



ACC Middle East Conference 2018

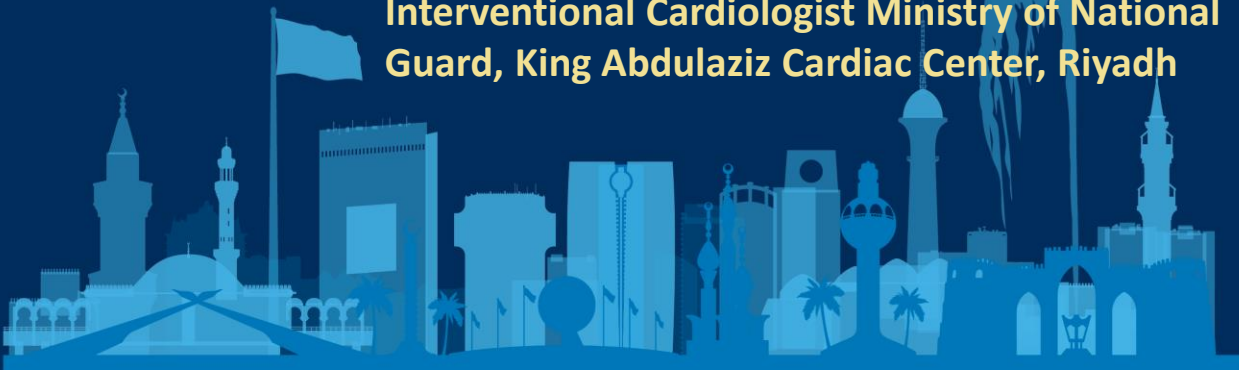
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جمعية القلب السعودية
Saudi Heart Association

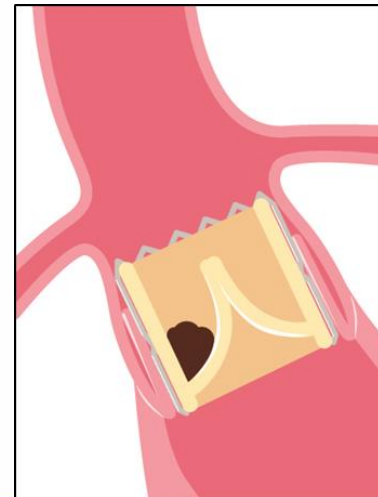
TAVR Valve Thrombosis

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Leaflet thrombosis

- Recently recognized as important mechanism of transcatheter heart valve failure.
- It is not known whether leaflet thrombosis after transcatheter aortic valve replacement (TAVR) has serious clinical consequences
- The prevalence of subclinical leaflet thrombosis after TAVI is 15% up to 40%



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leaflet thrombosis in TAVR

**Presence of acute- or subacute-onset of heart failure
Stroke/TIA symptoms**

Direct visualization of leaflet thrombosis on echocardiogram, or

Increase in mean gradient > 10 mmHg with no thrombus visible, or

Regression of elevated mean gradient after oral anticoagulation therapy or

Presence of reduced leaflet motion or hypoattenuated leaflet thickening on computed tomography angiogram or

Evidence of device thrombosis at autopsy or via examination of tissue during reoperation



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Thickened leaflets
Reduced motion



Thin leaflets
Normal motion



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Timing of presentation after TAVR

Acute (0-3 days)

Subacute (3 days to 3 months)

Late (3 months to 1 year)

Very late (> 1 year)

Outcomes:

Stroke or TIA

Cardiogenic shock (vasopressor or mechanical circulatory support)

Death from any cause



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- **Clinical or Symptomatic Leaflet Thrombosis Following Transcatheter Aortic Valve Replacement: Insights from the U.S. FDA MAUDE Database**

Abdul Moiz Hafiz , MD ORCID Icon, Ankur Kalra , MD ORCID Icon, Ronnie Ramadan , MD, Marie-France Poulin , MD, Ali Andalib , MD, Colin T. Phillips , MD ORCID Icon, show all
Pages 256-264 | Received 27 Jul 2017, Accepted 28 Jul 2017, Accepted author version posted online: 29 Aug 2017, Published online: 19 Sep 2017



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Methods: Data Collection

- Between January 2012 - October 2015, the MAUDE database was searched with identifier code, “NPT,” designated by the FDA to identify TAVR-related adverse events.
- Selected entries were searched further containing the following terms:
 - Leaflet
 - Central aortic regurgitation (AR)
 - Aortic stenosis
- The following data were recorded:
 - Presentation of leaflet thrombosis (aortic stenosis or regurgitation or mixed valve lesion)
 - Mode of diagnosis (echocardiography, computed tomography, surgical explantation, or autopsy)
 - Timing of onset after TAVR



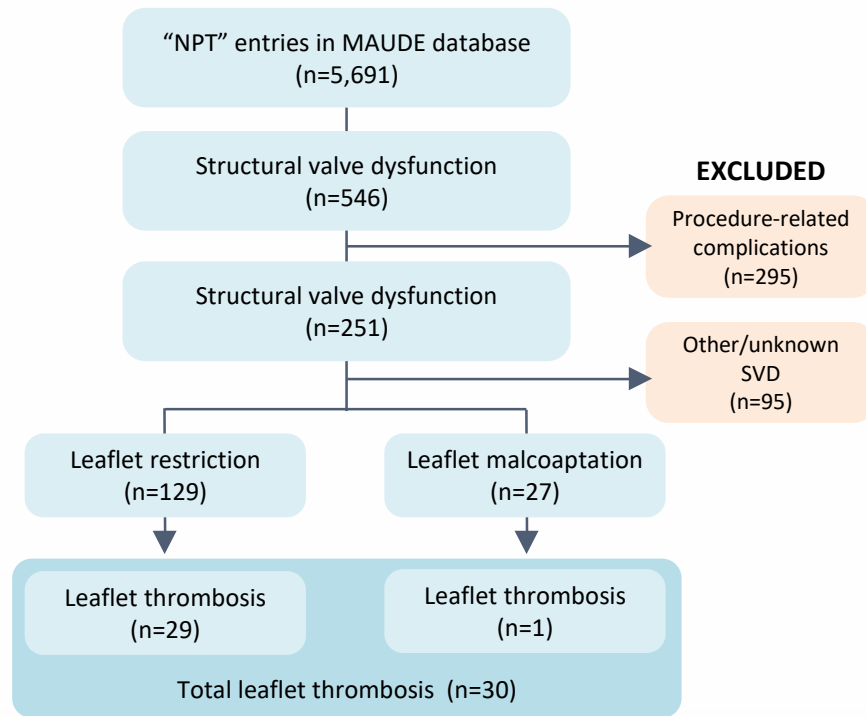
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Results

- There were **5,691** TAVR-related adverse events reported in MAUDE database.
- Of these, **546** adverse events were segregated based on pre-specified search terms.
- The final analysis included **156** adverse events of structural valve dysfunction:
 - Leaflet restriction (n=129)
 - Leaflet malcoaptation (n=27)
- Structural valve dysfunction due to leaflet thrombosis occurred in **30 cases**:
 - Edwards-Sapien = **20**
 - CoreValve® = **10**



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Results

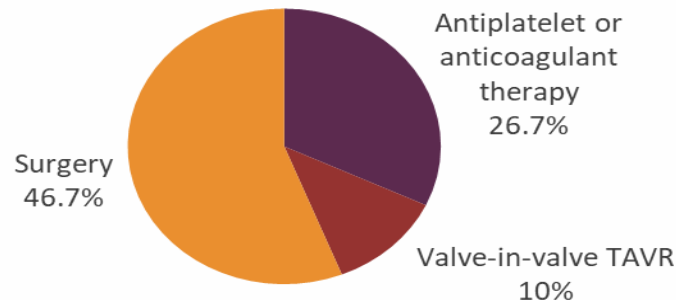
- **Interventions to address leaflet thrombosis:**

- Antiplatelet or anticoagulant therapy **26.7%** (8/30)
- Valve-in-valve TAVR **10.0%** (3/30)
- Surgery **46.7%** (14/30)
- Diuretics (n=1);
thrombus aspiration (n=1);
balloon aortic valvuloplasty (n=2);
no intervention (n=2)

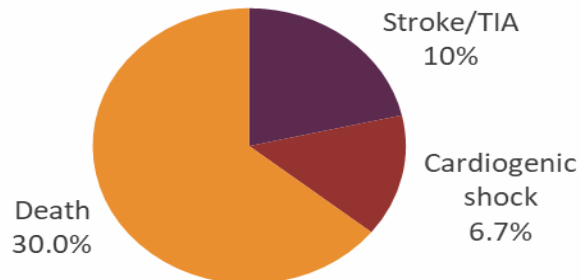
- **Outcome following leaflet thrombosis:**

- Stroke/TIA **10.0%** (3/30)
- Cardiogenic shock **6.7%** (2/30)
- Death **30.0%** (9/30)

Interventions



Outcomes

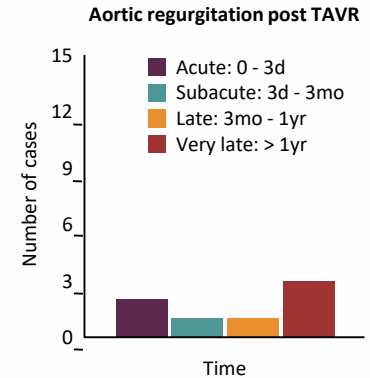
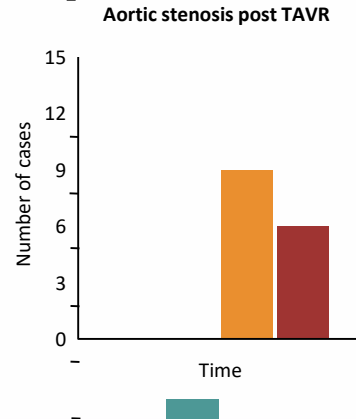
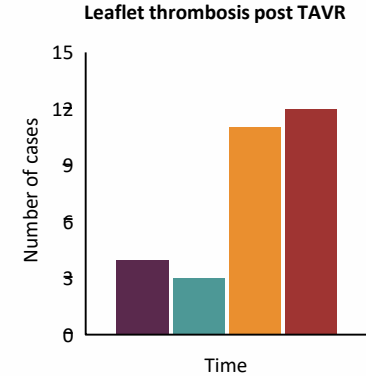
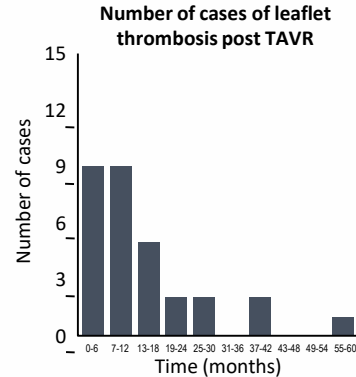


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Results

- **60% (18/30) cases** occurred in the **first year following TAVR**
- **40% (12/30) cases** occurred during 13-60 months
- Structural valve dysfunction presented as either:
 - Aortic stenosis **53.3% (16/30)**
 - Regurgitation **23.3% (7/30)**
 - Both **13.3% (4/30)**
- The remainder of **3/30** patients had stroke/TIA
- Timing of occurrence after TAVR:
 - Aortic stenosis 15.5 ± 12.2 months
 - Regurgitation 10.1 ± 10.9 months

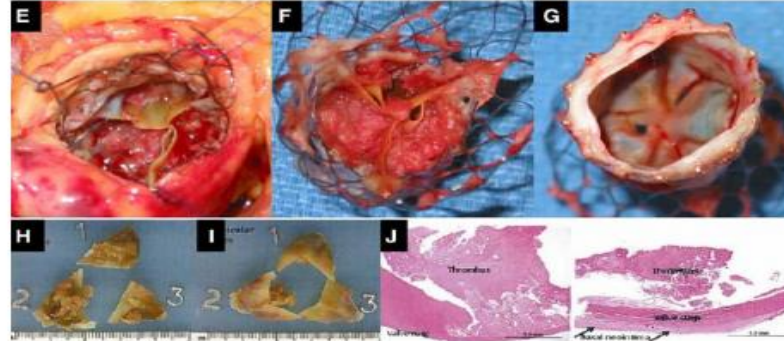


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Treatment and Clinical Outcomes of Transcatheter Heart Valve Thrombosis

Azeem Latib, MD*; Toru Naganuma, MD*; Mohamed Abdel-Wahab, MD; Haim Danenberg, MD;
Linda Cota, MD; Marco Barbanti, MD; Helmut Baumgartner, MD; Ariel Finkelstein, MD;
Victor Legrand, MD; José Suárez de Lezo, MD; Joelle Kefer, MD;
David Messika-Zeitoun, MD; Gert Richardt, MD; Eugenio Stabile, MD; Gerrit Kaleschke, MD;
Alec Vahanian, MD; Jean-Claude Laborde, MD; Martin B. Leon, MD; John G. Webb, MD;
Vasileios F. Panoulas, MD; Francesco Maisano, MD; Ottavio Alfieri, MD; Antonio Colombo, MD



- ✓ 26 cases on 4266 TAVI in 12 centres : 0.6%
- ✓ Sapien/ Sapien XT and Corevalve
- ✓ Median time : 181 days after TAVI
- ✓ No thrombogenic diathesis, no discontinuation of DAPT
- ✓ Echo : increased gradient, thickened leaflets, thrombus
- ✓ Restoration of normal THV function within 2 months of ACO

Circ Cardiovasc Interv. 2015 Apr;8(4)



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Symptomatic THV thrombosis exists,
noted in up to 1%, associated with
high transvalvular gradients @ echo.

ORIGINAL ARTICLE

N Engl J Med 2015;373:2015-24.

Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

R.R. Makkar, G. Fontana, H. Jilaihawi, T. Chakravarty, K.F. Kofoed, O. de Backer,
F.M. Asch, C.E. Ruiz, N.T. Olsen, A. Trento, J. Friedman, D. Berman, W. Cheng,
M. Kashif, V. Jelnin, C.A. Kliger, H. Guo, A.D. Pichard, N.J. Weissman, S. Kapadia,
E. Manasse, D.L. Bhatt, M.B. Leon, and L. Søndergaard



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PORTICO IDE Study

- ✓ RCT Portico versus commercial valves in US
- ✓ 4-dimensional volume rendered CT detected a reduced leaflet motion (RLM) in one patient with stroke
- ✓ 55 patients undergoing 4D-CT @ 30d after TAVI, were investigated
- ✓ 40% have a RLM, in all subgroups of devices
- ✓ All have hypoattenuating opacities @ 2D-CT, at the base of the valve leaflets
- ✓ Low mean gradient @ TT echo : 9 mmHg
- ✓ RLM less prevalent in patients receiving warfarin (vs DAPT)

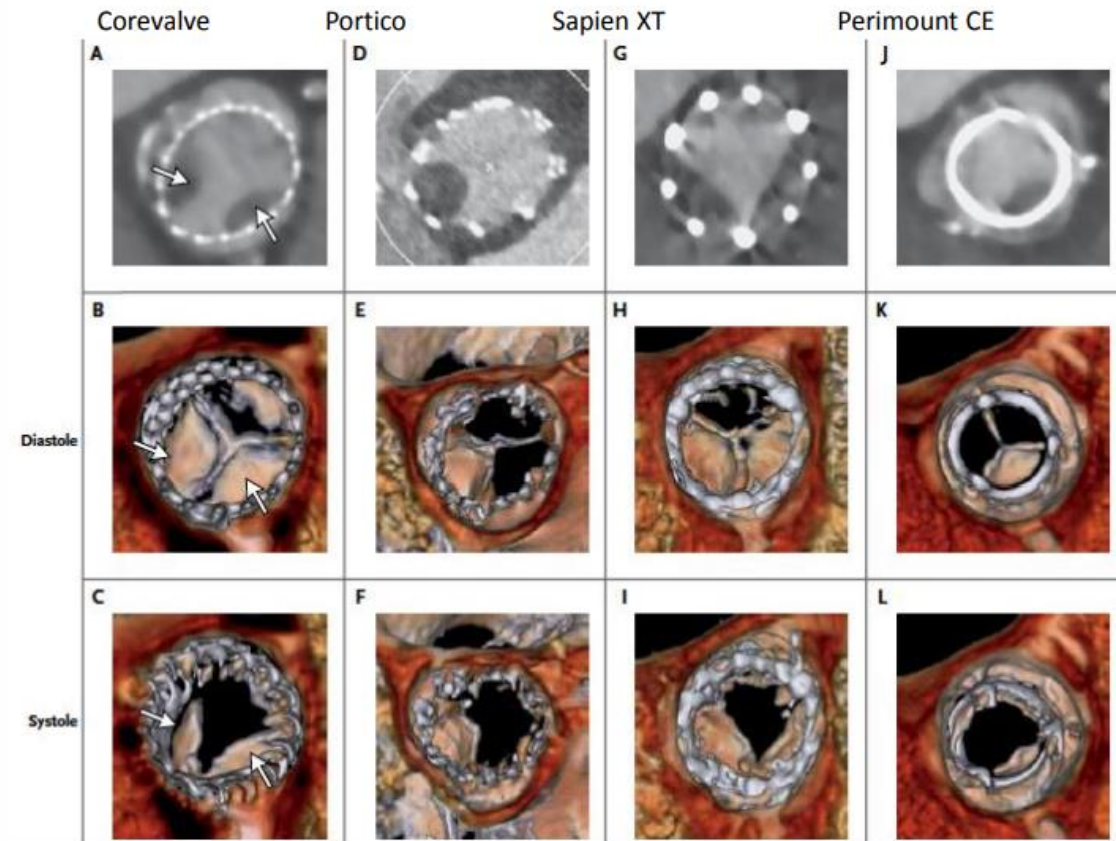
Pooled RESOLVE and SAVORY registries

- ✓ 132 patients in 2 centres : 4D-scan after TAVI
- ✓ RLM : 13% (14% TAVR ; 7% after SAVR)



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Outcome of patients with RLM

Table 3. Clinical Outcomes.

Outcome	Normal Leaflet Motion <i>number of patients</i>	Reduced Leaflet Motion <i>number of patients</i>	P Value*
PORTICO IDE study			
Patients in study	33	22	
Death†	1	2	0.56
Myocardial infarction‡	1	1	>0.99
Stroke or transient ischemic attack§	0	2	0.16
Stroke	0	2	0.16
Transient ischemic attack	0	0	>0.99
Pooled registries			
Patients in group	115	17	
Death	0	0	>0.99
Myocardial infarction	0	0	>0.99
Stroke or transient ischemic attack¶	1	3	0.007
Stroke	1	0	>0.99
Transient ischemic attack	0	3	0.002



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Possible subclinical leaflets thrombosis

- ✓ Reduced aortic valve leaflet motion
- ✓ Incidental finding by 4D-CT scan (hypoattenuated leaflets thickening)
- ✓ Hemodynamically subclinical at the time of detection
- ✓ Occured with several types of prostheses (SAVR and TAVR)
- ✓ Lower prevalence among patients ACO
- ✓ High rate of recovery after warfarin
- ✓ No histological confirmation



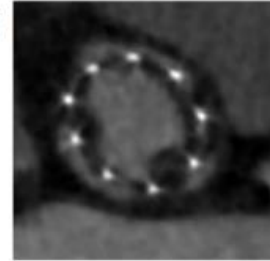
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HALT & HAM definitions

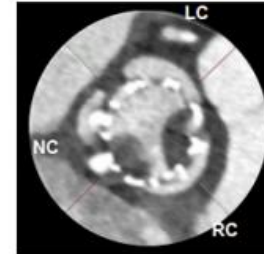
HALT: Hypo-Attenuating Leaflet Thickening

- Involving the periphery and base of the leaflet and extend to varying degrees to the edges of the leaflet



HAM: Hypo-Attenuation affecting Motion

- Reduction in leaflet motion in the presence of HALT
- A reduction in leaflet excursion of more than 50% was considered significant



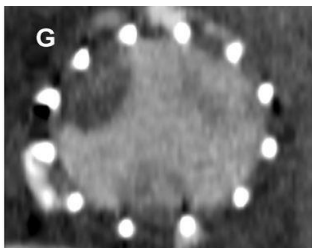
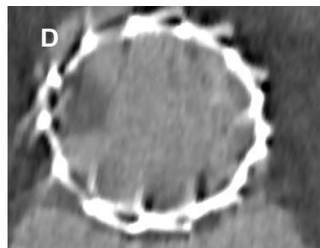
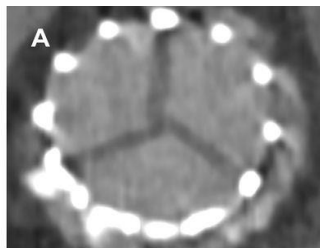
Sondergaard L, TVT 2016



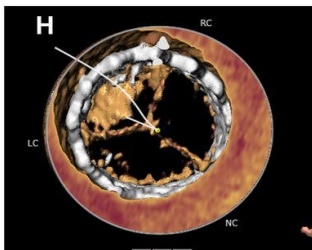
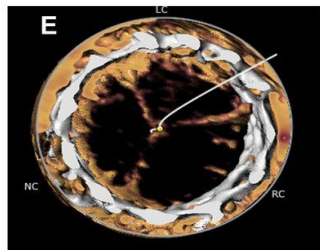
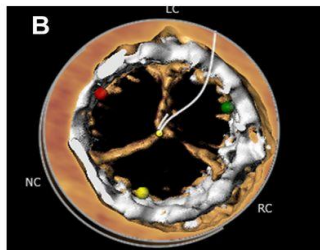
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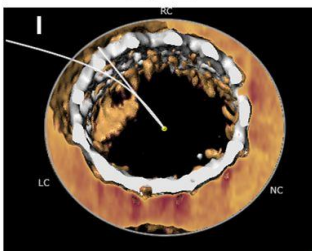
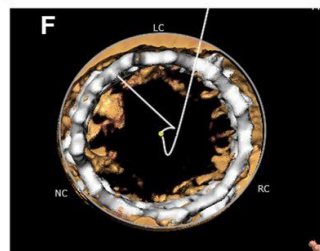
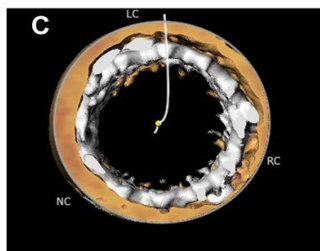
HALT



Diastole



Systole



Spectrum of Computed Tomographic Findings in Patients With Transcatheter Aortic Valves

(A to C) Normal valve: no hypoattenuating leaflet thickening (HALT) or hypoattenuation affecting motion (HAM). **(D to F) HALT positive, HAM negative:** presence of HALT (D), but no significant reduced leaflet motion (E,F). **(G to I) HALT positive, HAM positive:** presence of HALT (G) and reduced leaflet motion (H,I).

Raj Makkar, and Tarun Chakravarty JCIN 2018;11:1172-1174



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Medium-Term Follow-Up of Early Leaflet Thrombosis After Transcatheter Aortic Valve Replacement

Philipp Ruile, et al JACC: Cardiovascular Interventions

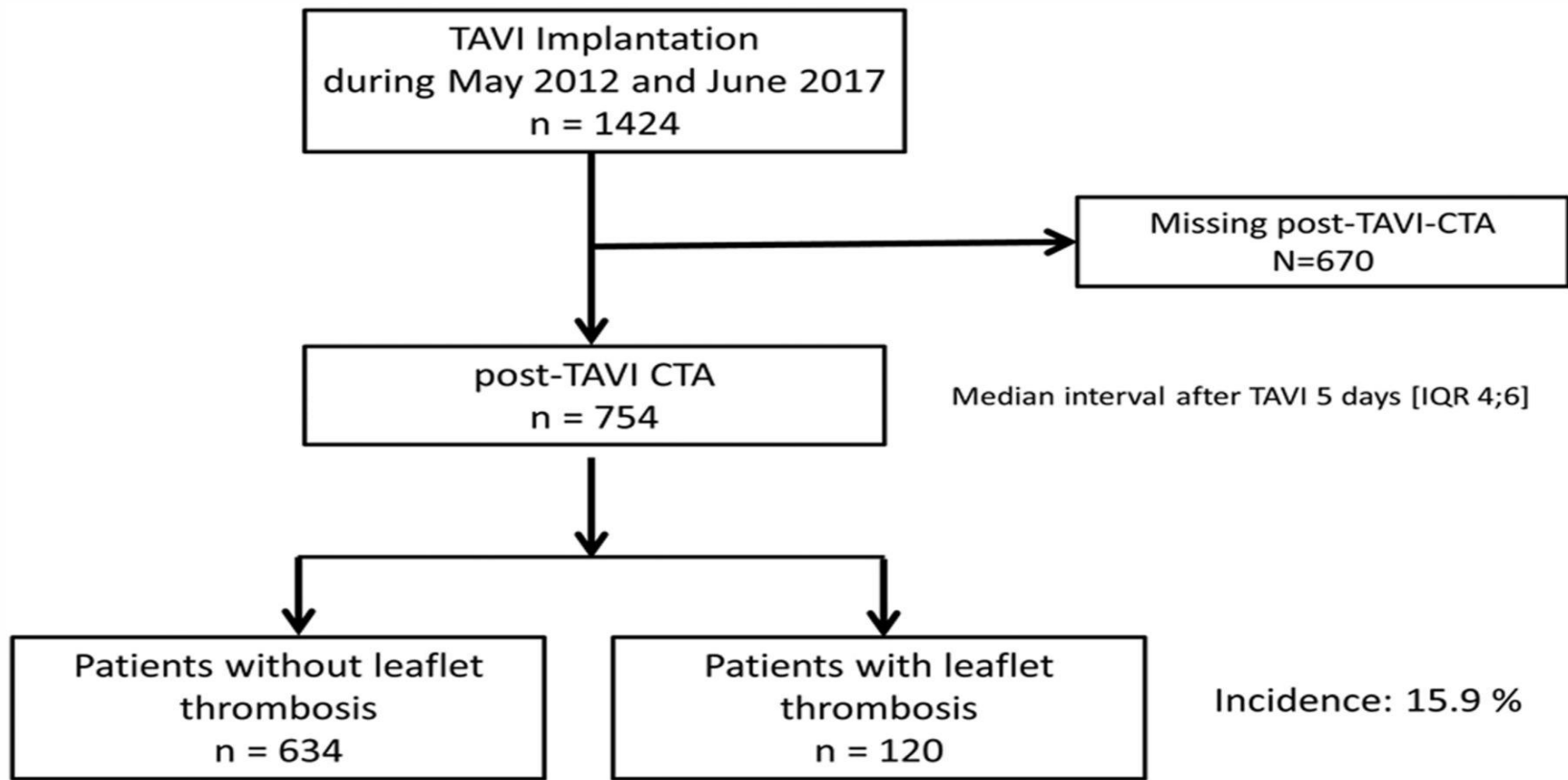
Volume 11, Issue 12, June 2018

- **Objectives** The aim of this study was to investigate medium-term outcomes in patients with leaflet thrombosis (LT).
- **Background** The clinical significance of early LT after transcatheter aortic valve replacement, diagnosed by computed tomography angiography in approximately 10% of patients, is uncertain.
- **Methods** In this observational study, computed tomographic angiography was performed a median of 5 days after transcatheter aortic valve replacement and assessed for evidence of LT. Follow-up consisted of clinical visits, telephone contact, or questionnaire.
- **Results** LT was diagnosed in 120 of 754 patients (15.9%). Patients with LT were less likely male (36.7% vs. 47.0%, $p = 0.045$), with a lower rate of atrial fibrillation (28.3% vs. 41.5%, $p = 0.008$). Peri- and post-procedural characteristics were comparable between groups (e.g., valve implantation technique; $p = 0.116$). During a median follow-up period of 406 days, there were no significant differences in the primary endpoint of all-cause mortality and the secondary combined endpoint of stroke and transient ischemic attack between patients with LT and those without LT (18-month Kaplan-Meier estimate for mortality 86.6% vs. 85.4%, $p = 0.912$; for stroke- or transient ischemic attack-free survival 98.5% vs. 96.8%, $p = 0.331$). In univariate and multivariate analyses, LT was not predictive of either endpoint, whereas male sex ($p = 0.03$), atrial fibrillation ($p = 0.002$), and more than mild paravalvular leak ($p = 0.015$) were associated with all-cause mortality.
- **Conclusions** In this prospective observational cohort undergoing post-transcatheter aortic valve replacement computed tomographic angiography, LT was not associated with increased mortality or rates of stroke over a follow-up period of 406 days.



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Philipp Ruile et al. JCIN 2018;11:1164-1171



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- **Peri- and post-procedural antithrombotic regime**

- Peri-interventional heparin 5,000 IU, with adjustment for high or low body weight, was administered in all patients. Before implantation, patients were administered either 400 mg effervescent aspirin (ASA) or a combination of 400 mg effervescent ASA and 600 mg clopidogrel. The peri- and post-interventional antiplatelet medication consisted of ASA (100 mg/day) alone from May 2012 to May 2014 and, since June 2014, dual-antiplatelet therapy with ASA (100 mg/day) plus clopidogrel (75 mg/day) for 6 months followed by lifelong ASA 100 mg/day. Anticoagulation treatment was paused as long as needed to achieve an international normalized ratio <2 in patients on vitamin K antagonist (phenprocoumon) or 24 h before TAVR for novel oral anticoagulant agents. One day after TAVR, anticoagulation was readministered in combination with clopidogrel.

- **Anticoagulation regimen in patients with LT**

- From May 2012 until May 2015, all patients with LT were treated with a modified antithrombotic regimen including a combination of phenprocoumon (target international normalized ratio 2 to 3) and clopidogrel 75 mg/day. Follow-up CTA was performed after 3 months, and phenprocoumon was stopped when signs of LT on CTA had resolved, unless anticoagulation was indicated for other reasons. Subsequently, patients were switched to dual-antiplatelet therapy. Repeat follow-up CTA was recommended at least 2 months after discontinuation of phenprocoumon. The results of this short-term follow-up have been published previously [\(5\)](#).
- From May 2015 onward, patients with LT received the same antithrombotic regimen as those without LT, and anticoagulation was initiated only when indicated for other reasons (e.g., atrial fibrillation). In case of clinical signs of thrombosis or a relevant increase in mean transvalvular gradient, patients received anticoagulation according to the decision of the treating physicians.



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Post-interventional echocardiographic assessment

- **Post-interventional echocardiographic assessment**
- Echocardiographic examinations were performed before discharge at the time of post-TAVR CTA by experienced cardiologists
- CTA was performed using a dual-source computed tomographic scanner
- Computed tomographic angiographic datasets were assessed by an experienced cardiac radiologist as part of routine post-TAVR clinical follow-up.
- In the presence of findings suspicious for LT, CTA was reassessed by a second radiologist blinded to the initial findings.
- Prosthesis leaflets were dynamically assessed on multiplanar reformations for the presence of LT throughout the cardiac cycle. LT was defined as hypoattenuated thickening with or without rigidity of 1 or more leaflet segments in at least 2 different multiplanar reformation projections and 2 different reconstruction time intervals.

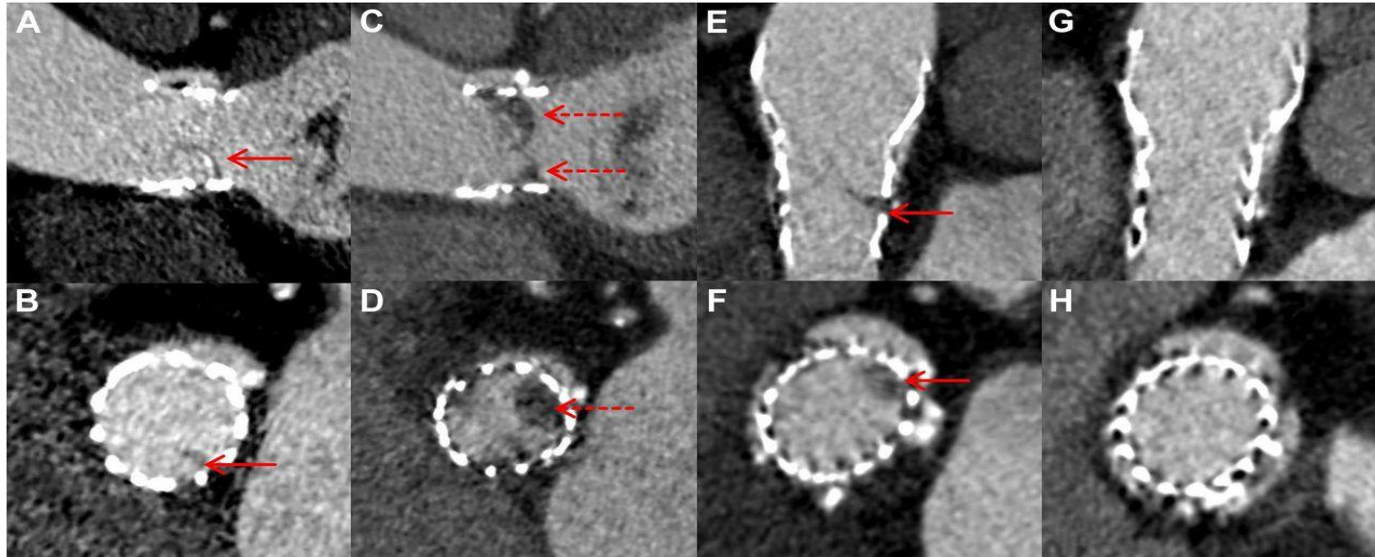


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A 89-year-old man with a SAPIEN 3 prosthesis

A 79-year-old woman with an Evolut R valve



Philipp Rulle et al. JCI 2018;11:1164-1171

Predictors of mortality and stroke or TIA

- **predictors of all-cause mortality were atrial fibrillation**
- **More than mild paravalvular leakage**
- **Male sex**
- **In contrast, LT was not significantly associated with an increased risk for all-cause mortality.**
- **In multivariate analysis atrial fibrillation, male sex, and more than mild paravalvular leakage remained predictors of all-cause mortality**



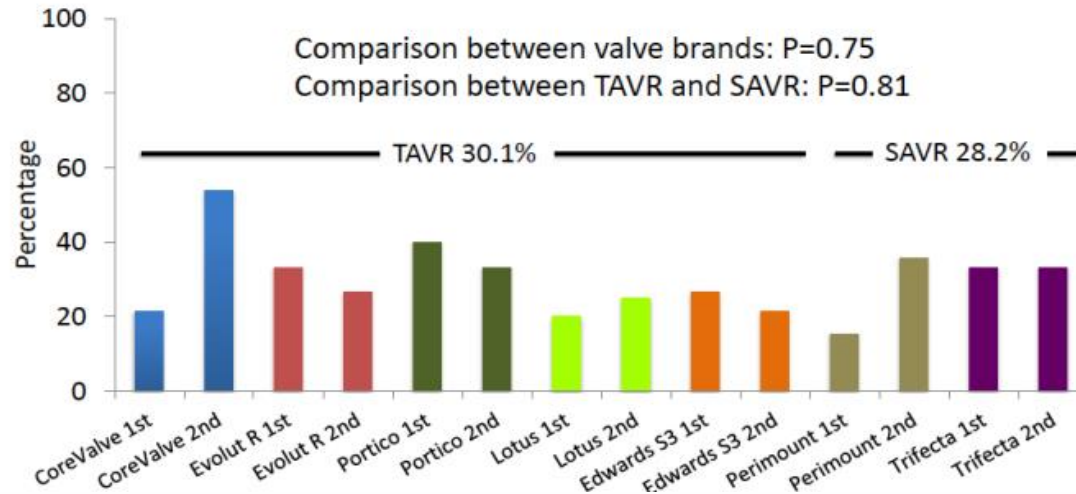
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The SAVORY registry in Copenhagen:

- 105 patients who underwent TAVR or SAVR

Prevalence of HALT *baseline and follow-up scan*



Sondergaard L, TVT 2016



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- The presence of leaflet thrombosis did not significantly affect mortality
- Strokes or TIAs
- Early leaflet thrombosis was not a predictor of mortality or strokes or TIAs in univariate or multivariate analysis.

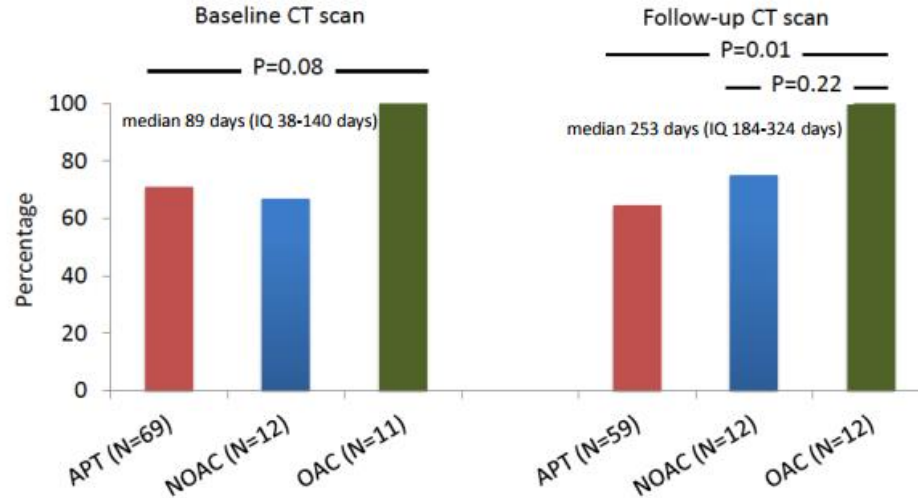


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VKA seems to prevent and resolve this phenomenon,
whereas APT and NOAC do not

Medication & freedom from HALT



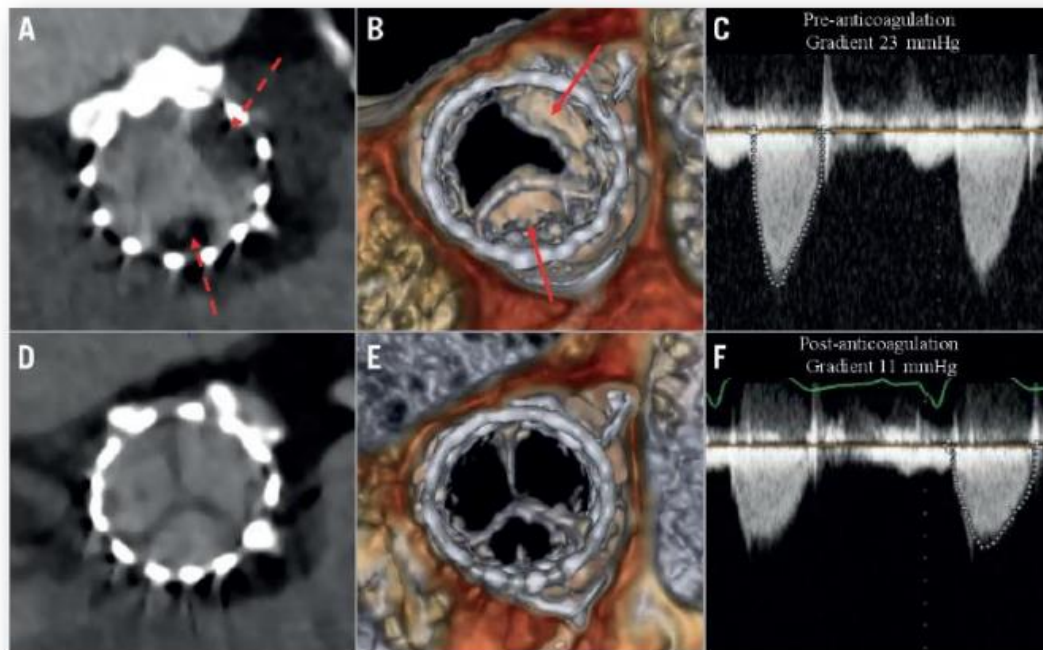
Sondergaard L, TVT 2016



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Resolution of HALT and RLM after warfarin



Makkar et al. *EuroIntervention* 2016

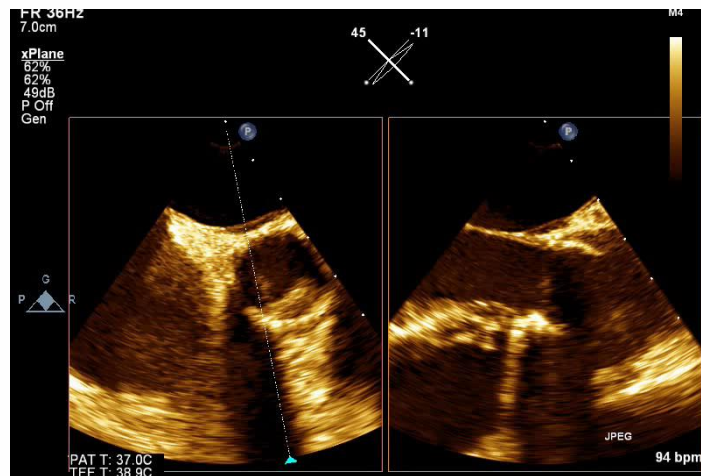


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Bioprosthetic Mitral Valve Thrombosis

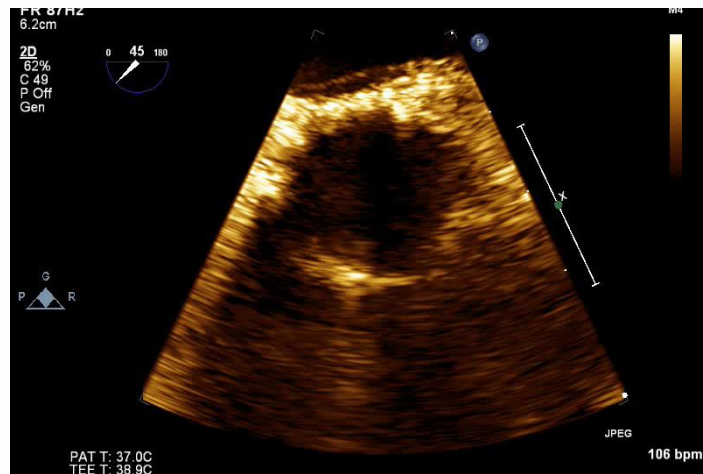


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Bioprosthetic Mitral Valve Thrombosis

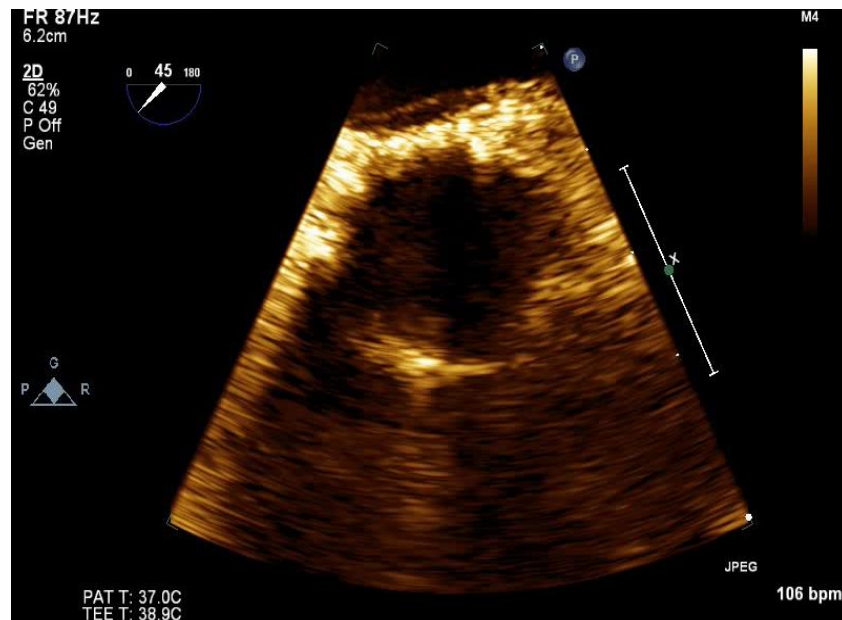


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Bioprosthetic Mitral Valve Thrombosis

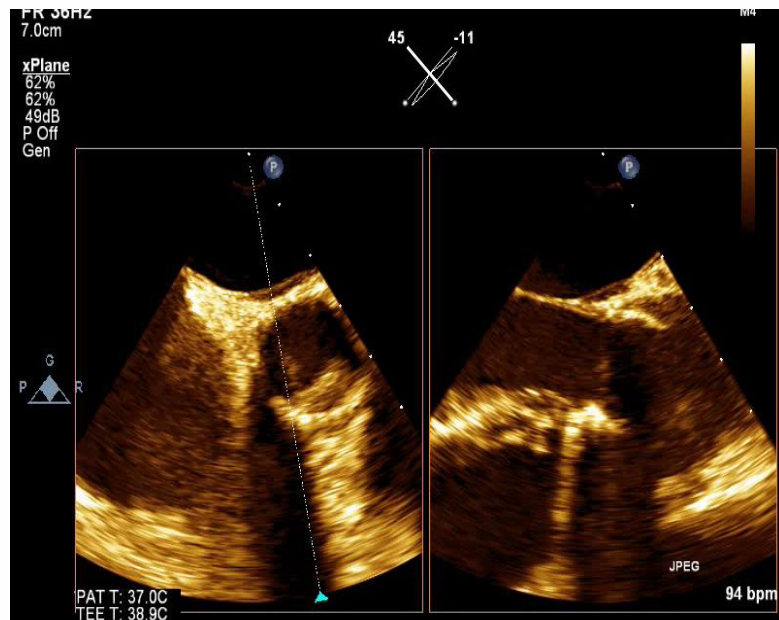


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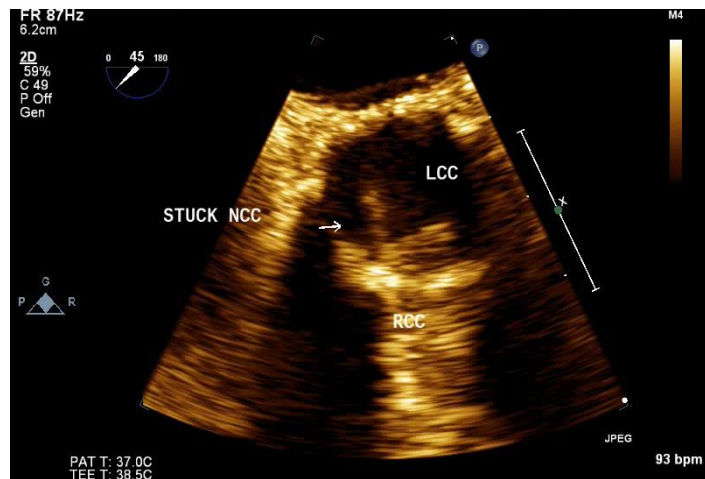


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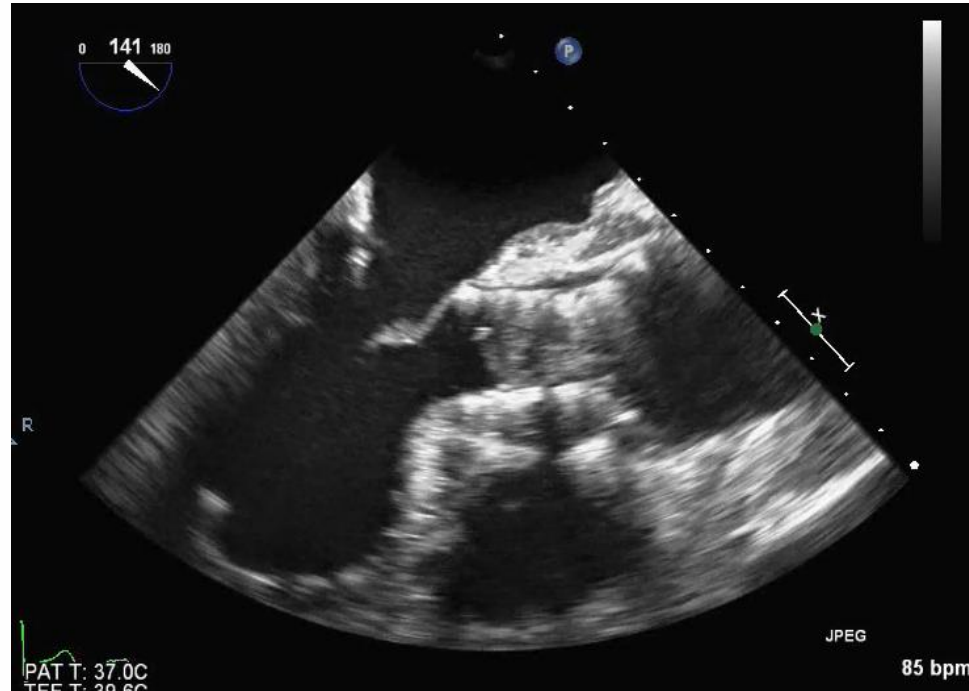


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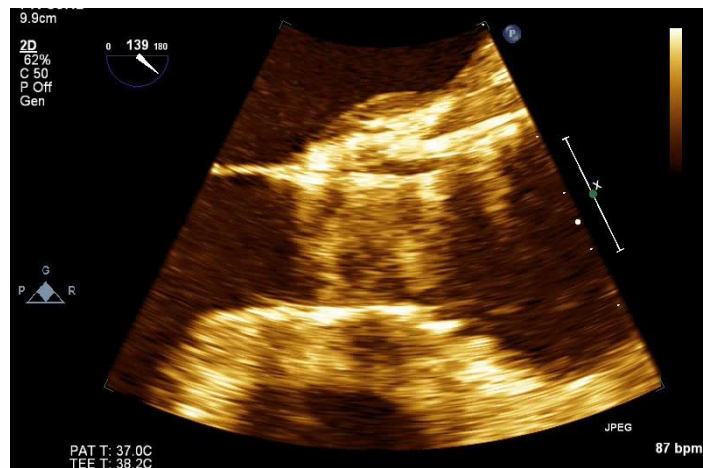
Thrombosis 8 M post-TAVR



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Thrombosis 8 M post-TAVR

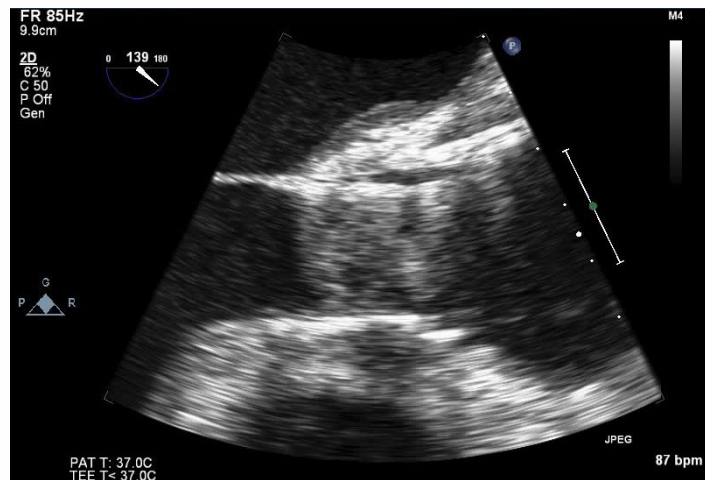


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Thrombosis 8 M post-TAVR



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Clinical implications

- ✓ No RLM or HALT in anticoagulated patients
- ✓ Restoration of normal THV after warfarin
- ✓ Should we give ACO in all patients after TAVI?
- ✓ Risk of bleeding
- ✓ No robust evidence for ACO after SAVR

Oral anticoagulation may be considered for the first three months after implantation of an aortic bioprosthesis.

IIb

C

2012 ESC guidelines

CLASS IIb

1. Anticoagulation, with a VKA, to achieve an INR of 2.5 may be reasonable for the first 3 months after bioprosthetic AVR (276).
(Level of Evidence: B)
2. Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily. (Level of Evidence: C)

2014 ACC/AHA guidelines



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ACO in all patients after TAVI ?

NO

- AF present in $\pm 1/3$ of patients TAVI
- Independently associated with CV morbi and mortality
- Driven by increased risk of bleeding relating to OAC (Vavuranakis et al. Curr Pharm Des 2016)
- PARTNER 1B : 1-yr mortality was quadrupled in AF patients experienced major bleedings



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Transcatheter Aortic Valve Replacement in Low-Risk Patients with Symptomatic Severe Aortic Stenosis

Ron Waksman, Toby Rogers, Rebecca Torguson, Paul Gordon, Afshin Ehsan, Sean R. Wilson, John Goncalves, Robert Levitt, Chiwon Hahn, Puja Parikh, Thomas Bilfinger, David Butzel, Scott Buchanan, Nicholas Hanna, Robert Garrett, Federico Asch, Gaby Weissman, Itsik Ben-Dor, Christian Shults, Roshni Bastian, Paige E. Craig, Hector M. Garcia-Garcia, Paul Kolm, Quan Zou, Lowell F. Satler and Paul J. Corso

Results We enrolled 200 low-risk patients with symptomatic severe aortic stenosis at 11 centers to undergo TAVR. We compared outcomes with an inverse probability weighting adjusted control cohort of 719 patients who underwent SAVR at the same institutions using the STS database. At 30 days, there was zero all-cause mortality in the TAVR group versus 1.7% mortality in the SAVR group. There was zero in-hospital stroke in the TAVR group versus 0.6% stroke in the SAVR group. Permanent pacemaker implantation rates were similar between TAVR and SAVR (5.0% versus 4.5%). The rates of new onset atrial fibrillation (3.0%) and length of stay (2.0 ± 1.1 days) were low in the TAVR group. One patient (0.5%) in the TAVR group had >mild paravalvular leak at 30 days. Fourteen percent of TAVR patients had evidence of subclinical leaflet thrombosis at 30 days.

Conclusions TAVR is safe in low-risk patients with symptomatic severe aortic stenosis, with low procedural complication rates, short hospital length of stay, zero mortality, and zero disabling stroke at 30 days. Subclinical leaflet thrombosis was observed in a minority of TAVR patients at 30 days.



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Conclusion

- Leaflet thrombosis is a serious adverse event following TAVR.
- Most cases occurred in the first year following TAVR, presented as aortic stenosis or regurgitation, and required surgery in 46.7% of cases.
- Clinically manifest leaflet thrombosis was associated with serious clinical manifestations including:
 - Stroke
 - Cardiogenic shock
 - Death
- Early diagnosis of leaflet thrombosis may be crucial for planning appropriate management and optimizing clinical outcome for patients.



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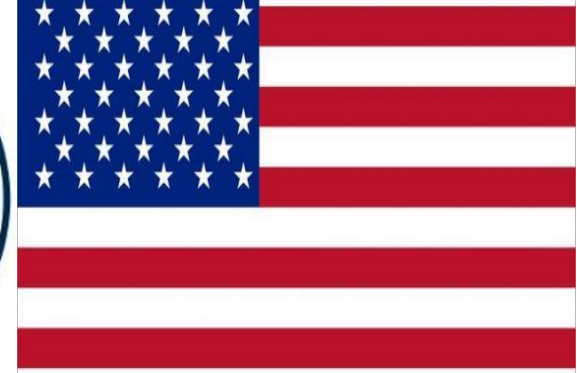


- Both of the low-risk TAVR trials for the Sapien 3 and the Evolut R include leaflet mobility substudies that involve cardiac CT. Two additional trials, GALILEO and ATLANTIS are studying the use of non-vitamin K oral anticoagulants (rivaroxaban and apixaban, respectively) to prevent valve thrombosis and other events in patients who have undergone transcatheter aortic valve replacement. The studies are designed to enroll approximately 1,500 patients each.



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Conclusions

- In a heterogeneous cohort of aortic bioprosthetic valves, the reduced leaflet motion occurred 12 % of the time on 4D CT.
- Patients undergoing SAVR, compared with TAVR, had lower incidence of reduced leaflet motion (3.6% vs. 12%; $p<0.04$). However, patients undergoing SAVR were different than TAVR reflecting contemporary practice with lower age and fewer comorbidities.
- Anticoagulation with both warfarin and NOACs ***and not DAPT which is the standard of care*** were effective in prevention and treatment of reduced leaflet motion.
- Majority of cases of subclinical leaflet thrombosis diagnosed by 4D CT are hemodynamically silent and hence missed by TTE



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Conclusions, *contd.*

Patients with subclinical leaflet thrombosis had a small but significant increase in transvalvular gradients compared to patients without subclinical leaflet thrombosis

A greater proportion of patients with subclinical leaflet thrombosis (15% vs. 1%) had hemodynamically significant increase in gradients (aortic valve gradients >20mmHg **and** increase in aortic valve gradients >10mmHg).

While the death, MI and stroke rates were not significantly different between the 2 groups, subclinical leaflet thrombosis was associated with increased rates of TIAs and strokes/TIAs.



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