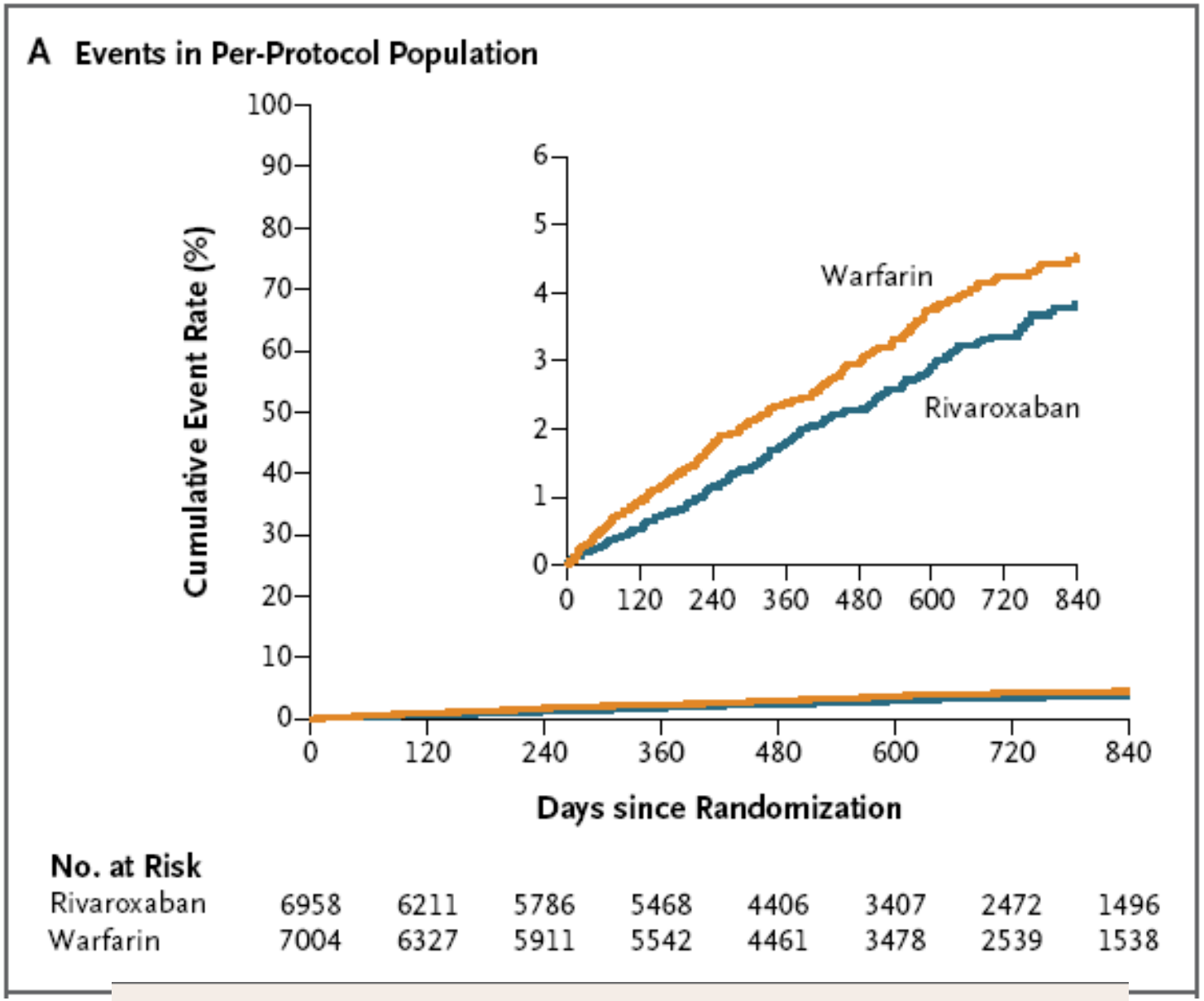
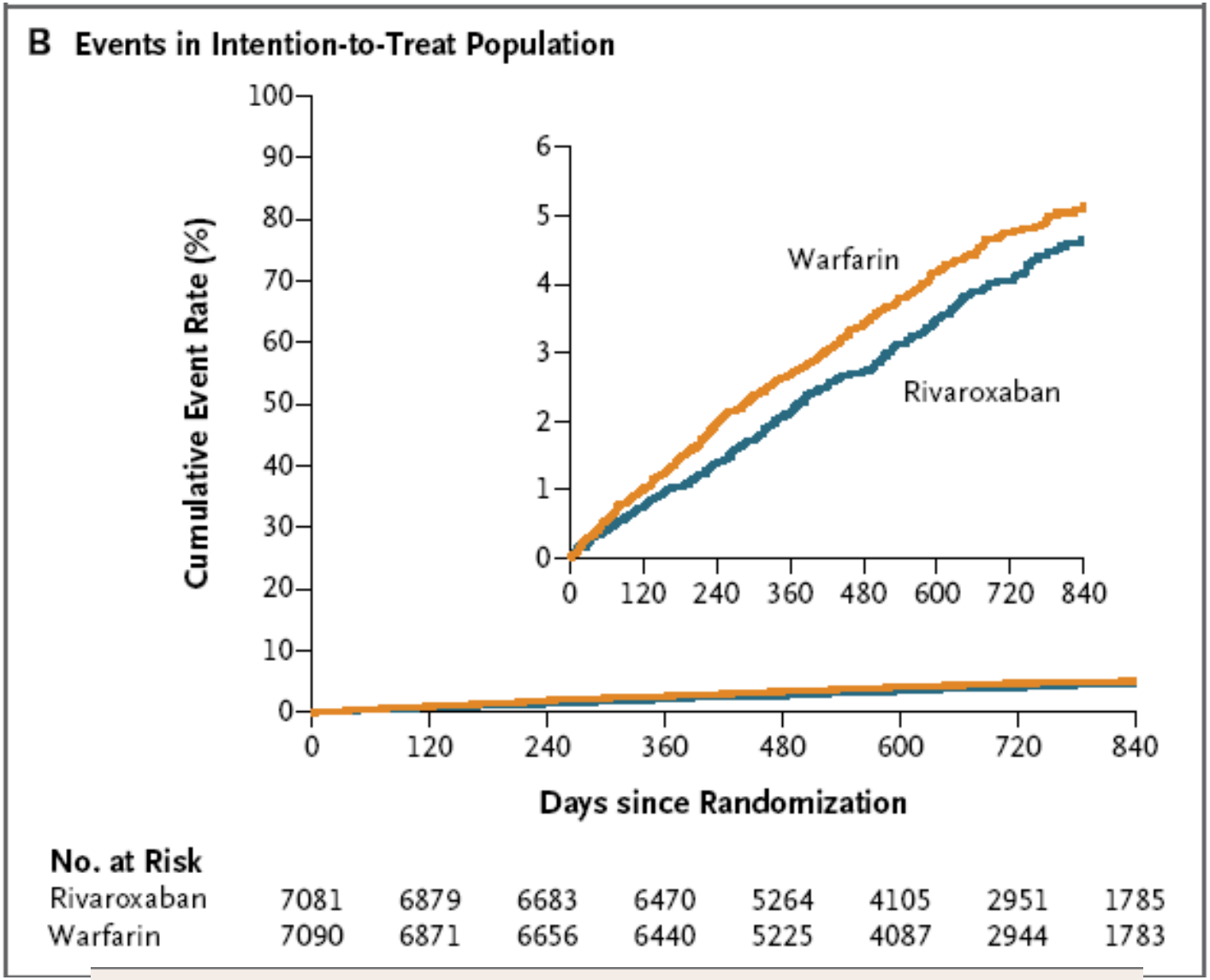


Figure 1. Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.



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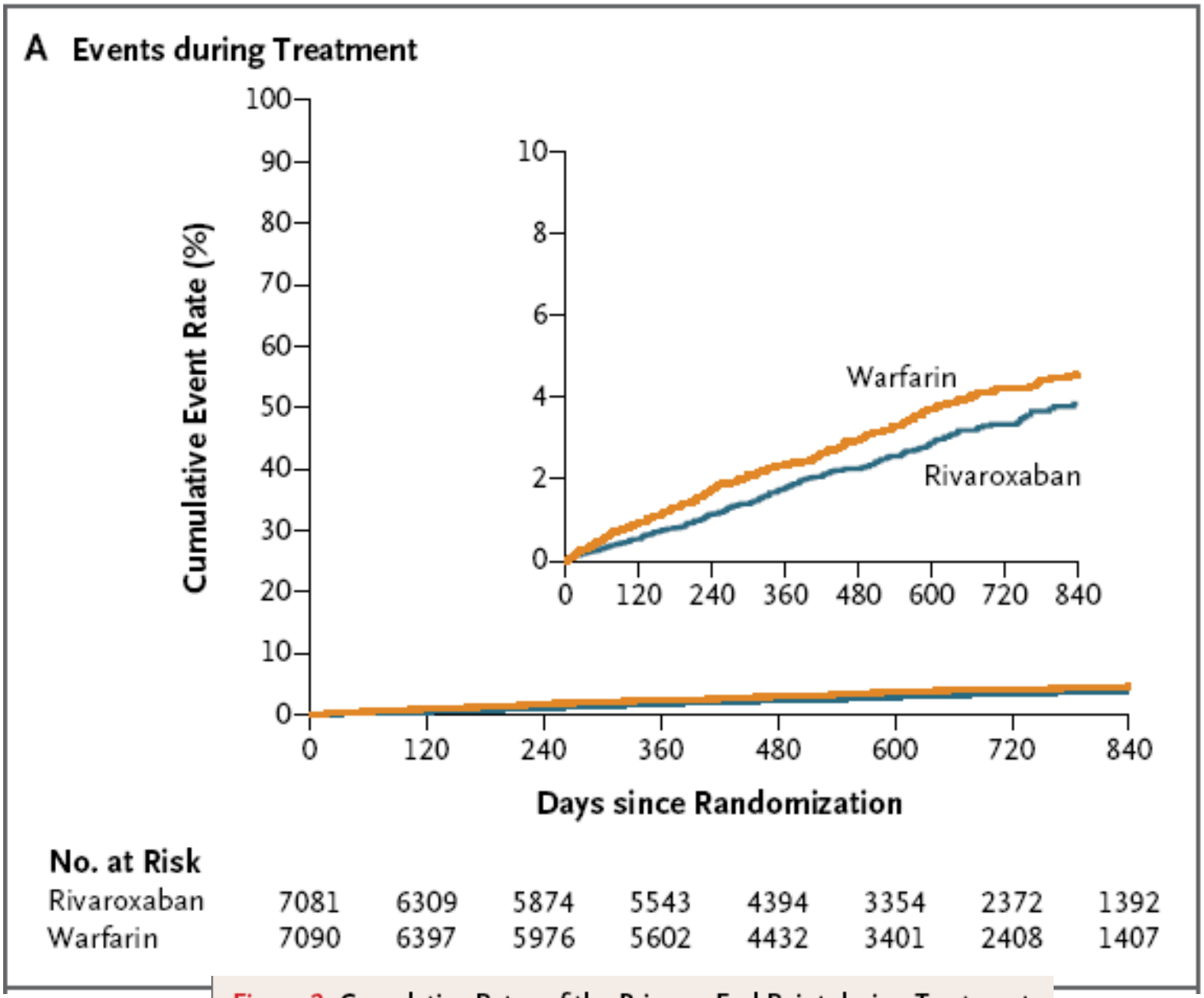

Figure 2. Cumulative Rates of the Primary End Point during Treatment and after Discontinuation in the Intention-to-Treat Population.

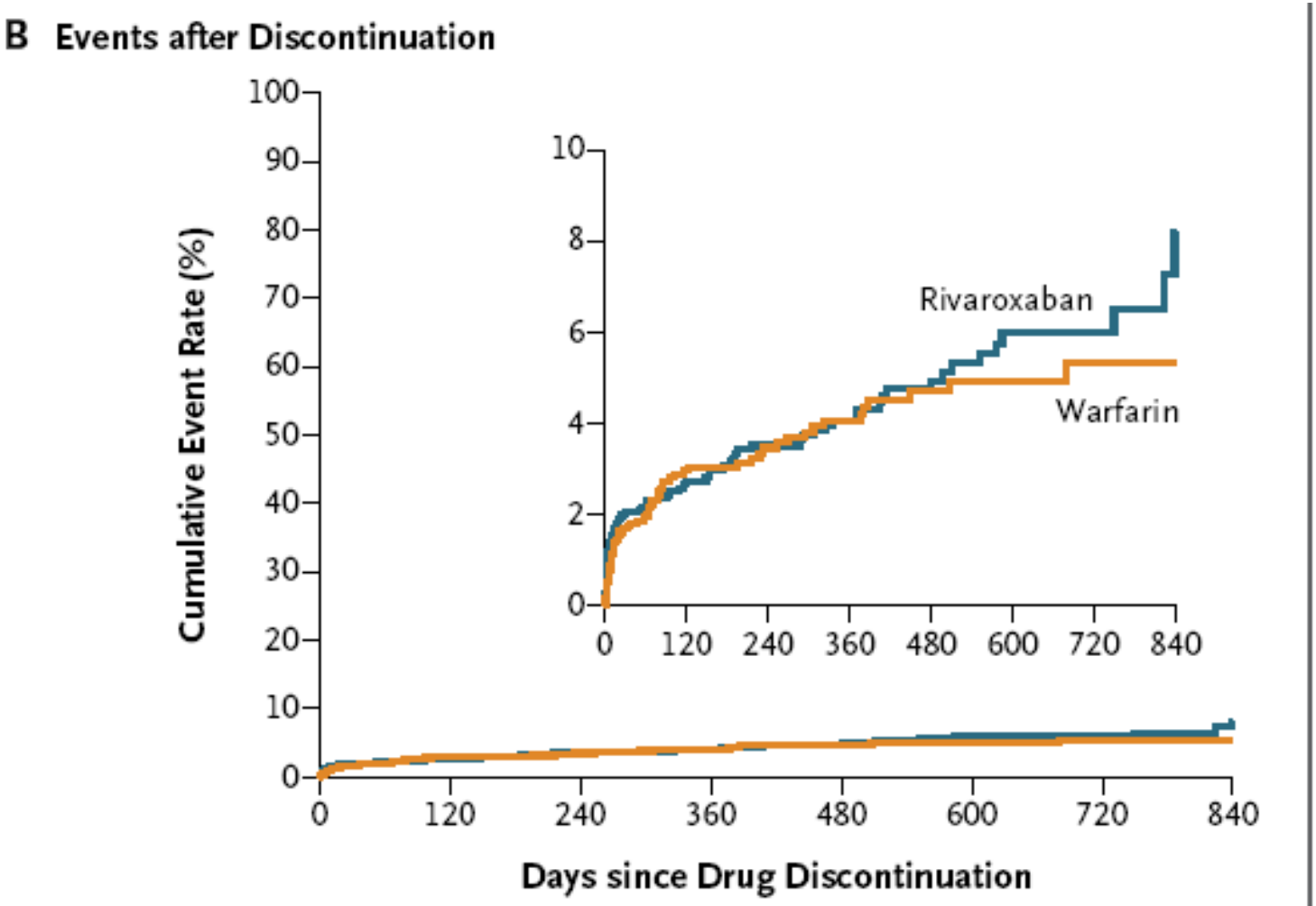

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Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

Conclusion

- Chez les patients ayant une ACFA, le rivaroxaban a une efficacité non inferieur à la warfarin pour la prevention de l'AVC ischémique ou emobolie systémique
- Pas de difference pour le risque hémorragique.
- Les hémorragies intracérébrales et fatales sont moins fréquentes dans le groupe rivaroxaban group.