A Rationale Approach to Adjunct Pharmacotherapy after TAVR

Susheel Kodali, MD

Co-Director, Heart Valve Center
Columbia University
New York, NY

TVT Transcatheter Valve Therapies (TVT)
A Multidisciplinary Approach

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Disclosure Statement of Financial Interest

Susheel Kodali, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support

- Steering Committee

- SAB (Equity)

Company

- Edwards Lifesciences

- Edwards Lifesciences, Claret Medical, Meril

- Thubrikar Aortic Valve, Inc

Background

- From a patient perspective, stroke is the most clinically meaningful complication following TAVR

- In cardiovascular medicine, pharmacologic efforts to reduce stroke must be balanced by increased bleeding risk

- In the elderly, comorbid population undergoing TAVR, both stroke and bleeding risks are significantly elevated
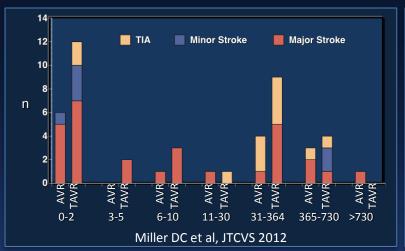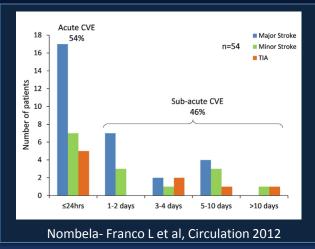
Questions

- Is DAPT necessary to reduce thrombotic risk after TAVR?

- Does thrombotic risk decrease over time?

- Does surgical data provide any guidance?

- Is there a role for anti-coagulation (either short tem or long term) after TAVR?

Background - Stroke

- 30 day stroke rates following TAVR average around 3%[1]

- ~50% of peri-procedural strokes occur >24 hours after TAVR

Miller DC et al, JTCVS 2012

Nombela- Franco L et al, Circulation 2012

- New and existing atrial arrhythmias are associated with doubling of stroke risk[2,3]

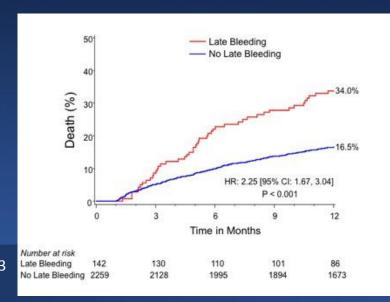- The occurrence of stroke results in worse one year outcomes with a more than 2-fold increase in mortality

[1]Rodes-Cabau J et al, JACC 2013
[2]Linke A et al, JACC 2012
[3]Nombela-Franco L et al, Circ 2012

Background - Bleeding

- Bleeding rates significant after TAVR
  - Major Bleeding – 15-32%, Life Threatening – 5-16%[1]
  - Majority but not all is related to procedure and is mechanical in nature

- Bleeding impacts mid-term mortality

- Late bleeding (major) occurs in ~5-6% and impacts mortality[2]

- Etiologies include gastrointestinal, trauma, genitourinary and neurologic[2]

Balancing Act

Thrombotic Events

Bleeding Events
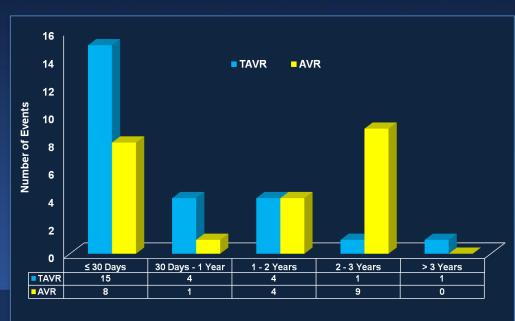
Nothing is gained for free!

Rationale for *Short-Term* DAPT

- Displacement of native leaflets into sinus creates areas of abnormal or slow flow

- Platelet activation due to vessel wall disruption or exposure of artificial surface may be mitigated

- Presence of metal within vascular tree results in higher thrombotic risk until endothelialization which takes ~3 months[1]

- There does not appear to be increased risk of late thrombotic events[2]

[1]Noble S et al, EuroIntervention 2009
[2]Thourani et al, ACC 2013

	≤ 30 Days	30 Days - 1 Year	1 - 2 Years	2 - 3 Years	> 3 Years
TAVR	15	4	4	1	1
AVR	8	1	4	9	0

Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation

Gian Paolo Ussia, MD[a,b,*], Marilena Scarabelli, MD[a], Massimiliano Mulè, MD[a], Marco Barbanti, MD[a], Kunal Sarkar, MD[a], Valeria Cammalleri, MD[a], Sebastiano Immè, MD[a], Patrizia Aruta, MD[a], Anna Maria Pistritto, MD[a], Simona Gulino, MD[a], Wanda Deste, MD[a], Davide Capodanno, MD[a,b], and Corrado Tamburino, MD, PhD[a,b]

- Single center, open label randomized study between ASA vs. ASA/Plavix for 3 months following TAVR
- 79 patients undergoing TAVR with CoreValve enrolled
- No significant difference in MACCE or Mortality at 30 days or 6 months between ASA alone vs ASA/Plavix
- No increased bleeding risk or acute procedural complications with Plavix

Study underpowered to answer question but no other large studies available

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Other Considerations

Original Investigation

Outcomes Following Transcatheter Aortic Valve Replacement in the United States

Michael J. Mack, MD; J. Matthew Brennan, MD, MPH; Ralph Brindis, MD, MPH; John Carroll, MD; Fred Edwards, MD; Fred Grover, MD; David Shahian, MD; E. Murat Tuzcu, MD; Eric D. Peterson, MD, MPH; John S. Rumsfeld, MD, PhD; Kathleen Hewitt, MSN; Cynthia Shewan, PhD; Joan Michaels, RN; Barb Christensen, RN; Alexander Christian; Sean O'Brien, PhD; David Holmes, MD; for the STS/ACC TVT Registry

What should be done with patients on oral anticoagulants prior to TAVR?

				Inoperable (n = 1559)	
				Trans-femoral (n = 1139)	Nontrans-femoral (n = 420)
				83 (77-88)	82 (77-87)
Male	3862 (50)	2053 (54)	992 (43)	616 (54)	201 (48)
STS PROM score, median (IQR), %	7 (5-11)	7 (5-11)	8 (5-12)	7 (4-10)	7 (4-11)
NYHA class III/IV heart failure	6272 (81)	3104 (81)	1884 (81)	962 (84)	322 (77)
Coronary artery disease	5316 (69)	2506 (66)	1706 (74)	793 (70)	311 (74)
No. of prior cardiac surgeries					
1	2045 (27)	905 (24)	700 (30)	309 (27)	133 (32)
≥2	400 (5)	164 (5)	140 (6)	71 (6)	25 (6)
Prior aortic valve intervention					
Balloon aortic valvuloplasty	1197 (16)	516 (13)	432 (19)	177 (16)	72 (17)
Surgical AVR	123 (2)	58 (2)	32 (1)	25 (2)	8 (2)
TAVR	14 (0.2)	7 (0.2)	4 (0.2)	2 (0.2)	1 (0.2)
Previous stroke	1004 (13)	503 (13)	321 (14)	130 (11)	50 (12)
Peripheral arterial disease	2416 (31)	898 (23)	1067 (46)	274 (24)	177 (42)
COPD					
Moderate	1081 (14)	511 (13)	358 (15)	154 (14)	58 (14)
Severe	1064 (14)	536 (14)	336 (15)	138 (12)	54 (13)
Oxygen-dependent lung disease	1135 (15)	569 (15)	347 (15)	161 (14)	58 (14)
Renal failure					
Dialysis-dependent	350 (5)	190 (5)	95 (4)	47 (4)	18 (4)
Serum creatinine level ≥3.0 mg/dL	361 (5)	194 (5)	103 (4)	47 (4)	17 (4)
5-m walk time >6 s	2198 (72)	1008 (73)	784 (73)	304 (70)	102 (57)
Atrial fibrillation	3148 (41)	1627 (42)	919 (40)	445 (39)	157 (37)
Permanent pacemaker/ICD	1500 (19)	774 (20)	433 (19)	215 (19)	78 (19)
Hostile chest	742 (10)	272 (7)	167 (7)	222 (19)	81 (19)

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Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators
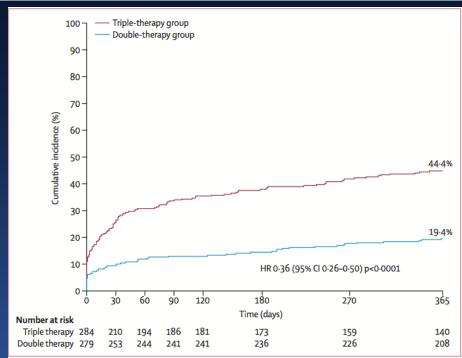
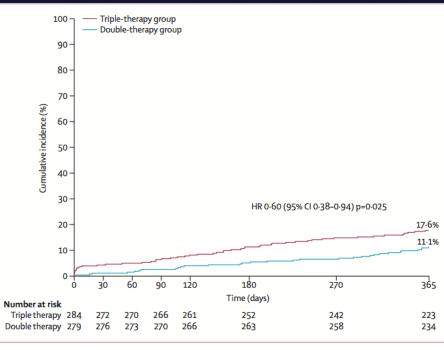Figure 2: Incidence of the primary endpoint (any bleeding)
HR=hazard ratio.

Figure 3: Cumulative incidence of the secondary endpoint (death, myocardial infarction, stroke, target-vessel revascularisation, and stent thrombosis)
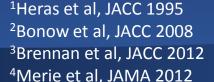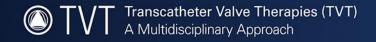HR=hazard ratio.

What have we learned from surgery?

- Risk of thromboembolic events is highest in first 3 months after bioprosthetic SAVR[1]

- Recommendation after surgery is ASA[2]

- However, several studies have suggested that addition of warfarin after surgery reduces thromboembolic events and CV death even in the absence of atrial fibrillation[3,4]

[1]Heras et al, JACC 1995
[2]Bonow et al, JACC 2008
[3]Brennan et al, JACC 2012
[4]Merie et al, JAMA 2012

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Proposed Algorithm Following TAVR

Does patient have another indication for DAPT?

— NO → **Is patient at high risk for bleeding or falls?**

— YES → **Aspirin 81mg lifelong**

Is patient at high risk for bleeding or falls? — NO ↓

Is patient on anticoagulation?

— NO → **Aspirin 81mg lifelong + Plavix 75mg (6 months)**

— YES ↓

ASA 81mg + Coumadin (or novel anticoagulants?)

Does patient have another indication for DAPT? — YES ↓

Proposed Algorithm Following TAVR

Does patient have another indication for DAPT (i.e. recent DES)?

↓ YES

Does patient have strong indication for anticoagulation?

→ YES → **Is patient at increased risk for bleeding or falls?** → YES → **ASA 81mg + Plavix 75mg for 3 months followed by ASA 81mg + coumadin**

↓ NO

ASA 81mg lifelong + Plavix 75mg for 6 months

↓ NO

ASA 81mg + Coumadin + 1-3 months of Plavix 75mg

Role for LAA Occluders?

Especially in patients with ACS or complex PCI

Unanswered Questions

- Does dual-antiplatelet therapy reduce the risk of stroke?

- What is the optimal duration of therapy?

- Can we predict patients at higher risk of embolic events?

- Is late embolic risk different for different devices?
  - More metal vs. Less metal vs. No Metal
  - Closed design vs Open design

- What is the role of LAA occluders?