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# Quel traitement anti-thrombotique après TAVI ?

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GRCI 2017  
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**CHU**  
ROUEN NORMANDIE

**UNIVERSITÉ**  
**DE ROUEN**  
NORMANDIE

**Speaker's name : Eric, DURAND, Rouen**

J'ai des liens d'intérêt potentiel à déclarer

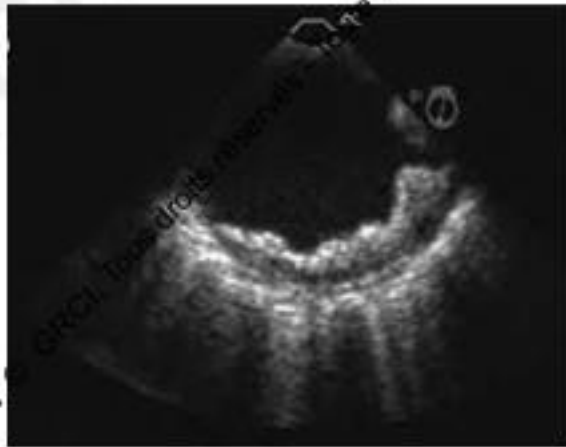
Honoraires: Servier, AstraZeneca, Bayer, Edwards Lifesciences, BMS

Consultant: ART, Robocath, Edwards Lifesciences

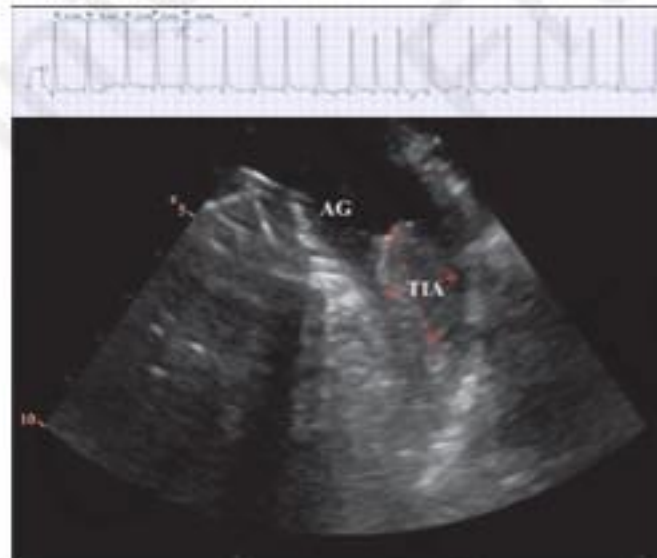
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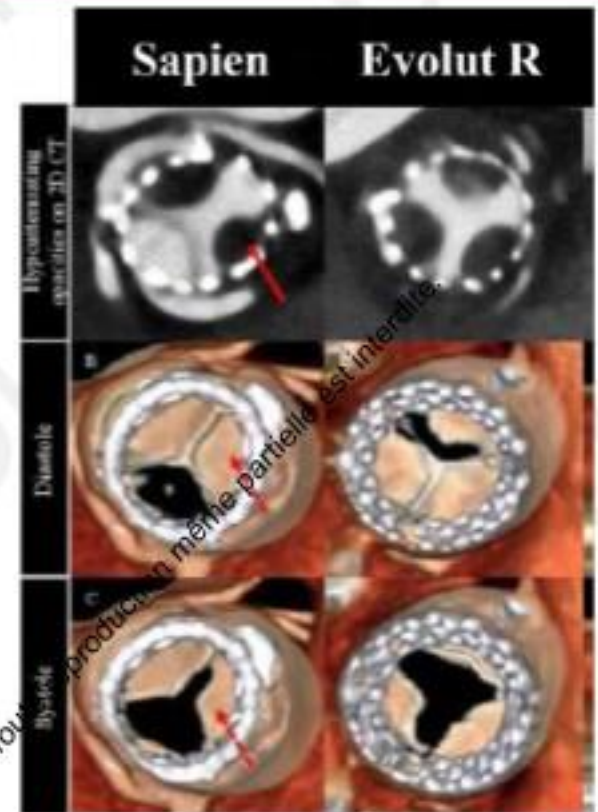
# Quels sont les substrats des complications thrombo-emboliques pendant/après un TAVI ?



Athérome aortique



Fibrillation auriculaire

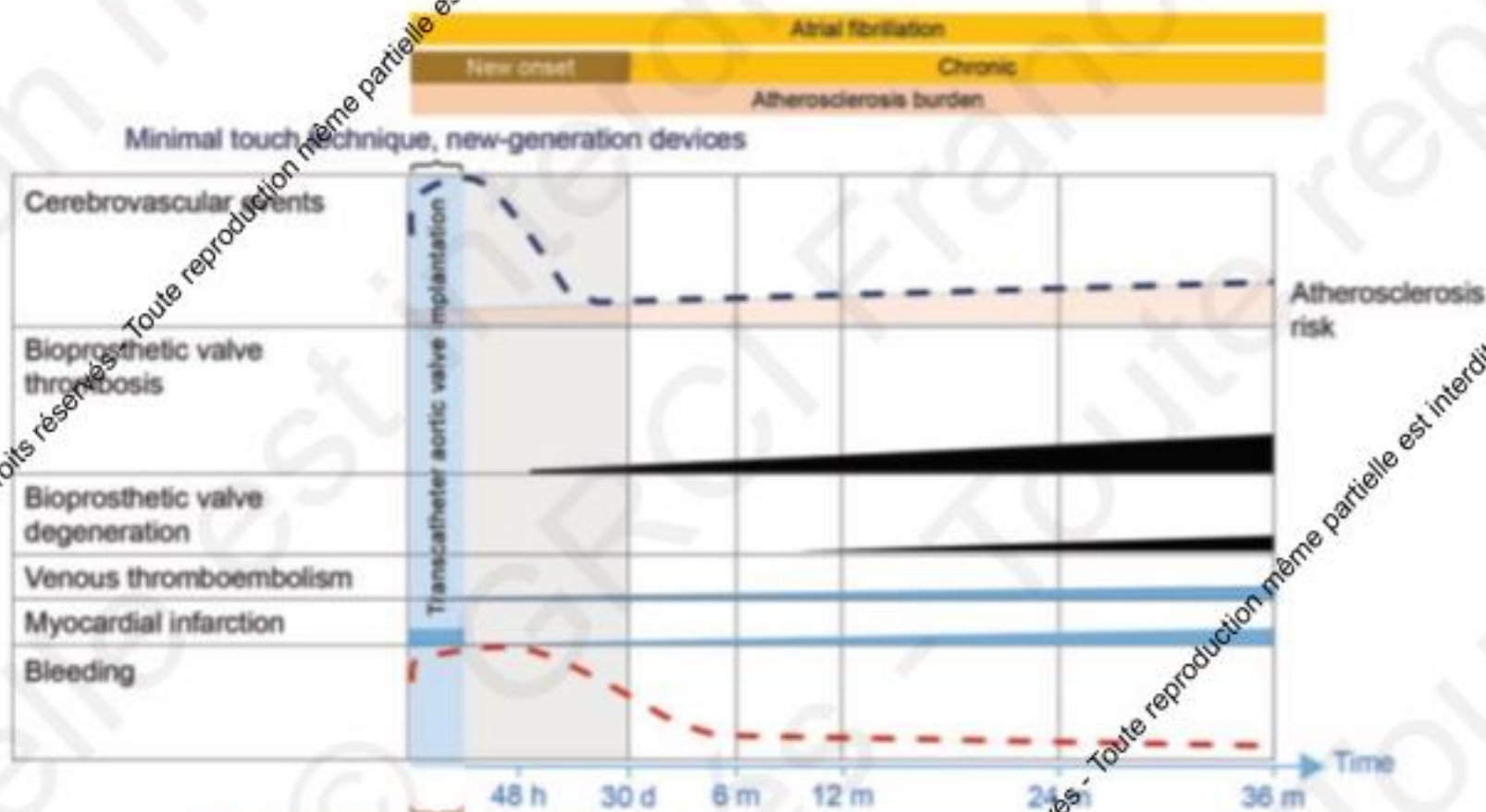


Thrombose valvulaire

2017

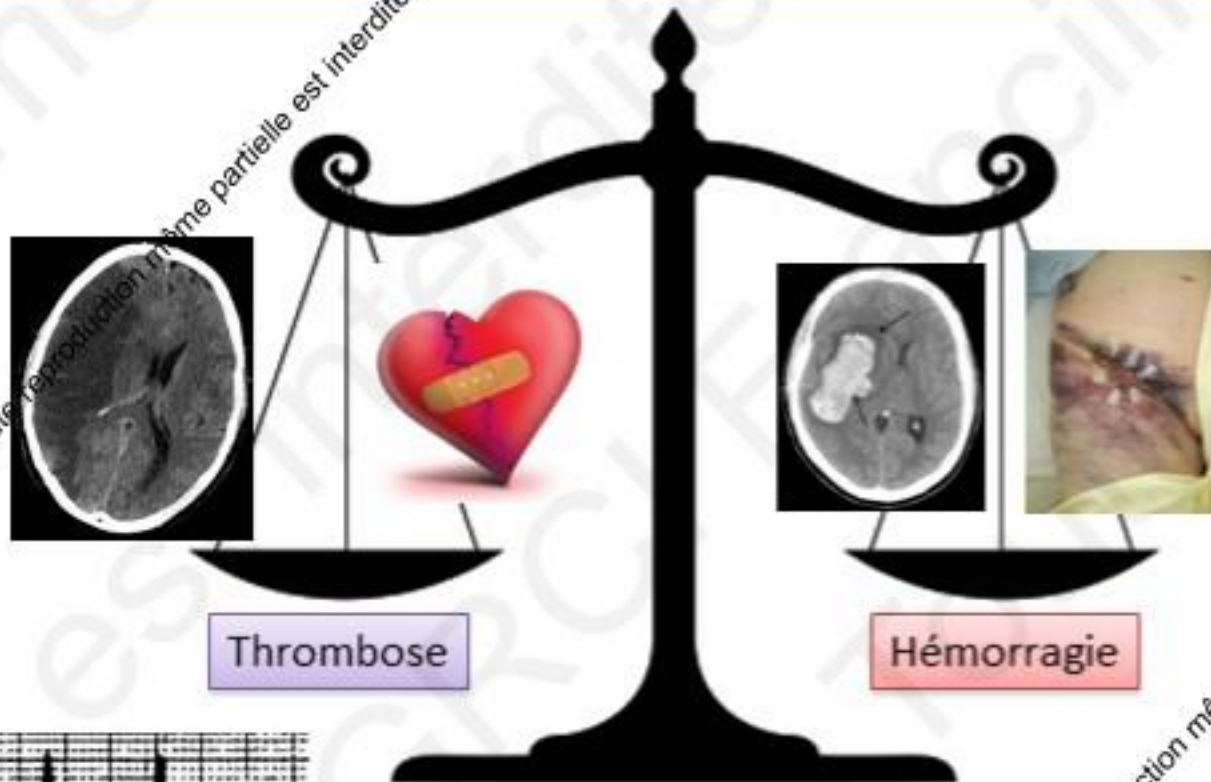
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# Risques Thrombotique/hemorragique



Delivery catheters and prostheses with smaller, less traumatic profile and surface

# Traitement anti-thrombotique post-TAVI: Problématiques



# Quel anticoagulant pendant la procédure ?

## Bravo 3 Study Flow



Phase III  
Open label,  
randomized

802 high-risk TAVR in  
7 countries / 31 sites

Sites in EU  
and North  
America

R  
1:1

**BIVALIRUDIN**  
(bolus 0.75 mg/kg + infusion 1.75 or  
1.4 or 1.0 mg/kg/h)

**Unfractionated Heparin\***  
(Recommended ACT  $\geq$  350)

### Co-Primary Endpoints

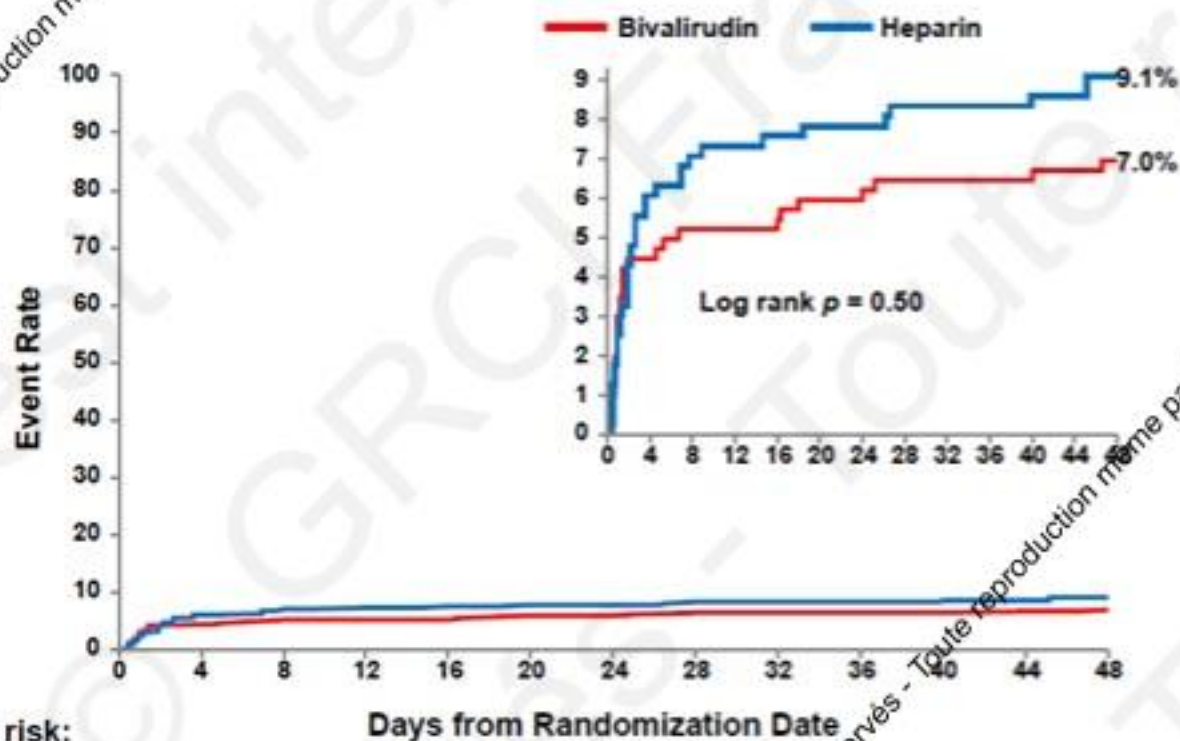
- BARC  $\geq$  3b major bleeding<sup>†</sup>, at 48 hours or hospital discharge whichever occurs earlier
- Net Adverse Clinical Events [NACE] (Death, MI, stroke and major bleeding) up to 30 days.

\*Heparin dosing and protamine use left at discretion of the operator

<sup>†</sup>Bleeding evaluated also according TIMI, GUSTO, ACUTY and VASA scales

# Quel anticoagulant pendant la procédure ?

## 48-h Major bleeding (BARC $\geq 3b$ )



Patients at risk:

	0	4	8	12	16	20	24	28	32	36	40	44	48
Bivalirudin	404	384	381	381	381	378	378	375	375	375	375	374	373
Heparin	398	371	367	366	365	364	364	361	361	360	360	360	358

# Quel anticoagulant pendant la procédure ?



- HNF (sans spécifier ACT ni protamine)

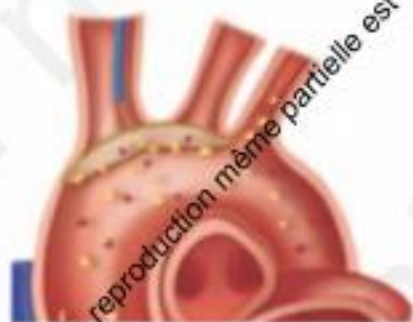


- HNF (ACT > 300 s) avec injection de protamine (1/1) en fin de procédure

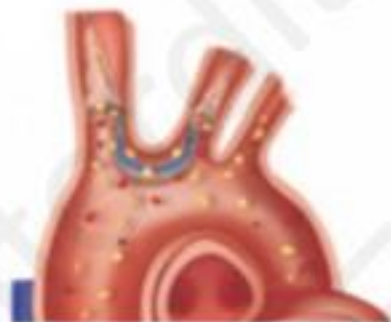


# Dispositifs de protection embolique

## EMBOLIC PROTECTION DEVICES AND TAVI



Embrella Deflector  
(Edwards LifeSciences)



Montage 2 Capture Device  
(Claret Medical)



Triguard Cerebral  
Deflector  
(Keystone Heart)

### EVIDENCE FROM RANDOMIZED TRIALS

#### PROTAVI-C

RODÉS-CABAU ET AL JACC CARDIOVASC  
INTERV. 2014

41 patients

↓ average volume of ischemic  
lesion

#### CLEAN-TAVI

HAUSSIG ET AL JAMA 2016

100 patients

↓ frequency of ischemic cerebral lesions

#### DEFLECT III TRIAL

LANSKY ET AL EUROPEAN HEART JOURNAL  
2015

85 patients

↓ new ischemic brain lesions and  
neurologic deficits

#### SENTINEL

KAPADIA ET AL JACC 2017

363 patients

No significant reduction of lesion volume on  
MRI

↑ cognitive function

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# Quel traitement antithrombotique après la procédure (pas d'indication à un TAC) ?



- DAPT pendant 3-6 mois puis SAPT à vie chez les patients sans indication à un TAC (IIa, C)
- SAPT chez les patients à haut risque hémorragique (IIb, C)



- Clopidogrel 75 mg pendant 6 mois et Aspirine (75-100 mg) à vie (IIb, C)
- AVK (INR cible 2,5) pendant 3 mois chez les patients à bas risque hémorragique (IIb, C)

# Quel traitement antithrombotique après la procédure (indication à un TAC) ?

	
<ul style="list-style-type: none"><li>• <b>AVK seul</b></li></ul>	<ul style="list-style-type: none"><li>• <b>Si indication à une DAPT*</b> AVK et Clopidogrel</li><li>• <b>Si pas d'indication à une DAPT:</b> AVK et Aspirine</li></ul>

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# Quel traitement antithrombotique après la procédure ? *Etudes en cours*

	No indication to OAC	Indication to OAC
Studies of antiplatelet strategies	<b>ARTE</b> (NCT01556298) ASA vs. DAPT	<b>AVATAR</b> (NCT02725902) ASA+VKA vs. no VKA
	<b>POPular TAVI</b> (NCT02247128) ASA vs. DAPT	<b>POPular TAVI</b> (NCT02247128) Clopidogrel+VKA vs. VKA
	<b>CLOE</b> (Announced) ASA vs. DAPT	<b>CLOE</b> (Announced) Clopidogrel+VKA vs. VKA
Studies of antiplatelet versus anticoagulant strategies	<b>AUREA</b> (NCT01642134) DAPT vs. VKA	
	<b>GALILEO</b> (NCT02556203) Rivaroxaban + ASA vs. DAPT	
	<b>ATLANTIS</b> (NCT02664649) Apixaban vs. Aspirin or DAPT	
Studies of anticoagulant strategies		<b>ATLANTIS</b> (NCT02664649) Apixaban vs. VKA
		<b>ENVISAGE TAVI</b> (NCT02943785) Edoxaban* vs. VKA*

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# Quel traitement antithrombotique après la procédure ?

	No indication to OAC	Indication to OAC
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Studies of antiplatelet versus anticoagulant strategies		
Studies of anticoagulant strategies		

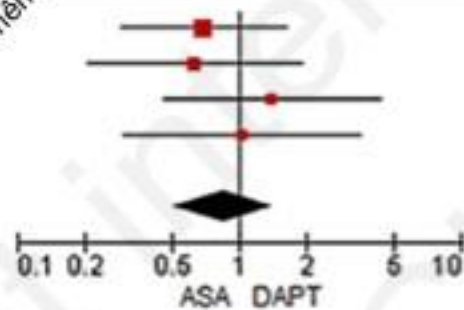
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# SAPT Vs. DAPT ?

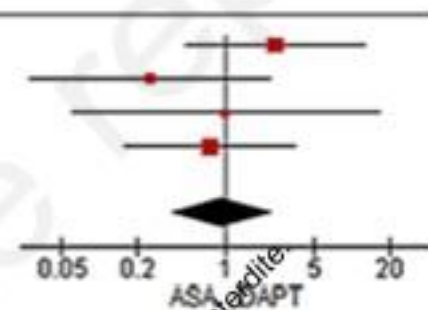
## NACE

Study	Odds Ratio (95% CI)
Durand et al (2014)	0.69 (0.30-1.62)
Poliacikova et al (2013)	0.63 (0.20-1.93)
Stabile et al (2014)	1.39 (0.45-2.27)
Ussia (2011)	1.03 (0.40-3.52)
<b>Overall</b>	<b>0.87 (0.48-1.43)</b>



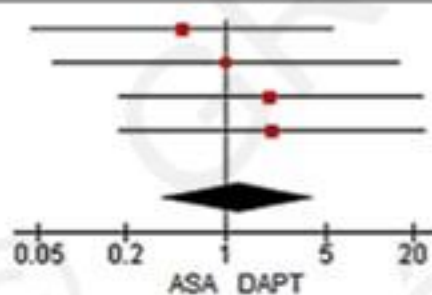
## All-cause mortality

Study	Odds Ratio (95% CI)
Durand et al (2014)	2.50 (0.49-12.89)
Poliacikova et al (2013)	0.25 (0.03-2.24)
Stabile et al (2014)	1.00 (0.06-16.37)
Ussia (2011)	0.75 (0.16-3.59)
<b>Overall</b>	<b>0.91 (0.36-2.27)</b>



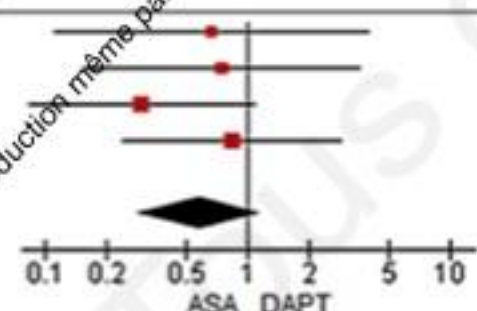
## Stroke

Study	Odds Ratio (95% CI)
Durand et al (2014)	0.50 (0.05-5.51)
Poliacikova et al (2013)	1.0 (0.06-15.99)
Stabile et al (2014)	2.03 (0.18-23.06)
Ussia (2011)	2.11 (0.18-24.24)
<b>Overall</b>	<b>1.21 (0.36-4.03)</b>



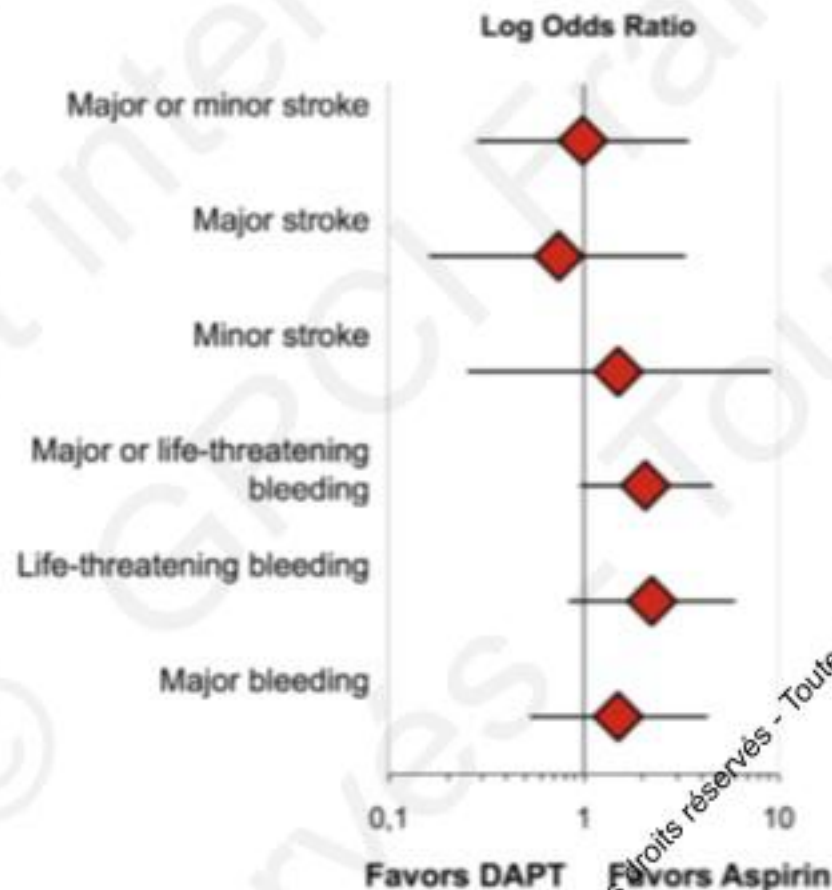
## LTB and major bleeding

Study	Odds Ratio (95% CI)
Stabile et al (2014)	0.83 (0.24-2.90)
Durand et al (2014)	0.30 (0.08-1.09)
Poliacikova et al (2013)	0.67 (0.11-3.99)
Ussia (2011)	0.75 (0.16-3.59)
<b>Overall</b>	<b>0.56 (0.28-1.09)</b>



# SAPT Vs. DAPT ?

Thirty-day outcomes of DAPT vs. Aspirin after TAVR.  
Meta-analysis of 421 patients from 3 RCTs



# DAPT/SAPT: Etude ARTE

Prospective, randomized, open label, multicenter study

Patients randomized  
(the day prior to the TAVR procedure)

**Aspirin 80-100mg/d**

- Start at least 24hrs before TAVR
- Continued for at least 6 months

**Aspirin 80-100mg/d + Clopidogrel 75mg/d**

**Clopidogrel treatment**

- Initial dose of 300 mg followed by 75 mg/d

**Transfemoral approach**

- Start within 24hrs before TAVR
- Continued for 3 months

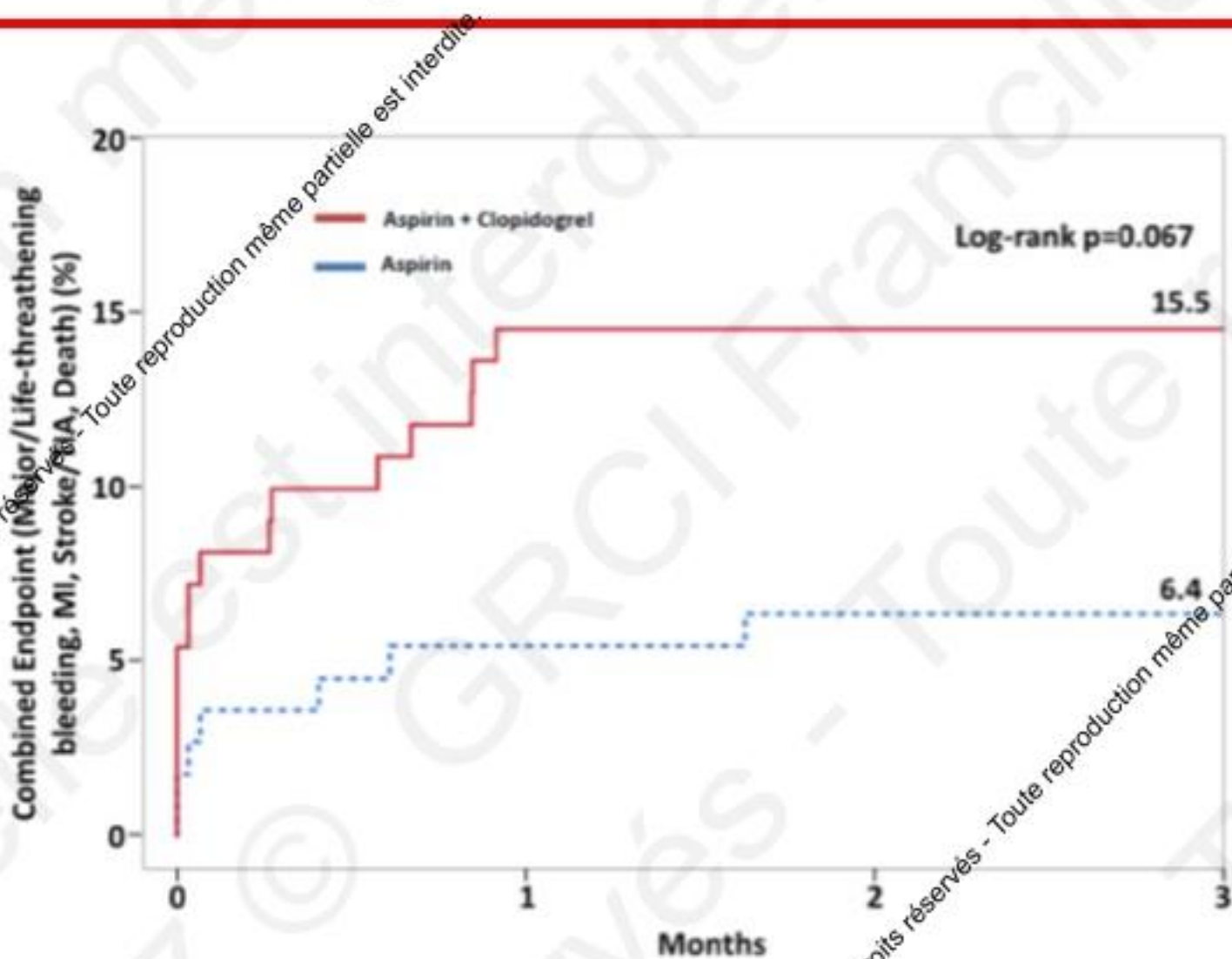
**Transapical/Transaortic/Transcatheter approach**

- Start within 24hrs after TAVR
- Continued for 3 months

Clinical visit/phone contact at 1- 3- and 12-month follow-up

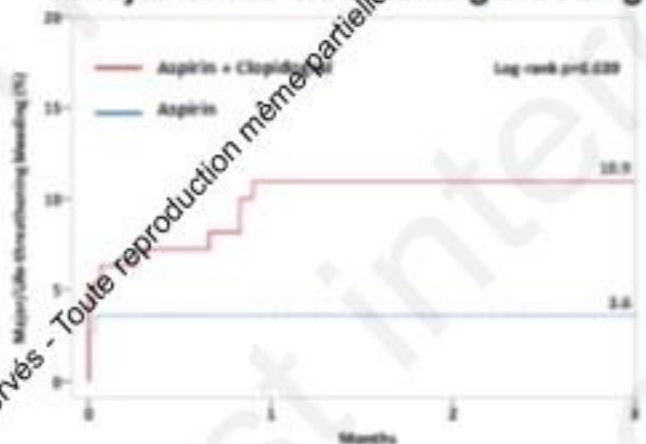


# DAPT/SAPT: Etude ARTE

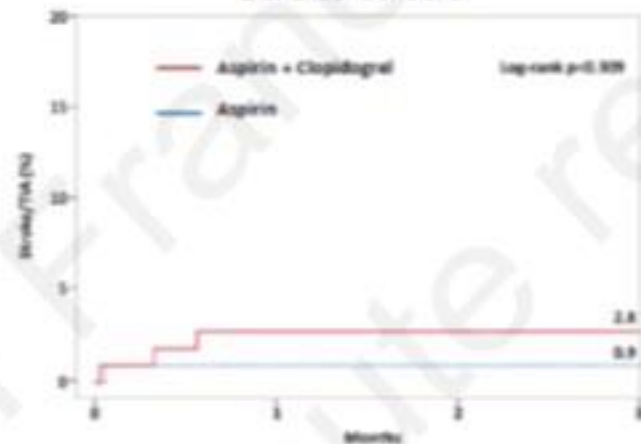


# DAPT/SAPT: Etude ARTE

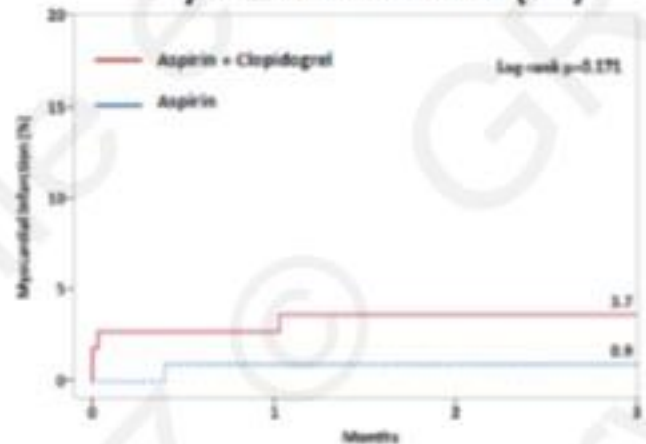
Major or life-threatening bleeding



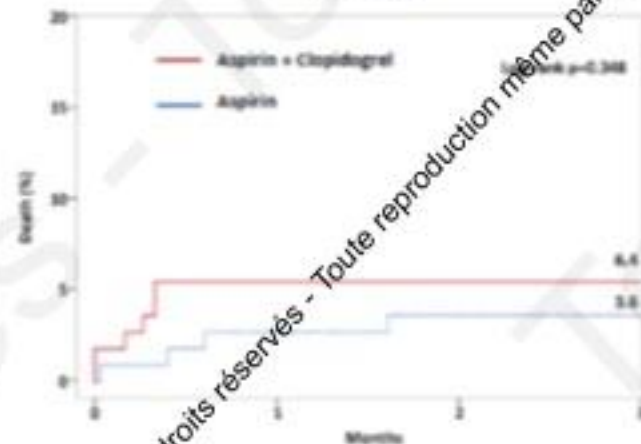
Stroke or TIA



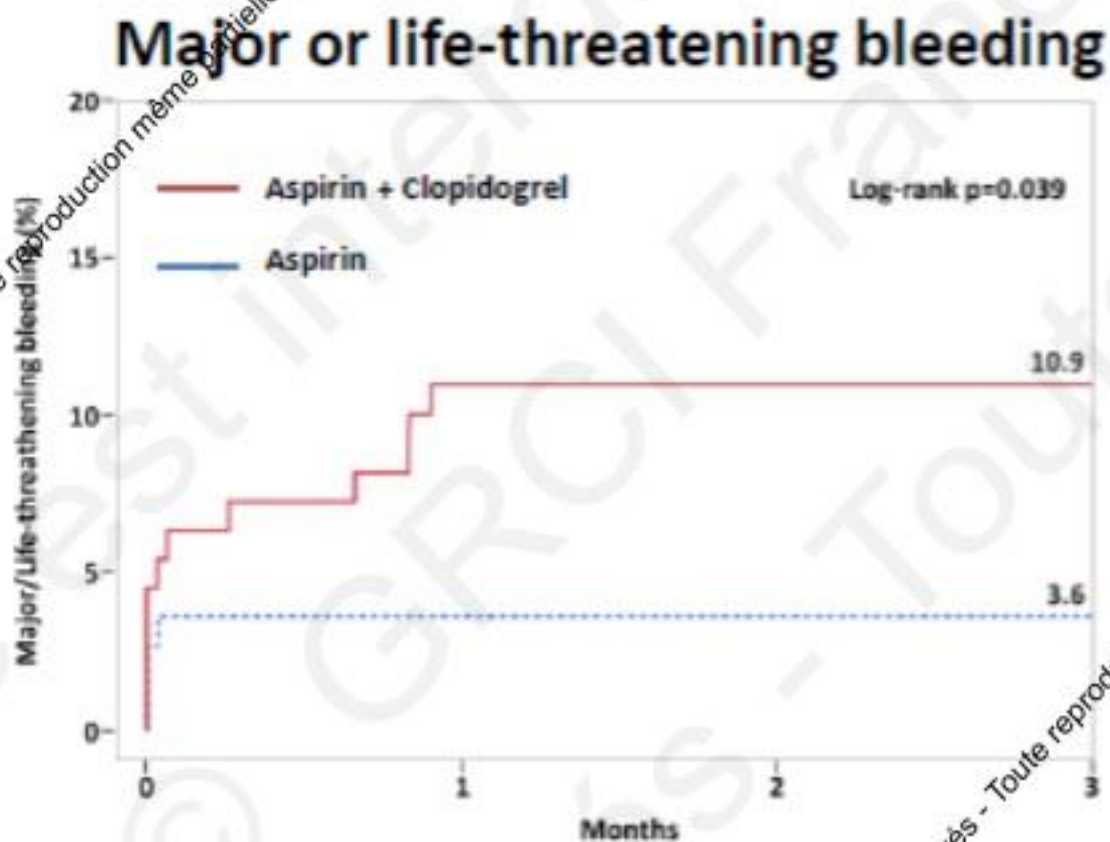
Myocardial infarction (MI)



Death



# DAPT/SAPT: Etude ARTE

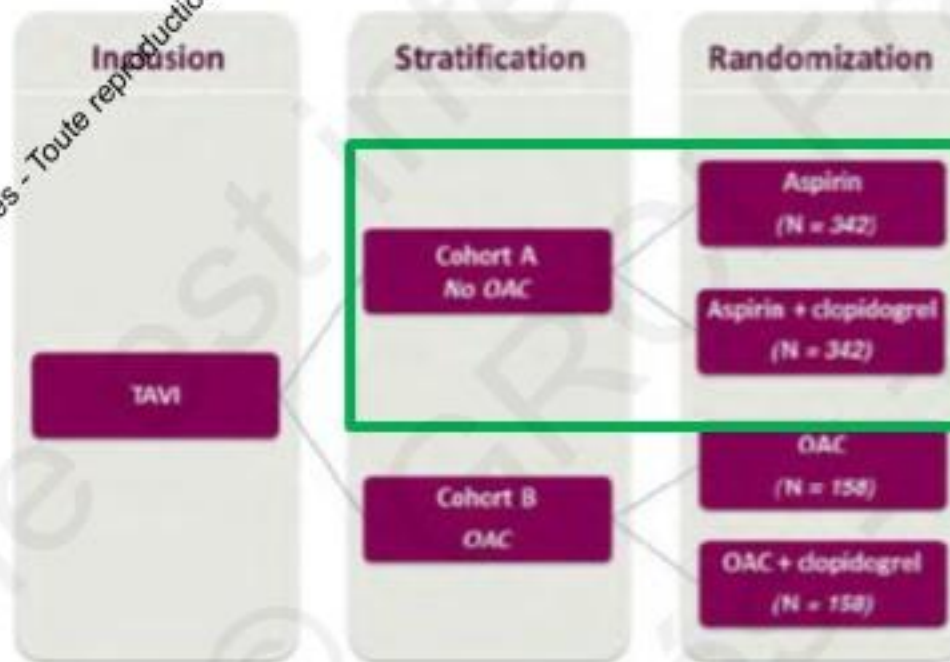


# DAPT/SAPT Etudes en cours

## POPULAR-TAVI

Nijenhuis et al. Am Heart J 2016;173:77-85

**Study Hypothesis: Monotherapy with Aspirin or OAC monotherapy is safer (non-procedure-related bleeding) than the addition of clopidogrel for 3 months**



Recruitment began in February 2014, and the trial will continue until a total of 1,000 patients (684 expected in cohort A and 316 in cohort B) are included and followed up for 1 year.



**Primary end-point: Freedom from all BARC-defined bleeding complications at 1 year after TAVI**

# Etudes en cours: CLOE

4000 patients  
traités par TAVI

Pas d'indication  
à un TAC

Indication  
à un TAC

Asp

Asp+Clap  
6 mois

AVK

Clap  
6 mois + AVK

- Critère de jugement principal efficacité: décès/IDM/AVC/MTV/Embolie systémique
- Critère de jugement principal sécurité: Hémorragies vitales/majeures

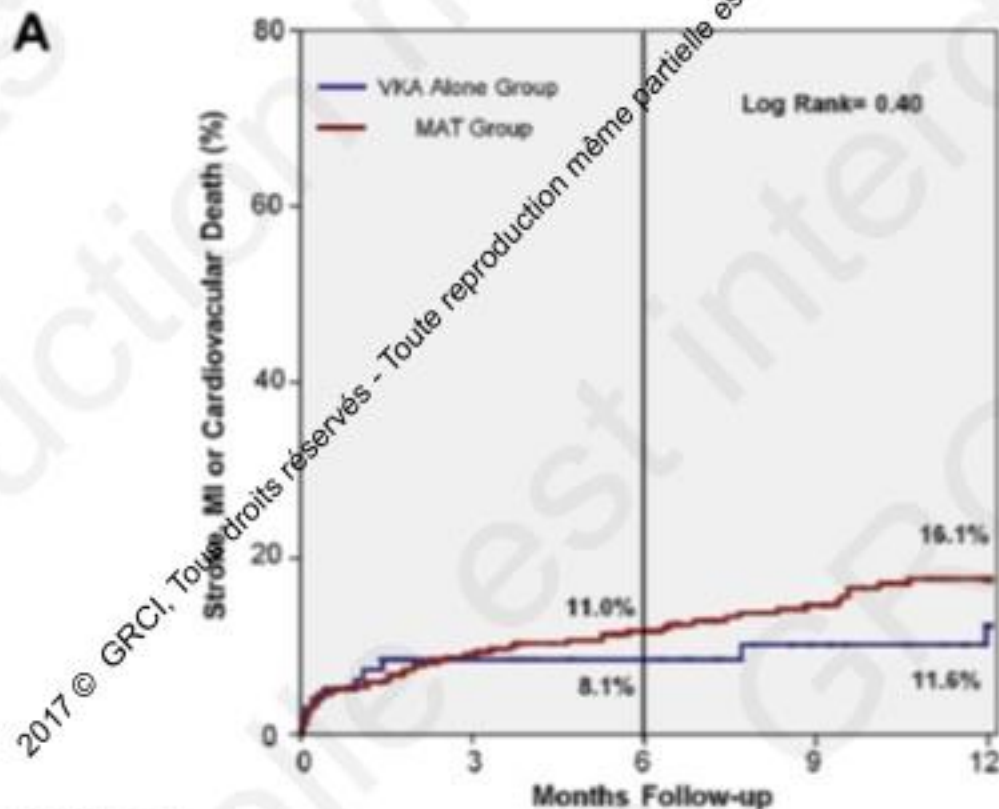
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Studies of anticoagulant strategies		

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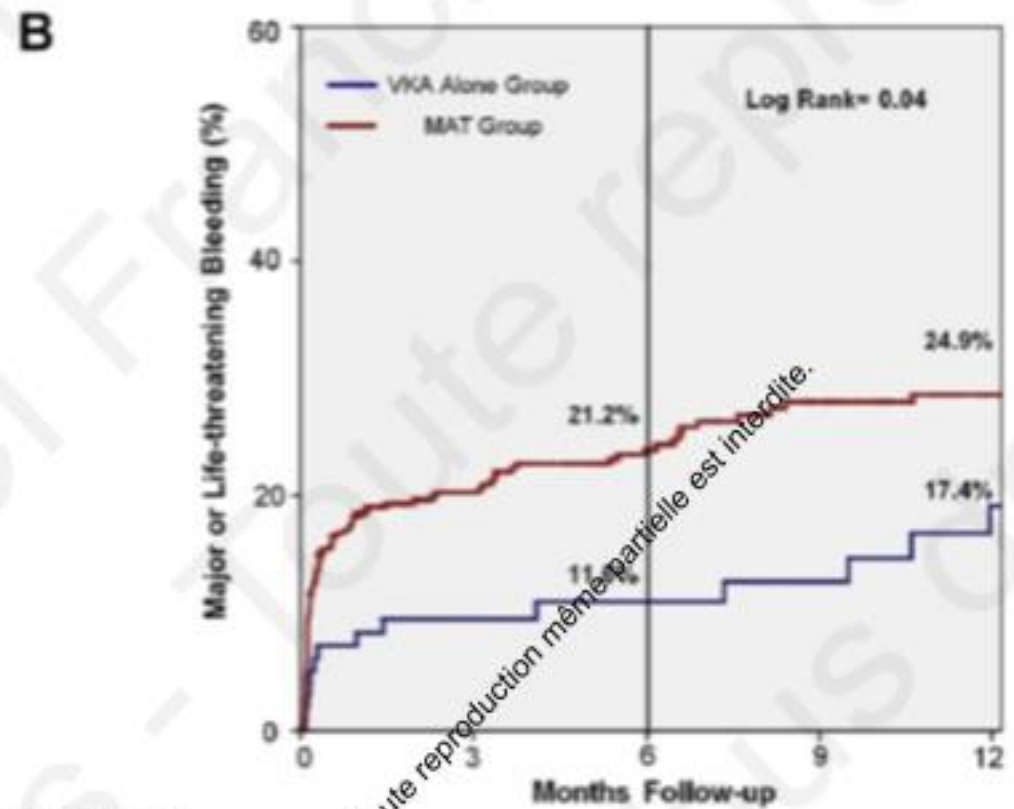
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# AKK seul ou AVK et antiagrégants ?



Patients at risk

Months Follow-up	0	3	6	9	12
VKA Alone Group	101	75	68	59	45
MAT Group	520	324	276	214	184

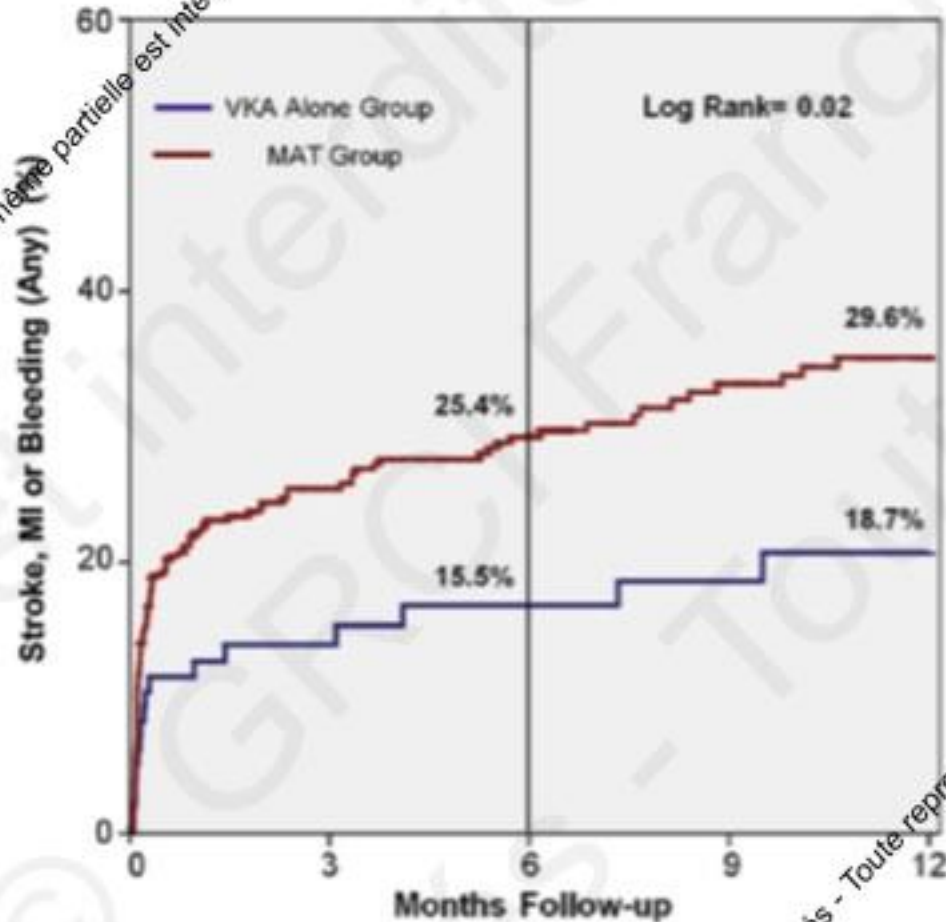


Patients at risk

Months Follow-up	0	3	6	9	12
VKA Alone Group	101	75	66	57	44
MAT Group	520	295	255	172	149

# AKK seul ou AVK et antiagrégants ?

C



Patients at risk  
 VKA Alone Group  
 MAT Group

101	71	64	55	43
520	281	239	185	141

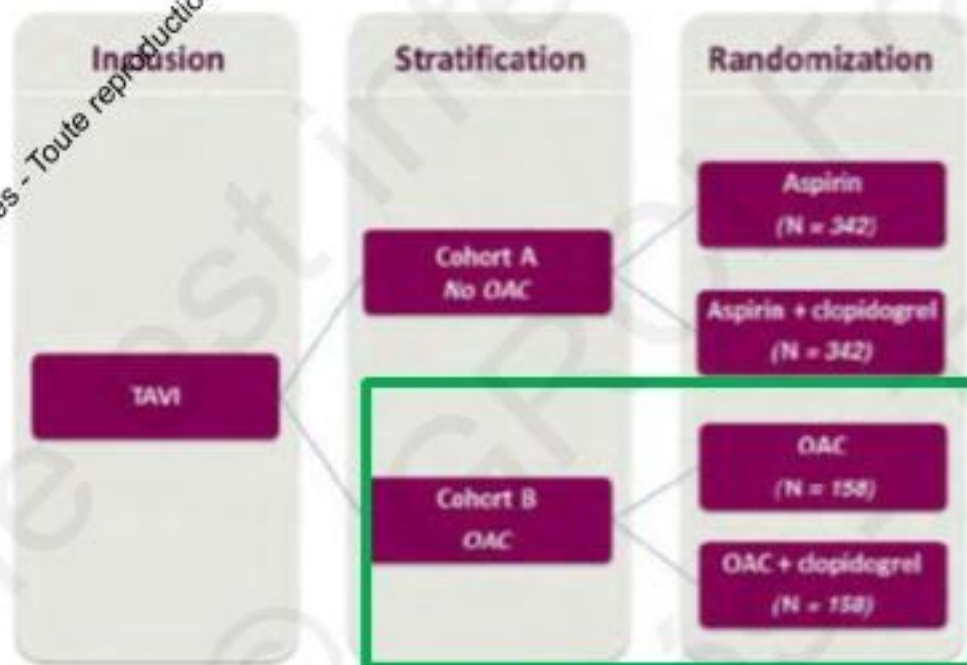


# Etudes en cours

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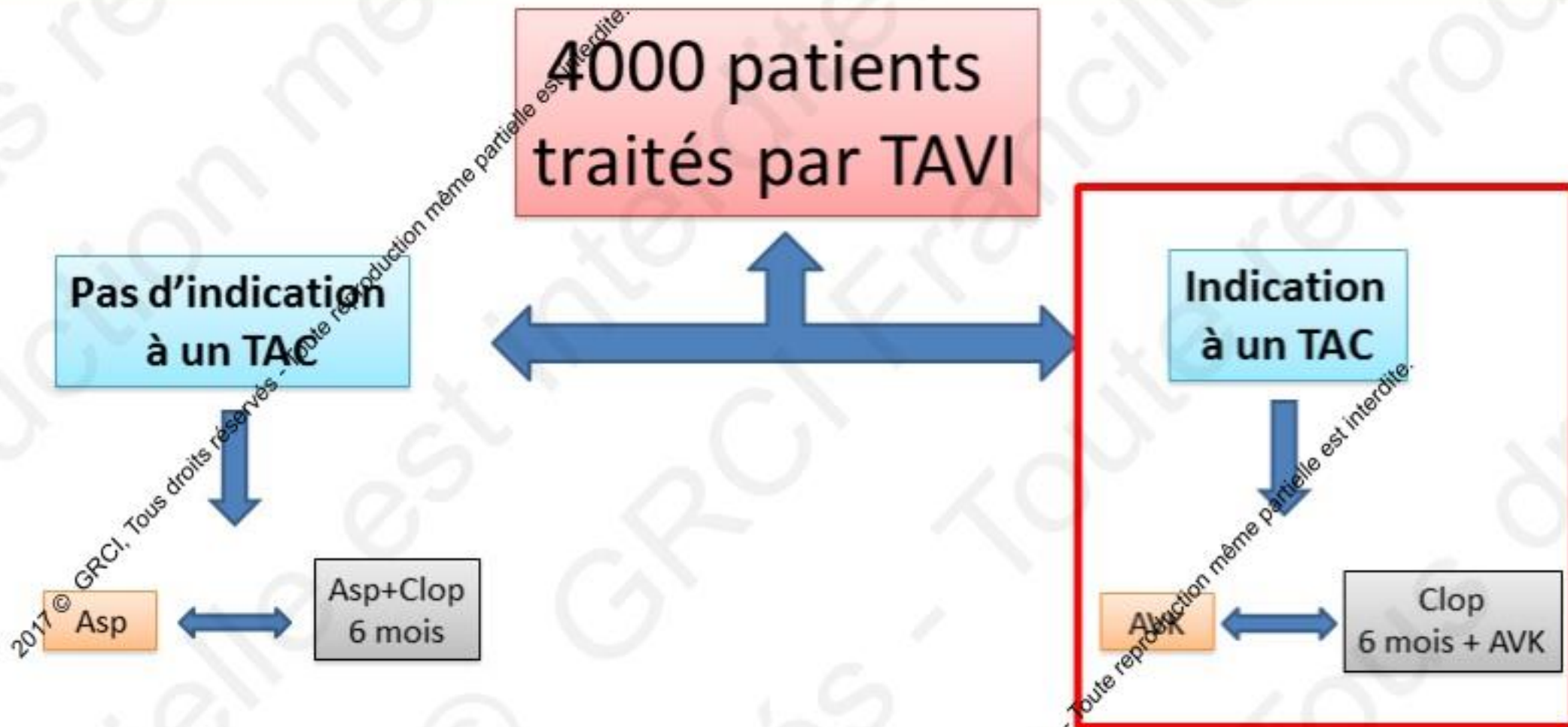


Recruitment began in February 2014, and the trial will continue until a total of 1,000 patients (684 expected in cohort A and 316 in cohort B) are included and followed up for 1 year.



**Primary end-point: Freedom from all BARC-defined bleeding complications at 1 year after TAVI**

# Etudes en cours: CLOE



- Critère de jugement principal efficacité: décès/IDM/AVC/MTV/Embolie systémique
- Critère de jugement principal sécurité: Hémorragies vitales/majeures

# Quel traitement antithrombotique après la procédure ?

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Studies of anticoagulant strategies		

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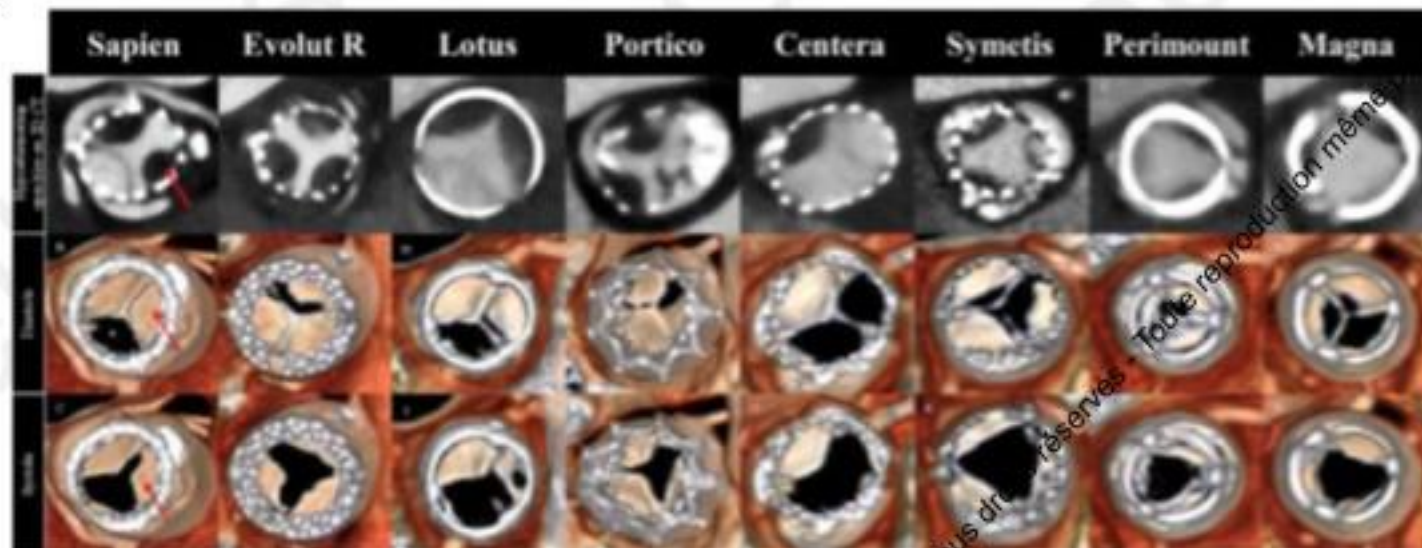
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# Chez les patients sans indication à un TAC: DAPT ou TAC ?

## SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

Chakravarty et al. Lancet 2017

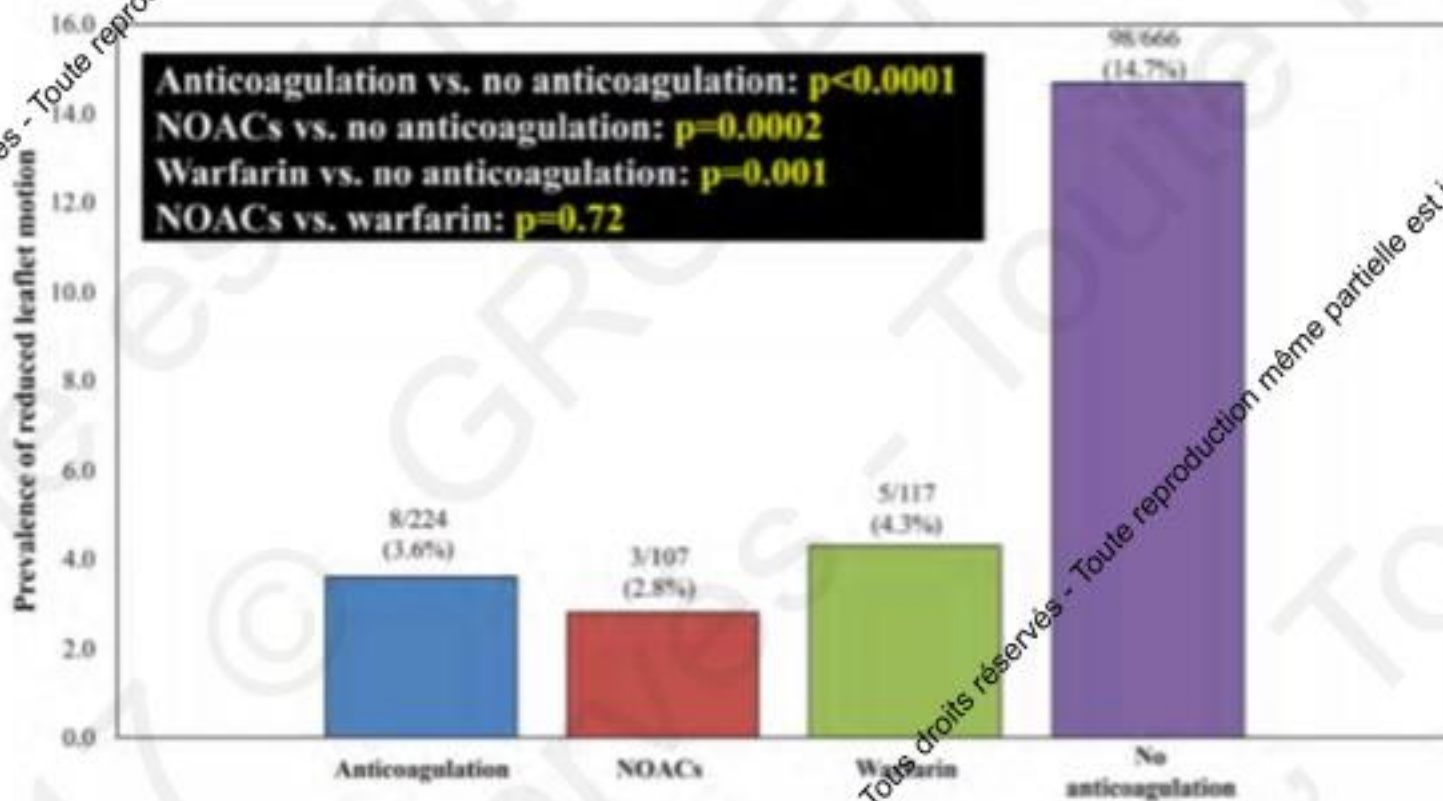
- 800 patients with interpretable CT scans were included (RESOLVE registry, n=626; SAVOR Registry, n=264)
- Incidence: **12%**: **4%** after SAVR and **13%** after TAVR ( $p < 0.001$ )



# Chez les patients sans indication à un TAC: DAPT ou TAC ?

## SUBCLINICAL LEAFLET THROMBOSIS IN BIOPROSTHETIC VALVES

Chakravarty et al. Lancet 2017



# Chez les patients sans indication à un TAC: DAPT ou TAC ?

## Impact of reduced leaflet motion on clinical outcomes

Only non-procedural events (>72 hours post-TAVR/SAVR) included

**No significant difference in strokes; but increased risk of TIAs**

	Normal leaflet motion (N=784)		Reduced leaflet motion (N=106)		Hazard ratio (95% CI)	p-value
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years		
<b>Non-procedural events</b>						
Death	34/784 (4.3%)	2.91	4/106 (3.8%)	2.66	0.96 (0.34-2.7)	0.94
Myocardial infarction	4/784 (0.5%)	0.34	1/106 (0.9%)	0.67	1.91 (0.31-17.08)	0.56
Strokes/TIAs	20/784 (2.6%)	1.75	8/106 (7.6%)	5.71	3.24 (1.43-7.50)	0.004
All strokes*	15/784 (1.9%)	1.31	4/106 (3.8%)	2.75	2.14 (0.71-6.44)	0.18
Ischemic strokes	14/784 (1.8%)	1.22	4/106 (3.8%)	2.75	2.29 (0.75-6.97)	0.14
TIAs	7/784 (0.9%)	0.60	5/106 (4.7%)	3.11	5.89 (1.87-18.60)	0.002

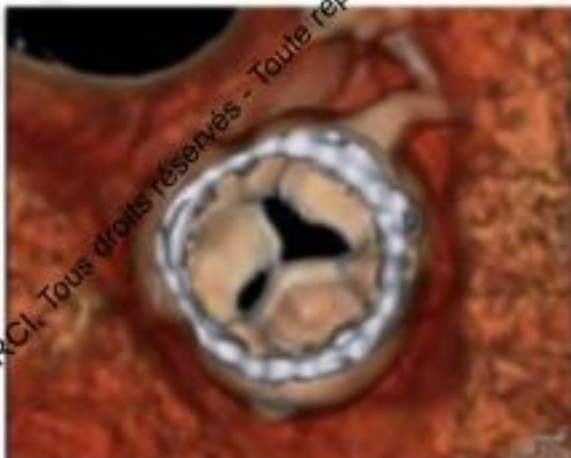
TIA=Transient ischemic attack

\* All strokes include hemorrhagic and ischemic strokes

# Chez les patients sans indication à un TAC: DAPT ou TAC ?

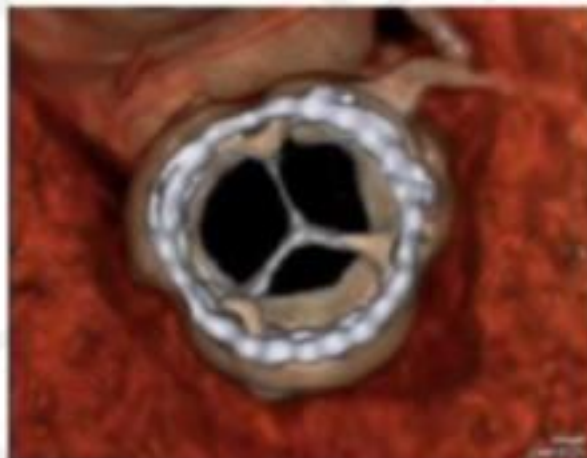
Baseline

Reduced leaflet motion



Rivaroxaban 10 mg  
For 3 months

Normal leaflet motion



6 months' rivaroxaban  
discontinuation

Reduced leaflet motion



**Reduced leaflet motion recurred in 4 out of 8 patients in whom anticoagulation was discontinued**

Mean time from discontinuation of anticoagulation to recurrence of reduced leaflet motion was  $164 \pm 109$  days

# ATLANTIS

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

1509 patients after successful TAVI procedure

Stratum 1  
Indication for OAT

Stratum 2  
No indication for OAT

R  
1:1

K  
1:1

VKA

Apixaban 5mg bid\*

DAAT/SAPT

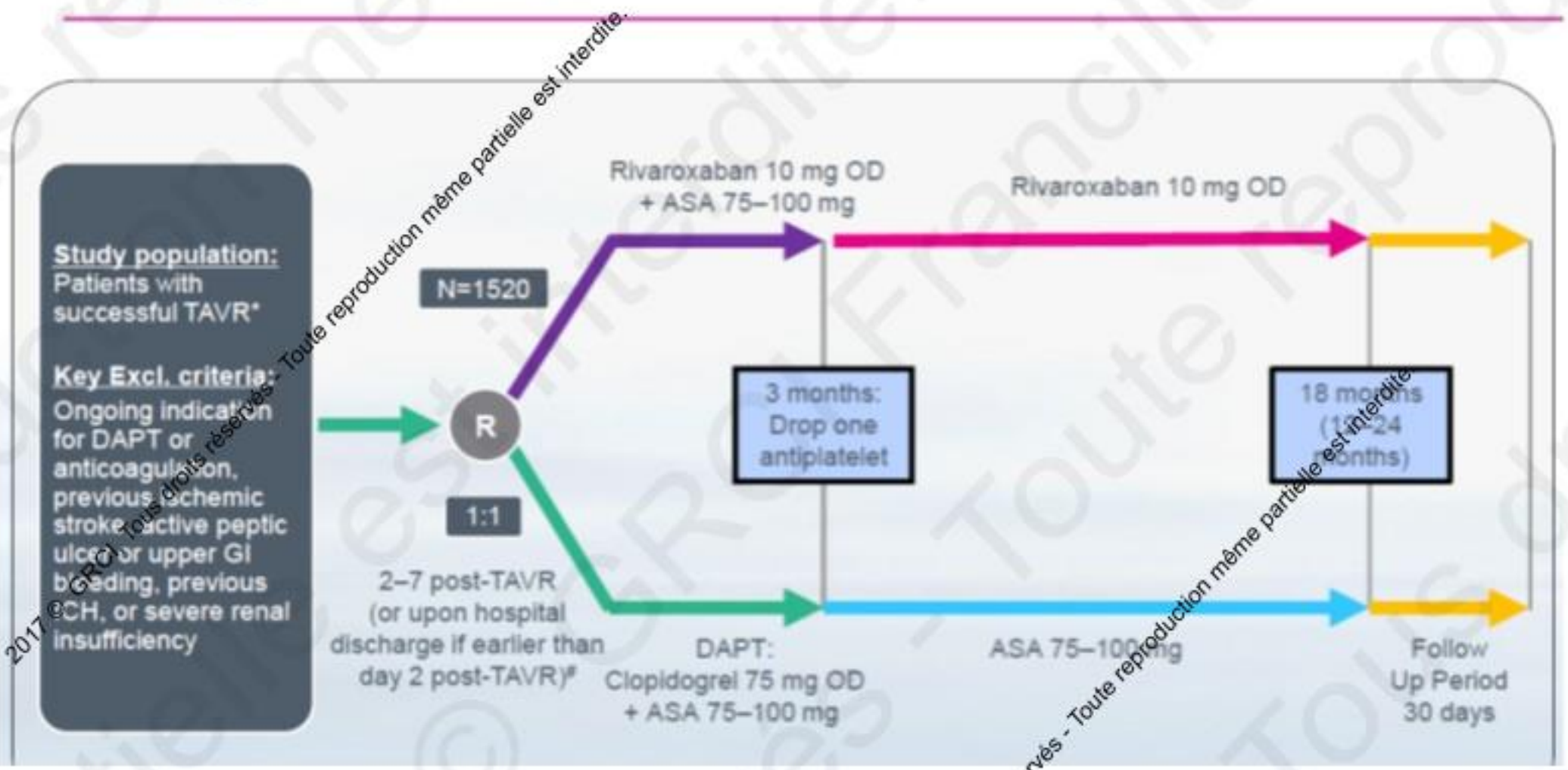
Primary end-point is a composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism, major bleedings over one year follow-up.

\*2.5mg bid if creatinine clearance 15-29ml/min or if two of the following criteria: age ≥ 80 years, weight ≤ 60kg or creatinine ≥ 1.5mg/dL (133 μmol/L).



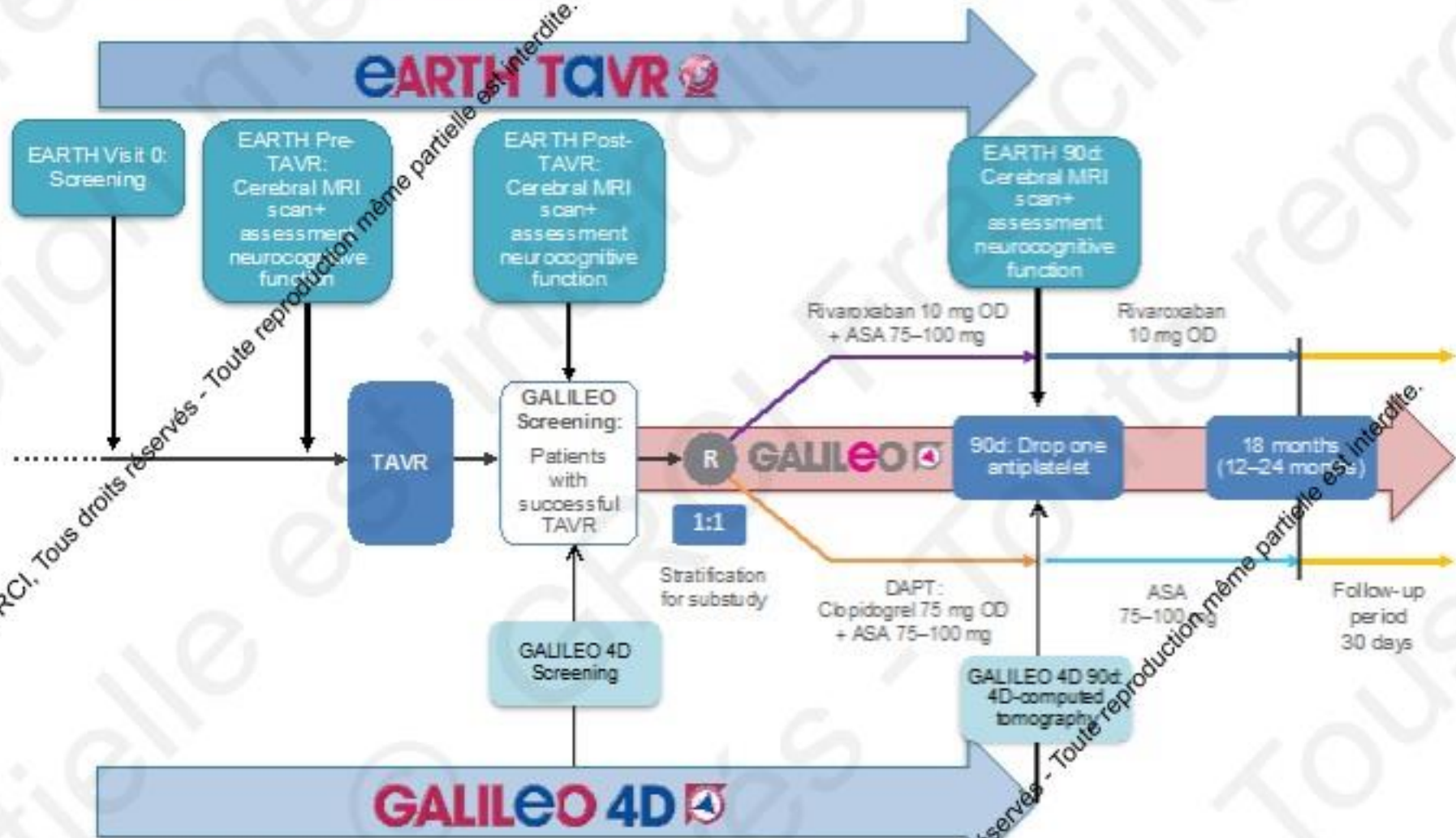


# Design overview



**Primary end-point:** Death or first adjudicated thrombo-embolic event defined as composite of all cause death and adjudicated any stroke, MI, symptomatic valve thrombosis, PE, DVT, or non-CNS SE (time frame: up to 25 months)

# EARTH, 4D CT, and GALILEO combined flow chart



<https://clinicaltrials.gov/ct2/show/NCT02833948> [accessed 10 May 2017];  
<https://clinicaltrials.gov/ct2/show/NCT02758964> [accessed 10 May 2017];  
<https://clinicaltrials.gov/ct2/show/NCT02556203> [accessed 10 May 2017]

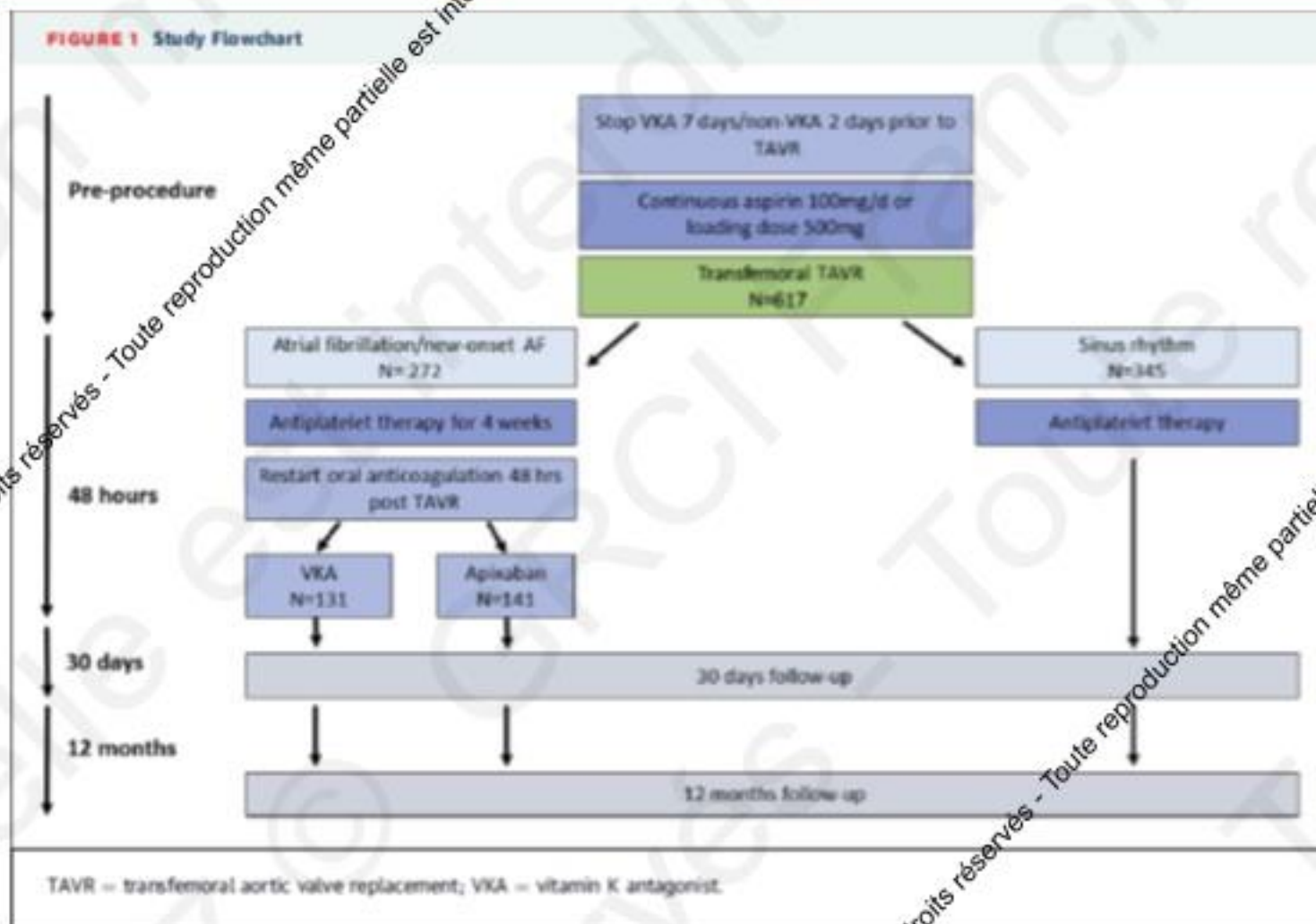
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Studies of anticoagulant strategies		<b>ATLANTIS</b> (NCT02264649) Apixaban vs. VKA <b>ENVISAGE TAVI</b> (NCT02043795) Edoxaban* vs. VKA*

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# AVK ou AOD ?



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# AVK ou AOD ?

**TABLE 5** Patients With Atrial Fibrillation: 30-Day Clinical Outcomes

	Apixaban (n = 141)	Vitamin K Antagonist (n = 131)	p Value
Early safety endpoint	13.5 (19)	30.5 (40)	<0.01
All-cause mortality	1.4 (2)	3.8 (5)	0.22
Disabling and nondisabling stroke	2.1 (3)	5.3 (7)	0.17
Intracerebral bleeding	0.7 (1)	0 (0)	0.34
Acute kidney injury stages 2 and 3	2.1 (3)	8.4 (11)	<0.01
Life-threatening bleeding	3.5 (5)	5.3 (7)	<0.01
Major vascular complications	3.5 (5)	7.6 (10)	0.09
Valve dysfunction requiring a repeat procedure	0 (0)	0 (0)	-
Endocarditis	0 (0)	0 (0)	-

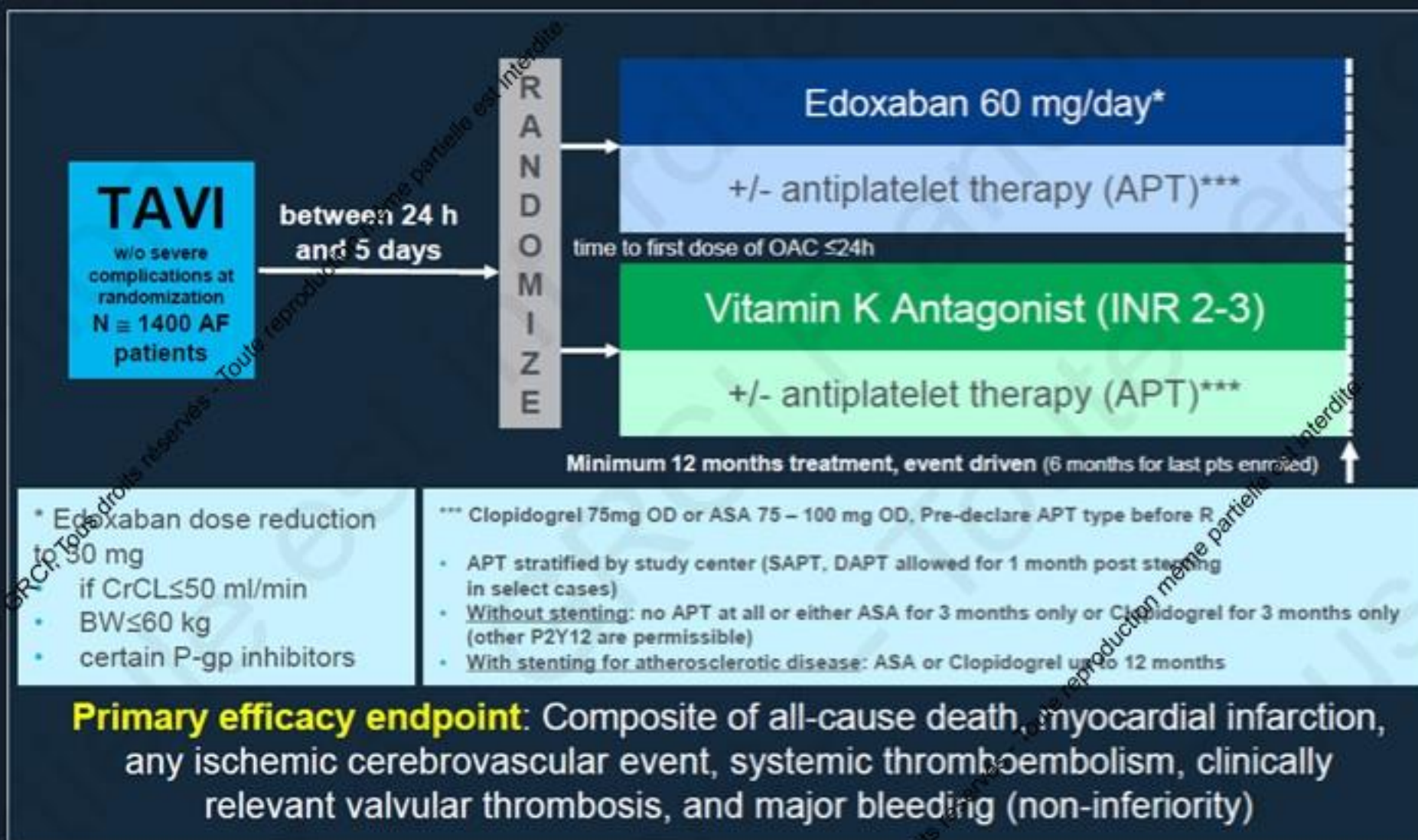
Values are % (n).

**TABLE 6** Patients With Atrial Fibrillation: 12-Month Follow-Up

	Apixaban (n = 81)	Vitamin K Antagonist (n = 50)	p Value
MACE	27.2 (22)	18.0 (9)	0.34
All-cause mortality	23.4 (19)	12.0 (6)	0.18
Disabling and nondisabling stroke	1.2 (1)	2.0 (1)	0.73
Rehospitalization	15.7 (14)	16.0 (8)	0.87
Secondary outcome measure*	24.7 (20)	14 (7)	0.23

Values are % (n). \*All-cause mortality and all stroke.  
MACE = major adverse cardiac event.

# ENVISAGE TAVI AF: Design Overview



# ATLANTIS

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

1509 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\*

DAPI/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 15-29ml/min or if two of the following criteria: age ≥ 80 years, weight ≤ 60kg or creatinine ≥ 1.5mg/dL (133 μmol/L).

# Conclusions

- **Le traitement anti-thrombotique est resté longtemps empirique après un TAVI**
- **De nombreuses études sont en cours pour préciser les meilleures stratégies thérapeutiques**
- **Chez les patients sans indication formelle à un TAC:**
  - SAPT Vs. DAPT: plutôt SAPT (ARTE, POPular TAVI, CHLOE)
  - DAPT Vs. AVK ou AOD (AUREA, ATLANTIS, GALILEO)
- **Chez les patients ayant une indication à un TAC:**
  - AVK Vs. AOD (ATLANTIS, ENVISAGE TAVI AF)
  - AVK Vs. AVK+Clopidogrel (AVATAR, POPular TAVI, CHLOE)



# MERCI POUR VOTRE ATTENTION



# Notre stratégie à Rouen

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- **Pas d'indication à un TAC**
  - Pas de dose de charge de clopidogrel (TF et TA)
  - Bas risque hémorragique: DAPT 1 mois puis SAPT
  - Haut risque hémorragique: SAPT
- **Indication à un TAC**
  - Reprise du tt habituel le jour même sans relai héparine ni association avec des antiagrégants
- **Cas particulier d'un stenting avant TAVI et TAC**
  - Pas de trithérapie
  - Clopidogrel et AVK/AOD si angioplastie < 1 an
  - AVK/AOD seul si angioplastie > 1 an

# Quel traitement antithrombotique après la procédure: Etudes en cours

	Pas d'indication à un TAC	Indication à un TAC
<b>Stratégies anti-agrégants</b>	<ul style="list-style-type: none"> <li>• <b>ARTE</b> (SAPT Vs. DAPT)</li> <li>• <b>POPular TAVI</b> (SAPT Vs. DAPT)</li> <li>• <b>CLOE</b> (SAPT Vs. DAPT)</li> </ul>	<ul style="list-style-type: none"> <li>• <b>AVATAR</b> (Asp+AVK Vs. AVK)</li> <li>• <b>POPular TAVI</b> (clopidogrel +AVK Vs. AVK)</li> <li>• <b>CLOE</b> (clopidogrel +AVK Vs. AVK)</li> </ul>
<b>Antiagrégants Vs. TAC</b>	<ul style="list-style-type: none"> <li>• <b>AUREA</b> (DAPT Vs. AVK)</li> <li>• <b>GALILEO</b> (Rivaroxaban+Asp Vs. DAPT)</li> <li>• <b>ATLANTIS</b> (Apixaban Vs. SAPT/DAPT)</li> </ul>	
<b>Stratégies anticoagulants</b>		<ul style="list-style-type: none"> <li>• <b>ATLANTIS</b> (Apixaban Vs. AVK)</li> <li>• <b>ENVISAGE TAVI</b> (Edoxaban Vs. AVK)</li> </ul>