
# 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

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AMERICAN COLLEGE of CARDIOLOGY

ClinicalTrials.gov number, NCT02664649

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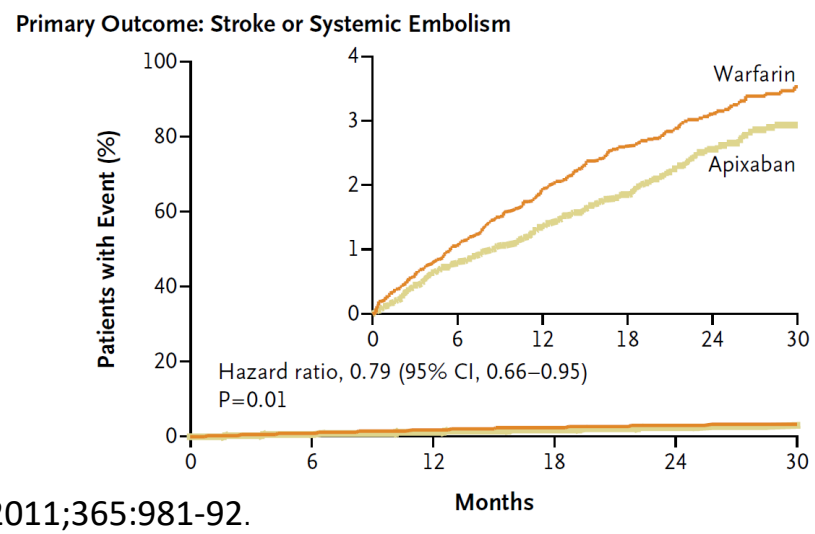
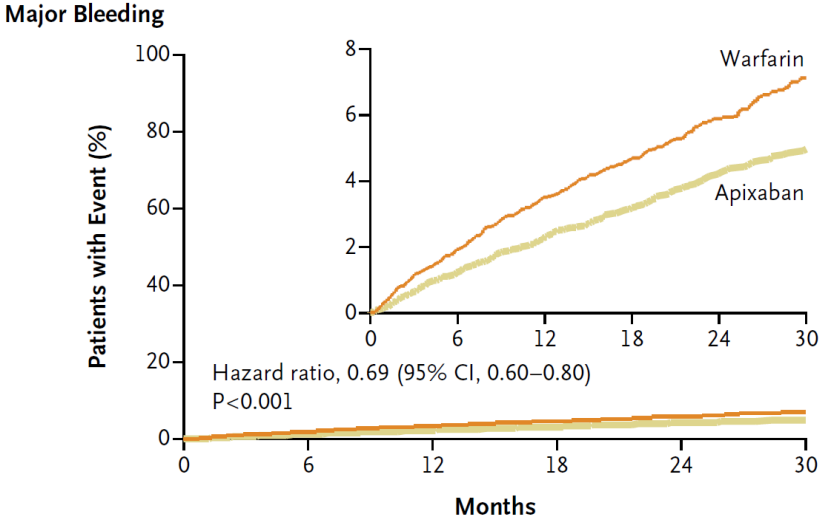
# Background

- 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



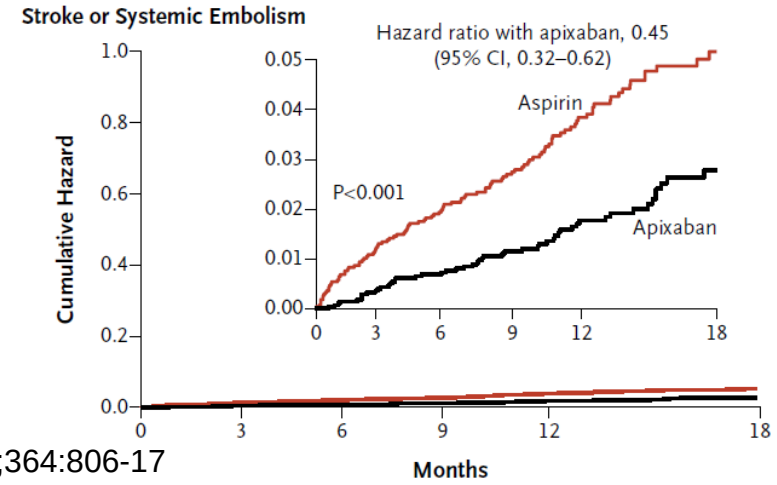



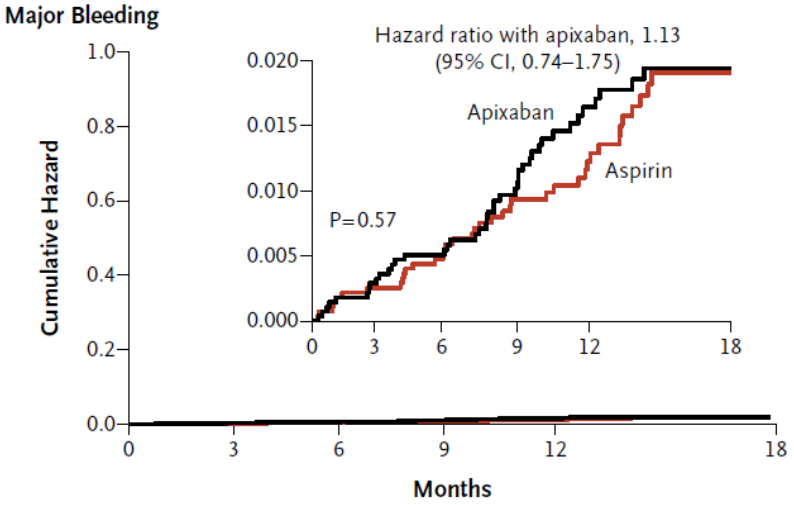

N Engl J Med 2011;365:981-92.

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)
- Jean-Jacques PORTAL (Independent Statistician)
- Karine BROCHARD (Project Manager)
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- Pr Eric VICAUT (Paris, France )
- Pr Eric VAN BELLE (Lille, France)
- Pr Franz-Joseph NEUMANN (Bad Krozingen,Germany)
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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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## Clinical Events Committee

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- Dr Pierre AUBRY
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# 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**mplantation for Aortic **S**tenosis

**1510 patients after successful TAVI procedure**

| Stratum 1<br>Indication for OAT | | Stratum 2<br>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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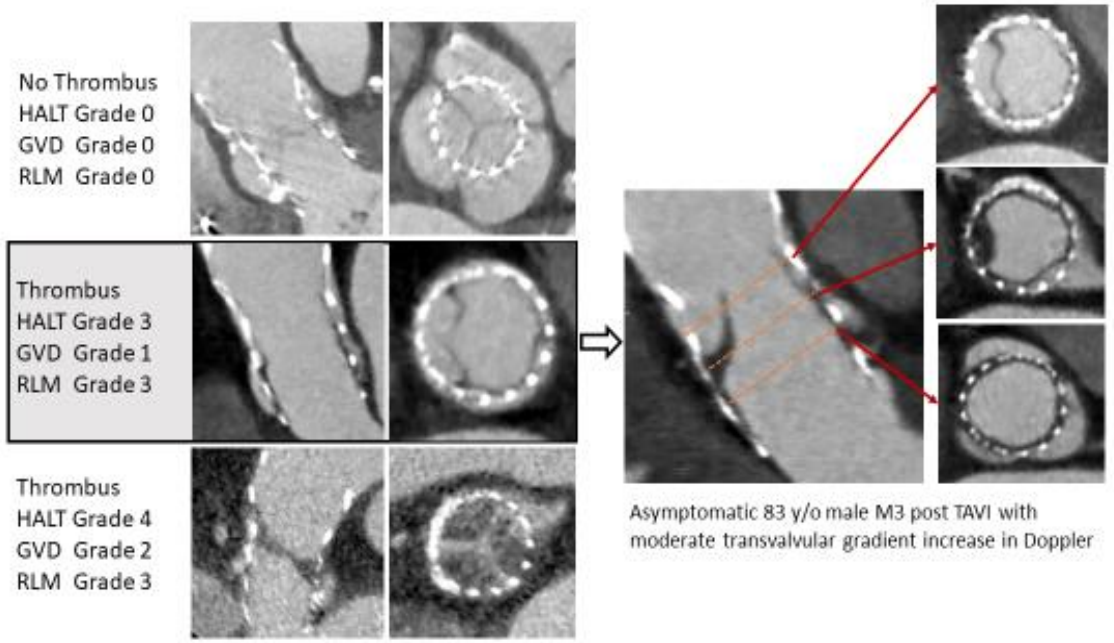
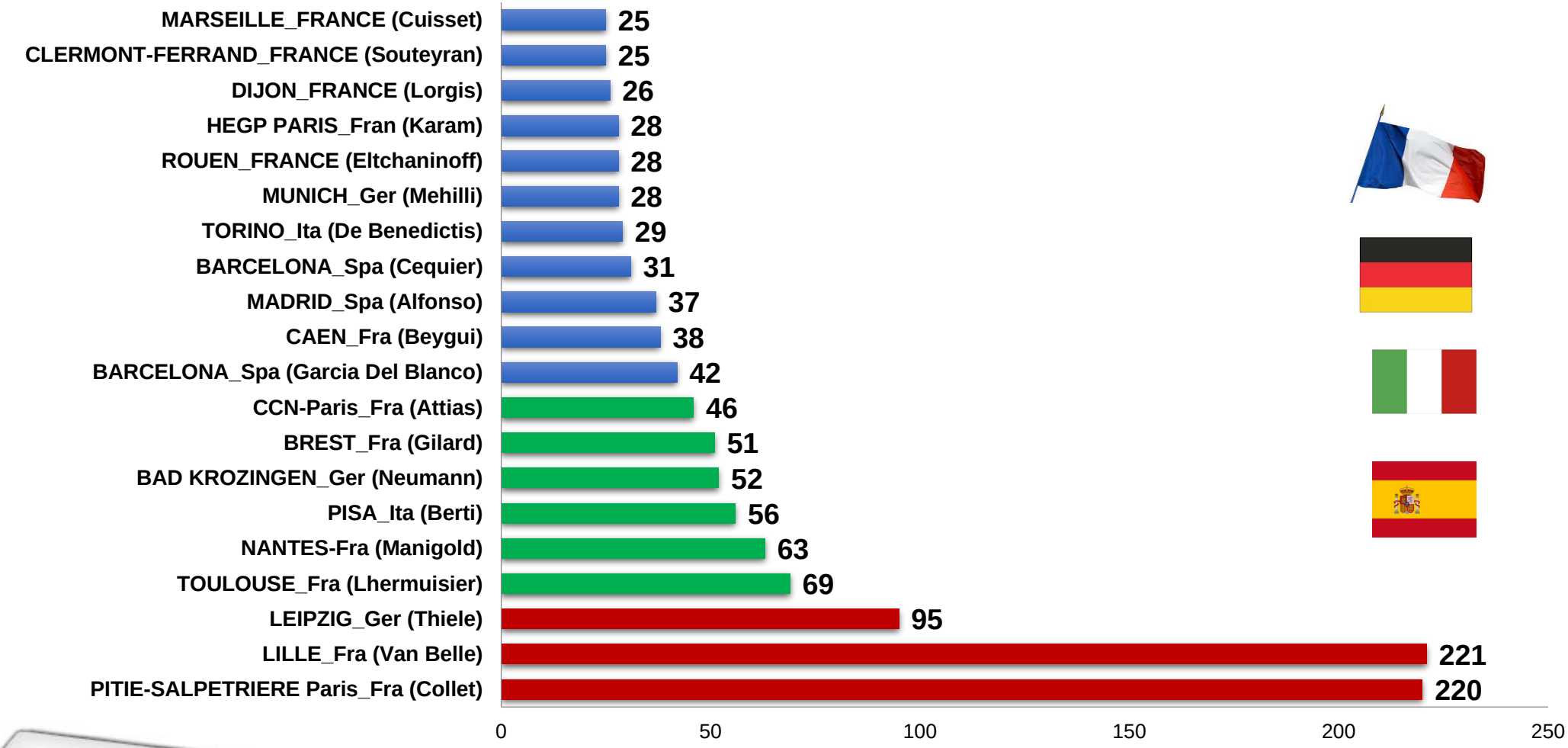
# CT and ECHO evaluation of subclinical leaflet thrombosis

- 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

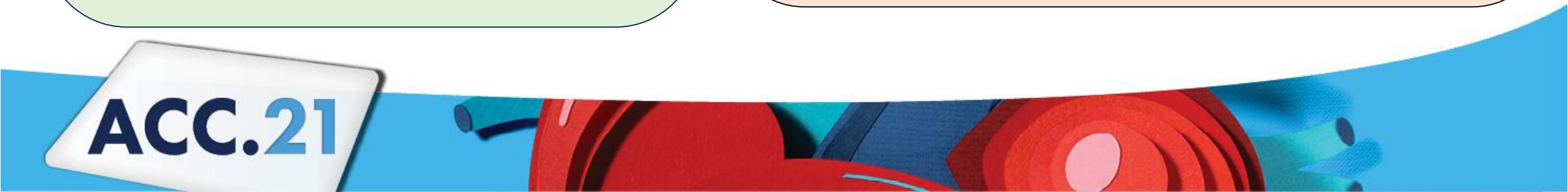
# Key Inclusion and exclusion criteria

## 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

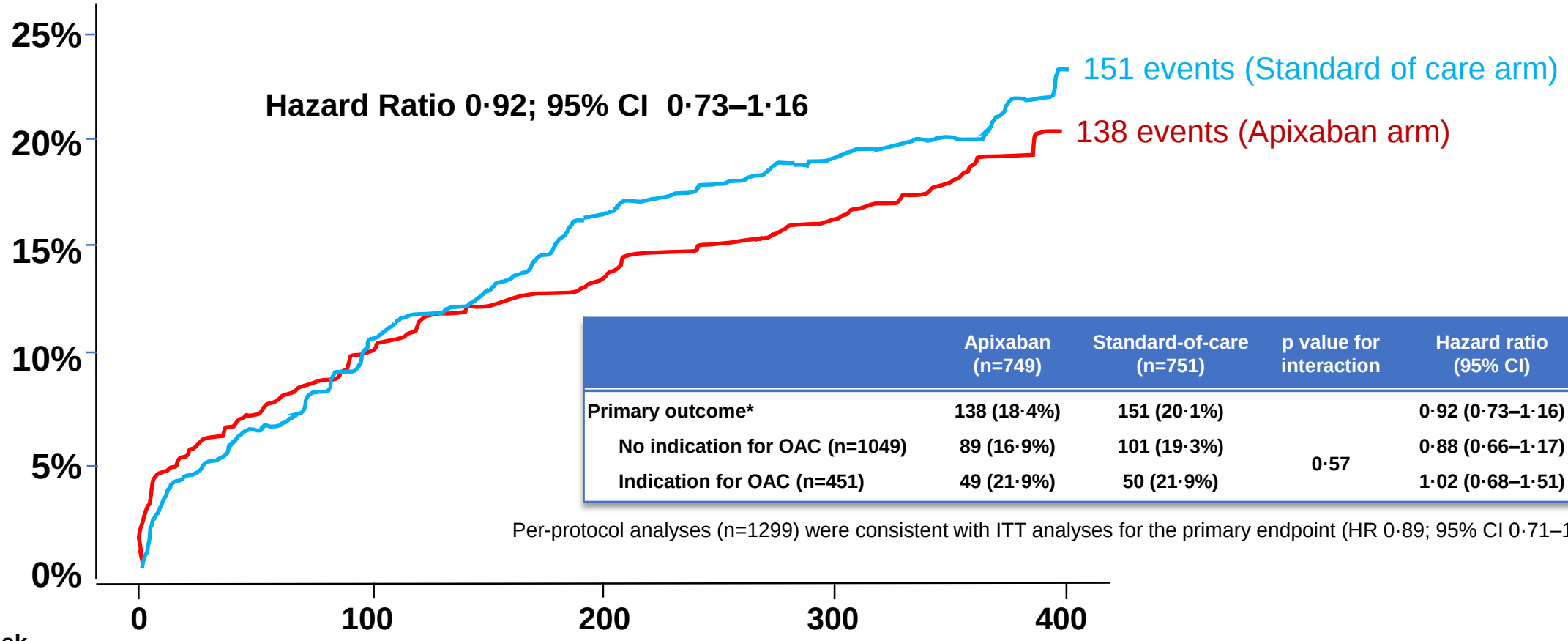
# Baseline Characteristics

| | 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/m$^2$† | 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<br>Balloon-expanding<br>Valve in valve<br>Mild PVR<br>Moderate to severe PVR | 395 (52·8%)<br>353 (47·2%)<br>40 (5·3%)<br>35 (15·4%)<br>3 (1·3%) | 386 (51·5%)<br>363 (48·5%)<br>35 (4·7%)<br>39 (16·6%)<br>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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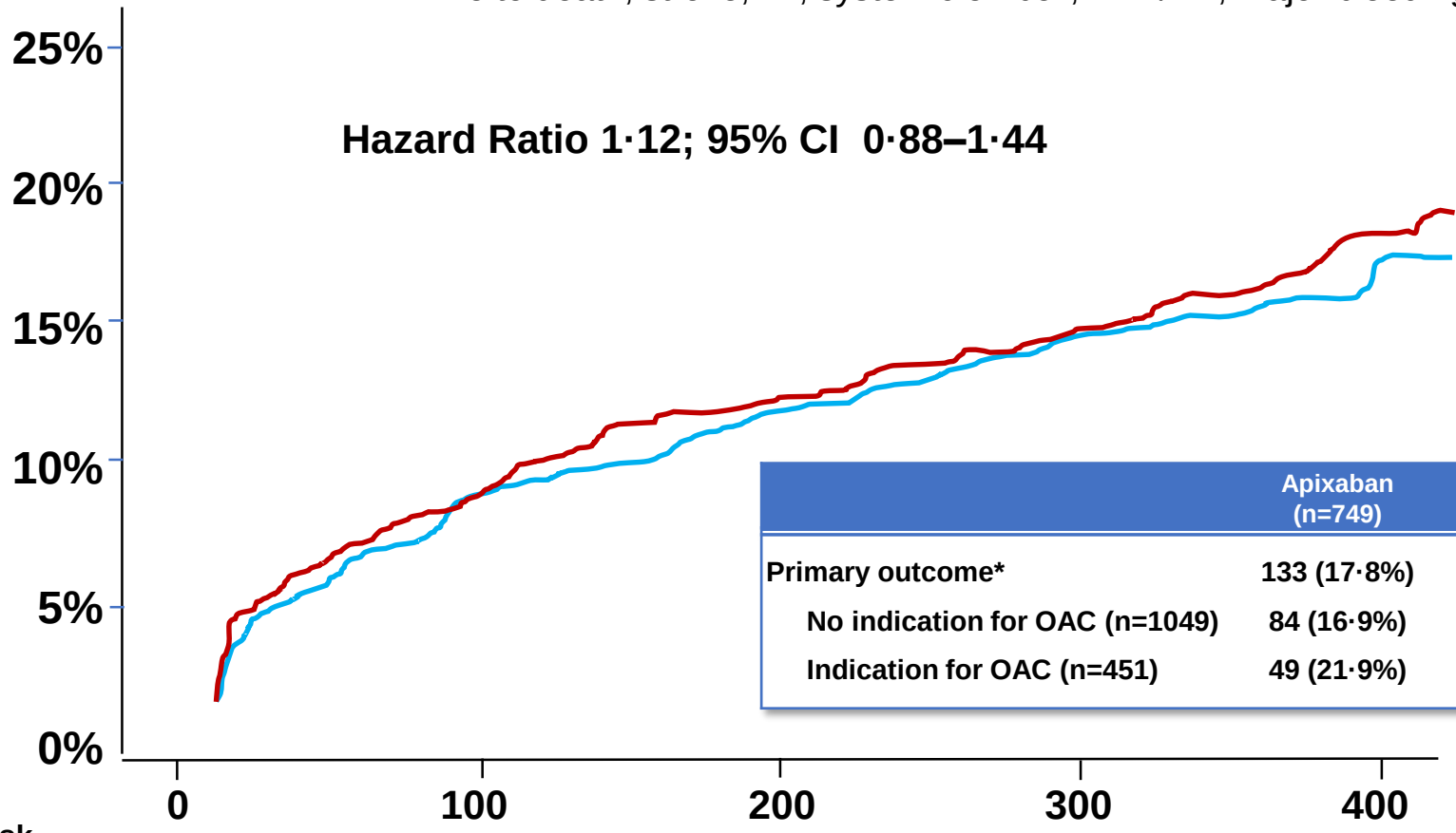
# Primary Endpoint without valve thrombosis

## (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) |

**Number at risk**

| | | | | | |
|---|---|---|---|---|---|
| SOC: | 751 | 656 | 615 | 584 | 43 |
| Apixaban: | 749 | 651 | 617 | 589 | 27 |

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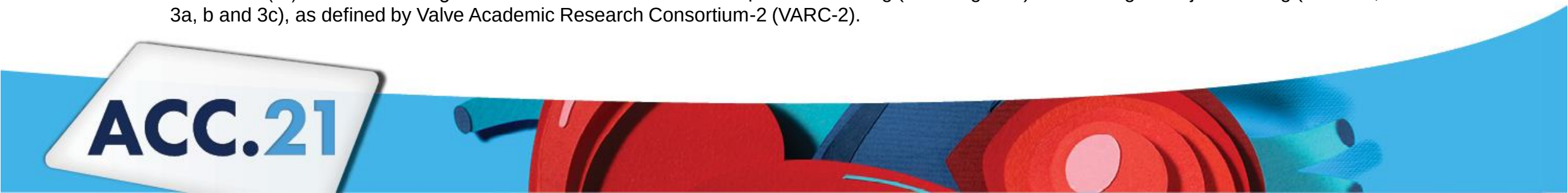
# Secondary outcomes

| | 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).

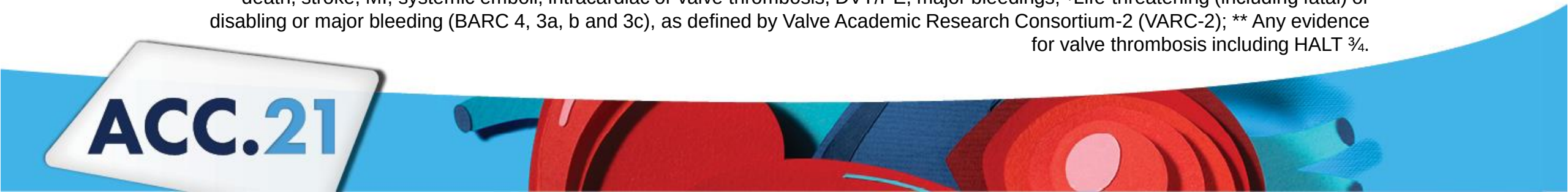


# Outcomes in stratum 1 (post-hoc)

## 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.

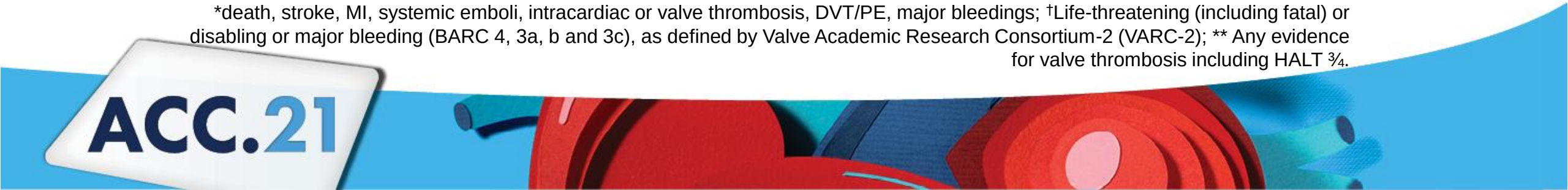


# Outcomes in stratum 2 (post-hoc)

## 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


Investigators from France

Jean-Philippe COLLET, Olivier BARTHELEMY, Rémi CHOUSSAT, Johanne SILVAIN, Pierre SABOURET, Richard ISNARD, Amel MAMERI, Florent HUANG, Lise LEGRAND, Lionel LEROUX, Pierre COSTE, Hervé LE BRETON, Dominique BOULMIER, Marc BEDUSSA, Vincent AUFFRET, Guillaume LEURENT, François SCHIELE, Nicolas MENEVEAU, Benoit GUILLON, Farzin BEYGUI, Rémi SABATIER, Mathieu BIGNON, Katrien BLANCHART, Clément BRIET, Adrien LEMAITRE, Pierre ARDOUIN, Vincent ROULE, Eric VAN BELLE, Flavien VINCENT, Hugues SPILLEMAEKER, Basile VERDIER, Francis JUTHIER, Cédric DELHAYE, Thibault LHERMUSIER, Didier CARRIE, Nicolas BOUDOU, Francisco CAMPELO-PARADA, Frédéric BOUISSET, Guillaume CAYLA, Laurent SCHMUTZ, Benoit LATTUCA, Hélène ELTCHANINOFF, Eric DURAND, Nicolas BETTINGER, Najime BOUHZAM, Thierry LEFEVRE, Bernard CHEVALIER, Hakim BENAMER, Philippe GAROT, Stéphanie CHAMPAGNE, Thierry UNTERSEEH, Antoinette NEYLON, Martine GILARD, Romain DIDIER, Pierre-Philippe NICOL, Christophe CAUSSIN, Géraud SOUTEYRAND, Nicolas COMBARET, Guillaume CLERFOND, Dominique HIMBERT, Marina URENA-ALCAZAR, Jérémie ABTAN, Thibaut MANIGOLD, Vincent LETOCART, Julien PLESSIS, Matthieu WARGNY, Juan Pablo MAUREIRA, Mazen ELFARRA, Thierry FOLLIGUET, Gilles RIOUFOL, Gérard FINET, Guillaume CELLIER, Florence LECLERCQ, Jean-Christoph MACIA, Delphine DELSENY, Thomas CUISSET, Pierre DEHARO, Nicolas JAUSSAUD, Marc LAMBERT, Stéphane CHASSAING, Didier BLANCHARD, Christophe BARBEY, Marc-Antoine ARNOULD, Olivier BAR, Nicolas DUMONTEIL, Didier TCHECHE, Nicole KARAM, Christian SPAULDING, Alain HAGEGE, Luc LORGIS, Philippe BUFFET, Thomas GOLDEN-BABE, David ATTIAS, Florent LAVEAU, Julien DREYFUS, Olivier VARENNE, Fabien PICARD, Alexandre LAFONT, Maximilien SOCHALA, Philippe DEGRELL, Olivier MOREL, Patrick OHLMANN, Karl ISAAZ, Sarah BALICHARD, Antoine GERBAY, Alexis CERISIER, Benjamain HABER, Said GHOSTINE

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