



**ACC.21**

# ATLANTIS 4D\_CT

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



[www.action-groupe.org](http://www.action-groupe.org)

Academic Research Organization



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AMERICAN  
COLLEGE of  
CARDIOLOGY

ClinicalTrials.gov number, NCT02664649

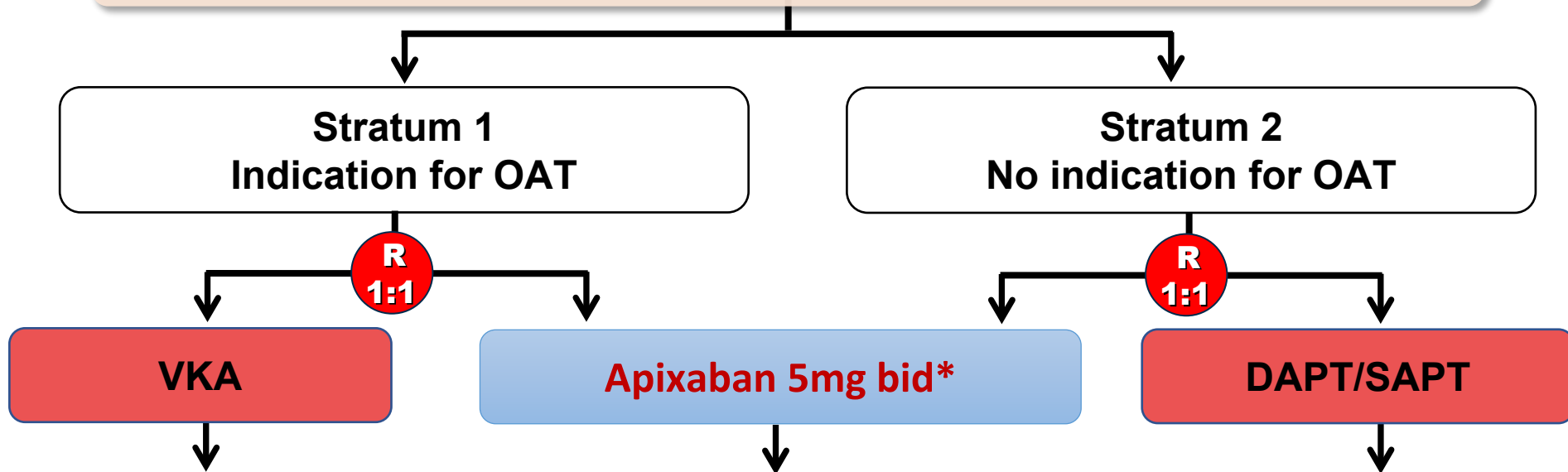


@ActionCoeur

# ATLANTIS Study design

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

**1510 patients after successful TAVI procedure**



**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.

## Academic Research Organization

- Pr Gilles MONTALESCOT (Scientific Director)
- Pr Jean-Philippe COLLET (Principal Investigator)
- Pr Eric VICAUT (Methodologist-statistician)
- Jean-Jacques PORTAL (Independent Statistician)
- Karine BROCHARD (Project Manager)
- Amel CHAMAM (Project Manager)



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## Sponsor



Assistance Publique des Hôpitaux de Paris

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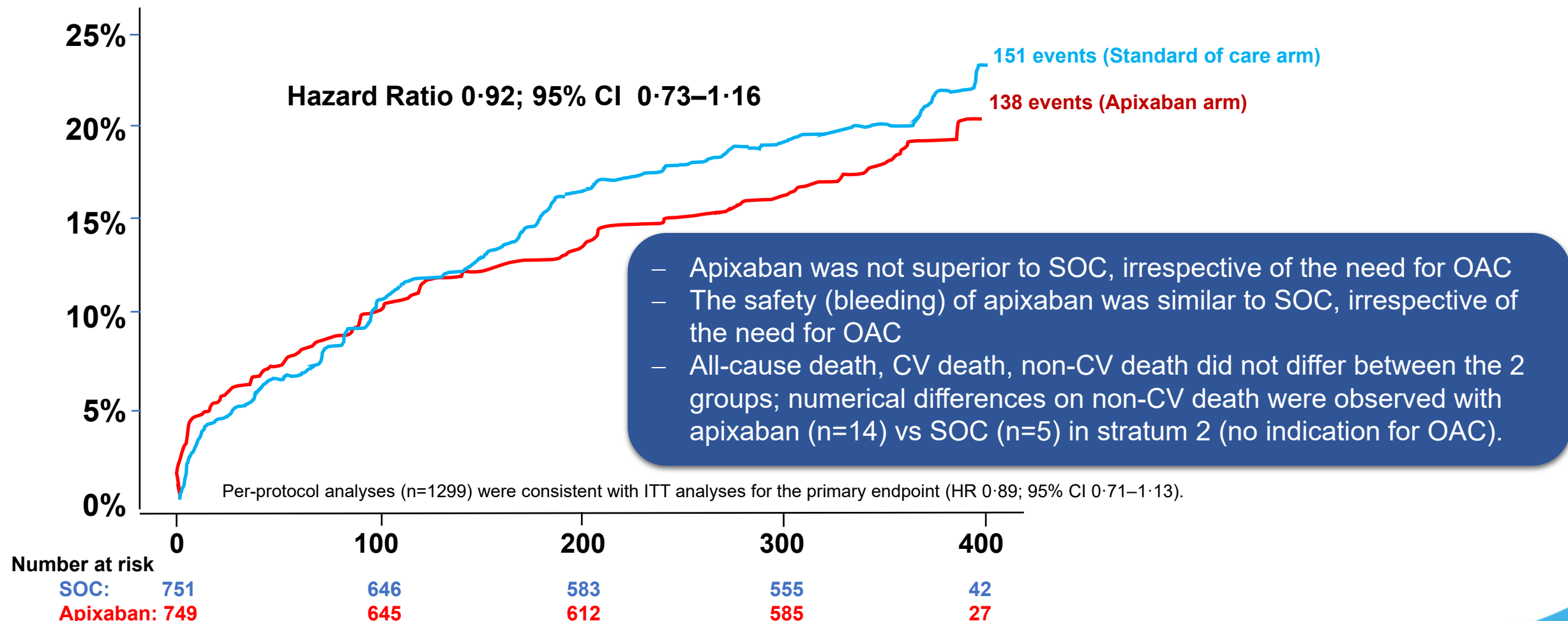
## Imaging Core Lab

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- Dr Etienne Charpentier
- Dr Khaoula Bouazizi,
- Dr Mikael Prigent
- Dr Paul Guedeney
- Dr Tomy Salloum



# Primary Endpoint (Intent-to-treat)

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

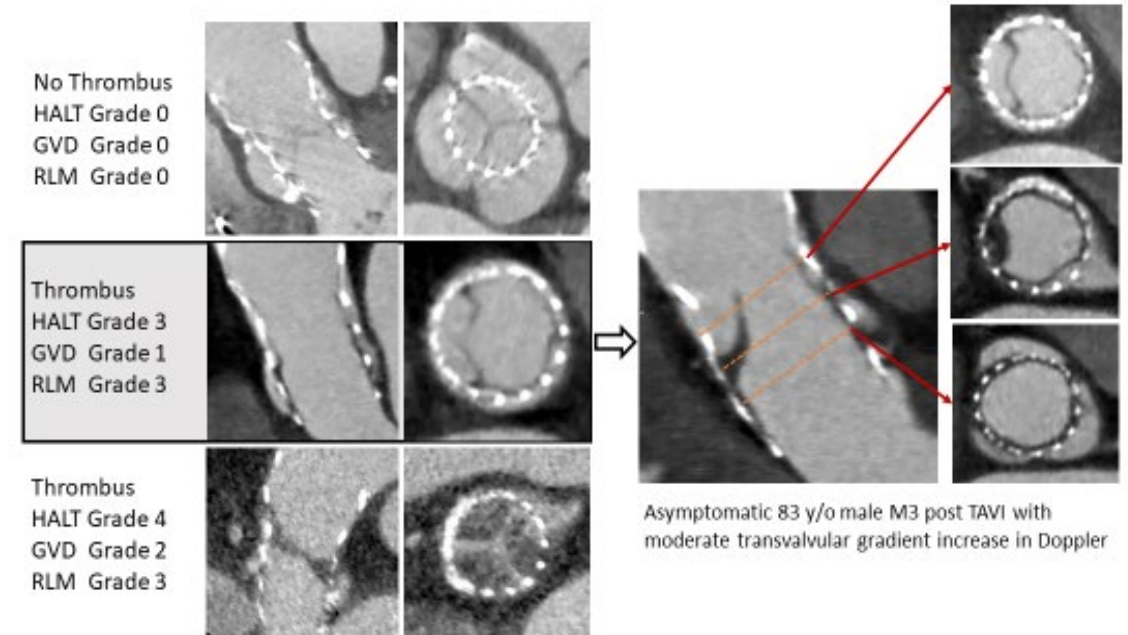


# 4D-Study Objectives

- **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.

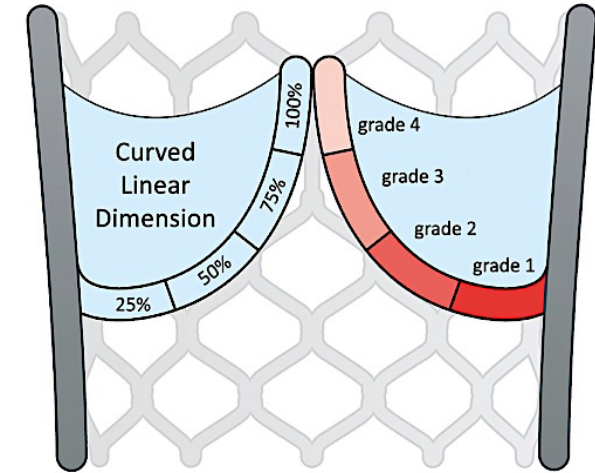
- 4D-CT scan was protocol mandated to identify subclinical valve thrombosis, a component of the primary endpoint
- 4D-CT analyses were all independently performed, at the ACTION Group Imaging Core Lab,\* by two expert investigators blinded to medical data and randomized treatment assignment.

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



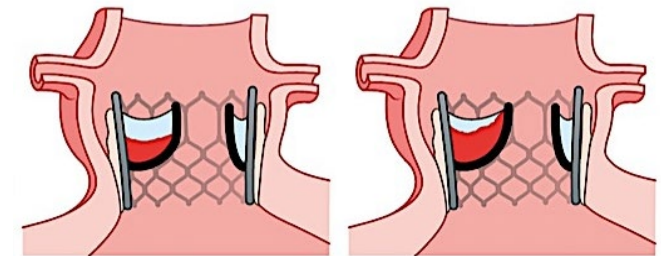
➤ Reduced leaflet motion (RLM) was defined as:

- **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.

➤ Hypoattenuated leaflet thickening (HALT) was defined as visually identifiable increased leaflet thickness on contrast-enhanced multi-planar reformats, and graded from 0 to 4.





## **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<sup>2</sup>
- The percentage of patients with RLM  $\geq$  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 .



- **Sample size for ATLANTIS-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 therapy

# 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 <sup>2</sup> †	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 <sub>2</sub> DS <sub>2</sub> VASc score	4.3 (1.4)	4.4 (1.4)

	Apixaban (n=370)	Standard-of-care (n=392)
<b>Procedural characteristics</b>		
Type of device		
Self-expanding	200 (54.2)	216 (55.4)
Balloon-expanding	169 (45.8)	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%)	<b><math>P_{int}=0.0375</math></b>	<b>0.65 (0.41-1.04)</b>
No indication for oral anticoagulation (n=558)	24/275 (8·7%)	45/283 (15·9%)	$P_{tt}=0.0111$	<b>0·51 (0·30–0·86)</b>
Indication for oral anticoagulation (n=204)	9/95 (9·5%)	6/109 (5·5%)	$P_{tt}=0.2841$	<b>1.80 (0.62 to 5.25)</b>

\*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)
<b>Primary outcome* no. / No. (%)</b>	33/370 (8·9%)	51/392 (13·0%)	<b>P<sub>int</sub>=0.0375</b>	<b>0.65 (0.41-1.04)</b>
<b>No indication for oral anticoagulation (n=558)</b>	24/275 (8·7%)	45/283 (15·9%)	<b>P<sub>tt</sub>=0.0111</b>	<b>0·51 (0·30–0·86)</b>
<b>Indication for oral anticoagulation (n=204)</b>	9/95 (9·5%)	6/109 (5·5%)	<b>P<sub>tt</sub>=0.2841</b>	<b>1.80 (0.62 to 5.25)</b>
<b>Main secondary outcome** no. / No. (%)</b>	<b>5/370 (1·4%)</b>	<b>28/392 (7·1%)</b>	<b>P<sub>int</sub>=0.1471</b>	<b>0.18 (0·07–0·47)</b>
<b>No indication for oral anticoagulation (n=558)</b>	<b>3/275 (1·1%)</b>	<b>24/283 (8·5%)</b>		<b>0·12 (0·03–0·40)</b>
<b>Indication for oral anticoagulation (n=204)</b>	<b>2/95 (2·1%)</b>	<b>4/109 (3·7%)</b>		<b>0·57 (0·10–3·15)</b>

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

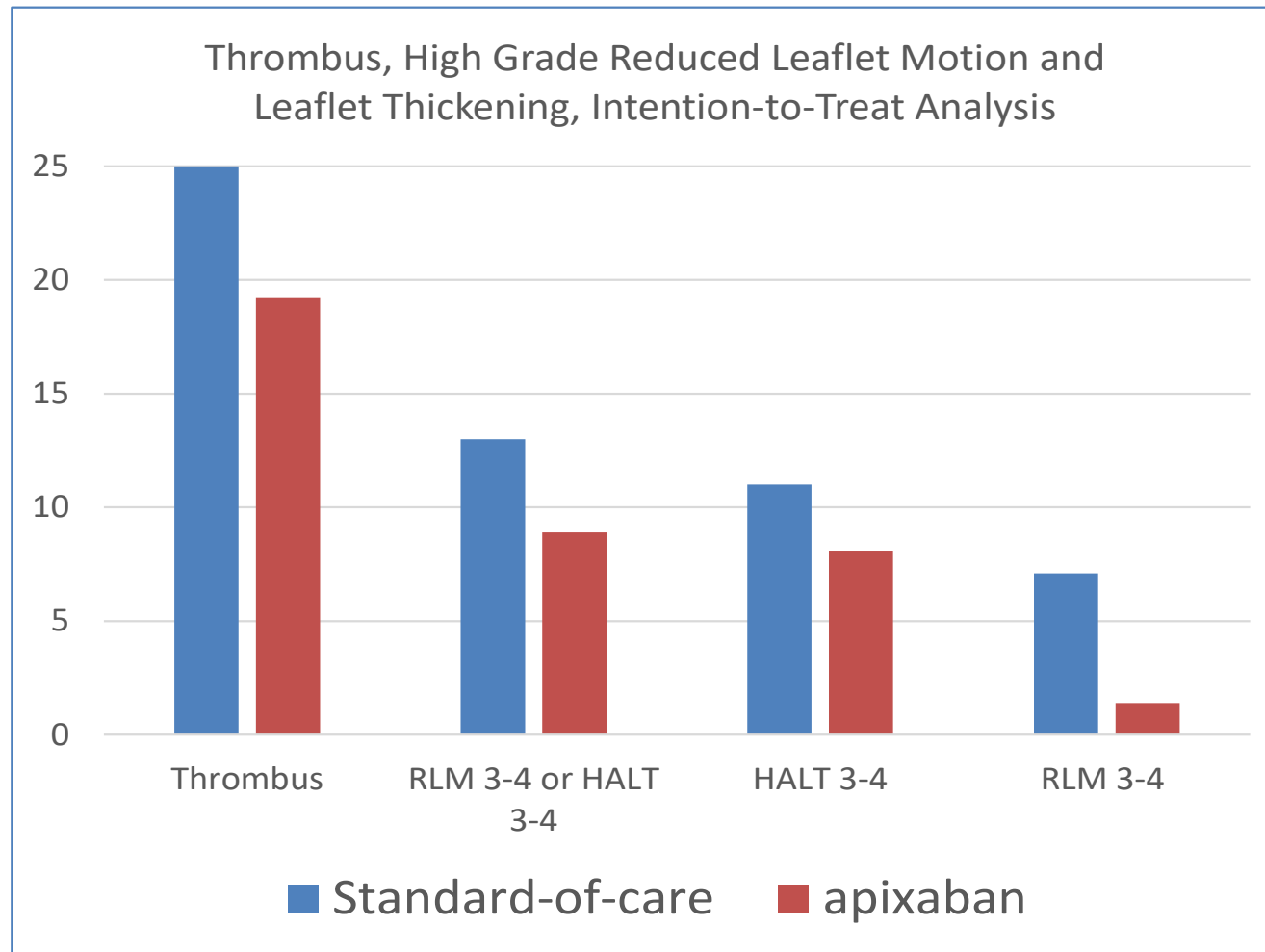
\*\*Patients with at least one prosthetic valve leaflet with RLM of grade 3 or 4,

# Other secondary outcomes

	Apixaban (n=379)	Standard-of-care (n=392)	p value for interaction	Odds ratio (95% CI)
<b>Patients with at least one leaflet with HALT <math>\geq 3</math> / No.(%)</b>	30/370 (8.1%)	43/392 (11.0%)	<b><math>P_{int}=0.0307</math></b>	<b>0.72 (0.44-1.16)</b>
No indication for oral anticoagulation (n=558)	22/275 (8.0%)	39/283 (13.8%)		<b>0.54 (0.31-0.94)</b>
Indication for oral anticoagulation (n=204)	8/95 (8.4%)	4/109 (3.7%)		<b>2.41 (0.70-8.29)</b>
<b>Patients with the presence of a thrombus no./No.(%)</b>	<b>71/370 (19.2%)</b>	<b>98/392 (25.0%)</b>	<b><math>P_{int}=0.011</math></b>	<b>0.71 (0.50-1.01)</b>
No indication for oral anticoagulation (n=558)	<b>47/275 (17.1%)</b>	<b>82/283 (29.0%)</b>		<b>0.51 (0.34-0.76)</b>
Indication for oral anticoagulation (n=204)	<b>24/95 (25.3%)</b>	<b>16/109 (14.7%)</b>		<b>1.97 (0.97-3.97)</b>

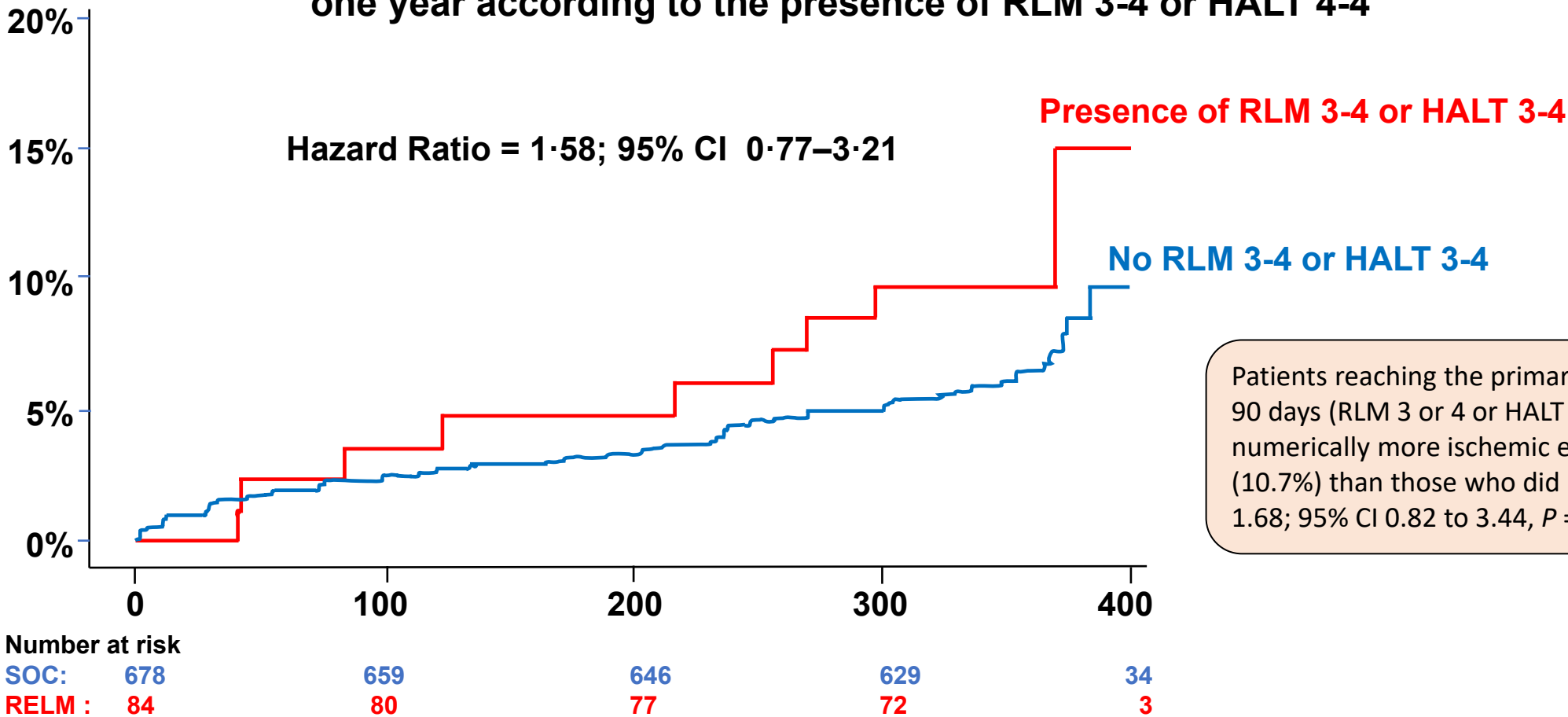


# Summary of study outcomes



# Outcomes according to RLM/HALT

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



# 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. antiplatelet 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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