

**ACC.21**

# 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



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



Jean-Philippe Collet, Eric Van Belle, Holger Thiele, Jean-Jacques Portal, Eric Vicaut, and Gilles Montalescot, for the ATLANTIS Investigators of the ACTION Group.



AMERICAN  
COLLEGE of  
CARDIOLOGY

ClinicalTrials.gov number, NCT02664649

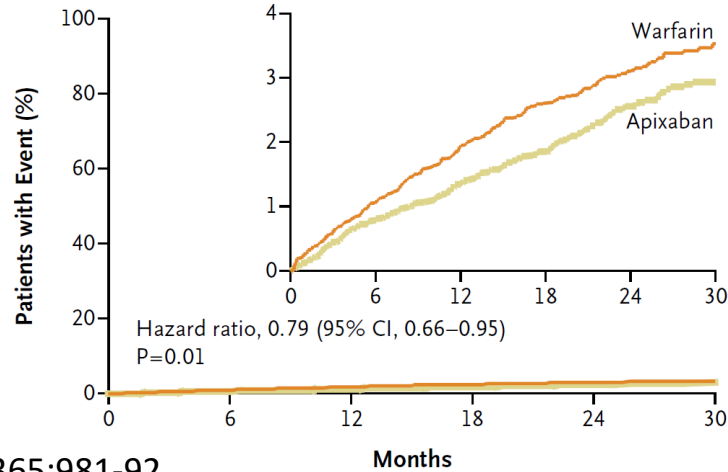


@ColletJeanphil1

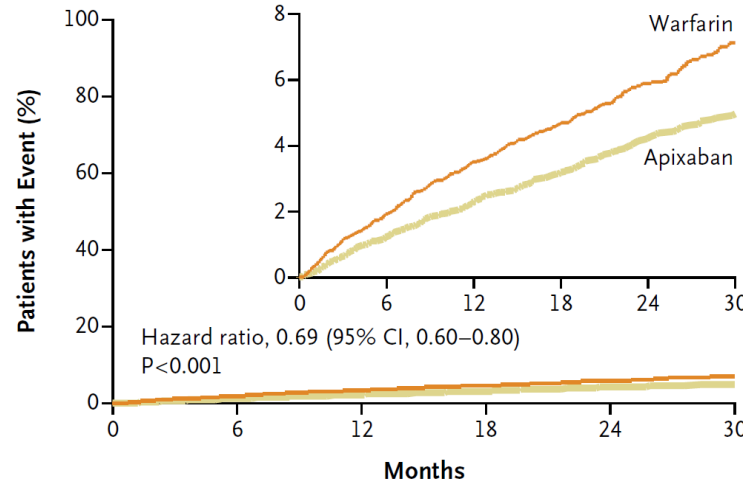
- Post-procedural thrombotic and bleeding events are frequent and negatively affect short-term survival.
- Thrombus formation on the implanted bioprosthesis adds to the potential hazards of TAVI.
- **SAPT alone** if no need for OAC and absence of recent stent implantation **is the safest option.**
- **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.

ARISTOTLE

Primary Outcome: Stroke or Systemic Embolism



Major Bleeding



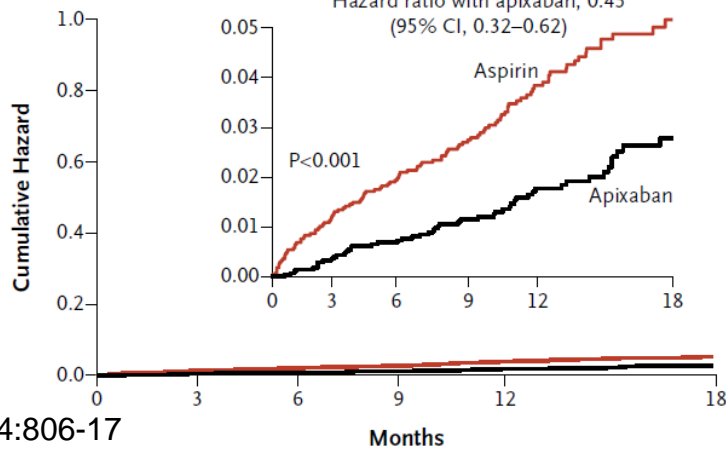
Apixaban vs. warfarin

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

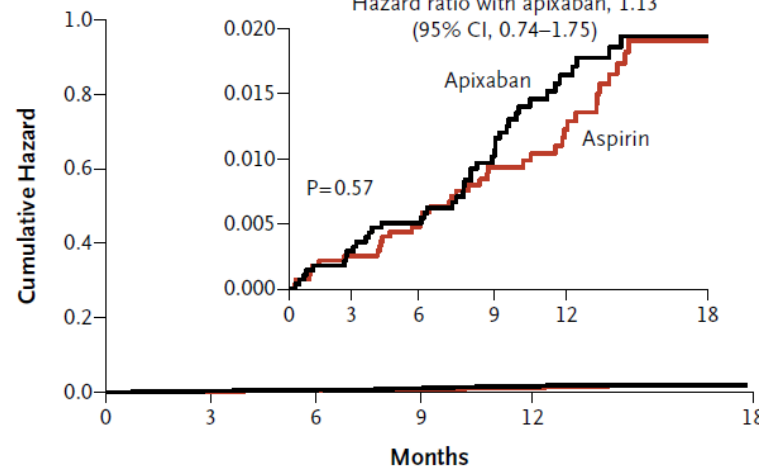
N Engl J Med 2011;365:981-92.

AVERROES

Stroke or Systemic Embolism



Major Bleeding



Apixaban vs. ASA

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

N Engl J Med 2011;364:806-17

\* Net clinical benefit

- **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.

## 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)



## Steering Committee

- Pr Jean-Philippe COLLET (Paris, France )
- Pr Gilles MONTALESCOT (Paris, France)
- Pr Eric VICAUT (Paris, France )
- Pr Eric VAN BELLE (Lille, France)
- Pr Franz-Joseph NEUMANN (Bad Krozingen, Germany)
- Dr Sergio BERTI (Massa, Italy)
- Pr Angel CEQUIER (Barcelona, Spain)
- Pr Pascal LEPRINCE (Paris, France)
- Dr Thierry LEFEVRE (Massy, France)

## Sponsor



Assistance Publique des Hôpitaux de Paris

- Damien VANHOYE - DRCI

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## DSMB

- Pr Alec VAHANIAN – Chair
- Dr Silvy LAPORTE
- Pr Christian HAMM

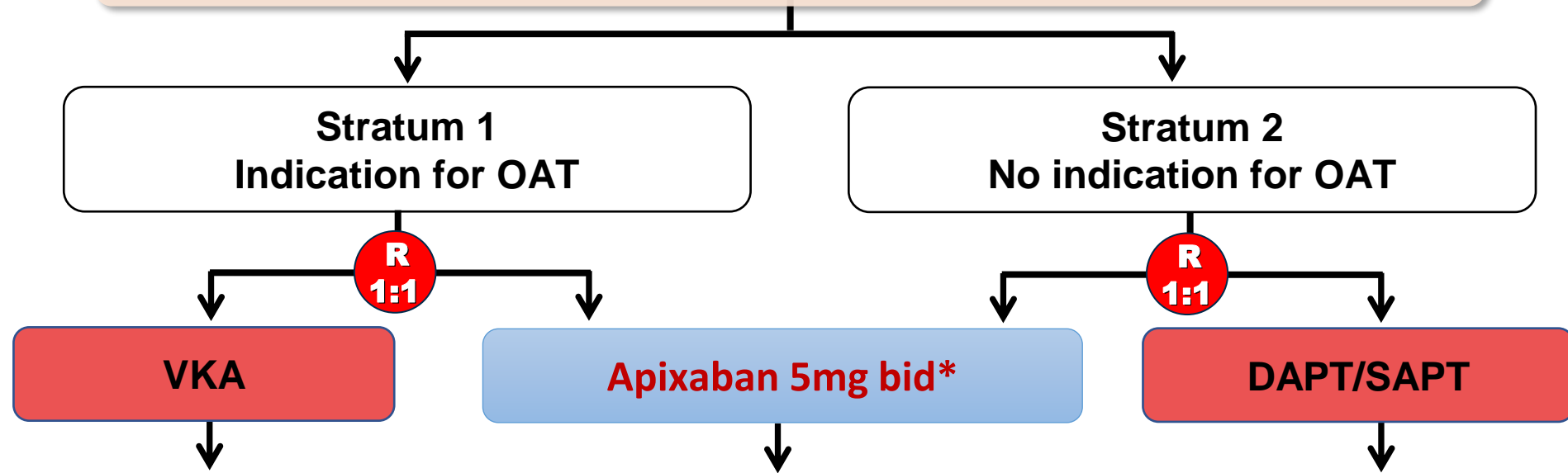
## Clinical Events Committee

- Dr Flore BARONNET
- Dr Pierre AUBRY
- Pr Patrick HENRY
- Dr Mohamad EL Khasty
- Dr Stéphane EDHERY

# 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



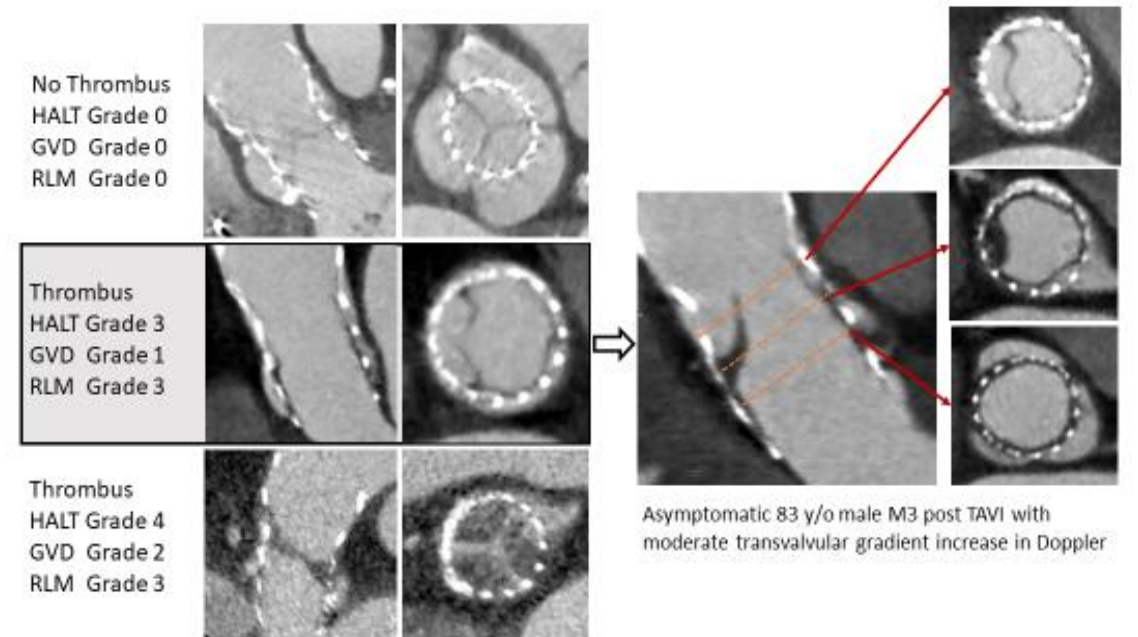
**Primary end-point** is a composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism, major bleedings **over one year follow-up**.

\*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.

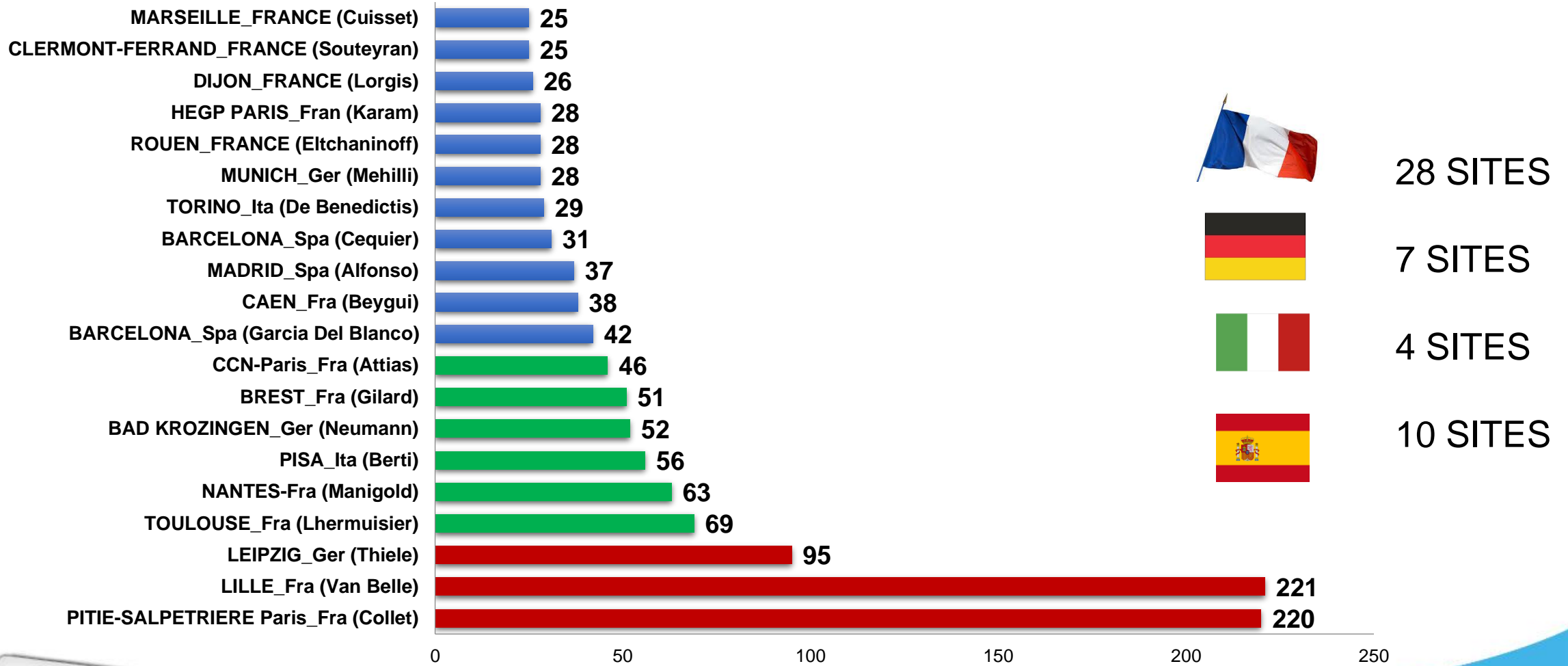
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# CT and ECHO evaluation of subclinical leaflet thrombosis

- 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  $\geq 10$  mmHg change from baseline (vs. hospital discharge) or  $> 20$  mmHg OR reduced leaflet mobility (RELM) grade 3 or 4 on at least one leaflet.



# Top recruiting centers





## 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.

- **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

## 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

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

## Primary outcome at one year

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

112 patients didn't complete the follow-up :

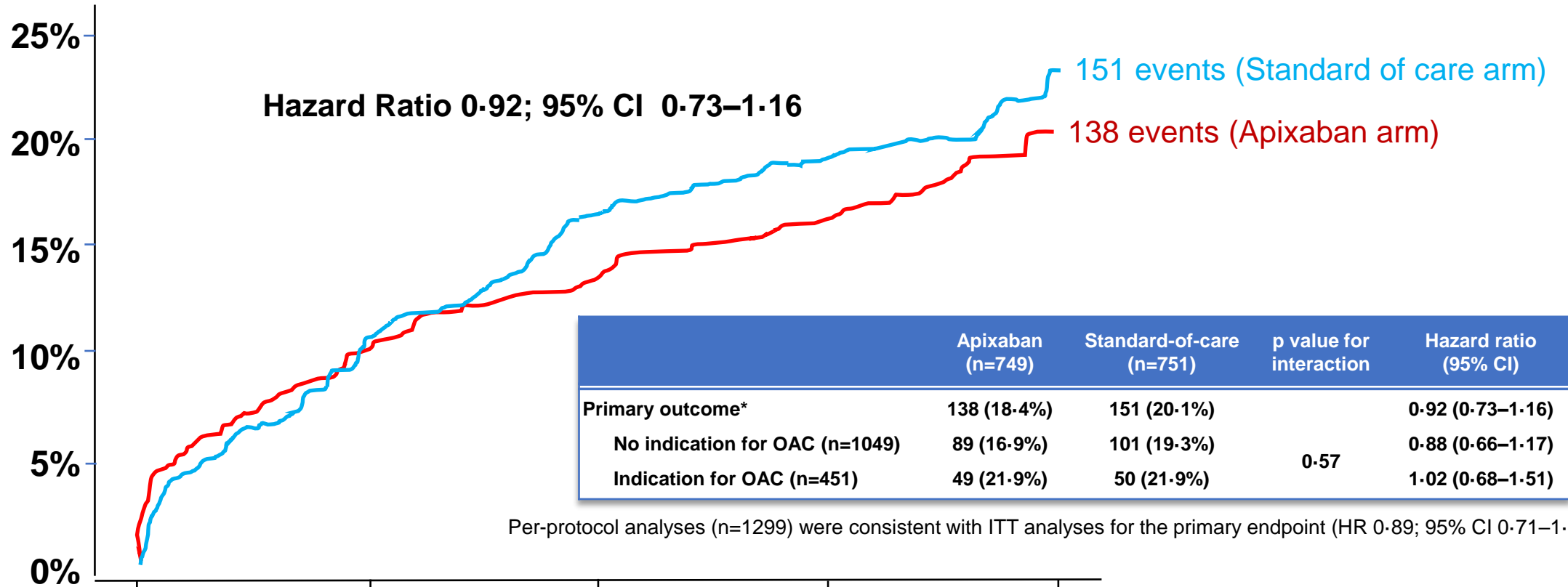
- n= 42 Death
- n= 28 Consent withdraw
- n= 7 Patient refuse to continue the study
- n= 29 Patient was lost to follow up
- n= 6 Other

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

	Apixaban (n=749)	Standard-of-care (n=751)
<b>Pre-TAVI antithrombotic treatment</b>		
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%)
<b>Procedural characteristics</b>		
Self-expanding	395 (52.8%)	386 (51.5%)
Balloon-expanding	353 (47.2%)	363 (48.5%)
Valve in valve	40 (5.3%)	35 (4.7%)
Mild PVR	35 (15.4%)	39 (16.6%)
Moderate to severe PVR	3 (1.3%)	1 (0.4%)
<b>Post-randomization antithrombotic treatment</b>		
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



Per-protocol analyses (n=1299) were consistent with ITT analyses for the primary endpoint (HR 0.89; 95% CI 0.71–1.13).

Number at risk

SOC: 751  
Apixaban: 749

100  
646  
645

200  
583  
612

300  
555  
585

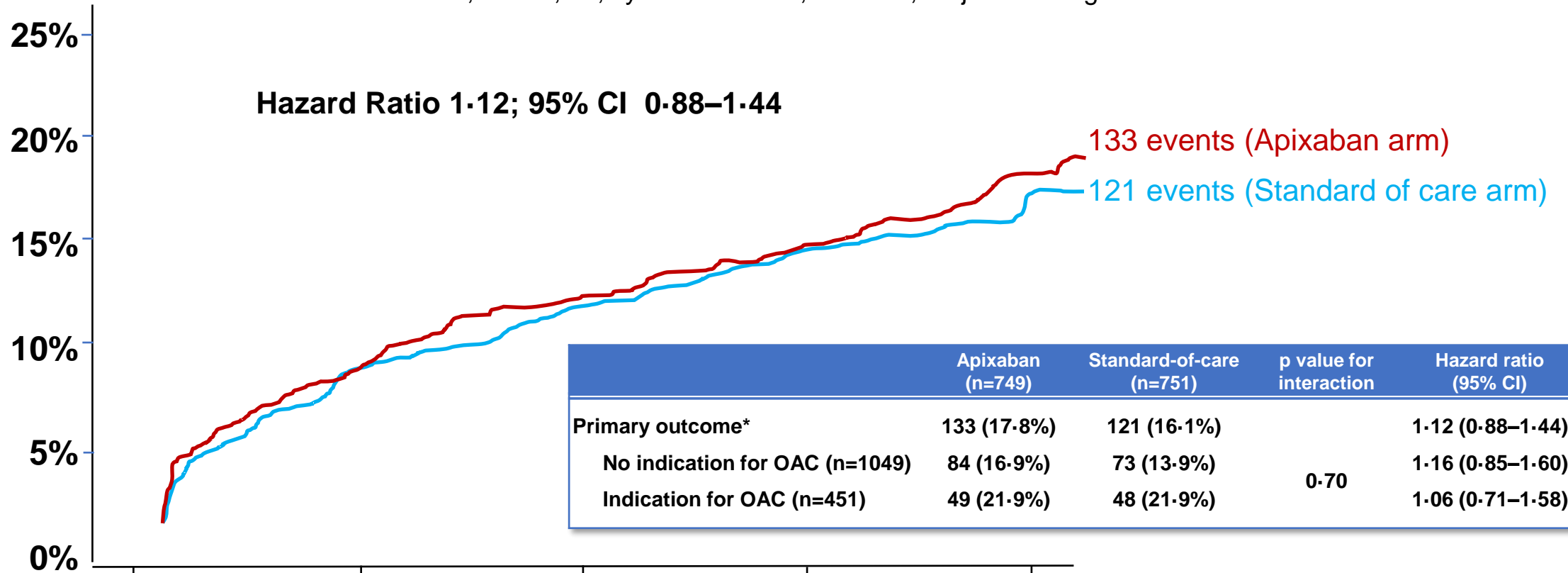
400  
42  
27



# 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)
<b>Primary outcome*</b>	<b>133 (17.8%)</b>	<b>121 (16.1%)</b>		<b>1.12 (0.88–1.44)</b>
No indication for OAC (n=1049)	84 (16.9%)	73 (13.9%)	<b>0.70</b>	<b>1.16 (0.85–1.60)</b>
Indication for OAC (n=451)	49 (21.9%)	48 (21.9%)		<b>1.06 (0.71–1.58)</b>

Number at risk

	0	100	200	300	400
SOC:	751	656	615	584	43
Apixaban:	749	651	617	589	27



# 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)
<b>Bioprosthetic thrombosis</b>	<b>8 (1.1%)</b>	<b>35 (4.7%)</b>	<b>0.23 (0.11–0.50)</b>
Intracardiac thrombus	3 (0.4%)	3 (0.4%)	1.11 (0.22–5.54)
<b>Deep vein thrombosis or pulmonary embolism</b>	<b>1 (0.1%)</b>	<b>11 (1.5%)</b>	<b>0.09 (0.01–0.72)</b>

	Apixaban (n=749)	Standard-of-care (n=751)	Hazard ratio (95% CI)
<b>Primary safety endpoint†</b>	<b>64 (8.5%)</b>	<b>64 (8.5%)</b>	<b>1.02 (0.72–1.44)</b>
<b>Life-threatening bleeding</b>	<b>19 (2.5%)</b>	<b>18 (2.4%)</b>	<b>1.06 (0.55–2.02)</b>
<b>Major bleeding</b>	<b>50 (6.7%)</b>	<b>48 (6.4%)</b>	<b>1.07 (0.72–1.59)</b>
<b>Minor bleeding (BARC 2 or 3a)</b>	<b>70 (9.3%)</b>	<b>78 (10.4%)</b>	<b>0.91 (0.66–1.26)</b>
<b>Any bleeding</b>	<b>174 (23.2%)</b>	<b>170 (22.6%)</b>	<b>1.05 (0.85–1.30)</b>

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).



## Need for oral anticoagulation

	Apixaban (n=223)	Standard of Care (n=228)	Hazard ratio (95% CI)
<b>Primary outcome*</b>	<b>49 (21.9%)</b>	<b>50 (21.9%)</b>	<b>1.02 (0.68-1.51)</b>
<b>Secondary efficacy outcomes</b>			
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)
<b>Safety outcomes</b>			
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)
<b>Any Valve Thrombosis**</b>	<b>2 (0.9%)</b>	<b>3 (1.3%)</b>	<b>0.67 (0.11-4.04)</b>

\*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)
<b>Primary outcome*</b>	<b>89 (16.9%)</b>	<b>101 (19.3%)</b>	<b>0.88 (0.66-1.17)</b>
<b>Secondary efficacy outcomes</b>			
Death, MI, any stroke/TIA	50 (9.5%)	35 (6.7%)	1.48 (0.96-2.30)
<b>Death, any stroke/TIA or systemic embolism</b>	<b>50 (9.5%)</b>	<b>33 (6.3%)</b>	<b>1.56 (1.01-2.43)</b>
<b>Death</b>	<b>31 (5.9%)</b>	<b>18 (3.4%)</b>	<b>1.86 (1.04-3.34)</b>
• <b>Cardiovascular death</b>	<b>17 (3.2%)</b>	<b>13 (2.5%)</b>	<b>1.42 (0.69-2.94)</b>
• <b>Non cardiovascular death</b>	<b>14 (2.66%)</b>	<b>5 (0.96%)</b>	<b>2.99 (1.07-8.35)</b>
<b>Safety outcomes</b>			
Primary safety endpoint <sup>†</sup>	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)
<b>Any Valve Thrombosis**</b>	<b>6 (1.1%)</b>	<b>32 (6.1%)</b>	<b>0.19 (0.08-0.47)</b>

\*death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings; <sup>†</sup>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 <sup>‡</sup>.

# 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 LECLERCO, 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-BABÉ, David ATTIAS, Florent LAVEAU, Julien DREYFUS, Olivier VARENNE, Fabien PICARD, Alexandre LAFONT, Maximilien SOCHALA, Philippe DEGRELLE, Olivier MOREL, Patrick OHLMANN, Karl ISAAZ, Sarah BALICHARD, Antoine GERBAY, Alexis CERISIER, Benjamain HABER, Said GHOSTINE

## Investigators from Germany

Franz-Josef NEUMANN, Dietmar TRENK, Stefan LEGGEWIE, Philipp RUILE, Roland KLINGENBERG, Christoph LIEBETRAU, Won-Keun KIM, Matthias RENKER, Arnaud VAN LINDEN, Mani ARSALAN, Holger THIELE, Axel LINKE, David HOLZHEY, Philipp KIEFER, Sergey LEONTYEV, Philipp HARTUNG, Steffen DESCH, Marcus SANDRI, Phillip MUNCH, Danilo OBRADOVIC, Julinda MEHILLI, Steffen MASSBERG, Sarah GSCHWENDTNER, Christian KUPATT, Ruth THALMANN, Sabine BLEIZIFFER, Uwe ZEYMER, Ralf ZAHN, Nicolas WERNER, Hueseyin INCE, Evren CAGLAYAN, Nina GERHARDT-KLEINFELDT, Christin MACHNEK, Alper ÖNER, Seyrani YÜCEL, Peter BOEKSTEGERS, Ralf MÜLLER, Christian DEGENHART

## Investigators from Italy

Sergio BERTI, Luigi PASTORMERLO, Alberto RANIERI DE CATERINA, Giuseppe TRIANNI, Marcello RAVANI, Marco DE CARLO, Paolo SPONTONI, Marco ANGELILLIS, Mauro DE BENEDICTIS, Marco PAVANI, Caterina GANDOLFO, Stefano CANNATA

## Investigators from Spain

Angel CEQUIER, Marcos ÑATO BENGUA, Guillem MUNTANE, José Maria HERNANDEZ, Antonio Jesus MUÑOZ GARCIA, Juan ALONSO BRIALES, Antonio DOMONGUEZ FRANCO, Ramiro TRILLO NOUCHE, Diego LOPEZ OTERO, Javier Martin MOREIRAS, Ignacio CRUZ GONZALEZ, Luis Javier RODRIGUEZ COLLADO, Alejandro DIEGO NIETO, Alberto SAN ROMAN CALVAR, Ignacio AMAT SANTOS, Silvio Humberto VERA VERA, Hipólito GUTIERREZ GARCIA, Francisco FERNANDEZ AVILES, Enrique GUTIERREZ IBANEZ, Felipe DIEZ DEL HOYO, Fernando ALFONSO, Teresa ALVARADO CASAS, Fernando RIVERO CRESPO, Francisco Javier CUESTA CUESTA, Maria Teresa BASTANTE VALIENTE, Ramon Francisco MARURI SANCHEZ, Bruno GARCIA DEL BLANCO, Vicenç SERRA GARCIA, Pedro Julio SUASNAVAR PORTILLO, Gerard MARTI AGUASCA, Carlos CUELLAS RAMON, Armando PEREZ de PRADO, Felipe FERNANDEZ VAZQUEZ, Maria LOPEZ BENITO, Tomas Fernando BENITO GONZALEZ, Manuel PAN ALVAREZ OSORIO, Francisco HIDALGO LESMES, Miguel Angel ROMERO MORENO, Soledad OJEDA PINEDA, Javier SUAREZ DE LEZO HERREROS