Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After TAVR: Main Results of The GALILEO Trial

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On The Behalf of The GALILEO Investigators

Disclosures

George Dangas, MD, PhD	Dr. Dangas reports grants from Bayer, during the conduct of the study; personal fees from Sanofi Aventis, personal fees from Bayer, personal fees from Janssen, grants and personal fees from Daiichi-Sankyo, other from Medtronic, outside the submitted work.
Jan Tijssen, PhD	Dr. Tijssen reports grants and personal fees from Bayer, during the conduct of the study.
Gennaro Giustino, MD	Dr. Giustino reports personal fees from Bristol-Myers-Squibb / Pfizer, outside the submitted work.
Marco Valgimigli, MD, PhD,	Dr. Valgimigli reports personal fees from Astra Zeneca, grants and personal fees from Terumo, personal fees from Alvimedica/CID, personal fees from Abbott Vascular, personal fees from Daiichi Sankyo, personal fees from Opsens , personal fees from Bayer, personal fees from CoreFLOW , personal fees from IDORSIA PHARMACEUTICALS LTD, personal fees from Universität Basel | Dept. Klinische Forschung, personal fees from Vifor, personal fees from Bristol Myers Squib SA, personal fees from iVascular , personal fees from Medscape, outside the submitted work.
Pascal Vranckx, MD	Dr. Vranckx reports personal fees from Bayer AG, during the conduct of the study; personal fees from Daichii Sankyo, personal fees from Astra Zeneca, personal fees from CLS Bhering, outside the submitted work.
Robert Welsh, MD,	Dr. Welsh reports grants and personal fees from Astra Zeneca, grants and personal fees from Bayer, grants and personal fees from Boerhinger Ingelheim, outside the submitted work.
Karen Thomitzek, MD	Dr. Thomitzek reports personal fees from Bayer, from null, outside the submitted work.
Peter Wildgoose, PharmD	Dr. Wildgoose reports and Employee of Janssen Pharmaceuticals, and stock holder in Johnson and Johnson.
Ronald Van Amsterdam, PhD	Dr. van Amsterdam has nothing to disclose.
Roxana Mehran, MD	Dr. Mehran reports grants from Bayer, during the conduct of the study; personal fees from Sanofi Aventis, personal fees from Bayer, personal fees from Janssen, grants and personal fees from Daiichi-Sankyo, other from Medtronic, outside the submitted work.
Stephan Windecker, MD	Dr. Windecker reports grants from Amgen , grants from Abbott, grants from Bayer, grants from BMS, grants from CSL Behring, grants from Boston Scientific, grants from Biotronik, grants from Medtronic, grants from Edwards Lifesciences, grants from Polares, grants from Sinomed, outside the submitted work.

Background

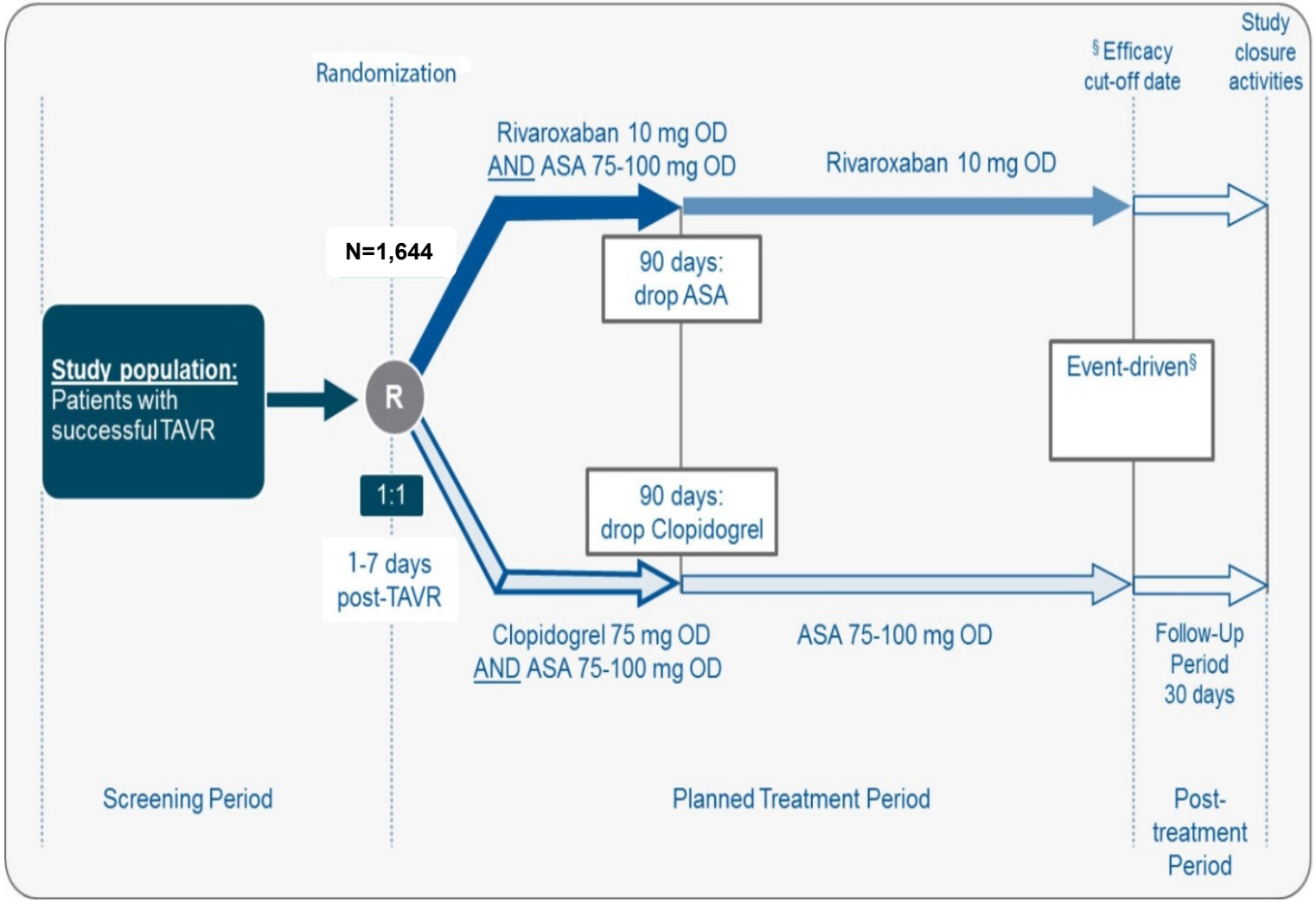
- Transcatheter Aortic Valve Replacement (TAVR) has been established as a standard of care for patients with severe symptomatic AS.
- Thromboembolic complications have been observed early and late after TAVR
- Subclinical leaflet thrombosis, observed with both TAVR and SAVR, has been associated with increased risk of cerebrovascular events in some observational studies
- Current guidelines recommend the use of DAPT after TAVR, however these are based only on expert consensus and small studies
- The oral Factor Xa inhibitor Rivaroxaban, at a 10 mg once daily dosage may be effective in reducing the risk of thromboembolic events post-TAVR
  - N.B. this dosage lower than the 20mg (15mg for renal dfxn) daily indicated for stroke prevention in A.Fib

Study Design

- Open label, international, multicenter, event-driven, randomized, controlled trial comparing a rivaroxaban-based antithrombotic strategy vs. an antiplatelet-based strategy post-successful TAVR

- **Primary efficacy endpoint**: death, stroke, MI, systemic thromboembolism, symptomatic valve thrombosis, or deep venous thrombosis or pulmonary embolism

- **Primary safety endpoint**: VARC-2 major, disabling or life-threatening bleeding



Key Inclusion and Exclusion Criteria

INCLUSION

1. Man or woman of **18 years of age or older**

2. Have a **successful transfemoral or trans-subclavian TAVR** of an aortic valve stenosis (either native of valve-in-valve), defined as:
   - Correct positioning of a single prosthetic heart valve into the proper anatomical location.
   - Intended performance of the prosthetic heart valve - presence of all 3 conditions post-TAVR:
     - Mean aortic valve gradient < 20 mmHg
     - Peak transvalvular velocity (aortic valve maximum velocity) < 3.0 m/s
     - No severe or moderate aortic valve regurgitation
   - Absence of major periprocedural complications

3. With **any approved/marketed TAVR device**

EXCLUSION

1. Atrial fibrillation with an indication for OAC
2. Need for chronic oral anticoagulation
3. Any ongoing absolute indication for DAPT
4. Contraindication to aspirin, clopidogrel or rivaroxaban; known bleeding diathesis
5. Routine use of NSAIDs
6. Planned coronary or vascular intervention or major surgery
7. Clinically overt stroke within 3 months
8. Severe renal impairment (eGFR<30) or on dialysis, or post-TAVR unresolved acute kidney injury
9. Moderate and severe hepatic impairment or any hepatic disease associated with coagulopathy
10. Active infective endocarditis
11. Active malignancy

Study Organization

Executive Committee
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Funding: Bayer & Janssen

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Study Statisticians & Programmers
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Clinical Coordinating Centers

Cardialysis, Rotterdam, the Netherlands	Europe
Mount Sinai Medical Center, New York NY	North America
Vigour Centre, Edmonton, Alberta	Canada

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D. Hildick-Smith	United Kingdom
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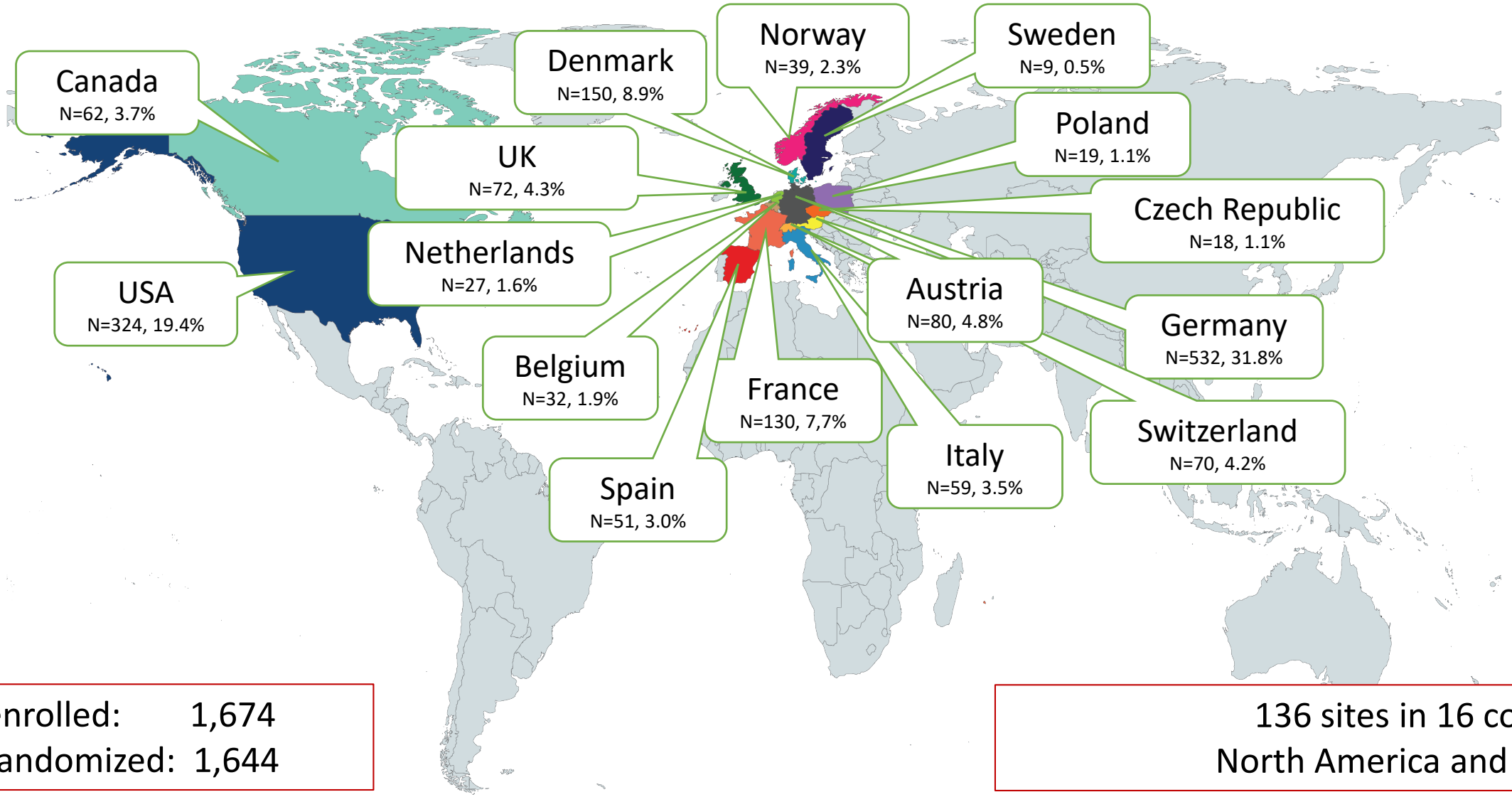
Enrolled population



Total enrolled: 1,674
Total randomized: 1,644

136 sites in 16 countries
North America and Europe

Top 20 performing sites

Site	Principal Investigator	Randomized
1. University of Ulm, Germany	Prof. J. Wöhrle	98
2. Rigshospitalet, University of Copenhagen, Denmark	Prof. L. Søndergaard	90
3. CHRU de Brest- La Cavalle Blanche University Hospital, Brest, France	Prof. M. Gilard	77
4. Mount Sinai Hospital, New York, USA	Prof. A. Kini	49
5. Aarhus University Hospital, Denmark	Dr. C.J. Terkelsen	45
6. St. Johannes Hospital, Germany	Prof. Dr. H. Möllmann	43
7. Cedars-Sinai Medical Center, Los Angeles, USA	Prof. R. Makkar	43
8. University of Pennsylvania, USA	Prof. H. Hermann	40
9. Kerckhoff Klinik GmbH, Bad Nauheim, Germany	Dr. W-K. Kim	39
10. Herz-Kreislauf-Zentrum Segeberger Kliniken GmbH, Germany	PD. Dr. R. Toelg	36
11. Universitätsklinikum Düsseldorf, Germany	Dr. A. Polzin	35
12. Medizinische Universität Graz, Austria	Ass. Prof. D. van Lewinski	31
13. Otto-von-Guericke-Universität Magdeburg, Germany	Dr. S. Meissler	31
14. Bern University Hospital, Switzerland	Prof. S. Windecker	28
15. Oslo Universitetssjukehus, Rikshospitalet, Norway	Prof. L. Gullestad	25
16. Hospital La Paz, Madrid, Spain	Dr. R. Moreno Gómez	24
17. Uniklinik Köln, Germany	PD Dr. M. Adam	22
18. Luzerner Kantonsspital, Switzerland	PD Dr. S. Toggweiler	22
19. Leeds General Infirmary, United Kingdom	Dr. M. Cunnington	22
20. Klinikum der Eberhard-Karls-Universität Tübingen, Germany	Prof. Dr. T. Geisler	21

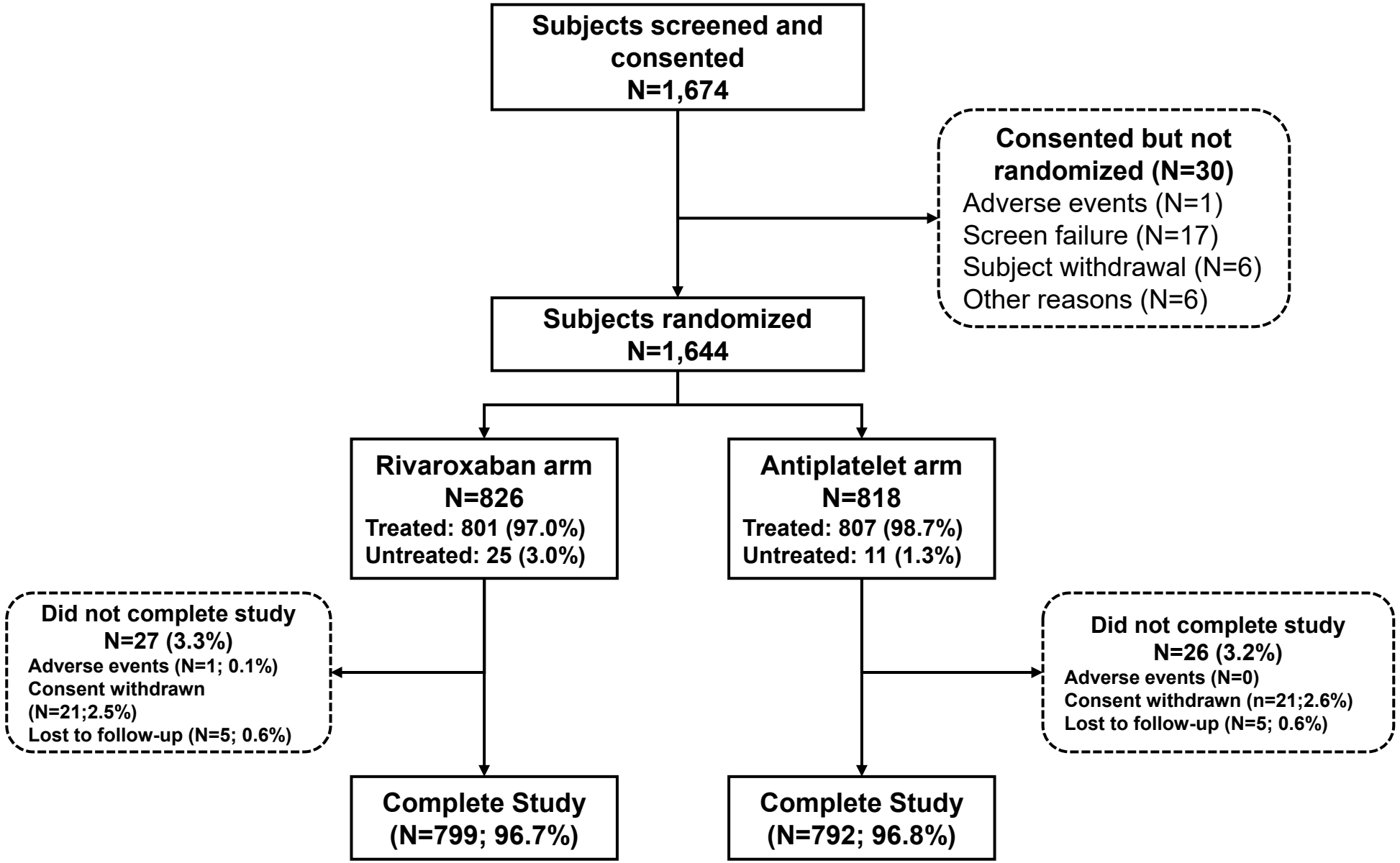
Statistical Methods

- The primary hypothesis of the trial was that the rivaroxaban-based strategy would be superior to the antiplatelet-based strategy with respect to incidence of death or thromboembolic events.
  - This testing was preceded by testing for non-inferiority in the on-treatment population.

- Original assumptions included an 18-month incidence of the composite primary endpoint of **33.0% under the antiplatelet-based regimen** and of **26.4% under the rivaroxaban-based regimen**, corresponding to an **HR of 0.7654**. We estimated that 440 composite primary outcomes, occurring in 27,360 patient-months of follow-up, would provide the trial with 80% power to statistically detect the expected effect at a one-sided significance level of 0.025

- The trial was terminated on August 13, 2018 (efficacy cut-off date) after the DSMB recommendation of 7 August 2018, due to safety concerns.
  - Only 183 patients had reached the primary efficacy outcome (42% of planned 440)

CONSORT Diagram



Baseline Characteristics

	Rivaroxaban Arm (N=826)	Antiplatelet Arm (N=818)
Clinical characteristics		
Age, years	80.4±7.1	80.8±6.0
Male sex	426 (51.6%)	405 (49.5%)
Diabetes mellitus	236 (28.6%)	235 (28.7%)
STS risk score	4.0±3.2	4.3±3.5
High risk (>8)	65 (7.9%)	74 (9.0%)
Intermediate risk (≥3 to ≤8)	383 (46.4%)	388 (47.4%)
Low (<3)	378 (45.8%)	356 (43.5%)
NYHA class III or IV	250 (30.3%)	222 (27.1%)
Coronary artery disease	325 (39.3%)	305 (37.3%)
Prior stroke	51 (6.2%)	35 (4.3%)
Peripheral artery disease	83 (10.0%)	82 (10.0%)
Permanent pacemaker	80 (9.7%)	80 (9.8%)
COPD	110 (13.3%)	88 (10.8%)
eGFR, mL/min/1.73m^2	73.4±23.8	73.2±23.2

	Rivaroxaban Arm (N=826)	Antiplatelet Arm (N=818)
Procedural characteristics		
Valve type		
Sapien XT valve	13 (1.6%)	13 (1.6%)
Sapien 3 valve	385 (46.6%)	346 (42.3%)
CoreValve	33 (4.0%)	35 (4.3%)
CoreValve Evolut R valve	206 (24.9%)	225 (27.5%)
Lotus valve	44 (5.3%)	40 (4.9%)
Portico valve	44 (5.3%)	40 (4.9%)
Acurate Neo valve	82 (9.9%)	89 (10.9%)
Valve-in-valve	42 (5.1%)	49 (6.0%)
Post-TAVR echo characteristics		
Aortic valve area, cm^2	1.8±0.6	1.9±0.5
Mean aortic valve gradient, mmHg	10.0±4.7	10.1±4.6
Left ventricular ejection fraction, %	57.4±10.9	58.2±11.2
Paravalvular aortic regurgitation		
Mild	157 (19.0%)	168 (20.5%)
Moderate or severe	10 (1.2%)	10 (1.2%)

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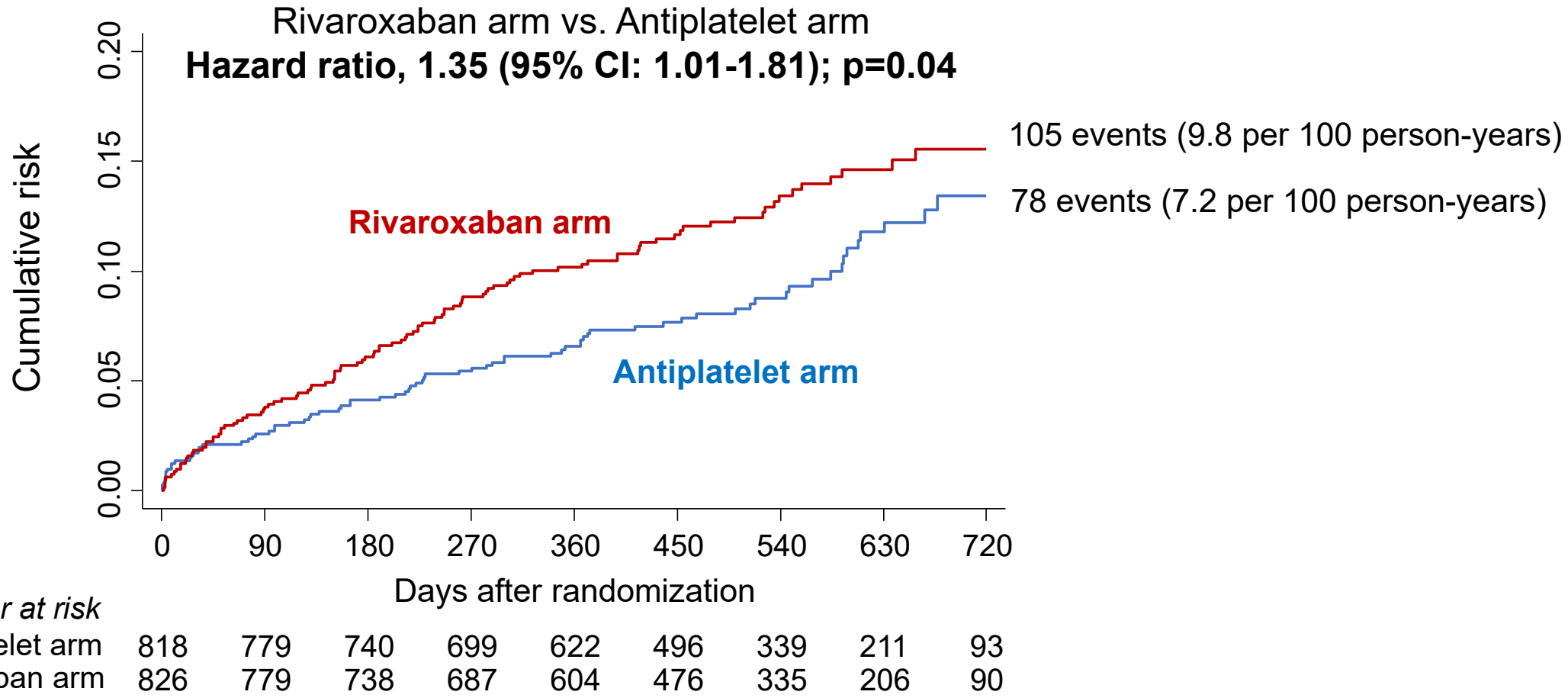
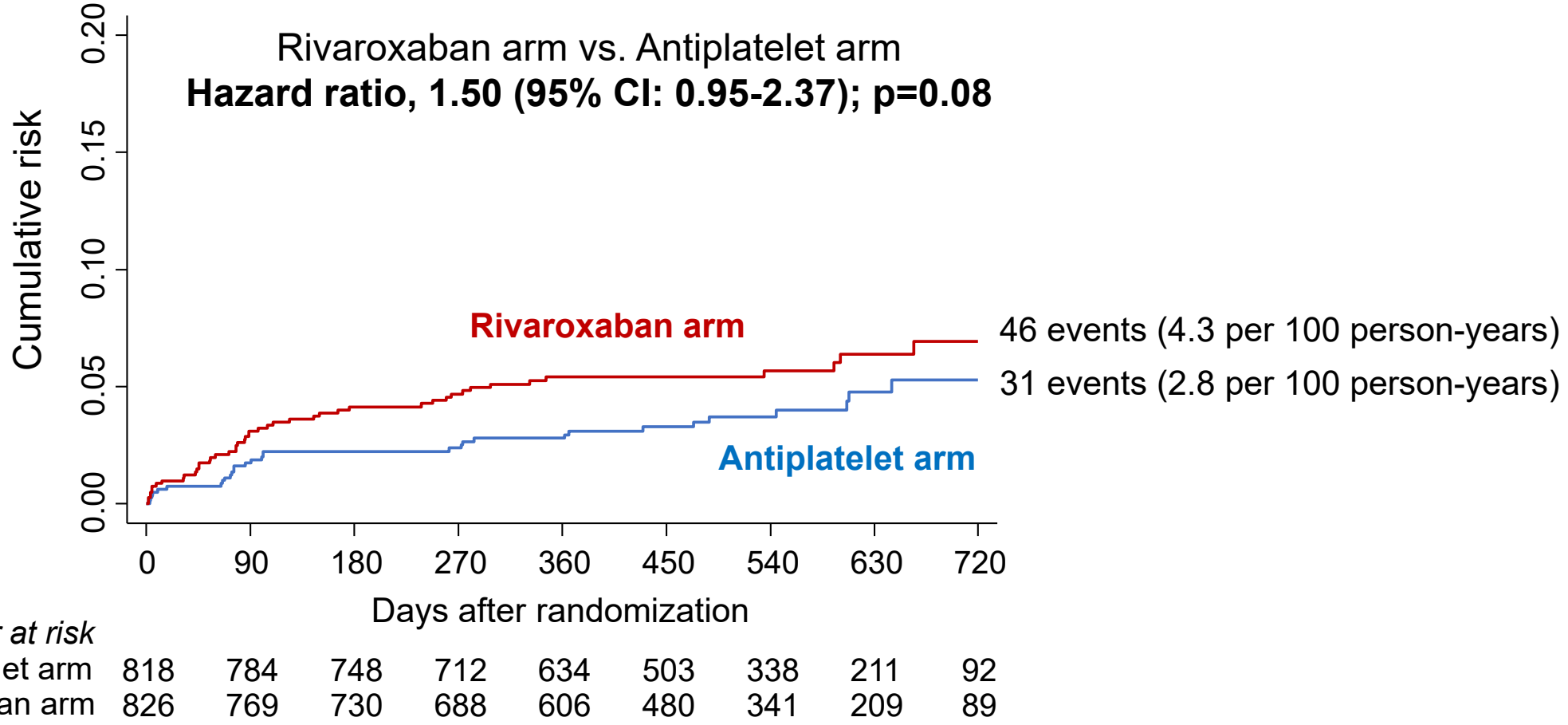
Primary Efficacy Endpoint (Intention-to-treat)

Time to death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis or systemic embolism

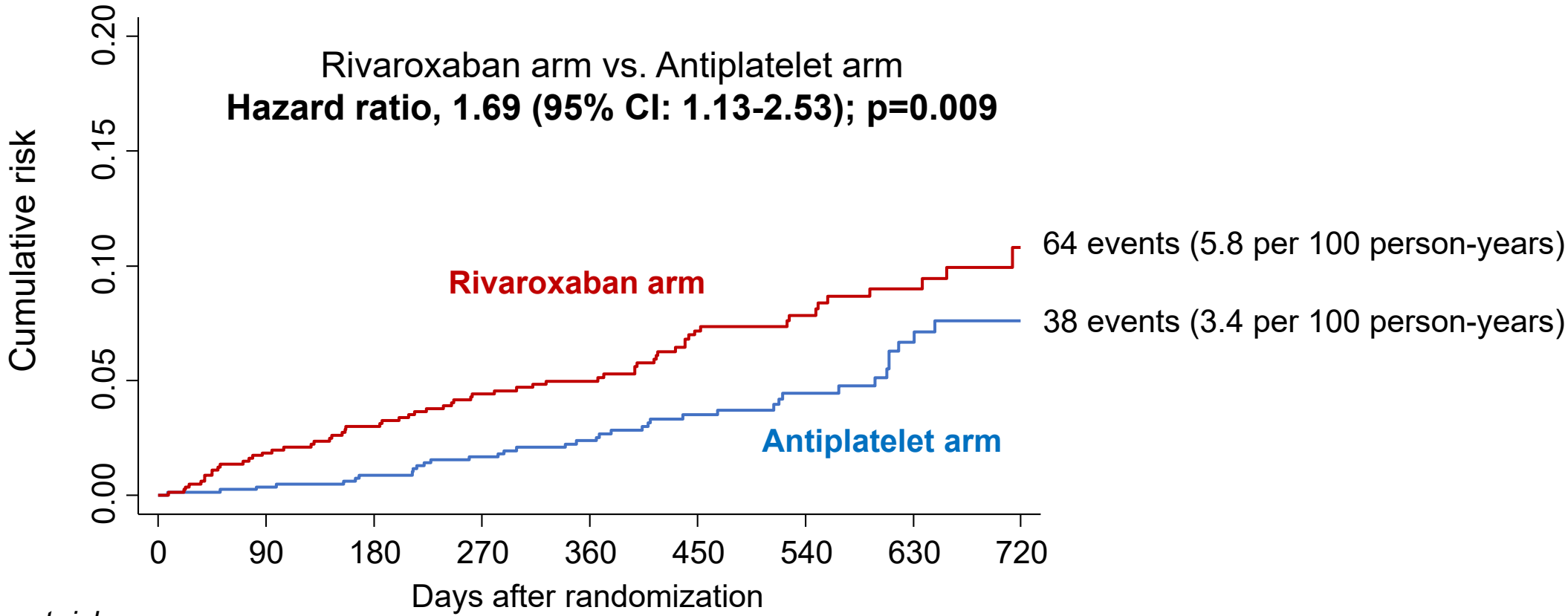


Primary Safety Endpoint (Intention-to-treat)

Time to VARC life-threatening, disabling or major bleeding



All-Cause Mortality (Intention-to-treat)



Number at risk

Antiplatelet arm	818	797	765	728	650	519	351	218	95
Rivaroxaban arm	826	793	759	718	636	499	356	219	92

Efficacy & Safety Endpoints (Intention-to-treat)

Outcome	Rivaroxaban arm (N=826)		Antiplatelet arm (N=818)		Incidence Rate Difference (95% CI)	Hazard Ratio (95% CI)
	n (%)	Incidence rate per 100 person-yrs	n (%)	Incidence rate per 100 person-yrs		
Efficacy Outcomes						
Primary efficacy outcome*	105 (12.7%)	9.8	78 (9.5%)	7.2	2.6 (0.1; 5.1)	1.35 (1.01-1.81)
Death	64 (7.7%)	5.8	38 (4.6%)	3.4	2.4 (0.6; 4.1)	1.69 (1.13-2.53)
Cardiovascular death	35 (4.2%)	3.2	27 (3.3%)	2.4	0.7 (-0.7; 2.1)	1.30 (0.79-2.14)
Non-cardiovascular death	29 (3.5%)	2.6	11 (1.3%)	1.0	1.6 (0.5; 2.7)	2.67 (1.33-5.35)
Stroke	30 (3.6%)	2.8	25 (3.1%)	2.3	0.5 (-0.8; 1.8)	1.20 (0.71-2.05)
Myocardial infarction	23 (2.8%)	2.1	17 (2.1%)	1.5	0.6 (-0.6; 1.7)	1.37 (0.73-2.56)
Symptomatic valve thrombosis	3 (0.4%)	0.3	7 (0.9%)	0.6	-0.4 (-0.9; 0.2)	0.43 (0.11-1.66)
Pulmonary embolism	3 (0.4%)	0.3	2 (0.2%)	0.2	0.1 (-0.3; 0.5)	1.49 (0.25-8.93)
Deep vein thrombosis	1 (0.1%)	0.1	4 (0.5%)	0.4	-0.3 (-0.7; 0.1)	0.25 (0.03-2.23)
Systemic embolism	1 (0.1%)	0.1	1 (0.1%)	0.1	0.0 (-0.3; 0.3)	0.98 (0.06-15.69)
Key secondary efficacy outcome†	83 (10.0%)	7.8	68 (8.3%)	6.3	1.5 (-0.8; 3.7)	1.22 (0.89-1.69)
Net Clinical Benefit‖	137 (16.6%)	13.2	100 (12.2%)	9.4	3.8 (0.9; 6.7)	1.39 (1.08-1.80)
Safety Outcomes						
Primary safety outcome**	46 (5.6%)	4.3	31 (3.8%)	2.8	1.5 (-0.1; 3.1)	1.50 (0.95-2.37)
VARC life-threatening or disabling bleeding	18 (2.2%)	1.6	17 (2.1%)	1.5	0.1 (-1.0; 1.2)	1.06 (0.55-2.06)
Fatal bleeding	2 (0.2%)	0.2	1 (0.1%)	0.1	0.1 (-0.2; 0.4)	2.01 (0.18-22.19)
VARC Major bleeding	30 (3.6%)	2.8	15 (1.8%)	1.4	1.4 (0.2; 2.6)	2.02 (1.09-3.76)
TIMI major or minor bleeding	42 (5.1%)	3.9	24 (2.9%)	2.2	1.7 (0.3; 3.2)	1.78 (1.08-2.94)
ISTH major bleeding	49 (5.9%)	4.6	30 (3.7%)	2.7	1.9 (0.2; 3.5)	1.66 (1.05-2.62)
BARC type 2, 3 or 5 bleeding	148 (17.9%)	15.4	85 (10.4%)	8.2	7.2 (4.2; 10.3)	1.84 (1.41-2.41)

*Defined as the composite of death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis or systemic embolism; p-value=0.04 (2-sided p-value for difference calculated following the failed non-inferiority hypothesis test); †Defined as the composite of cardiovascular death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis or systemic embolism; ‖Defined as the composite of Primary Efficacy of Primary Safety Outcomes; ** Defined as the composite of VARC life-threatening, disabling or major bleeding

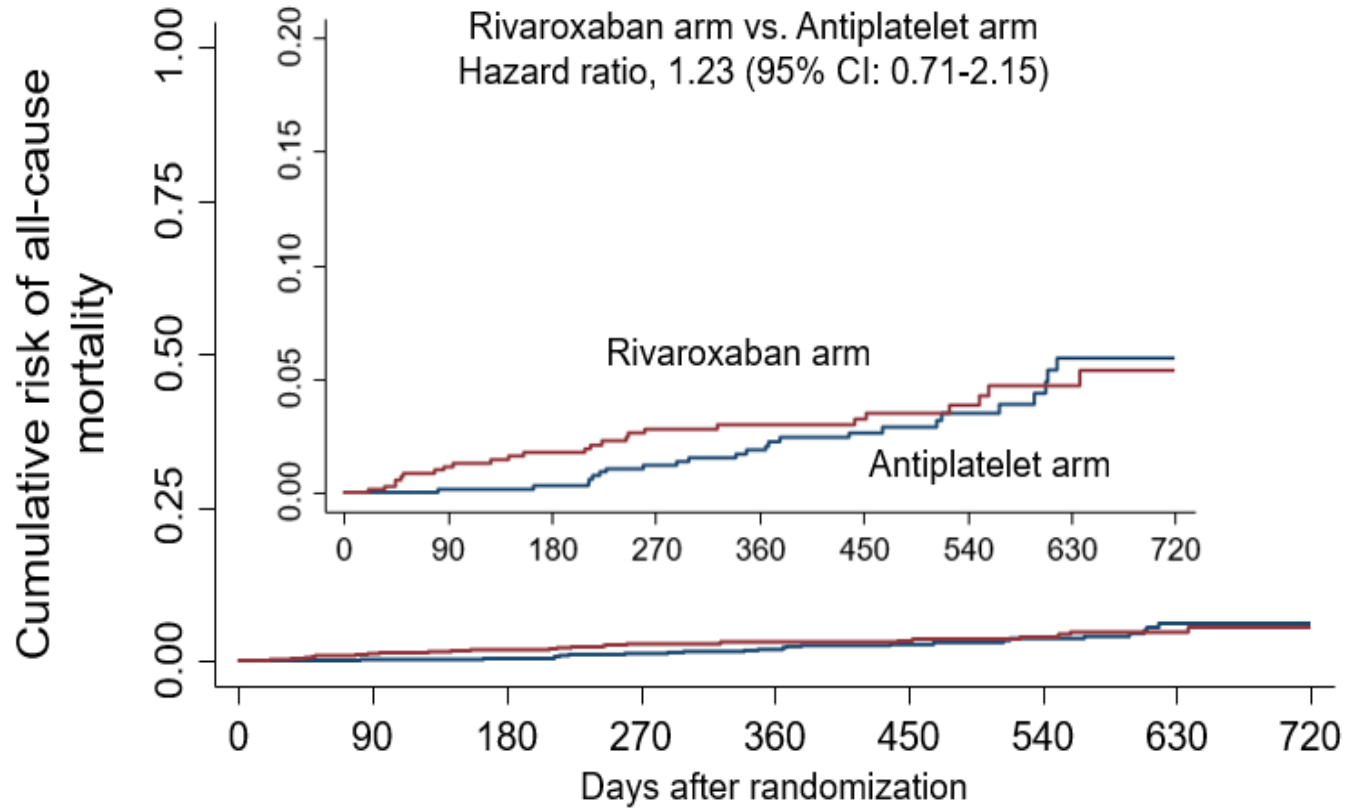
Efficacy & Safety Endpoints (On-Treatment Analysis)

Outcome	Rivaroxaban arm (N=826)		Antiplatelet arm (N=818)		Incidence Rate Difference (95% CI)	Hazard Ratio (95% CI)
	n (%)	Incidence rate per 100 person-yrs	n (%)	Incidence rate per 100 person-yrs		
Efficacy Outcomes						
Primary efficacy outcome*	68 (8.5%)	8.1	63 (7.8%)	6.6	1.5 (-1.0; 4.0)	1.21 (0.86-1.70)
Death	26 (3.2%)	3.0	24 (3.0%)	2.5	0.6 (-1.0; 2.1)	1.23 (0.71-2.15)
Stroke	24 (3.0%)	2.8	19 (2.4%)	2.0	0.9 (-0.6; 2.3)	1.40 (0.77-2.55)
Myocardial infarction	17 (2.1%)	2.0	14 (1.7%)	1.5	0.6 (-0.7; 1.8)	1.37 (0.67-2.78)
Symptomatic valve thrombosis	3 (0.4%)	0.4	6 (0.7%)	0.6	-0.3 (-0.9; 0.4)	0.58 (0.14-2.32)
Pulmonary embolism	2 (0.2%)	0.2	2 (0.2%)	0.2	0.0 (-0.4; 0.5)	1.06 (0.15-7.56)
Deep vein thrombosis	0	-	4 (0.5%)	0.4	-0.4 (-0.8; -0.0)	-
Systemic embolism	1 (0.1%)	0.1	0	-	0.1 (-0.1; 0.4)	-
Key secondary efficacy outcome†	61 (7.6%)	7.3	56 (6.9%)	5.9	1.4 (-1.0; 3.8)	1.22 (0.85-1.75)
Net Clinical Benefit‖	103 (12.9%)	12.5	84 (10.4%)	9.0	3.5 (0.4; 6.6)	1.36 (1.02-1.81)
Safety Outcomes						
Primary safety outcome**	39 (4.9%)	4.6	28 (3.5%)	2.9	1.7 (-0.1; 3.5)	1.53 (0.94-2.49)
VARC life-threatening or disabling bleeding	14 (1.7%)	1.7	16 (2.0%)	1.7	0.0 (-1.2; 1.2)	0.97 (0.47-1.98)
Fatal bleeding	1 (0.1%)	0.1	1 (0.1%)	0.1	0.0 (-0.3; 0.3)	1.06 (0.07-16.97)
VARC Major bleeding	26 (3.2%)	3.1	12 (1.5%)	1.2	1.8 (0.5; 3.2)	2.38 (1.20-4.71)
TIMI major or minor bleeding	35 (4.4%)	4.1	22 (2.7%)	2.3	1.9 (0.2; 3.5)	1.76 (1.03-3.00)
ISTH major bleeding	42 (5.2%)	5.0	27 (3.3%)	2.8	2.2 (0.3; 4.0)	1.71 (1.06-2.78)
BARC type 2, 3 or 5 bleeding	137 (17.1%)	17.1	74 (9.2%)	8.1	9.1 (5.7; 12.5)	2.04 (1.54-2.71)

*Defined as the composite of death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis or systemic embolism; †Defined as the composite of cardiovascular death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis or systemic embolism; ‖Defined as the composite of Primary Efficacy of Primary Safety Outcomes; ** Defined as the composite of VARC life-threatening, disabling or major bleeding

Non-inferiority for the primary efficacy outcome not met given upper bound of 95% CI of HR of 1.70 (pre-specified of 1.20)

On-Treatment Analysis. Time-to-Event Kaplan-Meier Curves for All-Cause Mortality



Number at risk

Antiplatelet arm	807	731	674	629	552	432	278	168	76
Rivaroxaban arm	801	660	597	548	473	361	245	147	56

Limitations

- This trial employed open-label treatment and is potentially subject to reporting and ascertainment bias.
- Prematurely terminated trial per DSMB recommendation; treatment effects and CIs need to be interpret with caution.
- On-treatment analyses are subject to bias due to the high rates of treatment discontinuation
- Patients undergoing TAVR with an established indication for anticoagulation were not included in this trial and treatment strategies for this patient population are being investigated in other clinical trials.

Conclusions

- In patients without an indication for oral anticoagulation after TAVR, a 10mg daily rivaroxaban-based antithrombotic strategy was associated with higher risk of death or thromboembolic events and bleeding compared to an antiplatelet-based antithrombotic strategy
  - Investigation on a lower dosage (2.5mg BID) may be a future endeavor

- The mechanism underlying the higher mortality in the rivaroxaban arm observed in the intention-to-treat analysis in this trial is unclear. The mortality rate differences were attenuated in the on-treatment analysis and occurred late after discontinuation of study drug.

- These results of GALILEO main trial are irrespective of potential effects on valve imaging findings (GALILEO 4D-CT Ancillary Study)


THANK YOU!