Conoscere e Curare il Cuore 2018

SABATO 17 MARZO

IL RISCHIO DI ICTUS DOPO TAVI. IL RUOLO DEI NAO

Raffaele De Caterina

Istituto di Cardiologia
Università degli Studi "G. d'Annunzio"
di Chieti - Pescara

Conoscere e Curare il Cuore 2018

XXXV Congresso di Cardiologia
del Centro per la Lotta contro l'Infarto Fondazione Onlus

Firenze, 16-18 marzo 2018

Palazzo dei Congressi

Simposio

LA VALVOLA AORTICA

17 marzo 2018 - ore 9:50-10:55

Il rischio di ictus dopo TAVI – Il ruolo dei NAO

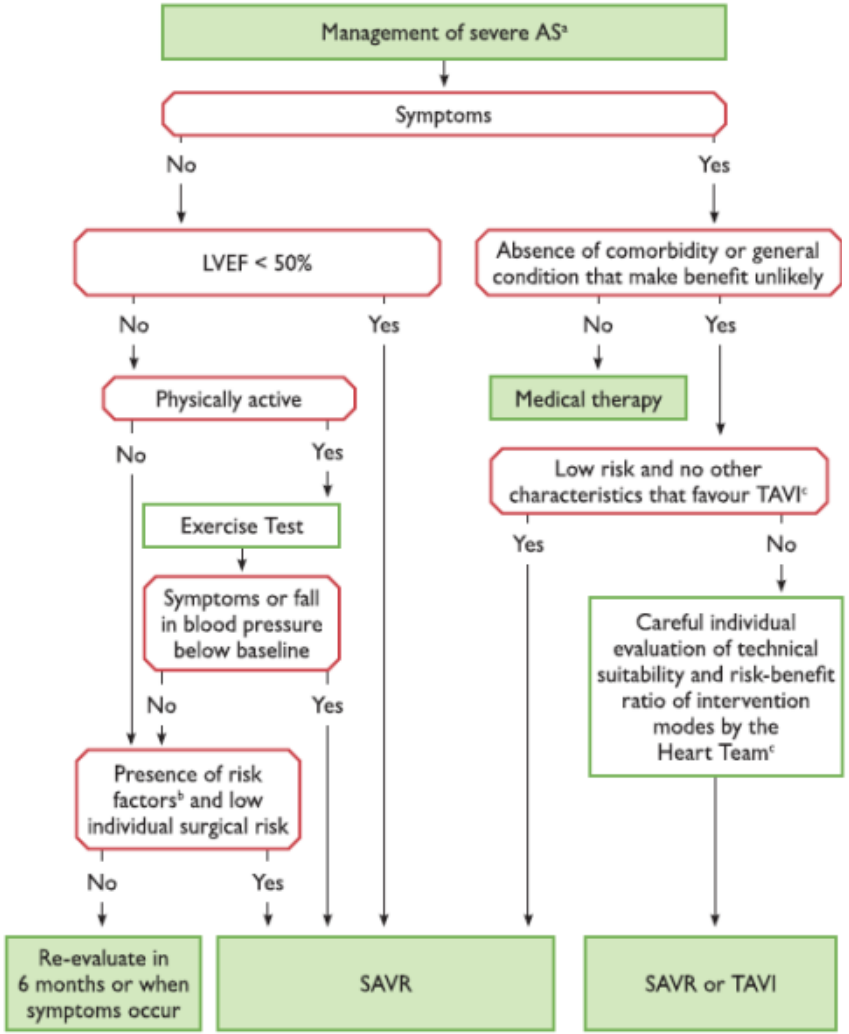
Raffaele De Caterina

Università "G. d'Annunzio" – Chieti e
Fondazione "G. Monasterio" – Pisa, Italia

17 marzo 2018, 10:05-10:20 - 15 min. + 20 min. disc.

Prof. Raffaele De Caterina
Conflitti d'interesse

- Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
- Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE AF-TIMI 38, Re-DUAL PCI
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck, Portola



TAVI have now a recognized role in the management of aortic stenosis

2017 ESC/EACTS Guidelines for the management of valvular heart disease

The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

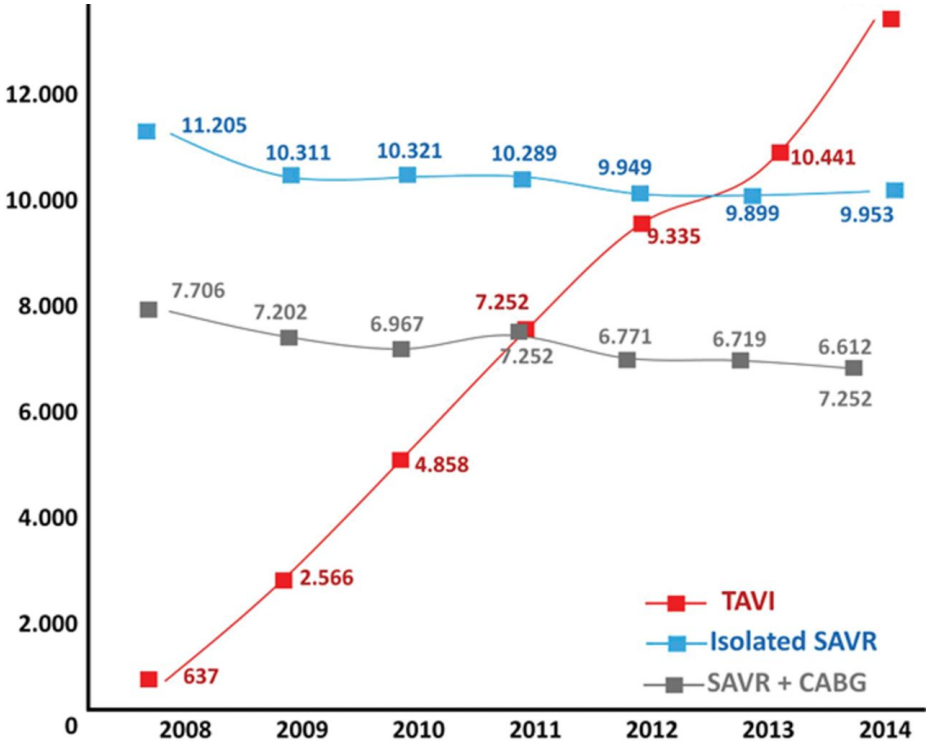
Baumgartner H et al., EHJ 2017 00, 1–53 doi:10.1093/eurheartj/ehx391

TAVI commercial approval in USA in 2011 for excessive-risk patients; in 2012 for high-risk; in 2016 for intermediate-risk patients

Perioperative risk of death – the Society of Thoracic Surgeons (STS) score

- low-risk: <4%
- intermediate-risk: 4-8%
- high-risk: >8%
- excessive-risk: >12%

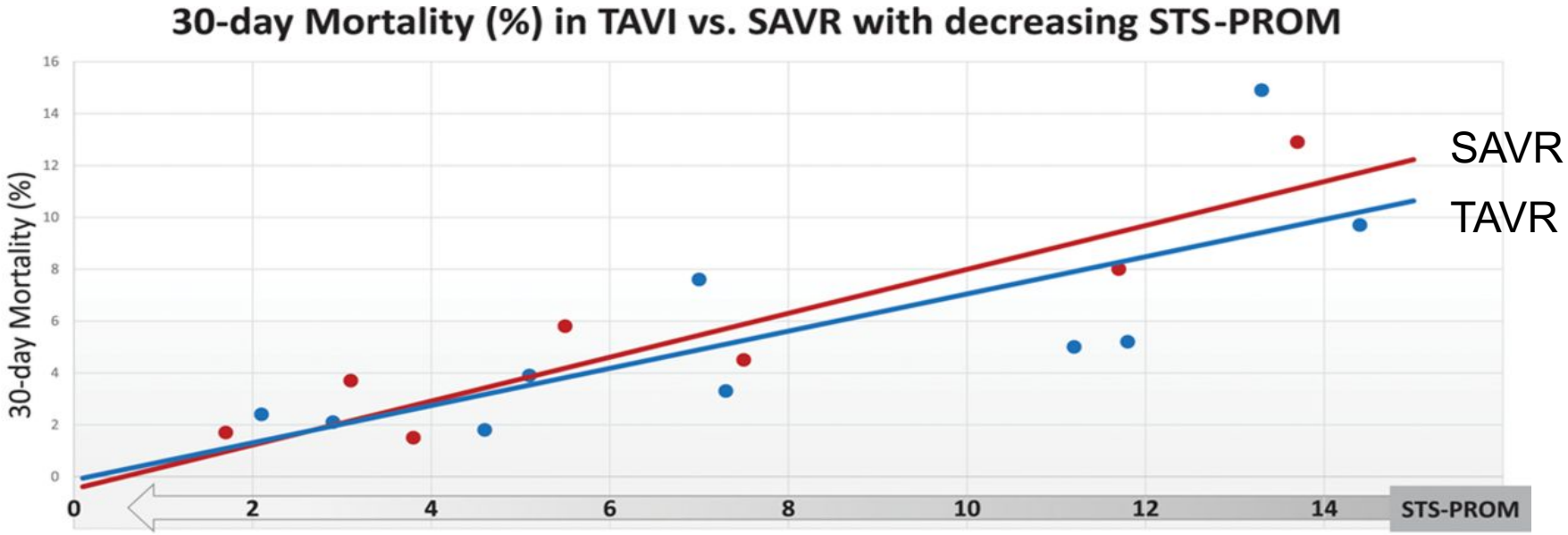
Temporal trends of transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) performance in Germany between 2008 and 2014



American Heart Association.

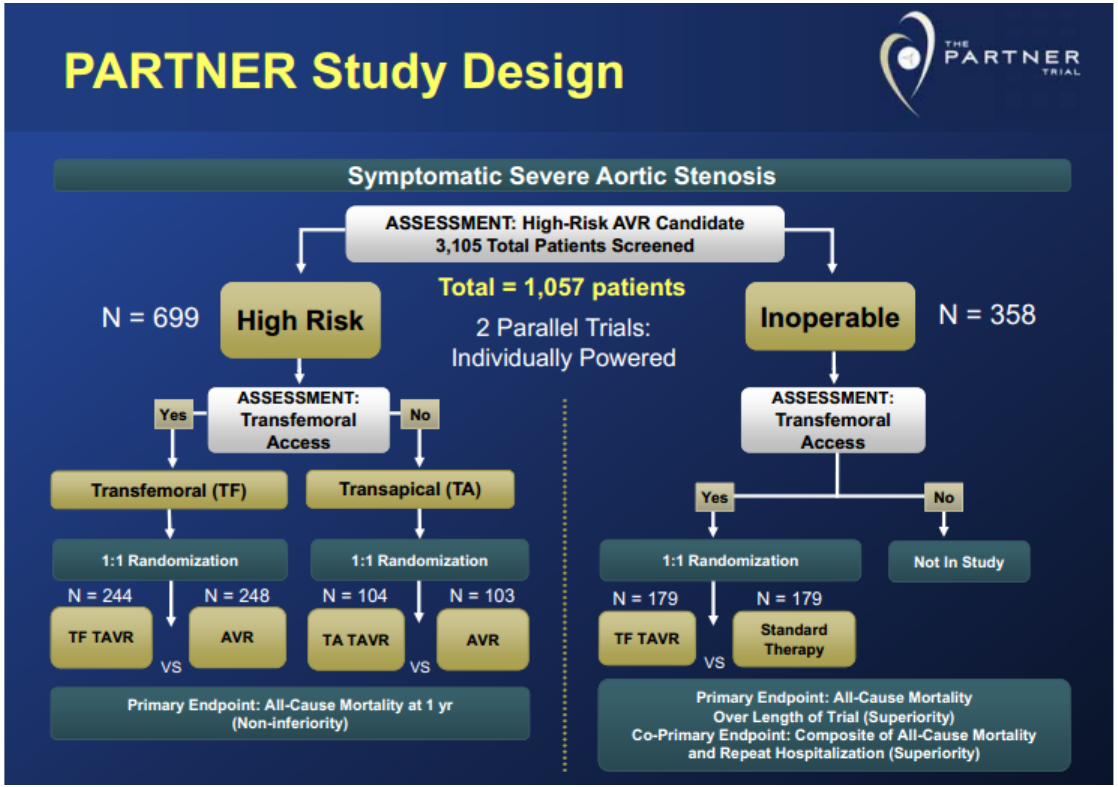
Abdelghani M, and Serruys PW - Circ Cardiovasc Interv. 2016;9:e002944

Mortality after transcatheter aortic valve implantation (TAVI) vs surgical aortic valve replacement (SAVR) with decreasing Society of Thoracic Surgeons-predicted risk of operative mortality (STS-PROM)



American Heart Association.

Abdelghani M, and Serruys PW - Circ Cardiovasc Interv. 2016;9:e002944



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2010 VOL. 363 NO. 17

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela S. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*

Leon M. et al.
N Engl J Med 2010;363:1597-1607.

Neurological Events at 30 Days and 1 Year
All Patients (N=699)

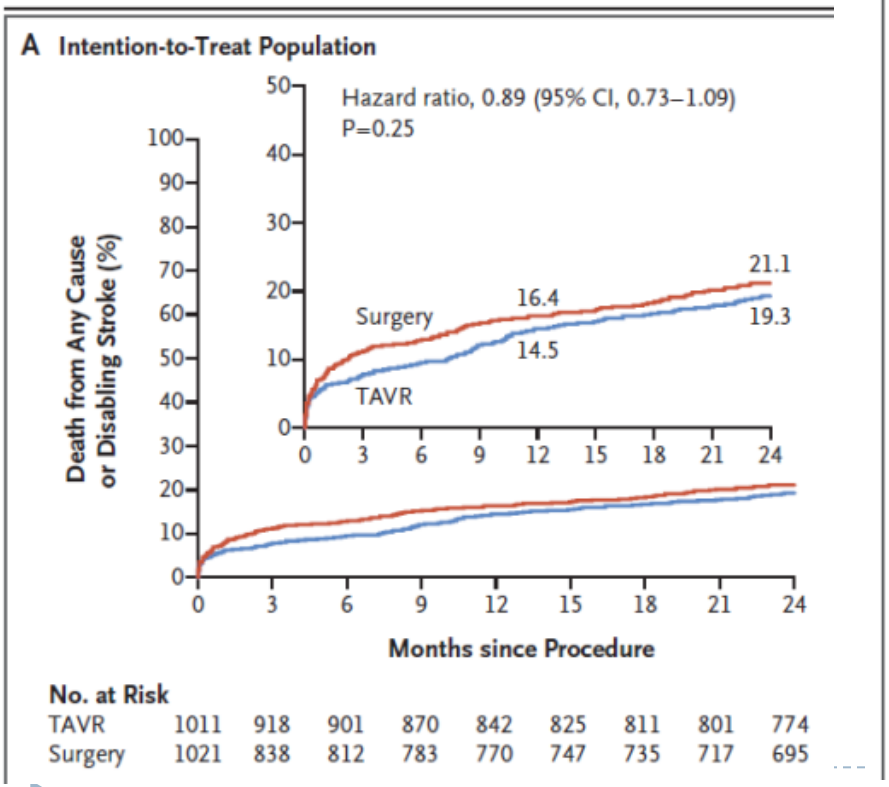
THE PARTNER TRIAL

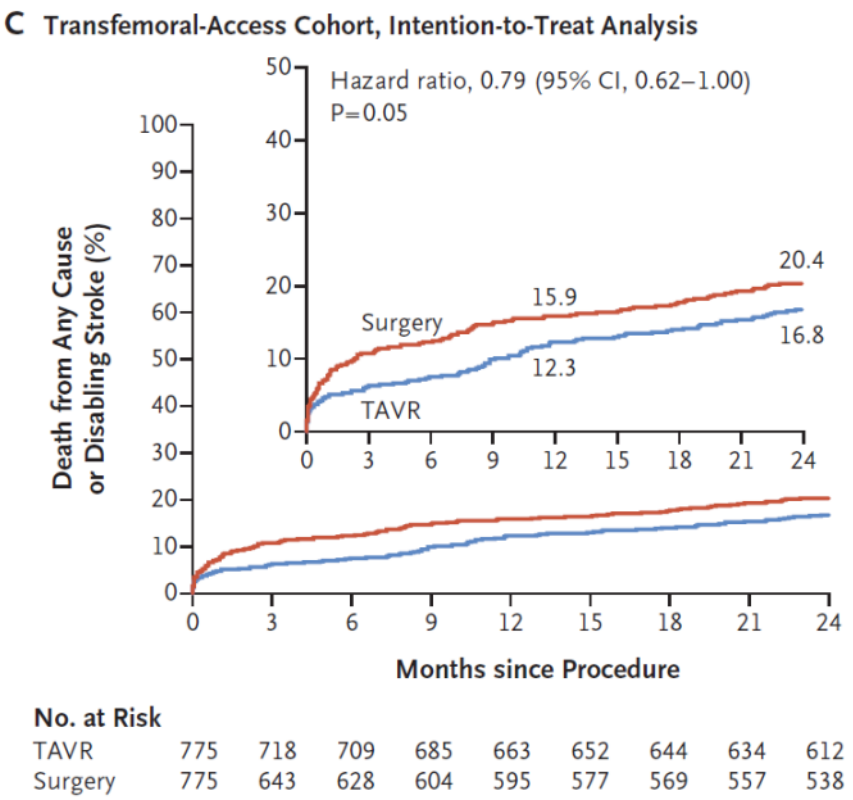
Outcome	30 Days TAVR (N = 348)	30 Days AVR (N = 351)	30 Days p-value	1 Year TAVR (N = 348)	1 Year AVR (N = 351)	1 Year p-value
All Stroke or TIA – no. (%)	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
TIA – no. (%)	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
All Stroke – no. (%)	16 (4.6)	8 (2.4)	0.12	20 (6.0)	10 (3.2)	0.08
Major Stroke – no. (%)	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07
Minor Stroke – no. (%)	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Death/maj stroke – no. (%)	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68

Results from the Placement of Aortic Transcatheter Valves (PARTNER) 1 high risk group randomized trial

Leon M. et al.
N Engl J Med 2010;363:1597-1607.

Results from the Placement of Aortic Transcatheter Valves (PARTNER) 2 cohort A randomized trial





Leon M. et al. N Engl J Med 2016;374:1609-20.

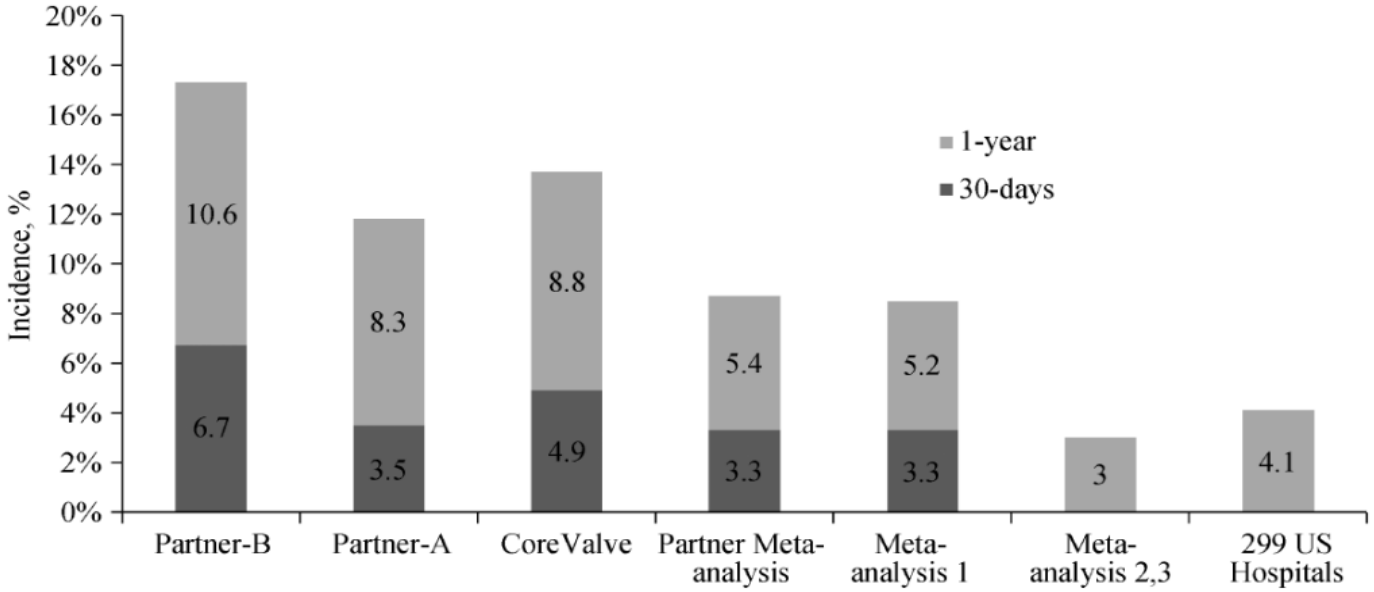
Comparable risk of stroke in TAVR vs surgery from the Placement of Aortic Transcatheter Valves (PARTNER) 2 cohort A randomized trial

Table 2. Clinical End Points at 30 Days, 1 Year, and 2 Years.*

End Point	At 30 Days			At 1 Year			At 2 Years		
	TAVR (N=1011)	Surgery (N=1021)	P Value	TAVR (N=1011)	Surgery (N=1021)	P Value	TAVR (N=1011)	Surgery (N=1021)	P Value
	no. of patients (%)			*no. of patients (%)*			*no. of patients (%)*		
Any stroke	55 (5.5)	61 (6.1)	0.57	78 (8.0)	79 (8.1)	0.88	91 (9.5)	85 (8.9)	0.67
Disabling stroke	32 (3.2)	43 (4.3)	0.20	49 (5.0)	56 (5.8)	0.46	59 (6.2)	61 (6.4)	0.83
Nondisabling stroke	23 (2.3)	18 (1.8)	0.43	30 (3.0)	24 (2.5)	0.44	33 (3.4)	27 (2.9)	0.51

Leon M. et al. N Engl J Med 2016;374:1609-20.

Decreasing rates of stroke in TAVI trials over time



Davlouros PA et al. *J Geriatr Cardiol* 2018; 15: 95-104

Incidence of stroke after TAVI

- Currently <5%.
- In an analysis examining the STS/American College of Cardiology Transcatheter Valve Therapy Registry from November 2011 to June 2013, stroke rate of 4.1% at 1 year in a large cohort of 12,182 patients.

Holmes DR,et al. JAMA 2015;313:1019.

Stroke after TAVI – still a major issue

- Increases mortality by 3.5 %
- Increases all-cause morbidity
- impacts on cognitive function and quality of life

Eggebrecht H, et al. EuroIntervention 2012;8:129–38.

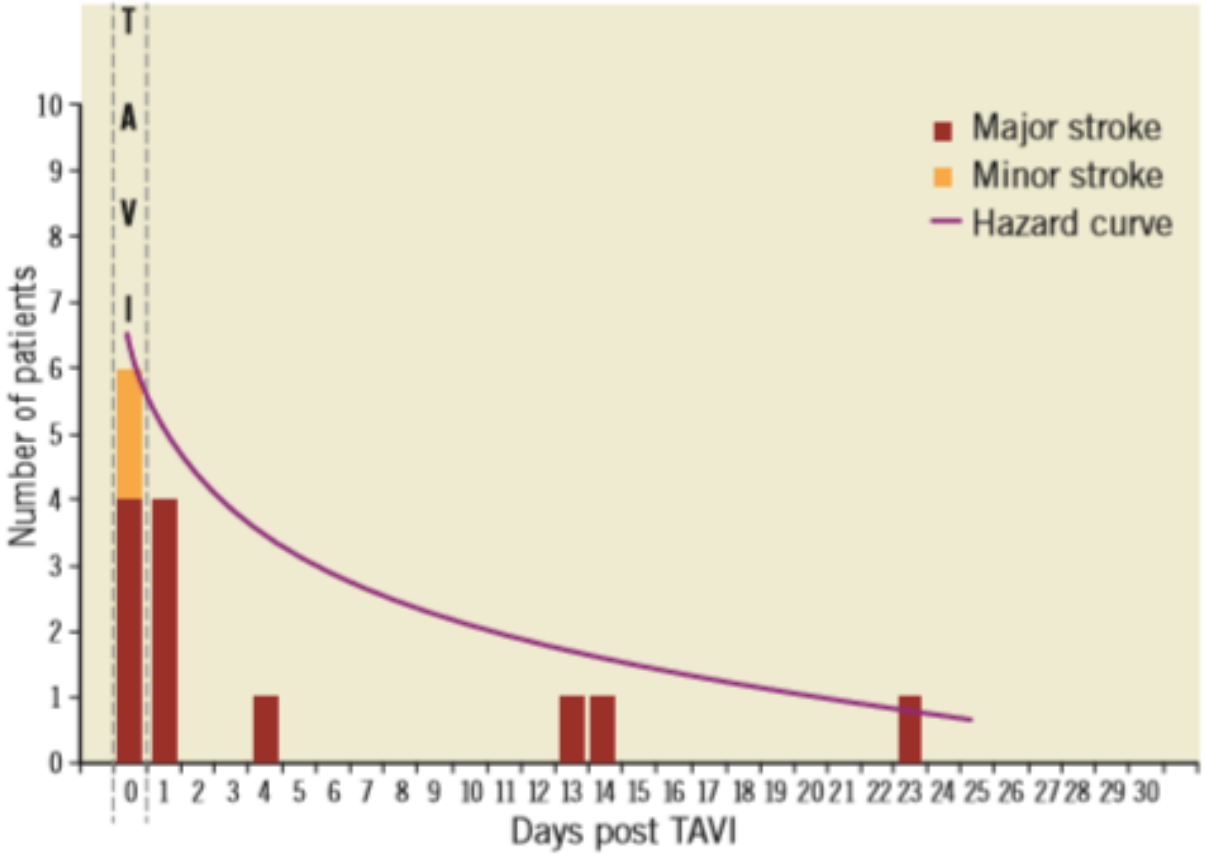


Figure 1. *Frequency distribution of cerebrovascular accidents within 30 days after transcatheter aortic valve implantation.*

Stortecky S. et al; EuroIntervention 2012;8:62-70

Stroke rates increase throughout the first year

In a meta-analysis of 10,037 patients who underwent TAVR (2004-2011) in Europe and North America, the incidence of stroke was

- 1.5% ± 1.4% at 24 hours
- 3.3% ± 1.8% at 30 days
- 5.2% ± 3.4% at 1 year

Eggebrecht H, et al. EuroIntervention 2012;8:129–38.

So, what can we do?

The multiple etiologies of stroke after TAVI

Procedural factors	Catheter manipulation within the proximal atheromatous thoracic aorta
Atheromatous and calcific emboli	Wire, catheter, and valve manipulation across a calcific aortic valve
	Balloon aortic valvuloplasty
	Valve deployment
	Balloon dilation of the deployed aortic valve
Alternative emboli	Air embolism
	Thromboembolism
Nonembolic issues	Watershed ischemia due to hypotension with hypoperfusion
	Acute hypertension after valve deployment
Nonprocedural factors	New atrial fibrillation
	Chronic atrial fibrillation
	Prior stroke
	Diabetes
	Atheromatous arterial disease
	Chronic hypertension

Nombela-Franco et al 2012
Freeman et al. 2014

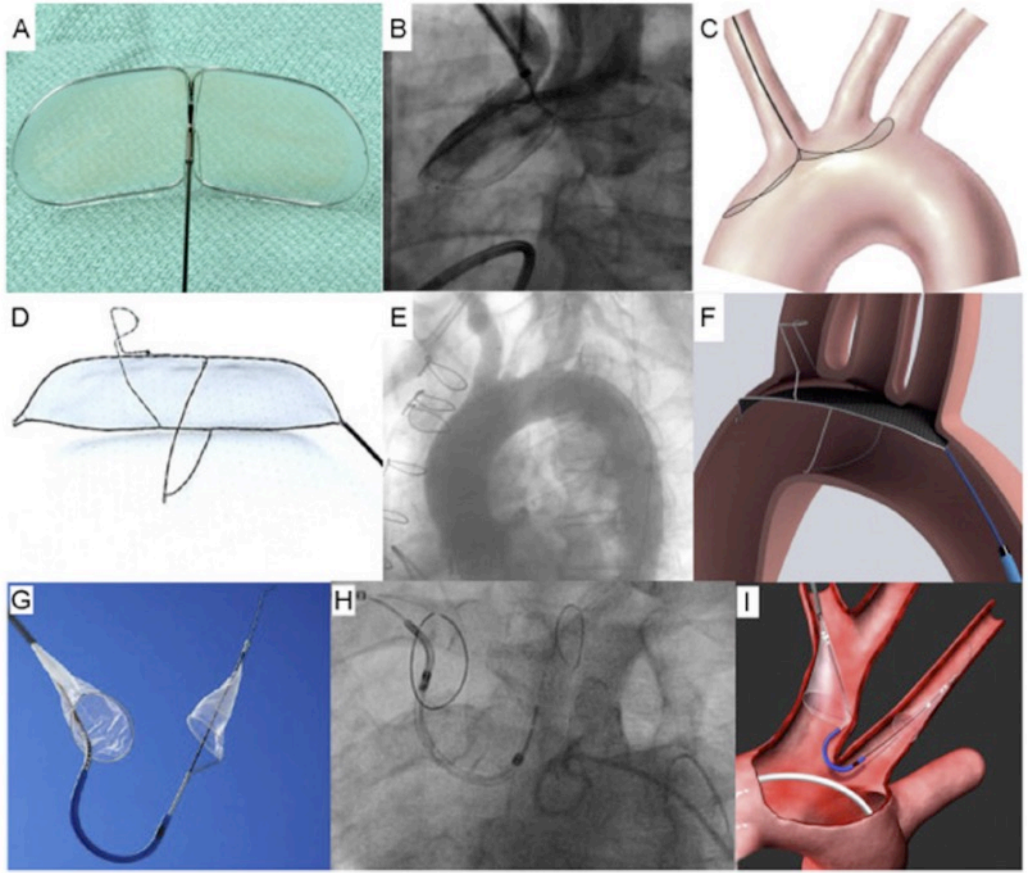
Procedure-dependent reasons for cerebral embolism during aortic valve replacement

Transfemoral TAVR	Transapical TAVR	SAVR
Manipulation through diagnostic catheters and large valve delivery systems	Air embolism through catheter changes and final catheter retrieval	Plaque dislocation due to - Insertion of the aortic cannula - Cross-clamping - Declamping
Balloon Valvuloplasty		Solid embolism during exercising the calcified leaflets
Positioning and implantation of the balloon-mounted valve		Air embolism through insufficient deairing
Balloon post-dilatation		
Hypoperfusion due to rapid passing		

TAVR: transcatheter aortic valve replacement; SAVR: surgical aortic valve replacement.

Grabert S et al, Interactive CardioVascular and Thoracic Surgery23(2016)469–476

Embolic protection devices



Histopathologic illustrations of captured debris retrieved from the Claret Montage Dual Filter

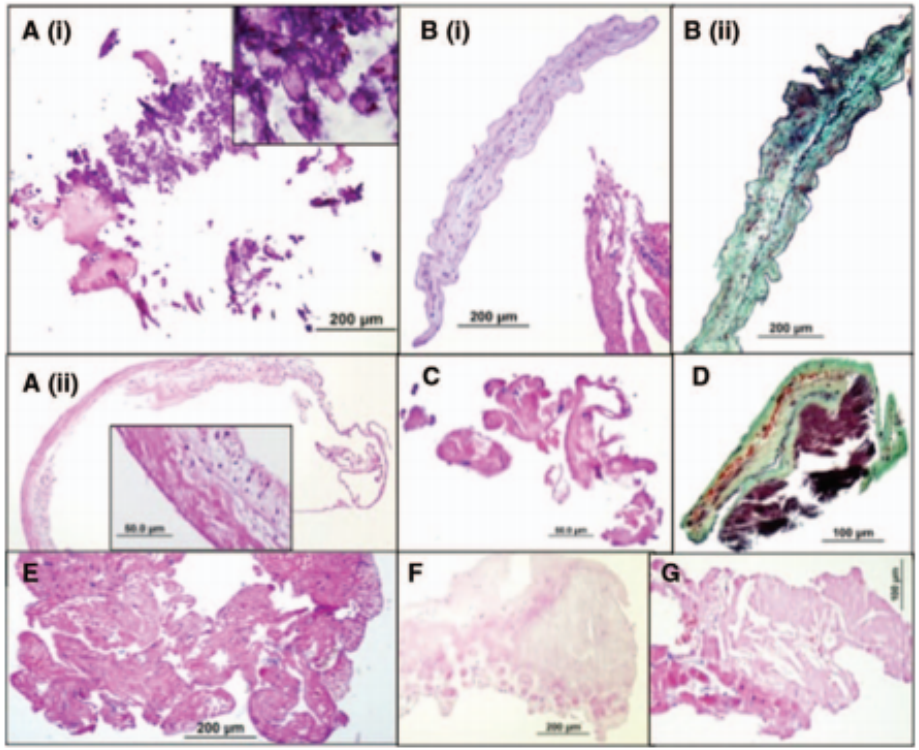
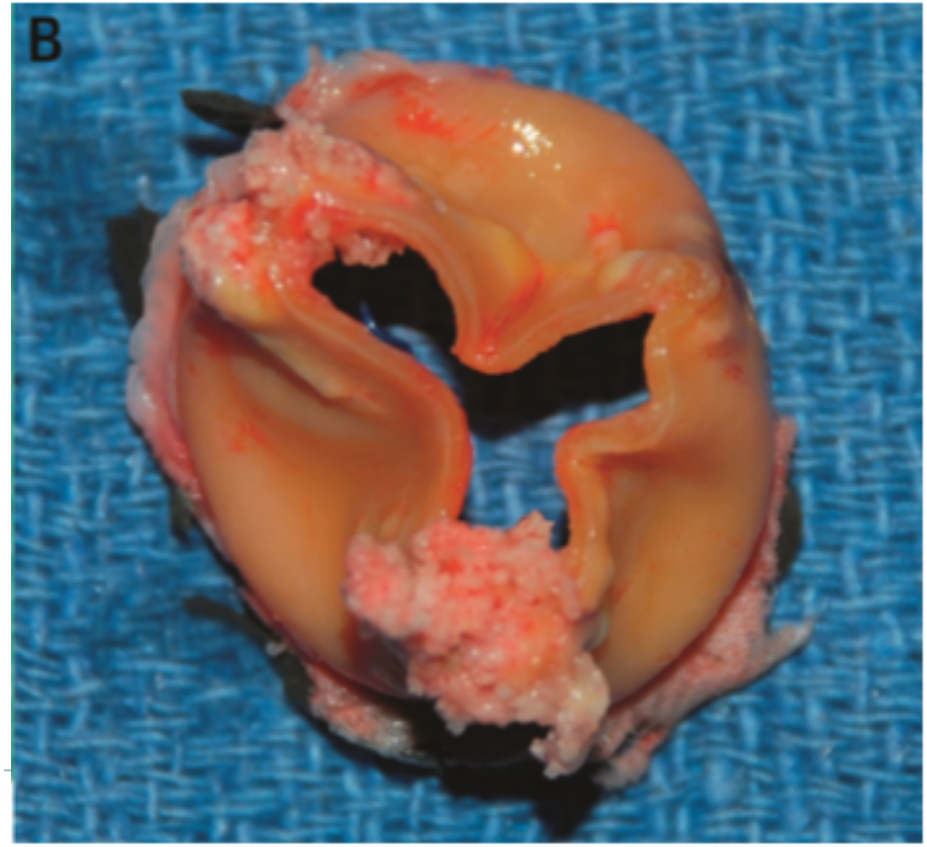


Figure 4. Histopathologic illustrations of captured debris retrieved from the Claret Montage Dual Filter. **A(i),** The calcium fragment. **A(ii),** The valve fragment. **B(i),** Valve fragments, H&E stained; note proteoglycan-rich matrix. **B(ii),** Elastic fibers and proteoglycans matrix are better appreciated on the Movat-stained section. **C,** Collagen fragments. **D,** Fragment of collagen and proteoglycan with thrombus (Movat stained). **E,** Thrombotic material consisting mostly of fibrin strands with trapped red blood cells and rare neutrophils. **F,** Valve tissue showing the presence of a nodule of Aranti. **G,** Necrotic material with thrombus, H&E stained. H&E indicates hematoxylin and eosin.

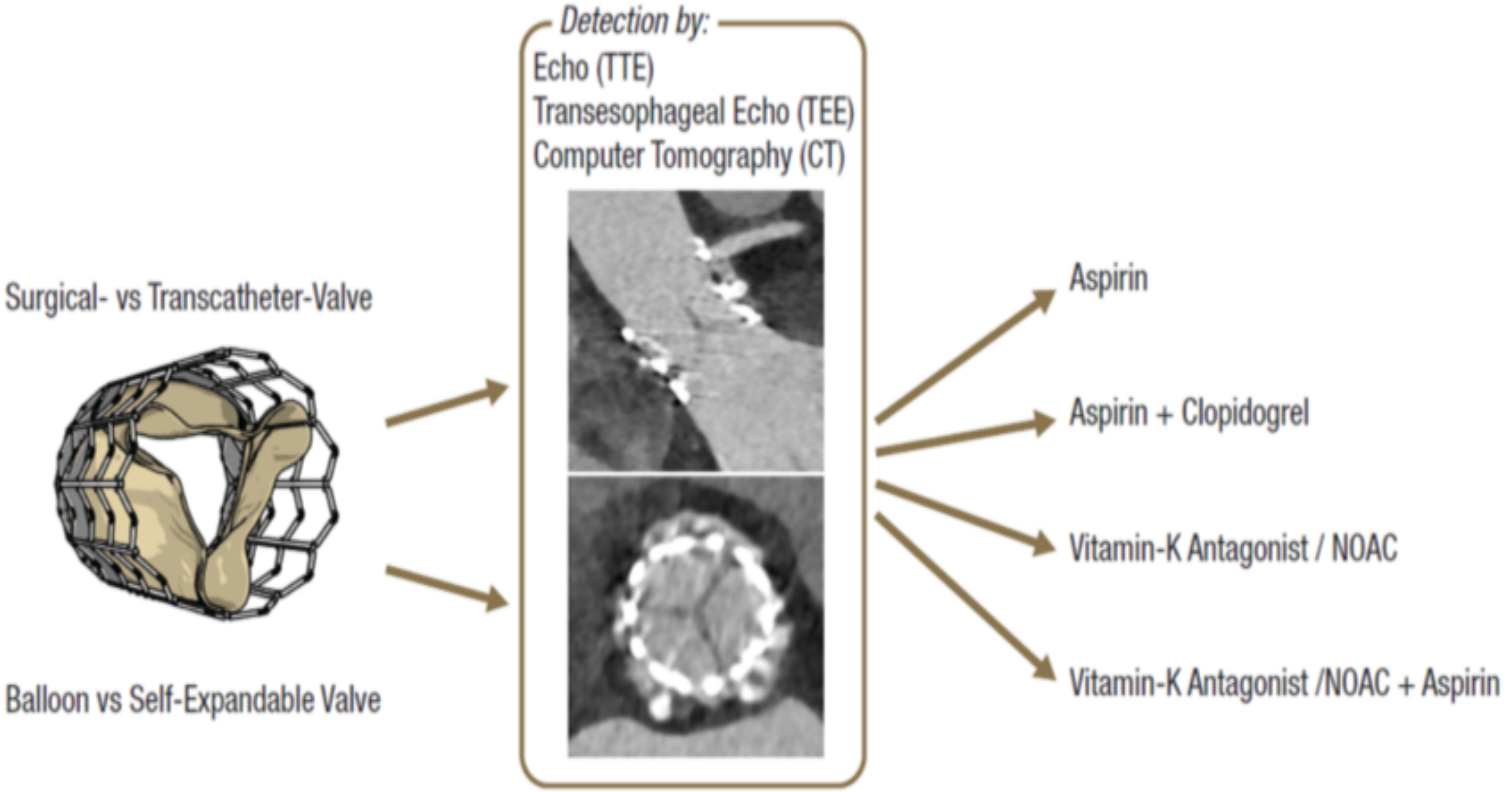
Van Mieghem NM et al, Circulation. 2013;127:2194-2201

An example of an explanted CoreValve with immobile leaflets due to the presence of thrombi on the aortic side

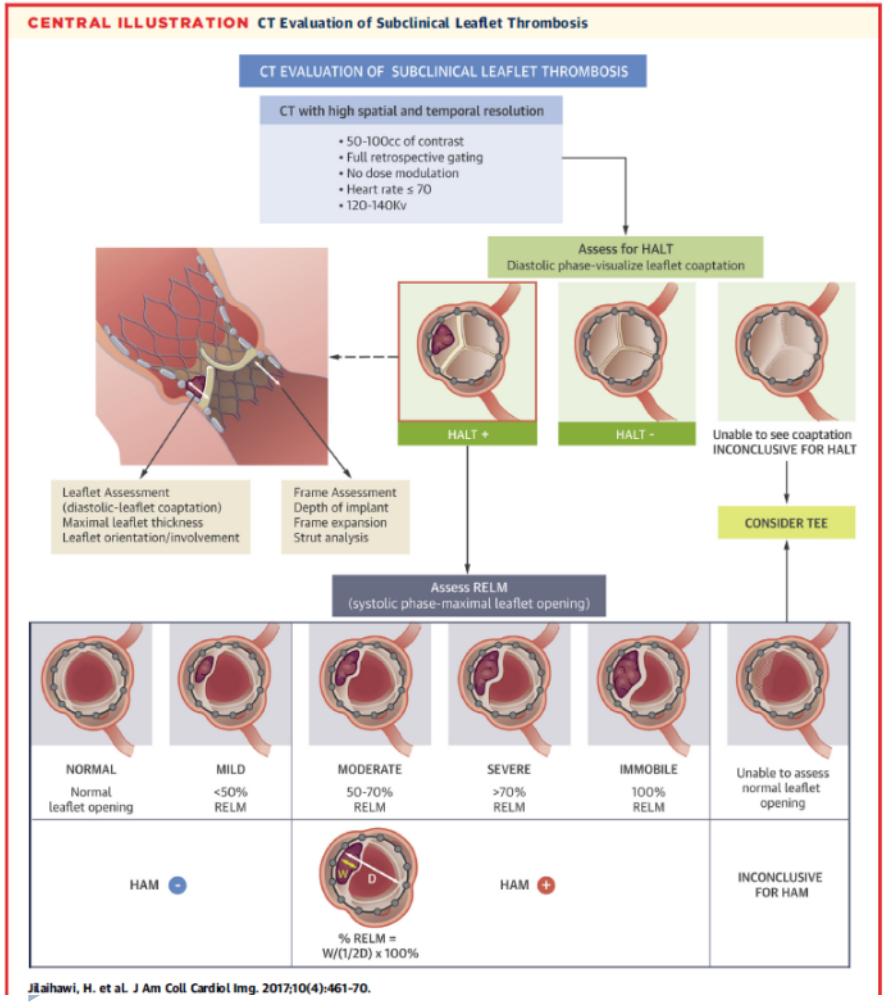


Puri R et al, JACC 2017

Thrombosis of TAVI prosthesis



Schirmer SH et al, Clin Res Cardiol (2017) 106:79–84



VIEWS

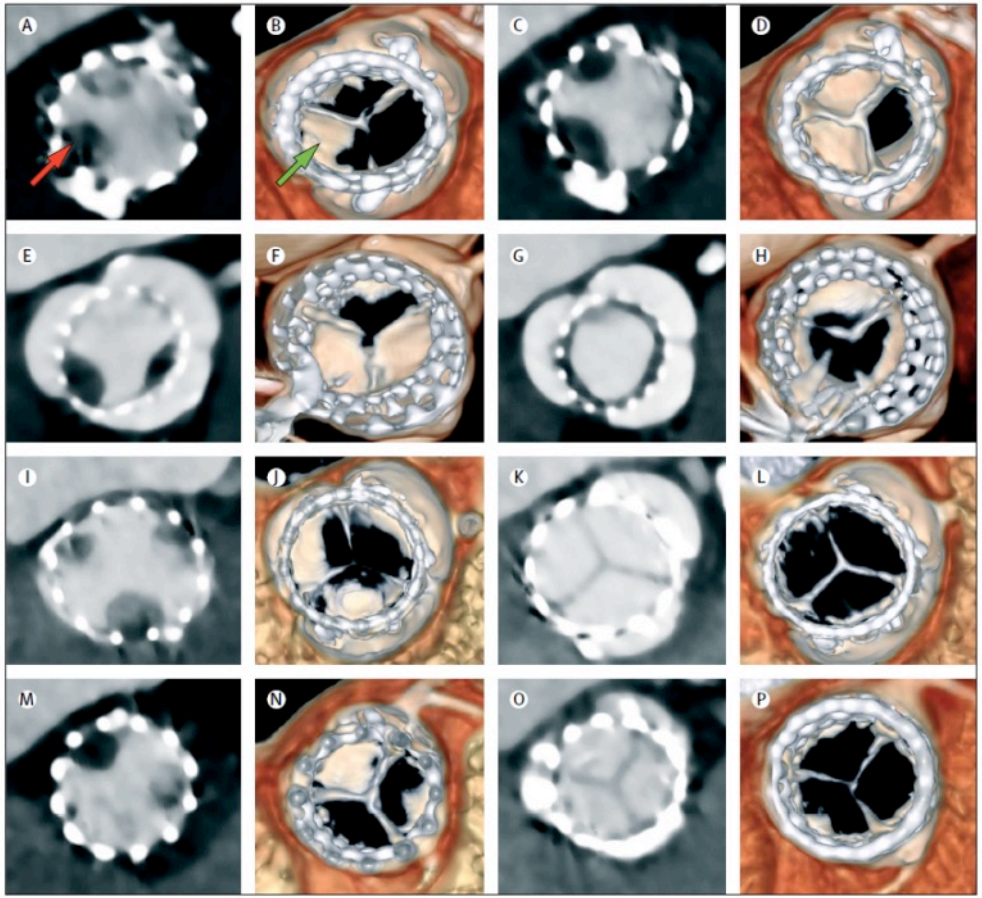
STATE-OF-THE-ART PAPERS

Systematic CT Methodology for the Evaluation of Subclinical Leaflet Thrombosis

Hasan Jilaihawi, MD,[a] Federico M. Asch, MD,[b] Eric Manasse, MD,[c] Carlos E. Ruiz, MD,[d] Vladimir Jelnin, MD,[d] Mohammad Kashif, MD,[e] Hiroyuki Kawamori, MD,[e] Yoshio Maeno, MD,[e] Yoshio Kazuno, MD,[e] Nobuyuki Takahashi, MD,[e] Richard Olson, BSME, MBA,[c] Joe Alkhatib, BSME,[c] Daniel Berman, MD,[e] John Friedman, MD,[e] Norman Gellada, RT, CRT,[e] Tarun Chakravarty, MD,[e] Raj R. Makkar, MD[e]

J Am Coll Cardiol Img
2017;10:461–70

Effect of dual antiplatelet therapy versus anticoagulation on hypoattenuating opacities and reduced leaflet motion



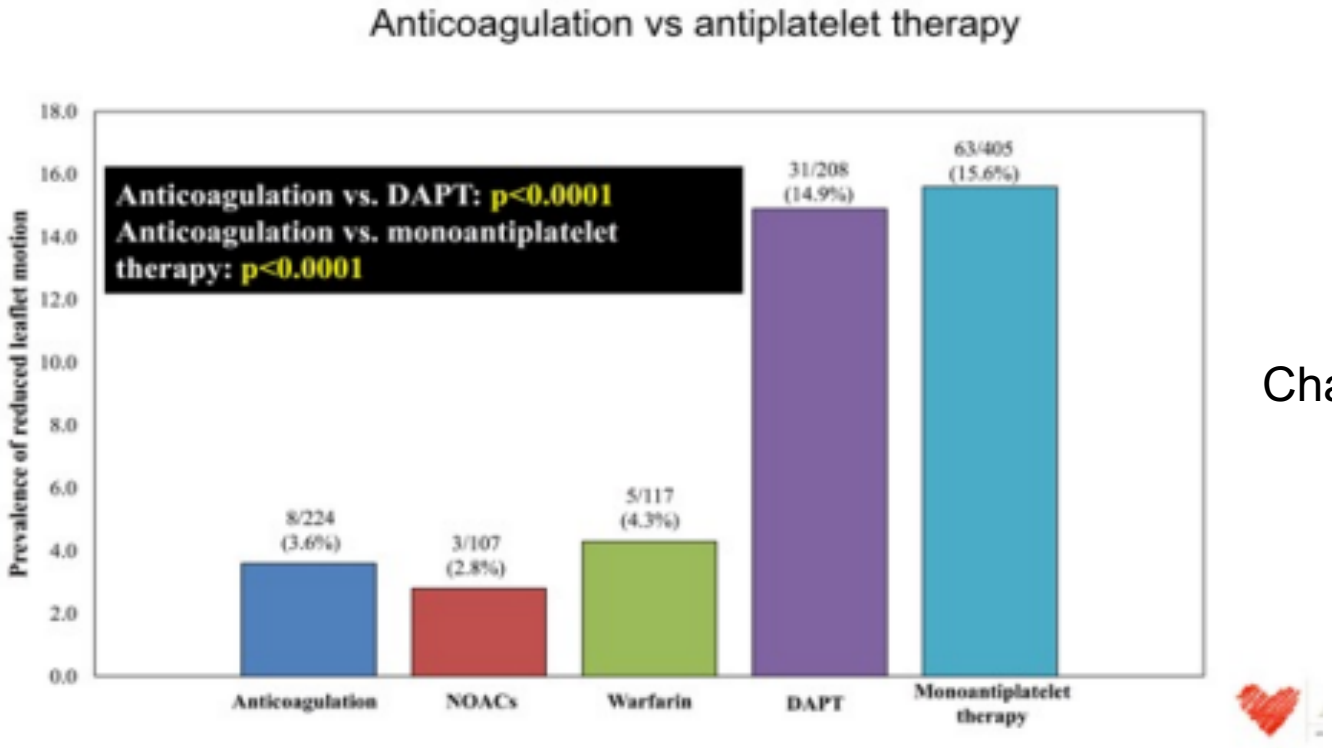
Chakravarty T. et al.,
***Lancet* 2017; 389: 2383–92**

Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study

- Subclinical leaflet thrombosis occurred frequently in bioprosthetic aortic valves, more frequently in transcatheter then in surgical valves
- Anticoagulation (both NOACs and warfarin), but not dual antiplatelet therapy, was effective in prevention or treatment of subclinical leaflet thrombosis
- Subclinical leaflet thrombosis was associated with increased rates of TIA and stroke +TIA
- Most patients with reduced leaflet motion detected with CT scanning had echocardiographic gradients of less than 20 mm Hg.
- Despite excellent outcomes after TAVI with the new generation valves, prevention and treatment of subclinical leaflet thrombosis might offer a potential opportunity for futher improvement in valve haemodynamics and clinical outcomes.

Chakravarty T. et al., *Lancet* 2017; 389: 2383–92

Anticoagulation and reduced leaflet motion



Chakravarty T et al. Lancet 2017

Chakravarty T et al. Lancet 2017 Mar 19. Epub ahead of print.

Atrial fibrillation and TAVI

- Pre-existing AF is common – 33.4% and affects all-cause mortality
- The incidence of new atrial fibrillation was 17.5%. It did not affect mortality after TAVI, but did increase risk of stroke significantly in the short-term
- Therefore up to >50% of TAVI patient may have AF!

Sannino A et al. Eurointervention 2016;12:e1047–56.

Current Antithrombotic Therapeutic Recommendations for Bioprosthetic Valve Implantation

	ACC/AHA Guidelines (19)	ESC/EACTS Guidelines (57)	ACCP Guidelines (56)	ACCF/AATS/SCAI/STS Expert Consensus (59)	CCS Position Statement (58)
SAVR MVR or repair	ASA 75–100 mg/d lifelong (IIa B) + VKA (INR of 2.5) for the first 3 months (IIa C for MVR or repair; IIb B for SAVR)	Low-dose ASA (IIa C) or VKA (IIb C) for the first 3 months post-SAVR VKA for the first 3 months after MVR or repair (IIa C)	ASA (50–100 mg/day) over VKA in the first 3 months post-SAVR (grade 2C) VKA (INR of 2.5) for the first 3 months post-MVR ASA over no therapy after 3 months in all cases (grade 2C)		
TAVR	ASA 75–100 mg/day lifelong + clopidogrel 75 mg/day for the first 6 months post-TAVR (IIb C)	DAPT (duration unspecified) In setting of OAC, avoid triple therapy and use warfarin with either ASA or clopidogrel	DAPT over VKA therapy and over no antiplatelet therapy in the first 3 months (grade 2C)	IV heparin with an ACT goal of 300 s during the procedure DAPT for 3–6 months, then ASA 81 mg indefinitely In setting of OAC, continue ASA, but not clopidogrel	DAPT for 1–3 months, then ASA 81 mg indefinitely In setting of OAC, avoid triple therapy

AATS = American Association for Thoracic Surgery; ACC = American College of Cardiology; ACCP = American College of Chest Physicians; ACT = activated clotting time; AHA = American Heart Association; ASA = aspirin; CCS = Canadian Cardiovascular Society; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; IV = intravenous; MVR = mitral valve replacement; SCAI = Society for Cardiovascular Angiography and Interventions; STS = Society of Thoracic Surgeons; VKA = vitamin K antagonist; other abbreviations as in Tables 1 and 3.

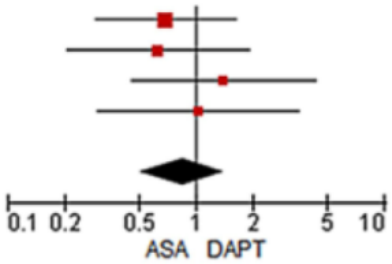
Puri R et al, JACC 2017; 2193– 211

DAPT Vs. Aspirin After TAVI: 30-Day FU

Hassell et al. *Heart* 2015;101:1118-25

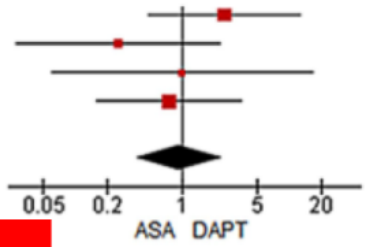
NACE

Study	Odds Ratio (95% CI)
Durand et al (2014)	0.69 (0.30-1.62)
Poliacikova et al (2013)	0.63 (0.20-1.91)
Stabile et al (2014)	1.39 (0.45-4.27)
Ussia (2011)	1.03 (0.30-3.52)
	0.83 (0.48-1.43)



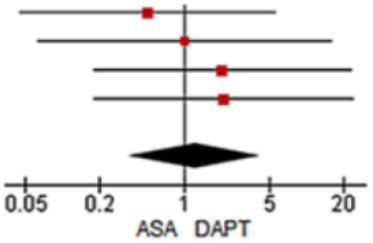
All-cause Death

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)
	0.91 (0.36-2.27)



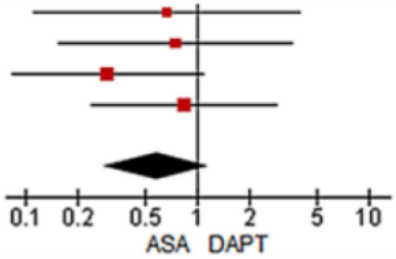
Stroke

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)
	1.21 (0.36-4.03)



LTB or 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)
	0.56 (0.28-1.11)



IPD analysis (N=672) of 2 RCT (N =199) and 2 non-matched cohorts (N=473)

ESC Guidelines 2017 for peri-TAVI antithrombotic therapy

Indications for antithrombotic therapy in patients with a prosthetic heart valve or valve repair

Recommendations	Class[a]	Level[b]
Bioprostheses		
Dual antiplatelet therapy should be considered for the first 3–6 months after TAVI, followed by lifelong single antiplatelet therapy in patients who do not need oral anticoagulation for other reasons.	IIa	C
Single antiplatelet therapy may be considered after TAVI in the case of high bleeding risk.	IIb	C
Oral anticoagulation may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis.	IIb	C

Baumgartner H et al., EHJ 2017
00, 1–53 doi:10.1093/eurheartj/ehx391

Ongoing studies comparing different antithrombotic regimes following TAVI (i)

Study	Acronym	NCT-number	Study arms	Primary endpoint	Planned pat. number	Sponsor	Timeline
Global study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to optimize clinical outcomes	GALILEO	NCT02556203	Rivaroxaban + aspirin vs. DAPT	Death/MI/stroke/ embolism/ prosthesis thrombus/major bleeding	1520	Bayer	Estimated completion 01/2018
Comparison of a rivaroxaban-based strategy with an antiplatelet-based strategy following successful TAVR for the prevention of leaflet thickening and reduced leaflet motion as evaluated by four-dimensional, volume-rendered computed tomography (4DCT)	GALILEO substudy	NCT02833948	As above	Leaft thickening and motion	300	ECRI/Bayer	Estimated completion 11/2017
Anti-thrombotic strategy after trans-aortic valve implantation for aortic stenosis	ATLANTIS	NCT02664649	Apixaban vs. DAPT or VKA	Death/MI/stroke/ embolism/ prosthesis thrombus/major bleeding	1509	Pfizer/BMS	Estimated completion 09/2018
Edoxaban compared to standard care after heart valve replacement using a catheter in patients with atrial fibrillation	ENVISAGE-TAVI AF	NCT02943785	Edoxaban vs. VKA	Death/MI/stroke/ embolism/ prosthesis thrombus/major bleeding	1400	Daiichi Sankyo	Estimated completion 11/2020

Schirmer SH et al, Clin Res Cardiol (2017) 106:79–84

Ongoing studies comparing different antithrombotic regimes following TAVI (ii)

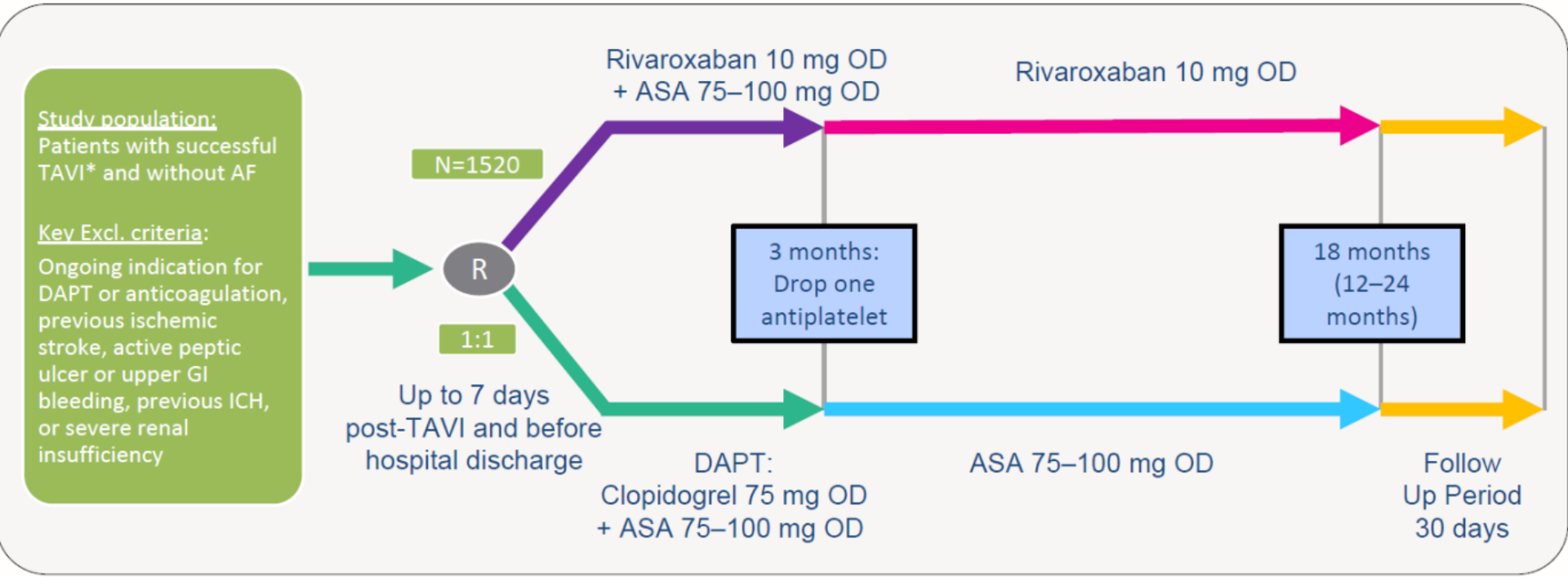
Antiplatelet therapy for patients undergoing transcatheter aortic valve implantation (POPular-TAVI)	POPular-TAVI	NCT02247128	Aspirin vs. DAPT vs. OAC vs. OAC + clopidogrel	Bleeding	1000	St. Antonius Hospital, Netherlands	Estimated primary complation 08/2016
Dual antiplatelet therapy versus oral anticoagulation for a short time to prevent cerebral embolism after TAVI	AUREA	NCT01642134	DAPT vs. acenocoumarol	Cerebral thrombo-emsolism (MRI)	–	Hospital de Meixoeiro, Spain	Estimated completion 04/2017
Anticoagulation alone versus anticoagulation and aspirin following transcatheter aortic valve interventions (1:1)	AVATAR	NCT02735902	Aspirin vs. aspirin + VKA	Death/MI/ stroke/valve thrombosis major bleeding	170	Nimes university Medtronic	Estimated start 04/2017
Aspirin versus aspirin + clopidogrel following transcatheter aortic valve implantation: the ARTE Trial	ARTE	NCT01559298	Aspirin vs. DAPT	Death/MI/ stroke/major bleeding	155	University Quebec/ Edwards Lifesciences	Estimated completion 01/2017

Information provided as provided on http://www.clinicaltrials.gov

DAPT dual antiplatelet therapy (i.e. aspirin + clopidogrel), *OAC* oral anticoagulation, *VKA* vitamin K antagonist, *MI* myocardial infarction, *MRI* magnetic resonance imaging

Schirmer SH et al, Clin Res Cardiol (2017) 106:79–84

GALILEO: Study Design Overview



~144 sites in Europe & North America (15 countries).

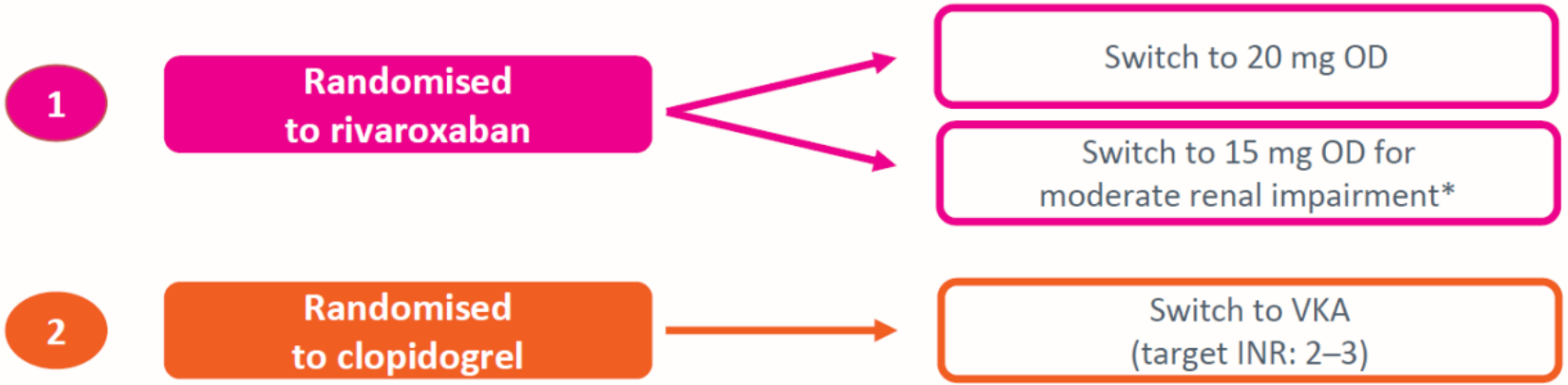
ASA=Acetylsalicylic acid; DAPT=Dual antiplatelet therapy; GI=Gastrointestinal; ICH=Intracranial haemorrhage; OD=Once daily; TAIR=Transcatheter aortic valve implantation

www.ClinicalTrials.gov Identifier: NCT02556203.

GALILEO

GALILEO: Treatment after new onset of AF (NOAF)[1]

- Approximately 15% of patients develop NOAF after randomisation[2, 3]



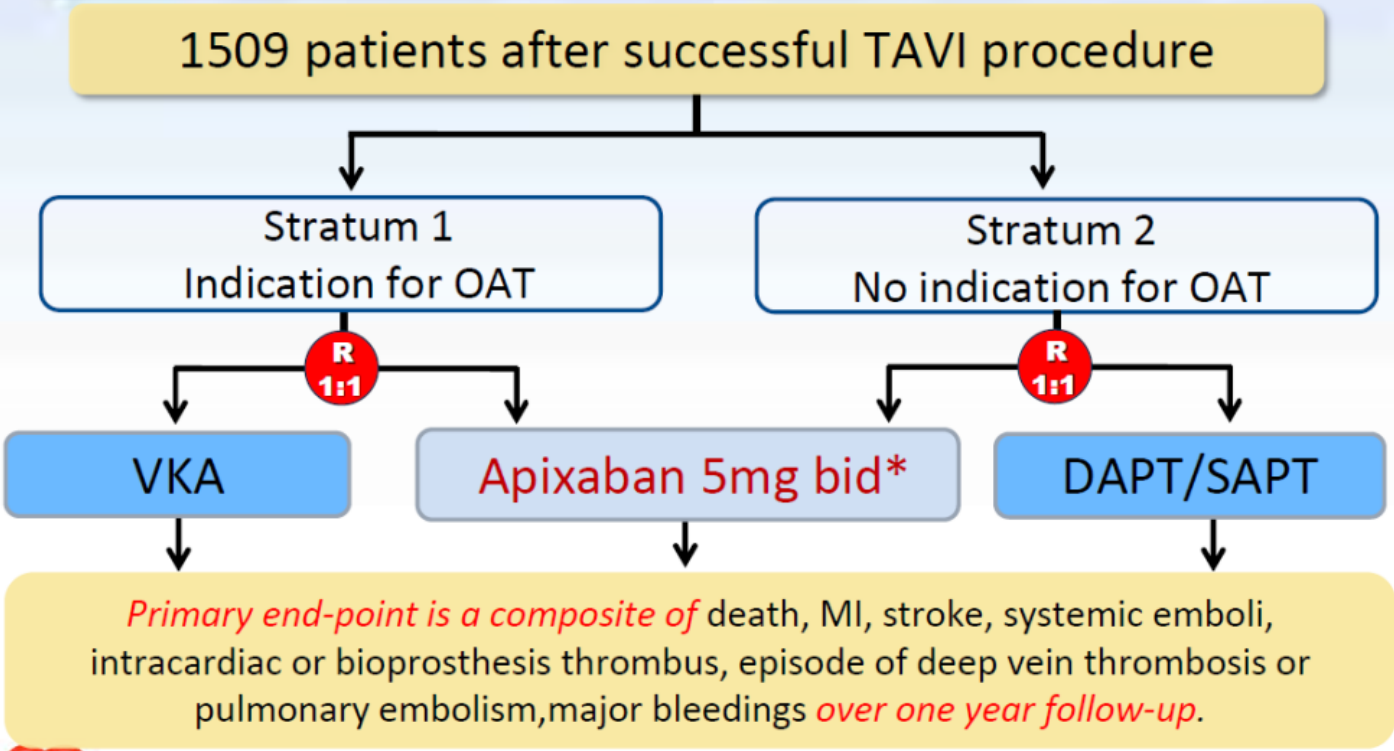
- Follow-up until end of study
  - Included in primary efficacy analysis (ITT)
  - Censoring in secondary analysis

i.e. CrCl=30–49 mL/min. CrCl=Creatinine clearance; INR=International normalised ratio; ITT=Intention to treat; NOAF=New onset atrial fibrillation; OD=Once daily; VKA=Vitamin K antagonist.

1. www.ClinicalTrials.gov Identifier: NCT02556203.; 2. Smith CR el al. *NEJM* 2011;364:2187–2198; 3. Adams DN et al. *NEJM* 2014;370:1790–1798

GALILEO

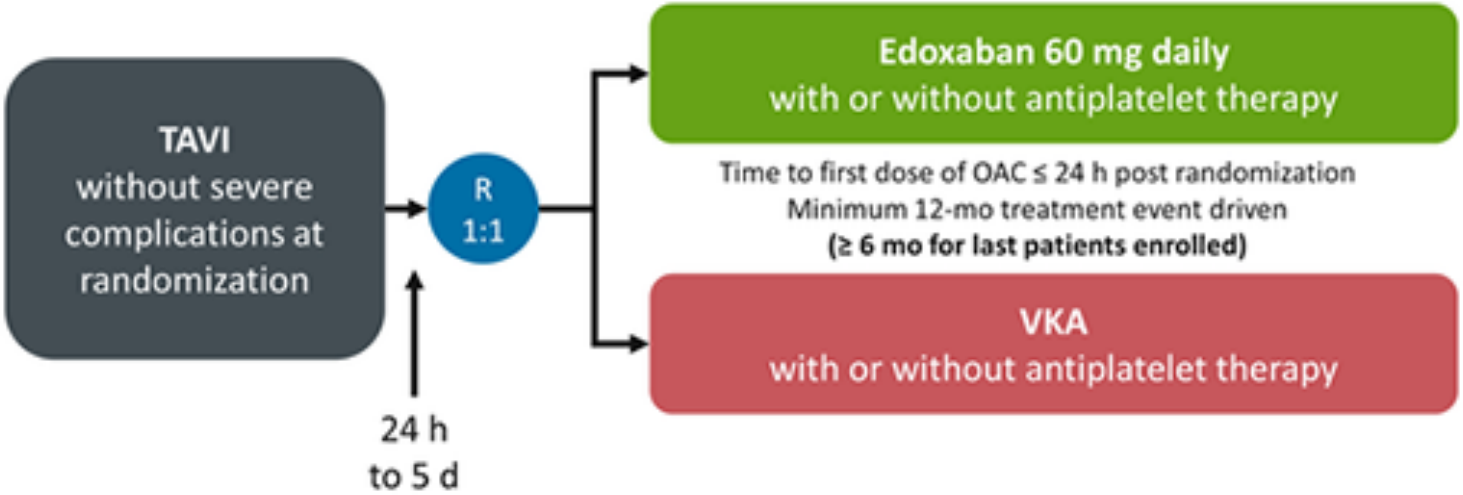
ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis)



*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 (133µMol).

ENVISAGE TAVI AF -- Study Design

Prospective, randomized, open-label, blinded evaluation of edoxaban vs VKA in approximately 1400 patients with AF indicated for chronic OAC after successful TAVI (~2500 patient-y)



Van Mieghem NM, et al. Am Heart J 2017

clinicaltrials.gov: NCT02943785; Van Mieghem NM, et al. *Am Heart J.* (Submitted)

Conclusion

- Excellent rationale for the possible use of NOACs with TAVI to avert stroke even in the absence of atrial fibrillation
- …pending the completion of ongoing studies

That’s all!