ATLANTIS 4D_CT

Apixaban and Valve Thrombosis after Transcatheter Aortic Valve Implantation: The ATLANTIS-4D-CT Substudy

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

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AMERICAN COLLEGE of CARDIOLOGY

ClinicalTrials.gov number, NCT02664649

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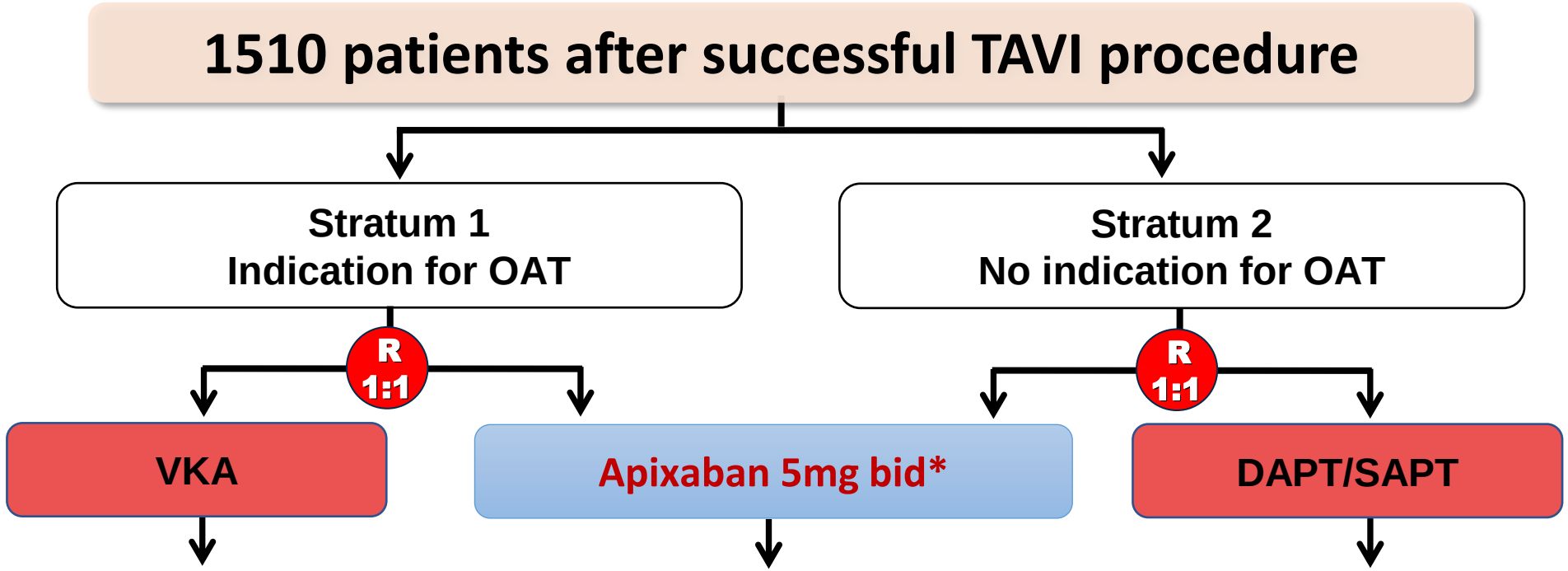
ATLANTIS Study design

Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis



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.

ACC.21

Study organization

Academic Research Organization

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- Pr Eric VICAUT (Méthodologist-statistician)
- Jean-Jacques PORTAL (Independent Statistician)
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Assistance Publique des Hôpitaux de Paris

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Imaging Core Lab

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- Dr Khaoula Bouazizi,
- Dr Mikael Prigent
- Dr Paul Guedeney
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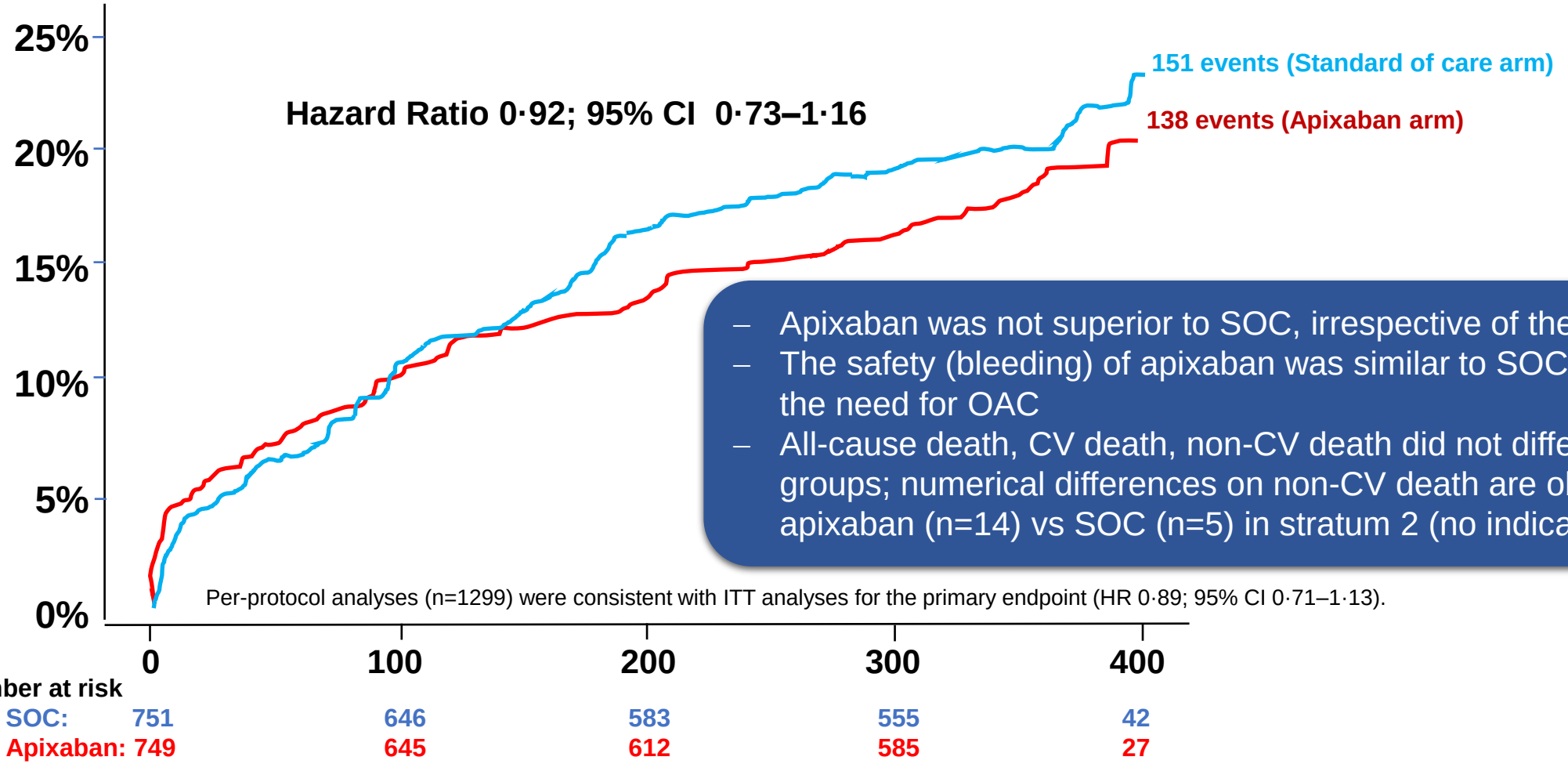
Primary Endpoint (Intent-to-treat)

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



- Apixaban was not superior to SOC, irrespective of the need for OAC
- The safety (bleeding) of apixaban was similar to SOC, irrespective of the need for OAC
- All-cause death, CV death, non-CV death did not differ between the 2 groups; numerical differences on non-CV death are observed with apixaban (n=14) vs SOC (n=5) in stratum 2 (no indication for OAC).

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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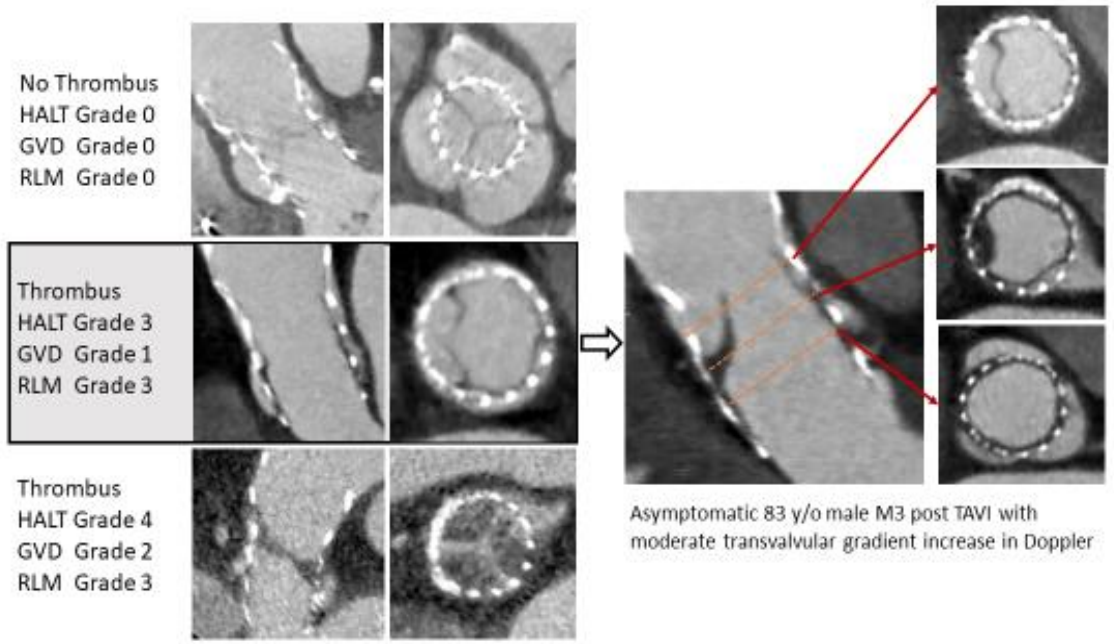
4D-Study Objectives

- Primary study objective → To evaluate the incidence of valve thrombosis at 3-6 months and to determine the effect of apixaban versus standard-of-care.

- Secondary objectives → To determine whether there was an interaction according to the presence of an indication for anticoagulation
  → To evaluate the relationship of valve thrombosis to clinical outcome at one year.

Methodology

- 4D-CT scan was protocol mandated to identify subclinical valve thrombosis, a component of the primary endpoint
- 4D-CT analyses were all independently performed, at the ACTION Group Imaging Core Lab,* by two expert investigators blinded to medical data and randomized treatment assignment.

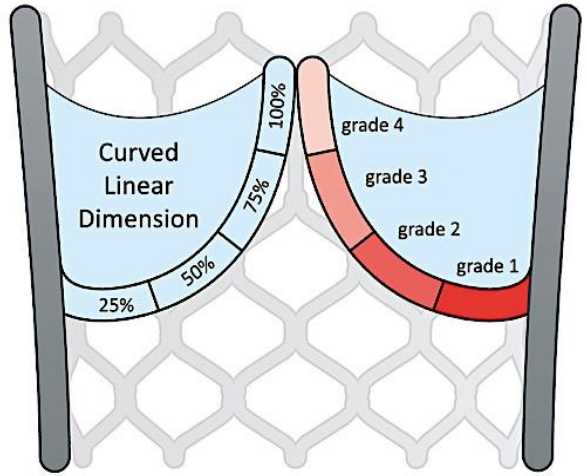


*Pitié-Salpêtrière Hospital, Institute of Cardiometabolism and Nutrition (ICAN) and Laboratoire d'Imagerie Biomédicale (INSERM), Paris, France

Study Methodology – 4DCT analysis

- Reduced leaflet motion (RLM) was defined as:

  - **Grade 0**: normal/unrestricted
  - **Grade 1**: minimally restricted (<25%)
  - **Grade 2**: mildly restricted (25-50%)
  - **Grade 3**: moderately restricted (50-75%)
  - **Grade 4**: largely immobile (>75%)



Blanke P, et al. JACC Cardiovasc Imaging. 2019;12:1-24.

4D-Study endpoints

Primary endpoint

- The percentage of patients with at least one prosthetic valve leaflet with RLM of grade 3 or 4, *or* HALT of grade 3 or 4

Secondary endpoints

- The percentage of patients with a thrombus
- The systolic valve area measured by planimetry in cm^2
- The percentage of patients with RLM ≥ grade 3
- The percentage of patients with (i) death, myocardial infarction, stroke or peripheral embolism, and (ii) death, myocardial infarction, and any stroke/transient ischemic attack at 1 year .

Statistical considerations

- **Sample size for ALTLANTIS-4D-CT** → no specific power calculation for the ATLANTIS-4D-CT substudy as it was part of the study protocol.

- **Primary analyses** → Analyses of the percentage of patients with at least one prosthetic valve leaflet with RLM of grade 3 or 4 or HALT of grade 3 or 4, the percentage of patients with a thrombus on the 4D-CT, and the percentage of patients with RLM 3 or 4 were performed by a multivariate logistic model, with treatment, stratum, interaction treatment x stratum and age as covariables.

- **Secondary analyses**
  - The analysis of global thickening on an ordinal scale was made using an ordinal logistic regression model with the same factors.
  - The analysis of the percentage of valve leaflets with RLM of grade 3 or 4 was performed using a mixed multivariate logistic regression model, with treatment, stratum, interaction treatment x stratum, age and patient as random factors.

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

630 CT not done/received

870 scans collected

108 CT scans not exploitable:
-12 unreadable exams
-84 without multiphase
-12 with missing information

762 CT scans complete for all endpoints

370 patients randomized to apixaban

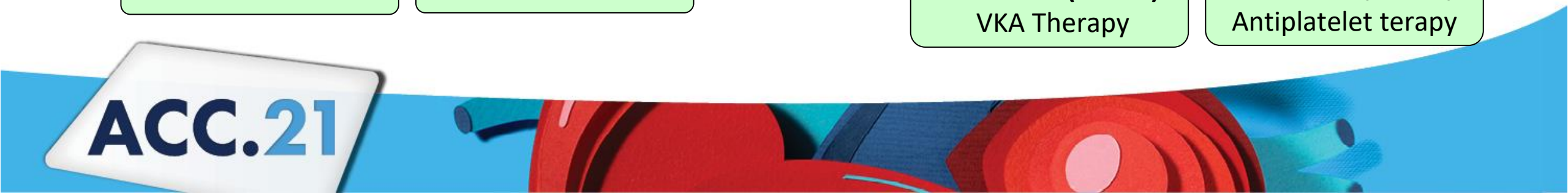
Stratum 1 (n=95)

Stratum 2 (n=275)

392 patients randomized to standard of care

Stratum 1 (n=109)
VKA Therapy

Stratum 2 (n=283)
Antiplatelet terapy

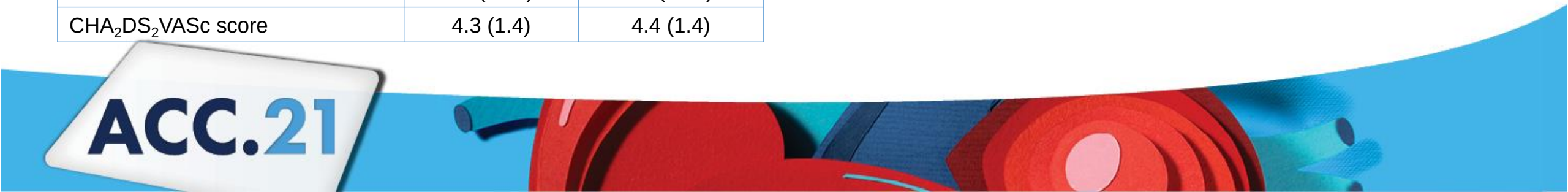


Baseline Characteristics

	Apixaban (n=370)	Standard-of-care (n=392)
Age, years	81·5 (6·1)	82·3 (6·4)
Female	200 (54·1%)	212 (54·1%)
Body mass index, kg/m^2†	27·4 (5·4)	27·1 (4·7)
Diabetes mellitus	110 (29·7%)	114 (29·1%)
Hypertension	294 (79·5%)	301 (79·1%)
STS risk score	4·9 (4·2)	5.0 (4.3)
Glomerular filtration rate, mL/min	62.1 (24.5)	61.8 (25.2)
Congestive heart failure	139 (37.6)	144 (36.7)
Prior myocardial infarction	37 (10.0)	38 (9.7)
Prior PCI	102 (27.6)	95 (24.2)
PCI <1 month	17 (4.6)	20 (5.1)
Prior CABG	31 (8.9)	29 (7.7)
Peripheral artery disease	43 (11.6)	56 (14.3)
Prior stroke	40 (10.8)	51 (13.0)
Atrial fibrillation	94 (25.4)	97 (24.7)
CHA_2DS_2VASc score	4.3 (1.4)	4.4 (1.4)

	Apixaban (n=370)	Standard-of-care (n=392)
Procedural characteristics		
Type of device Self-expanding Balloon-expanding	 200 (54.2) 169 (45.8)	 216 (55.4) 174 (44.6)

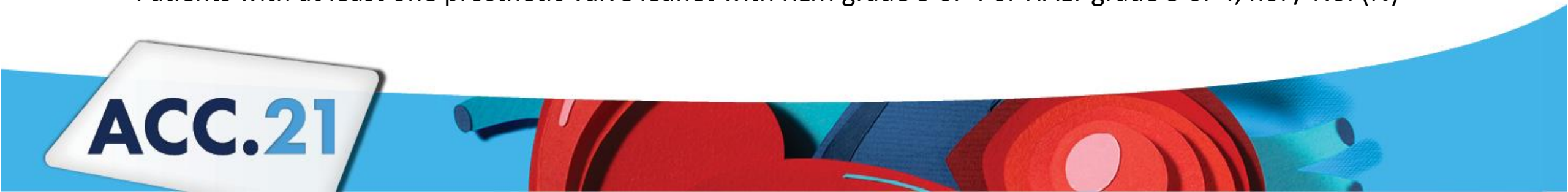
No difference found in baseline characteristics between patients with or without 4D-CT scan performed.



Primary outcome*

	Apixaban (n=379)	Standard-of-care (n=392)	p value for interaction	Odds ratio (95% CI)
Primary outcome* no. / No. (%)	33/370 (8·9%)	51/392 (13·0%)	P_{int}=0.0375	0.65 (0.41-1.04)
No indication for oral anticoagulation (n=558)	24/275 (8·7%)	45/283 (15·9%)	P_{tt}=0.0111	0·51 (0·30–0·86)
Indication for oral anticoagulation (n=204)	9/95 (9·5%)	6/109 (5·5%)	P_{tt}=0.2841	1.80 (0.62 to 5.25)

*Patients with at least one prosthetic valve leaflet with RLM grade 3 or 4 or HALT grade 3 or 4, no. / No. (%)



Main secondary outcome**

	Apixaban (n=379)	Standard-of-care (n=392)	p value for interaction	Odds ratio (95% CI)
Primary outcome* no. / No. (%)	33/370 (8·9%)	51/392 (13·0%)	**P_{int}=0.0375**	**0.65 (0.41-1.04)**
No indication for oral anticoagulation (n=558)	24/275 (8·7%)	45/283 (15·9%)	**P_{tt}=0.0111**	**0·51 (0·30–0·86)**
Indication for oral anticoagulation (n=204)	9/95 (9·5%)	6/109 (5·5%)	**P_{tt}=0.2841**	**1.80 (0.62 to 5.25)**
Main secondary outcome no. / No. (%)**	**5/370 (1·4%)**	**28/392 (7·1%)**	**P_{int}=0.1471**	**0.18 (0·07–0·47)**
No indication for oral anticoagulation (n=558)	**3/275 (1·1%)**	**24/283 (8·5%)**		**0·12 (0·03–0·40)**
Indication for oral anticoagulation (n=204)	**2/95 (2·1%)**	**4/109 (3·7%)**		**0·57 (0·10–3·15)**

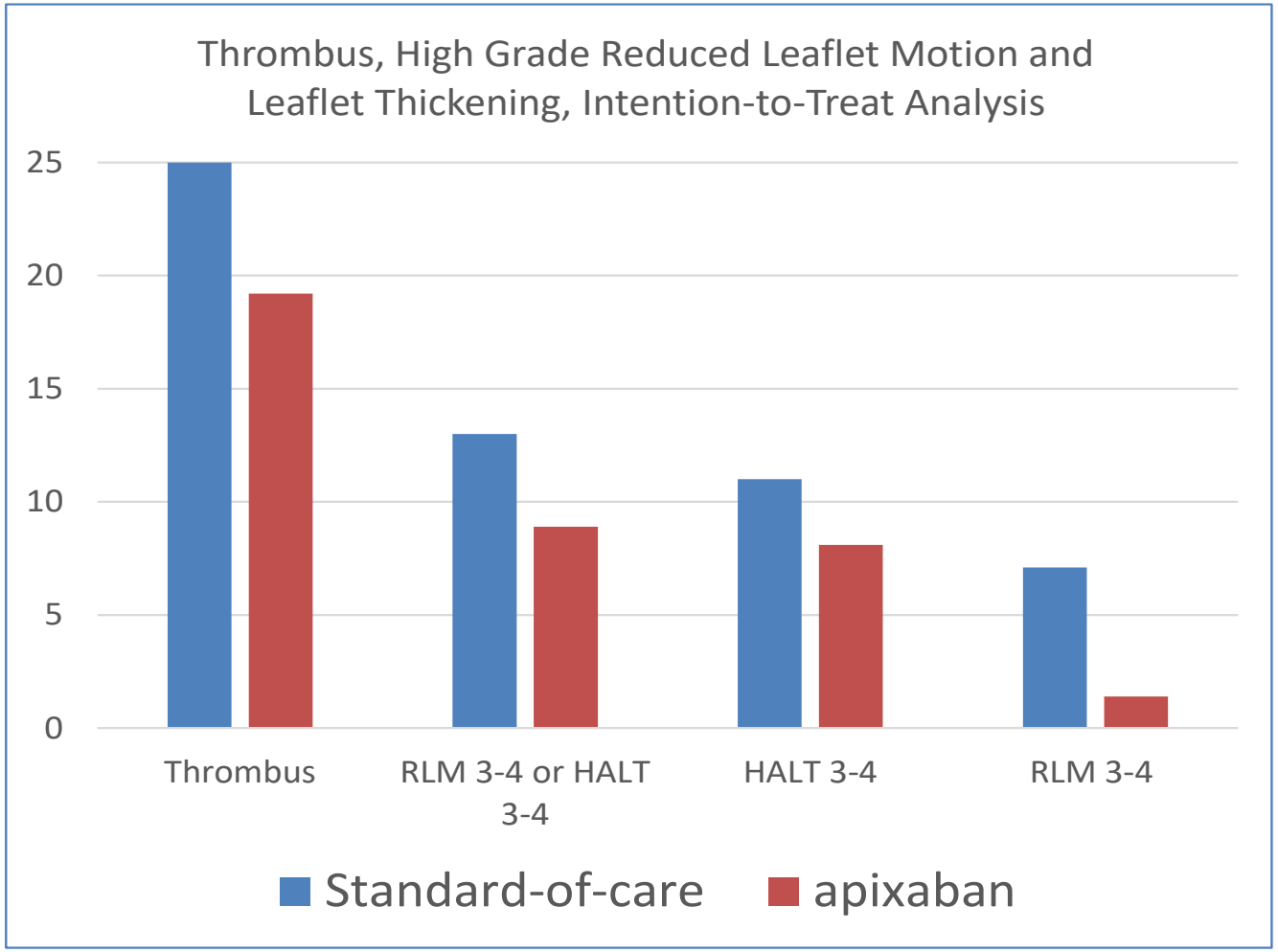
*Patients with at least one prosthetic valve leaflet with RLM grade 3 or 4 or HALT grade 3 or 4,

**Patients with at least one prosthetic valve leaflet with RLM of grade 3 or 4,

Other secondary outcomes

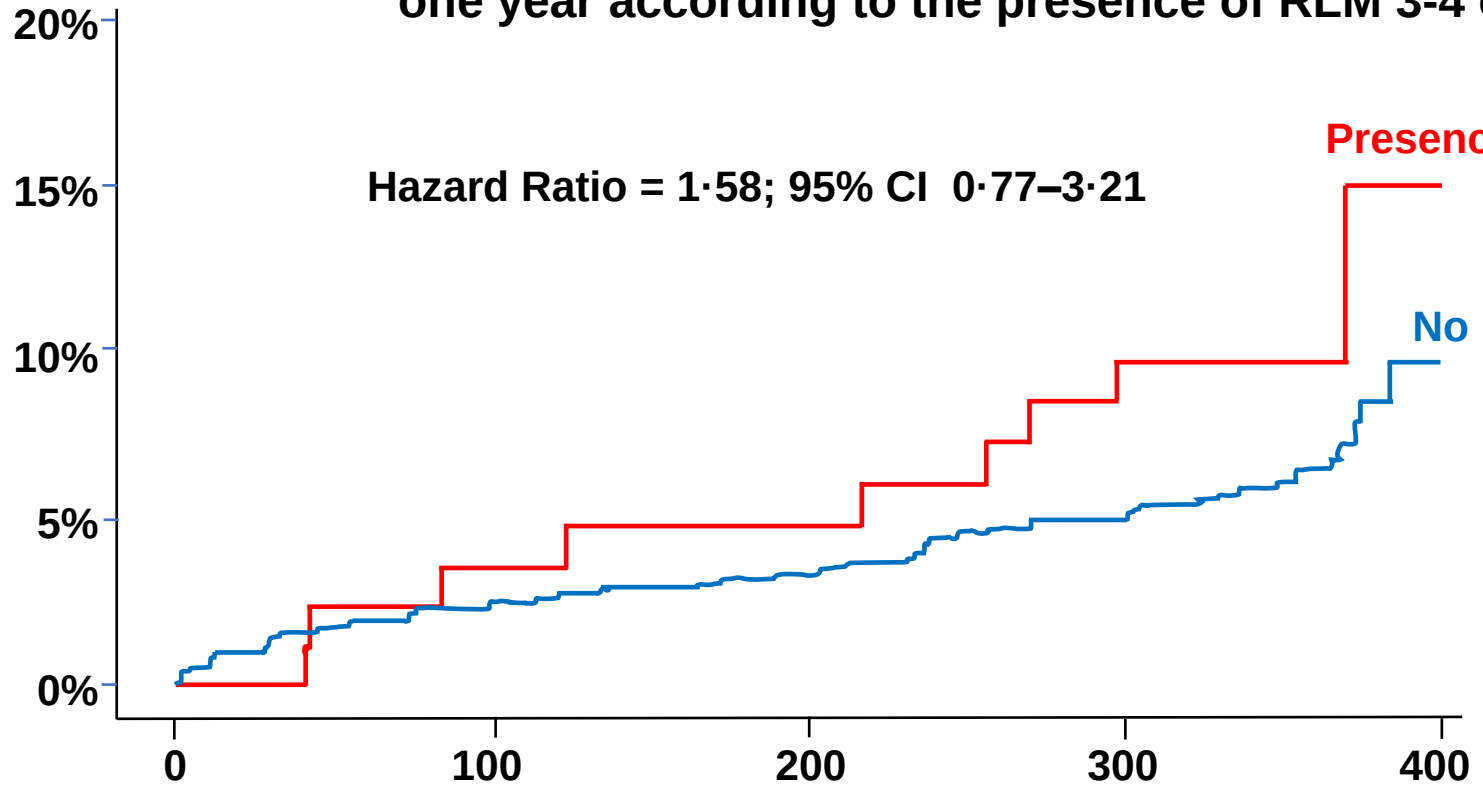
	Apixaban (n=379)	Standard-of-care (n=392)	p value for interaction	Odds ratio (95% CI)
Patients with at least one leaflet with HALT ≥ 3 / No.(%)	30/370 (8·1%)	43/392 (11·0%)	P_{int}=0.0307	**0.72 (0.44-1.16)**
No indication for oral anticoagulation (n=558)	22/275 (8·0%)	39/283 (13·8%)		**0·54 (0·31–0·94)**
Indication for oral anticoagulation (n=204)	8/95 (8·4%)	4/109 (3·7%)		**2·41 (0·70–8·29)**
Patients with the presence of a thrombus no./No.(%)	**71/370 (19·2%)**	**98/392 (25·0%)**	P_{int}=0.011	**0.71 (0.50-1.01)**
No indication for oral anticoagulation (n=558)	**47/275 (17·1%)**	**82/283 (29·0%)**		**0·51 (0·34–0·76)**
Indication for oral anticoagulation (n=204)	**24/95 (25·3%)**	**16/109 (14·7%)**		**1·97 (0·97–3·97)**

Summary of study outcomes



Outcomes according to RLM/HALT

Death, myocardial infarction, stroke of peripheral embolism over one year according to the presence of RLM 3-4 or HALT 4-4



Number at risk					
SOC:	678	659	646	629	34
RELM :	84	80	77	72	3

Patients reaching the primary endpoint at 90 days (RLM 3 or 4 or HALT 3 or 4) had numerically more ischemic events at 1 year (10.7%) than those who did not (7.1%) (HR 1.68; 95% CI 0.82 to 3.44, *P* = NS)

Ischemic outcomes at one year

	Apixaban (n=379)	Standard-of-care (n=392)	Difference (95% CI)	Hazard ratio (95% CI)
Death, myocardial infarction, stroke or peripheral embolism, No. (%)	**32 (8.6)**	**25 (6.4)**	**2.3 (-1.5 to 6.0)**	**1.44 (0.85 to 2.43)**
Death, myocardial infarction, any stroke/TIA, No. (%)	**31 (8.4)**	**23 (5.9)**	**2.5 (-1.1 to 6.2)**	**1.52 (0.88 to 2.61)**

Clinical outcomes did not differ between the two treatment groups

Conclusions

- **Apixaban reduces valve thrombosis** in the majority of patients who undergo TAVI and do not have an established indication for anticoagulation **(vs. antiplatetelet therapy)**

- **This effect is not observed vs. vitamin K antagonist** in the cohort of patients with an indication for anticoagulation

- The **reduction of valve thrombosis at 3 months** with apixaban in the cohort of patients without an indication for oral anticoagulation is **NOT** associated with a clinical benefit at 1 year follow-up.

Thank you to all patients and ATLANTIS investigators

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