ORIGINAL ARTICLE

Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation

V.J. Nijenhuis, J. Brouwer, R. Delewi, R.S. Hermanides, W. Holvoet, C.L.F. Dubois,
P. Frambach, B. De Bruyne, G.K. van Houwelingen, J.A.S. Van Der Heyden,
P. Toušek, F. van der Kley, I. Buysschaert, C.E. Schotborgh, B. Ferdinande,
P. van der Harst, J. Roosen, J. Peper, F.W.F. Thielen, L. Veenstra,
D.R.P.P. Chan Pin Yin, M.J. Swaans, B.J.W.M. Rensing, A.W.J. van 't Hof,
L. Timmers, J.C. Kelder, P.R. Stella, J. Baan, and J.M. ten Berg

Anticoagulation with or without Clopidogrel after TAVI

OPEN-LABEL RANDOMIZED TRIAL

313 Patients undergoing TAVI and receiving oral anticoagulation

Anticoagulation Only (N=157)

Anticoagulation + Clopidogrel 75 mg daily for 3 mo (N=156)

All bleeding at 12 mo	34 Patients (21.7%)	54 Patients (34.6%)

Risk Ratio, 0.63; 95% CI, 0.43 to 0.90; P=0.01

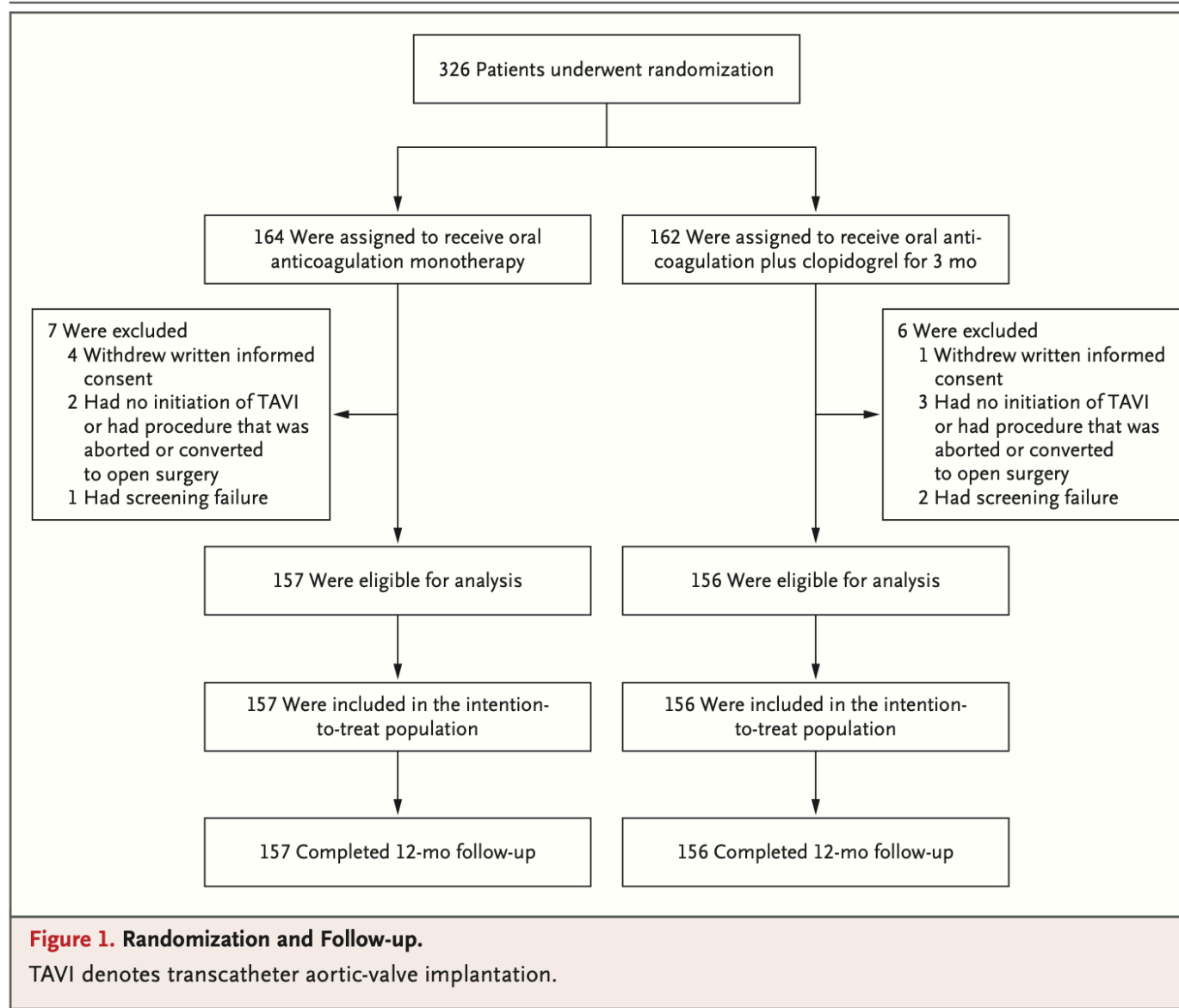| Non–procedure-related bleeding at 12 mo	34 Patients (21.7%)	53 Patients (34.0%)

Risk Ratio, 0.64; 95% CI, 0.44 to 0.92; P=0.02

Oral anticoagulation alone was associated with fewer bleeding events than oral anticoagulation plus clopidogrel.

Figure 1. Randomization and Follow-up.

TAVI denotes transcatheter aortic-valve implantation.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Oral Anticoagulation (N=157)	Oral Anticoagulation plus Clopidogrel (N=156)
Age — yr	80.9±6.2	81.0±5.5
Female sex — no. (%)	69 (43.9)	73 (46.8)
NYHA class III or IV — no. (%)	119 (75.8)	110 (70.5)
Body-mass index†	27.4±5.3	27.5±5.1
Logistic EuroSCORE — %‡		
Median	15.6	14.1
IQR	9.2–23.8	10.6–22.8
Society of Thoracic Surgeons risk score — %§		
Median	3.2	3.1
IQR	2.2–4.8	2.3–4.5
Indication for TAVI — no. (%)		
Normal-flow, high-gradient aortic stenosis	98 (62.4)	98 (62.8)
Low-flow, low-gradient aortic stenosis	51 (32.5)	50 (32.1)
Pure aortic regurgitation	6 (3.8)	4 (2.6)
Combination of above	2 (1.3)	4 (2.6)
Atrial fibrillation — no. (%)¶	150 (95.5)	147 (94.2)
Hypertension — no. (%)	115 (73.2)	105 (67.3)
Diabetes mellitus — no. (%)	43 (27.4)	46 (29.5)

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Oral Anticoagulation (N=157)	Oral Anticoagulation plus Clopidogrel (N=156)
Coronary artery disease — no. (%)	65 (41.4)	69 (44.2)
Previous myocardial infarction — no. (%)	14 (8.9)	20 (12.8)
Peripheral artery disease — no. (%)	30 (19.1)	28 (17.9)
Previous stroke — no. (%)	15 (9.6)	15 (9.6)
Estimated glomerular filtration rate — ml/min/1.73 m^2‖	53.4±17.7	55.6±17.1
Chronic obstructive pulmonary disease — no. (%)	33 (21.0)	30 (19.2)
Previous coronary-artery bypass grafting — no. (%)	30 (19.1)	30 (19.2)
Previous aortic-valve surgery — no. (%)	7 (4.5)	9 (5.8)
Left ventricular ejection fraction — no. (%)		
>50%	91 (58.0)	97 (62.2)
31–50%	54 (34.4)	46 (29.5)
≤30%	12 (7.6)	13 (8.3)

Table 2. Primary and Secondary Outcomes.*

Outcome	Oral Anticoagulation (N=157)	Oral Anticoagulation plus Clopidogrel (N=156)	Risk Ratio (95% CI)	Absolute Difference (95% CI)	P Value
	number (percent)			percentage points	
Primary outcomes					
All bleeding	34 (21.7)	54 (34.6)	0.63 (0.43 to 0.90)		0.01
Non–procedure-related bleeding	34 (21.7)	53 (34.0)	0.64 (0.44 to 0.92)		0.02
Secondary outcomes					
Secondary composite 1†					
Noninferiority analysis	49 (31.2)	71 (45.5)		−14.3 (−25.0 to −3.6)	
Superiority analysis	49 (31.2)	71 (45.5)	0.69 (0.51 to 0.92)		
Secondary composite 2‡					
Noninferiority analysis	21 (13.4)	27 (17.3)		−3.9 (−11.9 to 4.0)	
Superiority analysis	21 (13.4)	27 (17.3)	0.77 (0.46 to 1.31)		
Death from any cause	21 (13.4)	24 (15.4)	0.87 (0.51 to 1.50)		
Death from cardiovascular causes	13 (8.3)	20 (12.8)	0.65 (0.33 to 1.25)		
Stroke	9 (5.7)	9 (5.8)	0.99 (0.41 to 2.44)		
Ischemic	8 (5.1)	9 (5.8)	0.88 (0.35 to 2.23)		
Hemorrhagic	1 (0.6)	0			
Myocardial infarction	1 (0.6)	1 (0.6)	0.99 (0.06 to 15.75)		
VARC-2 bleeding					
Life-threatening or disabling bleeding	6 (3.8)	13 (8.3)	0.46 (0.18 to 1.18)		
Major bleeding	8 (5.1)	13 (8.3)	0.61 (0.26 to 1.43)		
Major, life-threatening, or disabling bleeding	14 (8.9)	26 (16.7)	0.54 (0.29 to 0.99)		
Minor bleeding	20 (12.7)	28 (17.9)	0.71 (0.42 to 1.21)		

Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation
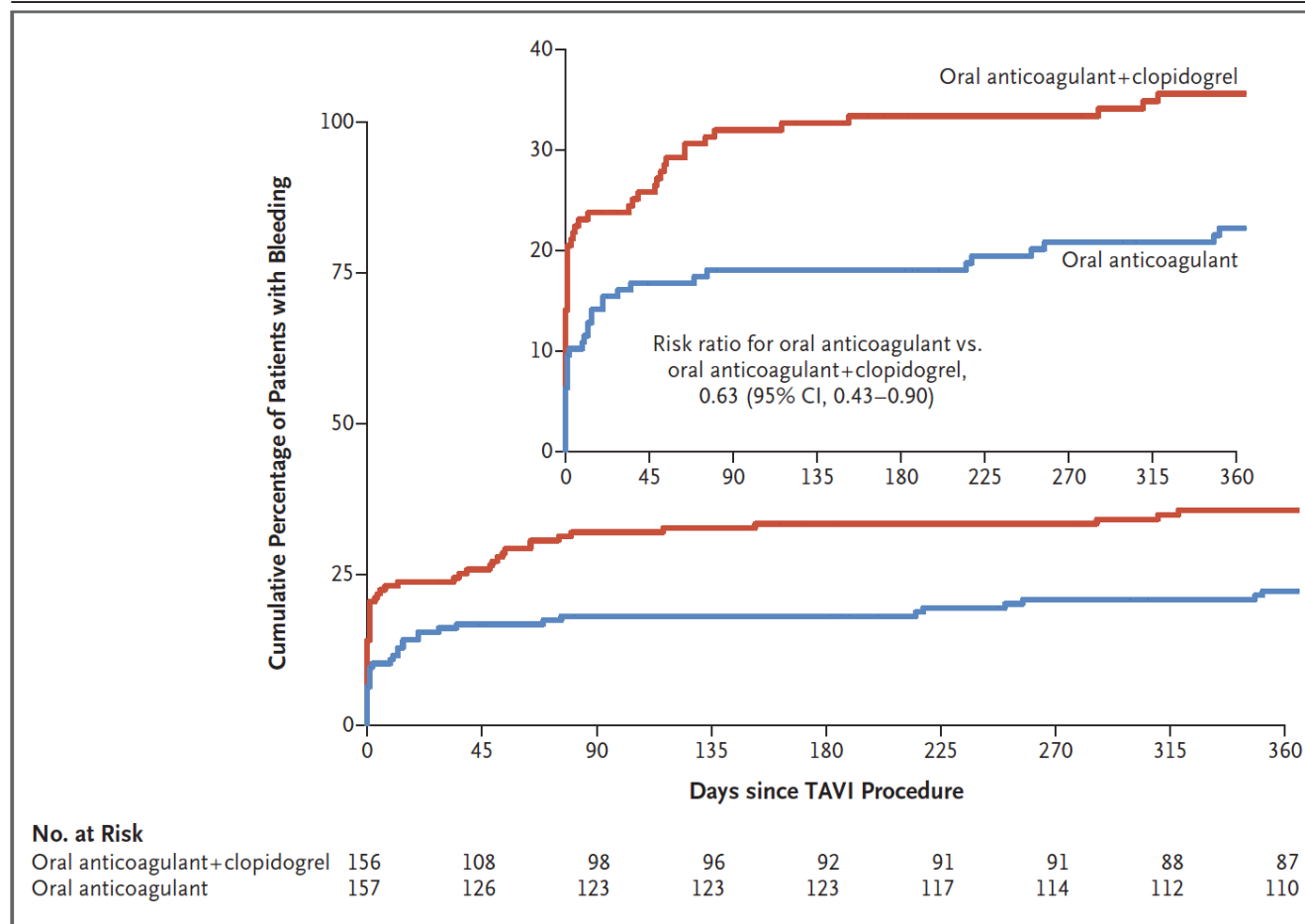

Figure 2. Primary Outcome of All Bleeding.

Shown are time-to-event Kaplan–Meier curves of the primary outcome of all bleeding. The inset shows the same data on an enlarged y axis. Given the nonproportionality of the hazards during the follow-up period, a post hoc risk-ratio analysis with 95% confidence intervals was performed. Results of a post hoc Cox proportional-hazards analysis over a period of 1 month for the primary outcome are shown in Table S10.

Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation

A Death from Cardiovascular Causes, Non–Procedure-Related Bleeding, Stroke, or MI (Secondary Composite 1)

B Death from Cardiovascular Causes, Ischemic Stroke, or MI (Secondary Composite 2)
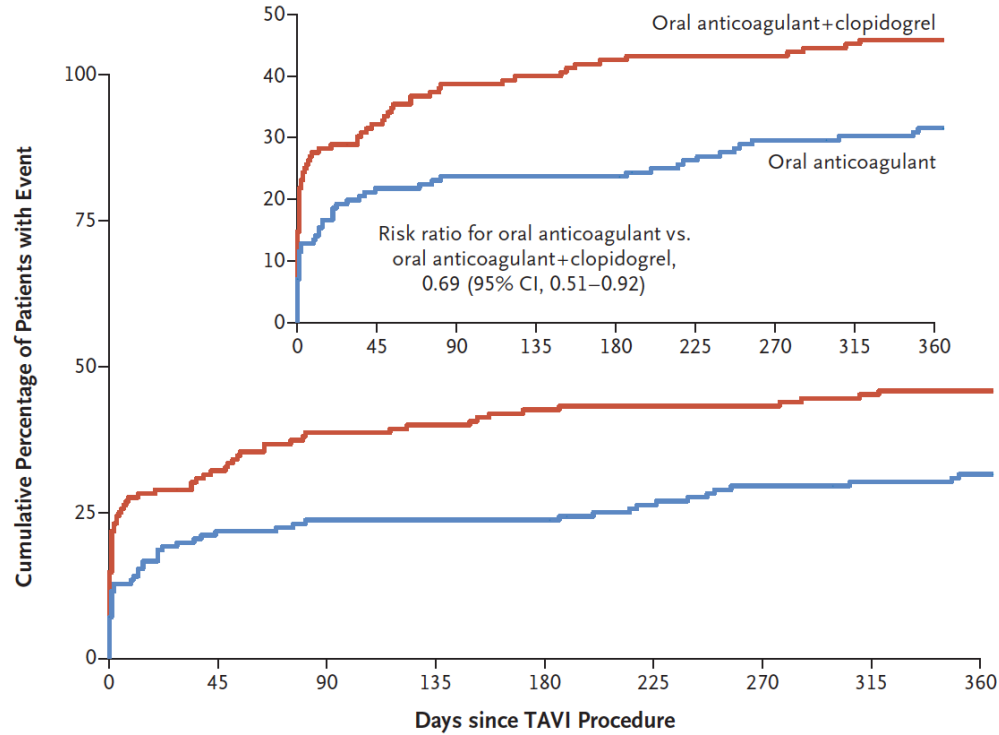
No. at Risk

Oral anticoagulant+clopidogrel	156	104	94	92	88	87	87	84	83
Oral anticoagulant	157	122	119	119	119	113	108	106	104
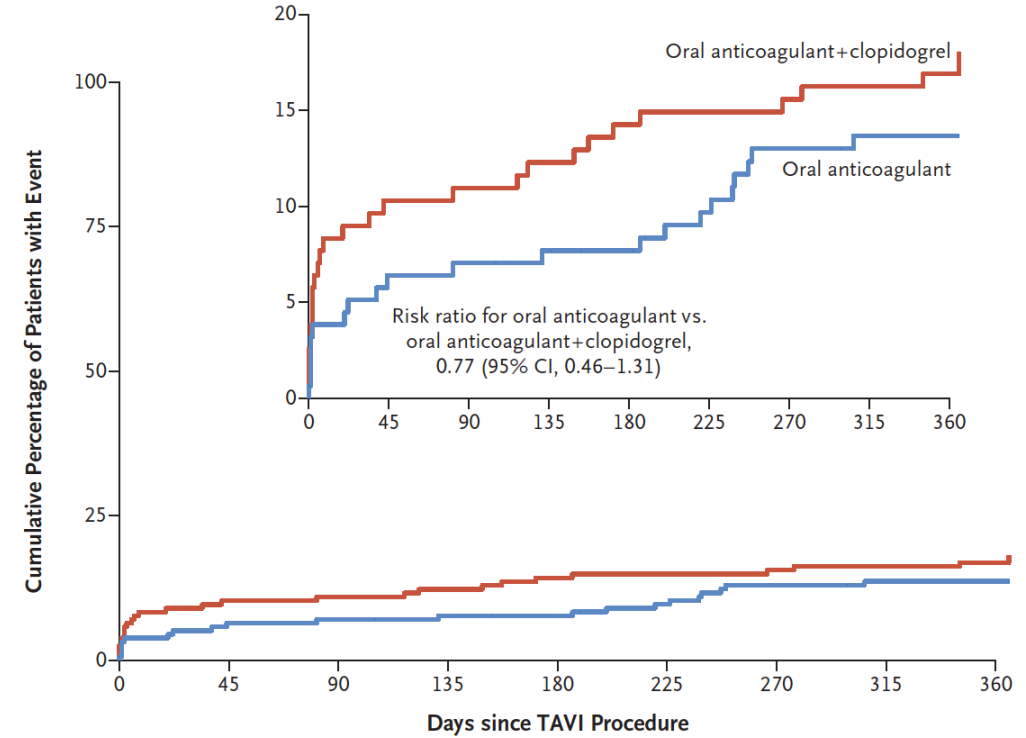
No. at Risk

Oral anticoagulant+clopidogrel	156	136	135	133	130	129	128	127	124
Oral anticoagulant	157	146	145	143	141	136	131	129	129