ATLANTIS

Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis : a randomized, open-label, phase 3 trial

ACTION Group
www.action-groupe.org
Academic Research Organization

SORBONNE UNIVERSITÉ
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AMERICAN COLLEGE of CARDIOLOGY

ClinicalTrials.gov number, NCT02664649

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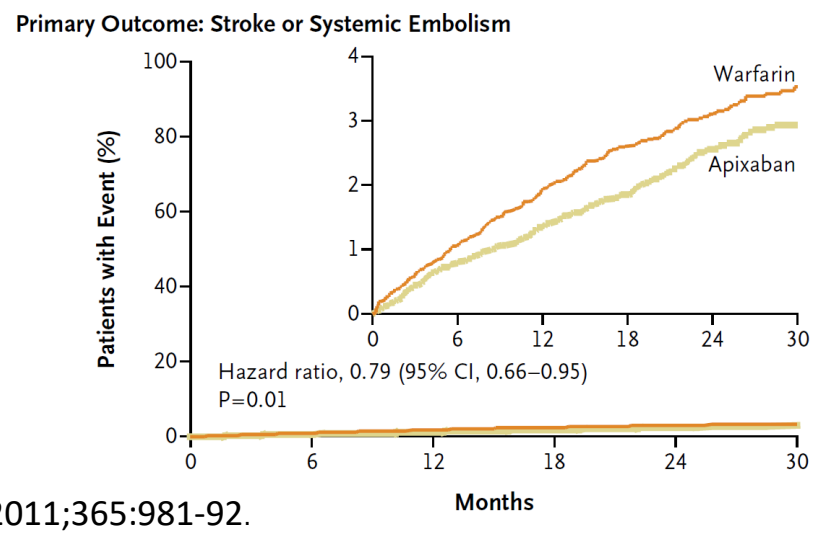
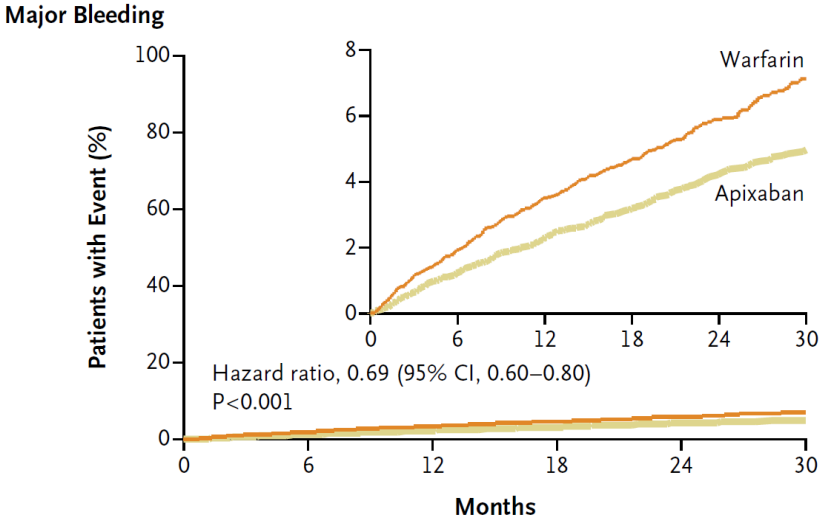
Background

- Post-procedural thrombotic and bleeding events are frequent and negatively affect short-term survival.
- Thrombus formation on the implanted bioprosthesis adds to the potential hazards of TAVI.
- **SAPT alone** if no need for OAC and absence of recent stent implantation **is the safest option**.
- **VKA alone are safer than when combined with antiplatelet therapy in** patients requiring OAC.
- There is **no evidence that NOAC could replace antiplatelet therapy or VKA after TAVI**.
- GALILEO demonstrated **more harm than benefit with low-dose rivaroxaban** compared with APT.

Net clinical benefit of apixaban in Atrial Fibrillation

ARISTOTLE



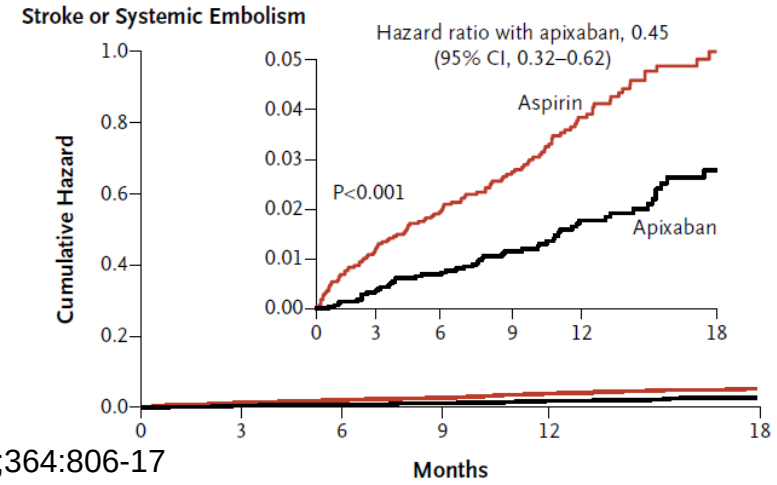


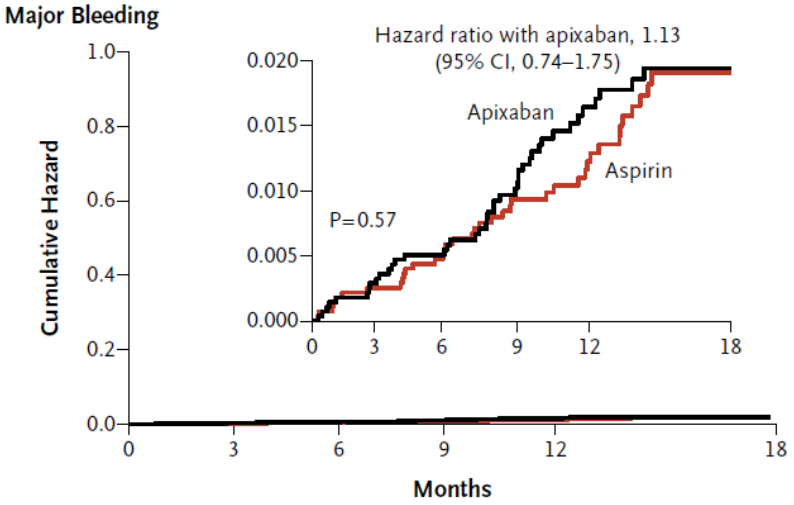
N Engl J Med 2011;365:981-92.

Apixaban vs. **warfarin**

NCB*: 3.2% vs 4.1%
p<0,001

AVERROES





N Engl J Med 2011;364:806-17

Apixaban vs. **ASA**

NCB*: 5.3 vs 7.2%
p=0,003

* Net clinical benefit

Study Objectives

- Primary study objective → to demonstrate superiority of apixaban 5mg bid compared to standard-of-care, comprising either antiplatelet or VKA therapy after successful TAVI.

- Secondary objective → to determine whether there was an interaction between treatment and outcomes according to the presence or absence of an indication other than TAVI for anticoagulation.

Study organization

Academic Research Organization

- Pr Gilles MONTALESCOT (Scientific Director)
- Pr Jean-Philippe COLLET (Principal Investigator)
- Pr Eric VICAUT (Méthodologist-statistician)
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Sponsor

Assistance Publique des Hôpitaux de Paris

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Funding

ACTION fonds and Alliance BMS/Pfizer

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Study design

Anti-**T**hrombotic Strategy to **L**ower **A**ll cardiovascular and **N**eurologic Ischemic and Hemorrhagic Events after **T**rans-Aortic Valve **I**mplantation for Aortic **S**tenosis

1510 patients after successful TAVI procedure

Stratum 1 Indication for OAT		Stratum 2 No indication for OAT	
R 1:1		R 1:1	
VKA	Apixaban 5mg bid*	DAPT/SAPT	

Primary end-point is a composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism, major bleedings over one year follow-up.

*2.5mg bid if creatinine clearance 15–29 mL/min or if two of the following criteria: age ≥80 years, weight ≤60kg or creatinine ≥1.5mg/dL (133µMol/L) or if concomitant antiplatelet therapy (ACS or recent stenting) or physician's choice.

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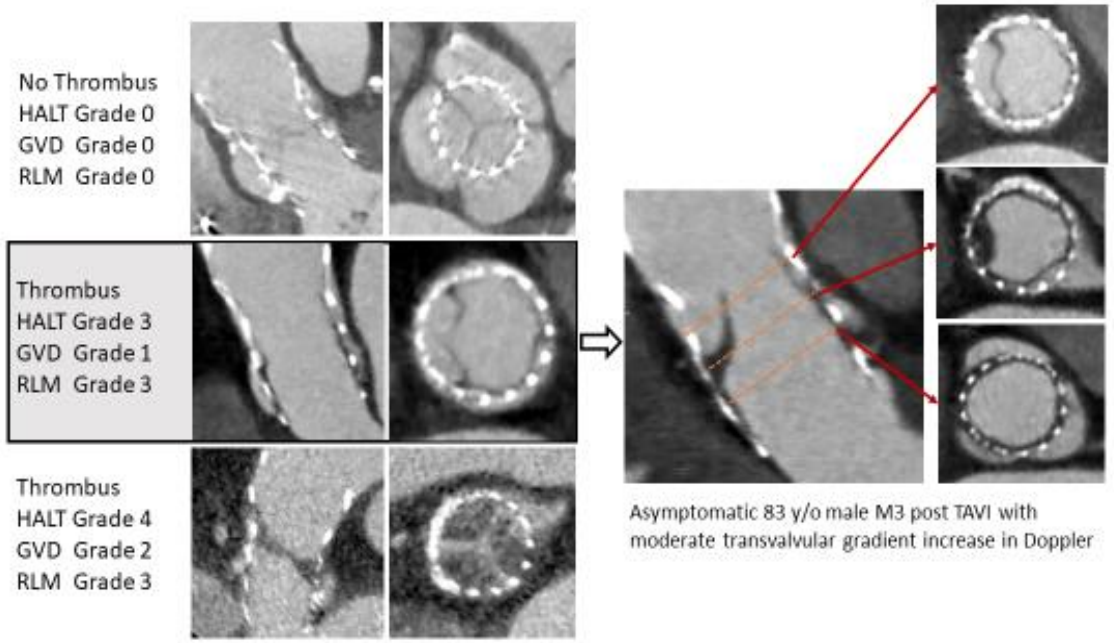
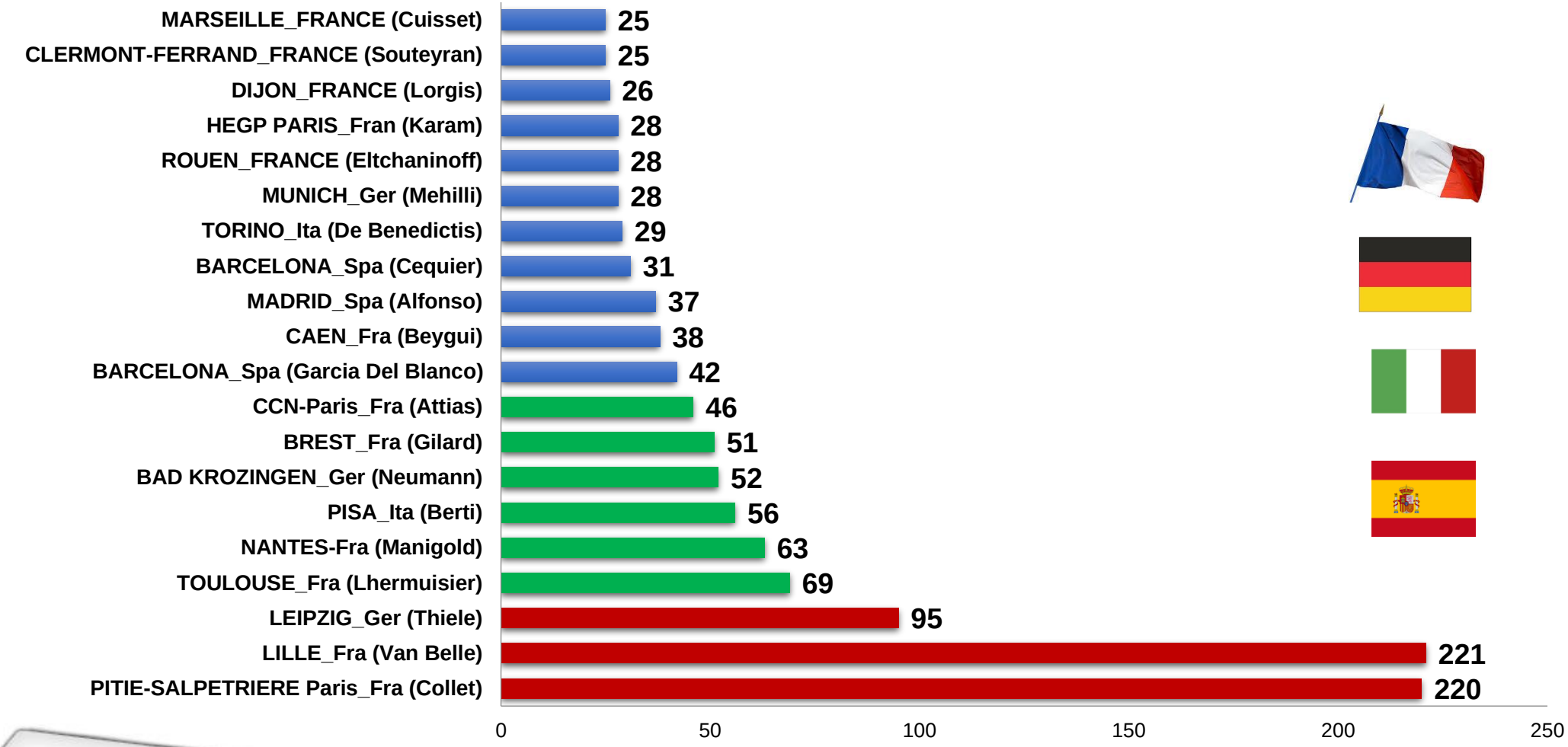
CT and ECHO evaluation of subclinical leaflet thrombosis

- 4D-CT scan was protocol mandated to identify subclinical valve thrombosis, a component of the primary endpoint
- **Definition**: visible thrombosis on TTE or 4D-CT scan AND mean transprosthetic gradient ≥10 mmHg change from baseline (vs. hospital discharge) or > 20mmHg OR reduced leaflet mobility (RELM) grade 3 or 4 on at least one leaflet.



Top recruiting centers



28 SITES

7 SITES

4 SITES

10 SITES

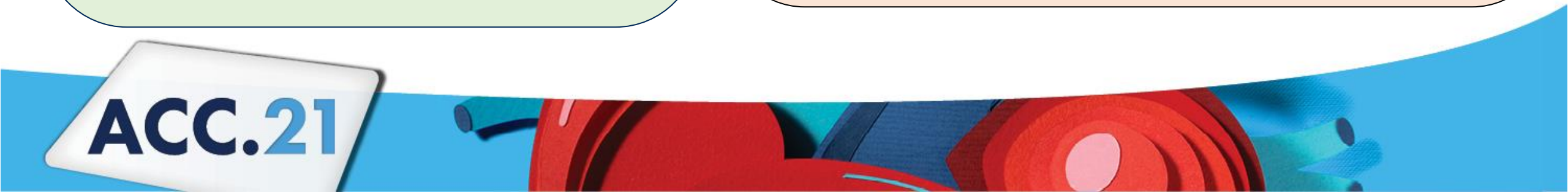
Key Inclusion and exclusion criteria

INCLUSION

1. Man or woman of **18 years of age or older**
2. **Successful TAVI** of an aortic valve stenosis (native of valve-in-valve)
3. **Irrespective of prior antithrombotic therapy**
4. Written Informed consent obtained at enrolment into the study
5. **With any approved/marketed TAVR device**

EXCLUSION

1. Creatinine Clearance < 15mL/min or dialysis.
2. Mechanical valves.
3. Severe mitral valve stenosis requiring an intervention.
4. Unsuccessful TAVI requiring re-intervention.
5. Ongoing major bleeding or vascular complication
6. Prior history of intracranial haemorrhage.
7. Recent stroke/TIA on anticoagulant therapy (<6 weeks).
8. Planned major surgery during follow-up
9. Expected survival less than one year.
10. Concomitant use of prasugrel or ticagrelor.
11. Coronary stent implantation <2 weeks prior to randomization
12. Concomitant treatments that are potent inhibitors of CYP3A4
13. Any coagulopathy and significant risk of bleeding.



Statistical considerations

- **Sample size** → a one-year incidence in the composite primary endpoint of 15% in the SOC, 686 patients per group (total number of events E=167) was determined to allow an 80% power to detect a 30% relative difference in event rate using a log-rank test with a 5% two-sided significance level.

- **Testing for the primary endpoint**
  - A test of difference was first performed.
  - Interaction according to the need for oral anticoagulation was then tested.

- **Secondary criteria → hierarchical strategy of testing**
  - Tests for significance of difference with a two-sided 5% alpha value were performed only if the primary hypothesis of superiority was verified.
  - Each criterion was tested only if a significant difference was found for the previous one; otherwise, only 95% CI of the HR were reported.
    - (i) death, MI, stroke
    - (ii) death, stroke/TIA or peripheral embolism
    - (iii) all cause death

1510 patients underwent randomisation (10 withdrew consent immediately and refuse the collection of any data in the database)

1500 patients were randomly assigned to treatment group

749 were assigned to the apixaban group

- 739 (98.7%) received apixaban
- 10 (1.3 %) did not receive apixaban

749 patients analyzed in the intention to treat and safety populations

105 patients didn't complete the follow-up :

- n= 54 Death
- n= 1 Decision of the investigator
- n= 25 Consent withdraw during the study
- n= 13 Patient refuse to continue the study
- n= 9 Patient was lost to follow up
- n= 3 Other

751 were assigned to the standard-of-care group

Stratum 1 (n=228)

- 202 (88.6%) received VKA±APT
- 20 (8.8%) received APT
- 6 (2.6%) unknown

Stratum 2 (n=523)

- 484 (92.5%) received APT
- 36 (6.9%) received VKA±APT
- 3 (0.6%) unknown

751 patients analyzed in the intention to treat and safety populations

112 patients didn't complete the follow-up :

- n= 42 Death
- n= 28 Consent withdraw
- n= 7 Patient refuse to continue the study
- n= 29 Patient was lost to follow up
- n= 6 Other

Primary outcome at one year

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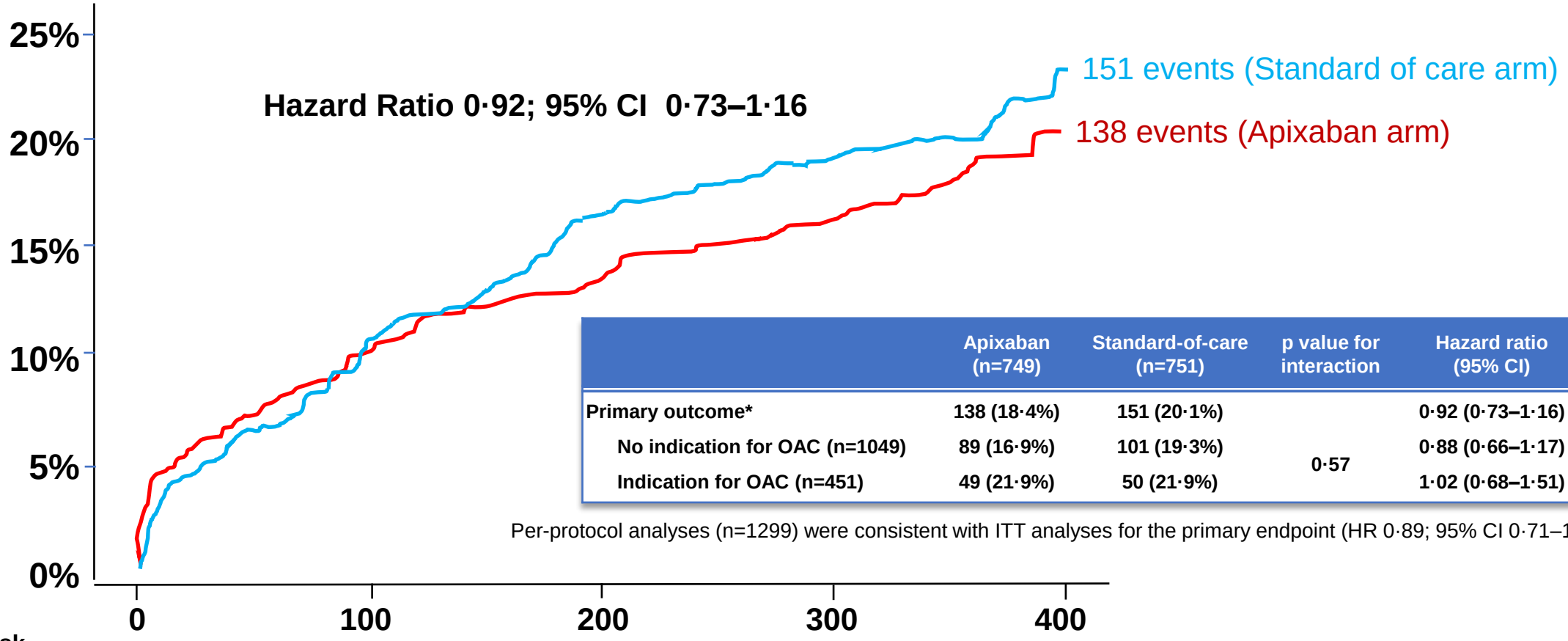
Baseline Characteristics

	Apixaban (n=749)	Standard-of-care (n=751)
Age, years	81·6 (6·1)	82·3 (6·4)
Male	344 (45·9%)	360 (47·9%)
Body mass index, kg/m²†	27·52 (5·45)	27·33 (5·16)
Diabetes mellitus	221 (29·5%)	214 (28·5%)
Hypertension	606 (80·9%)	601 (80·0%)
STS risk score	5·14 (5·02)	5·14 (5·38)
Glomerular filtration rate, mL/min	62·87 (30·75)	61·58 (31·00)
Congestive heart failure	292 (39·0%)	284 (37·8%)
Prior myocardial infarction	83 (11·1%)	90 (12·0%)
Prior PCI	202 (27·0%)	188 (25·0%)
PCI <1 month	38 (5·1%)	36 (4·8%)
Prior CABG	65 (9·1%)	56 (7·8%)
Peripheral artery disease	90 (12·0%)	111 (14·8%)
Prior stroke	78 (10·4%	89 (11·9%)
Atrial fibrillation	212 (28·3%)	199 (26·5%)
CHA_2DS_2VASc score	4·4 (1·4)	4·3 (1·4)

	Apixaban (n=749)	Standard-of-care (n=751)
Pre-TAVI antithrombotic treatment		
VKA	123 (16·4%)	111 (14·8%)
Non-VKA oral anticoagulant	66 (8·8%)	55 (7·3%)
Single antiplatelet therapy	428 (57·1%)	443 (59·0%)
Dual antiplatelet therapy	104 (13·9%)	94 (12·5%)
Procedural characteristics		
Self-expanding Balloon-expanding Valve in valve Mild PVR Moderate to severe PVR	395 (52·8%) 353 (47·2%) 40 (5·3%) 35 (15·4%) 3 (1·3%)	386 (51·5%) 363 (48·5%) 35 (4·7%) 39 (16·6%) 1 (0,4%)
Post-randomization antithrombotic treatment		
Apixaban 2,5mg bid	258 (34·4%)	
Apixaban 5mg bid	491 (65·6%)	
VKA alone		155 (20.6%)
SAPT (single antiplatelet therapy)		112 (14.9%)
DAPT (Dual antiplatelet therapy		427 (56.9%)
DAT (Dual therapy)		54 (7,2%)
Triple therapy		3 (0,4%)

Primary Endpoint (Intent-to-treat)

Time to death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings



	Apixaban (n=749)	Standard-of-care (n=751)	p value for interaction	Hazard ratio (95% CI)
Primary outcome*	138 (18·4%)	151 (20·1%)		0·92 (0·73–1·16)
No indication for OAC (n=1049)	89 (16·9%)	101 (19·3%)	0·57	0·88 (0·66–1·17)
Indication for OAC (n=451)	49 (21·9%)	50 (21·9%)		1·02 (0·68–1·51)

Per-protocol analyses (n=1299) were consistent with ITT analyses for the primary endpoint (HR 0·89; 95% CI 0·71–1·13).

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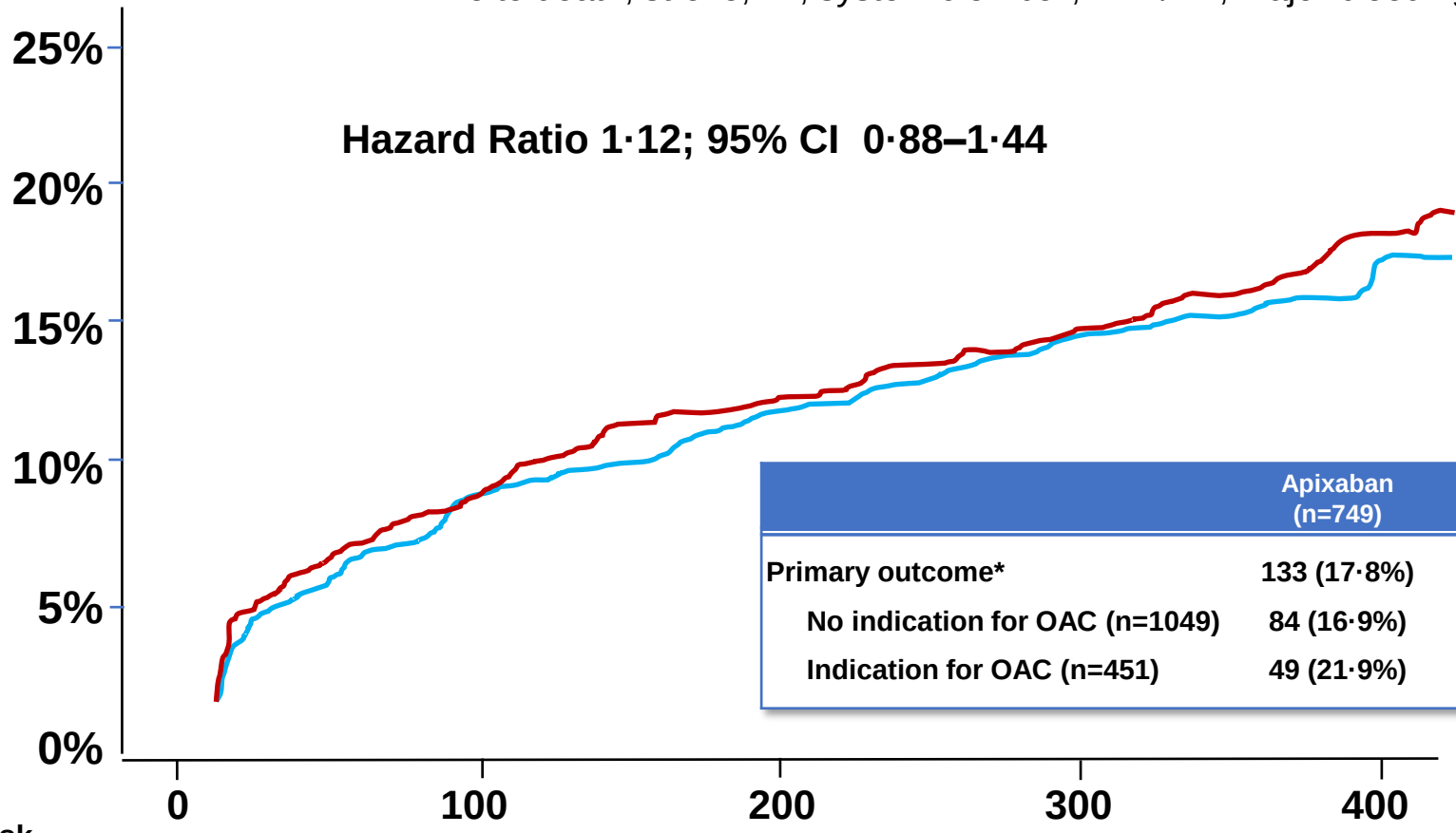
Primary Endpoint without valve thrombosis

(Post-Hoc sensitivity analysis)

Time to death, stroke, MI, systemic emboli, DVT/PE, major bleedings



	Apixaban (n=749)	Standard-of-care (n=751)	p value for interaction	Hazard ratio (95% CI)
Primary outcome*	133 (17·8%)	121 (16·1%)		1·12 (0·88–1·44)
No indication for OAC (n=1049)	84 (16·9%)	73 (13·9%)	0·70	1·16 (0·85–1·60)
Indication for OAC (n=451)	49 (21·9%)	48 (21·9%)		1·06 (0·71–1·58)

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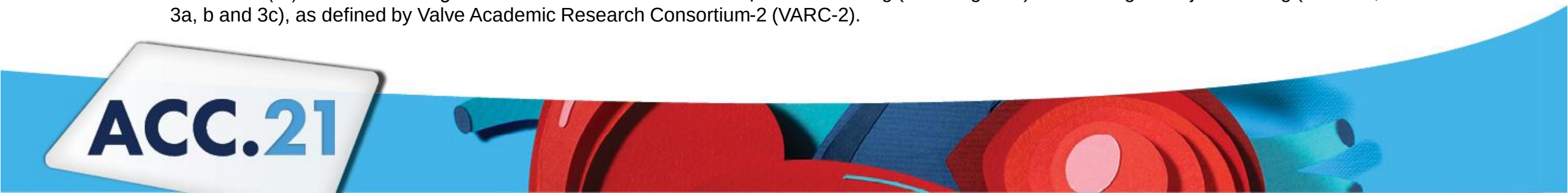
Secondary outcomes

	Apixaban (n=749)	Standard-of-care (n=751)	Hazard ratio (95% CI)
Death, MI, any stroke/TIA	**79 (10·5%)**	**62 (8·26%)**	**1·32 (0·95–1·85)**
Death, any stroke/TIA or systemic embolism	**78 (10·4%)**	**60 (8·0%)**	**1·35 (0·96–1·90)**
Death	**54 (7·2%)**	**41 (5·5%)**	**1·39 (0·92–2·09)**
From cardiovascular causes	38 (5·1%)	28 (3·7%)	1·42 (0·87–2·32)
From non-cardiovascular causes	16 (2·1%)	13 (1·8%)	1·33 (0·63–2·77)
Myocardial infarction	**6 (0·8%)**	**5 (0·7%)**	**1·22 (0·37–4·00)**
Stroke or TIA	**28 (3·7%)**	**21 (2·8%)**	**1·38 (0·78–2·44)**
Systemic embolism	**2 (0·3%)**	**3 (0·4%)**	**0·65 (0·11–3·91)**
Bioprosthetic thrombosis	**8 (1·1%)**	**35 (4·7%)**	**0·23 (0·11–0·50)**
Intracardiac thrombus	**3 (0·4%)**	**3 (0·4%)**	**1·11 (0·22–5·54)**
Deep vein thrombosis or pulmonary embolism	**1 (0·1%)**	**11 (1·5%)**	**0·09 (0·01–0·72)**

Safety analysis

	Apixaban (n=749)	Standard-of-care (n=751)	Hazard ratio (95% CI)
Primary safety endpoint†	64 (8·5%)	64 (8·5%)	1·02 (0·72–1·44)
Life-threatening bleeding	19 (2.5%)	18 (2.4%)	1·06 (0·55–2·02)
Major bleeding	50 (6·7%)	48 (6·4%)	1·07 (0·72–1·59)
Minor bleeding (BARC 2 or 3a)	70 (9·3%)	78 (10·4%)	0·91 (0·66–1·26)
Any bleeding	174 (23·2%)	170 (22·6%)	1·05 (0·85–1·30)

Data are n (%). BARC=Bleeding Academic Research Consortium. †Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, b and 3c), as defined by Valve Academic Research Consortium-2 (VARC-2).

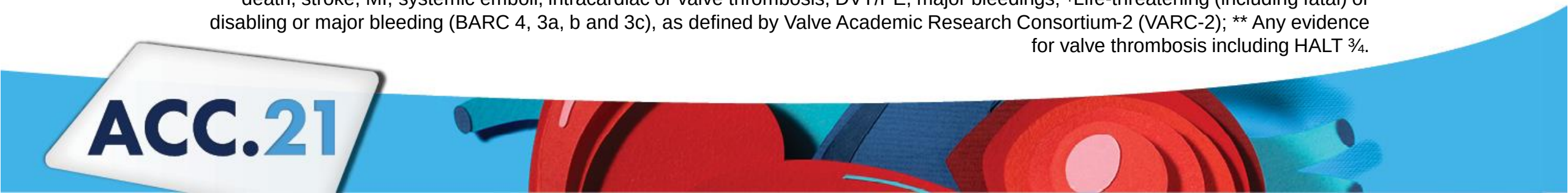


Outcomes in stratum 1 (post-hoc)

Need for oral anticoagulation

	Apixaban (n=223)	Standard of Care (n=228)	Hazard ratio (95% CI)
Primary outcome*	**49 (21·9%)**	**50 (21·9%)**	**1.02 (0.68-1.51)**
Secondary efficacy outcomes			
Death, MI, any stroke/TIA	29 (13·0%)	27 (11·8%)	1.13 (0.67-1.91)
Death, any stroke/TIA or systemic embolism	28 (12·6%)	27 (11·8%)	1.09 (0.64-1.85)
Death	23 (10·3%)	23 (10·1%)	1.04 (0.58-1.86)
Safety outcomes			
Primary safety endpoint†	23 (10·3%)	26 (11·4%)	0.92 (0.52-1.60)
Minor bleeding (BARC 2 or 3a)	21 (9·5%)	27 (10·4%)	0.79 (0.44-1.39)
Any bleeding	59 (26·4%)	58 (25·4%)	1.05 (0.73-1.51)
Any Valve Thrombosis**	**2 (0·9%)**	**3 (1·3%)**	**0.67 (0.11-4.04)**

*death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings; †Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, b and 3c), as defined by Valve Academic Research Consortium-2 (VARC-2); ** Any evidence for valve thrombosis including HALT ¾.

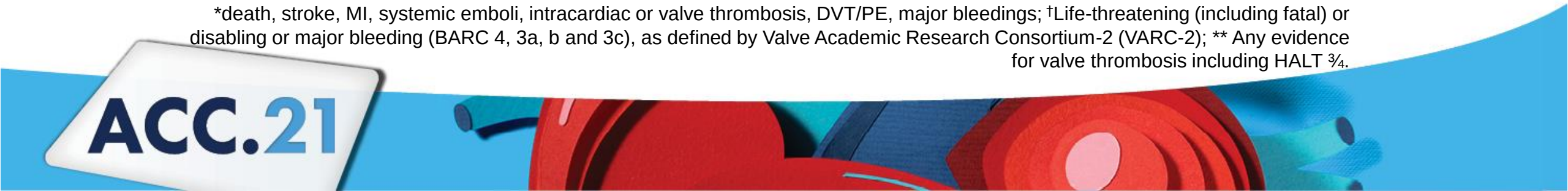


Outcomes in stratum 2 (post-hoc)

No need for oral anticoagulation

	Apixaban (n=526)	Standard of Care (n=523)	Hazard ratio (95% CI)
Primary outcome*	**89 (16·9%)**	**101 (19·3%)**	**0.88 (0.66-1.17)**
Secondary efficacy outcomes			
Death, MI, any stroke/TIA	50 (9·5%)	35 (6·7%)	1.48 (0.96-2.30)
Death, any stroke/TIA or systemic embolism	**50 (9·5%)**	**33 (6·3%)**	**1.56 (1.01-2.43)**
Death	**31 (5·9%)**	**18 (3·4%)**	**1.86 (1.04-3.34)**
• **Cardiovascular death**	**17 (3.2%)**	**13 (2·5%)**	**1·42 (0·69-2·94)**
• **Non cardiovascular death**	**14 (2·66%)**	**5 (0·96%)**	**2·99 (1·07-8·35)**
Safety outcomes			
Primary safety endpoint†	41 (7·8%)	38 (7·3%)	1.09 (0.69-1.69)
Minor bleeding (BARC 2 or 3a)	49 (9·3%)	51 (9·7%)	0.96 (0.65-1.42)
Any bleeding	115 (21·%)	112 (21·8%)	1.04 (0.80-1.35)
Any Valve Thrombosis**	**6 (1·1%)**	**32 (6·1%)**	**0.19 (0.08-0.47)**

*death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings; †Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, b and 3c), as defined by Valve Academic Research Consortium-2 (VARC-2); ** Any evidence for valve thrombosis including HALT ¾.



Limitations

- Open-label trial subject to reporting and ascertainment biases, although outcomes were prespecified and adjudicated by an independent blinded clinical-events committee.

- Apply only to patients who underwent a successful TAVI procedure and not to those scheduled for a TAVI or any other valve procedure.

- ATLANTIS results cannot draw definitive conclusions on efficacy.

Conclusions

- Apixaban after a TAVI procedure is not superior to SOC antithrombotic treatment in terms of net clinical benefit, globally and in each stratum (indication for OAC or not).
- The safety (bleeding) of apixaban is similar to that of current SOC, globally and in each stratum.
- Subclinical valve thrombosis is decreased with apixaban (but not statistically demonstrated) , a reduction driven by the stratum of patients without an indication for anticoagulation.
- A signal on non-cardiovascular mortality is observed only versus antiplatelet therapy in the stratum of patients without an indication for anticoagulation.

Thank you to all patients and ATLANTIS investigators

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