TCT Asia-Pacific
Seoul, April 26, 2012

TAVI – Current State & Future Perspectives

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Disclosure of Financial Interest

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

Physician Name	Company/Relationship
Eberhard Grube, MD	Medtronic, CoreValve: C, SB, AB, OF Sadra Medical: E, C, SB, AB Direct Flow: C, SB, AB Mitralign: AB, SB, E Symetis: AB Boston Scientific: C, SB, AB Biosensors: E, SB, C, AB Cordis: AB Abbott Vascular: AB Capella: SB, C, AB InSeal Medical: AB Valtec: E, SB Claret, SB

Key
G = Grant and or Research Support E = Equity Interests S = Salary, AB = Advisory Board
C = Consulting fees, Honoraria R = Royalty Income I = Intellectual Property Rights
SB = Speaker's Bureau O = Ownership OF = Other Financial Benefits

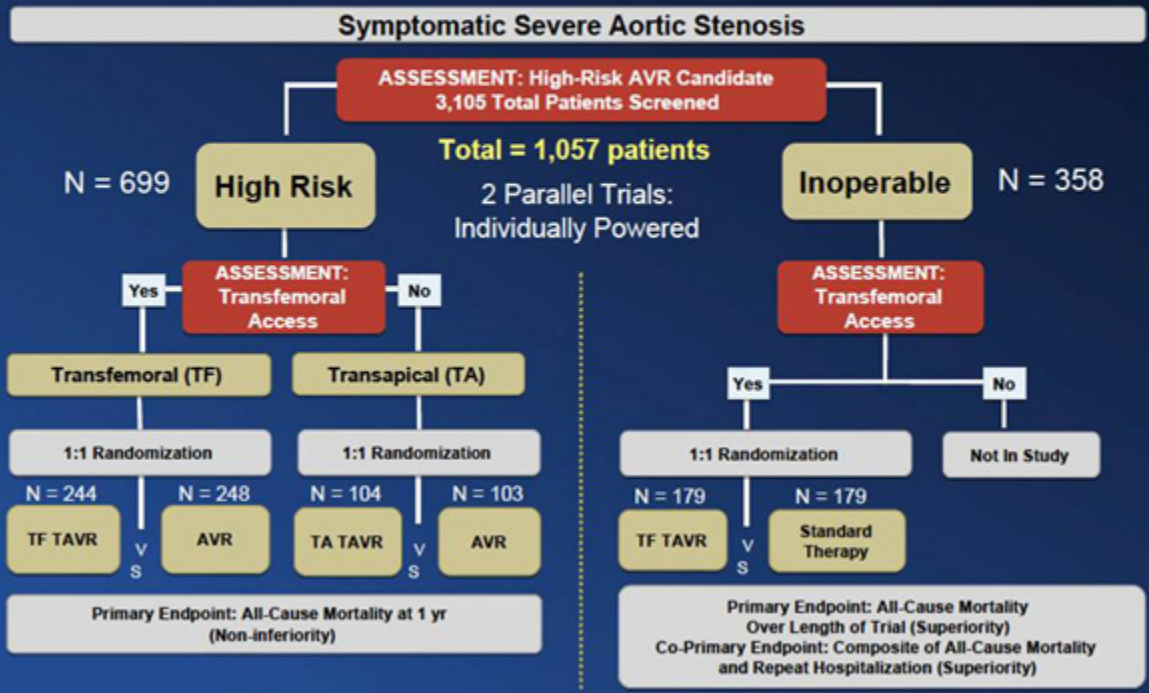
TAVR: 6 Months in Review

- Balloon Expandable TAVR:
  - PARTNER B: 2 Year Outcomes
  - PARTNER A: Quality of Life (TA v. TF)
- Self Expanding TAVR:
  - National Registries → Meta-analysis
- Risk Creep with Commercial TAVR
- Imaging Updates
- TAVR Complications:
  - Stroke
  - PPM Updates
  - Vascular Access
  - Perivalvular Leaks
  - Early Thrombosis-Restenosis
  - New Onset Atrial fibrillation

Enrolling Study Sites

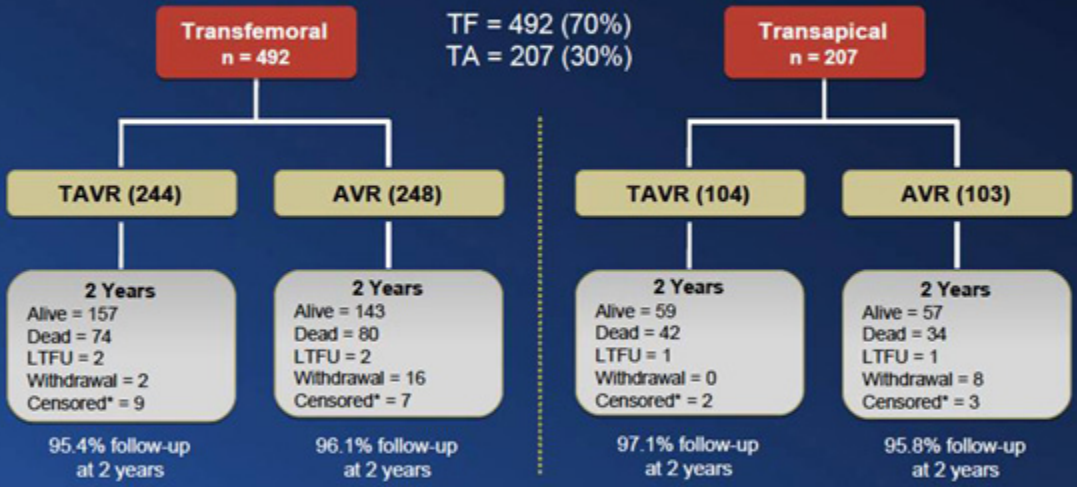
n = 699 patients
25 investigator sites
22 USA, 2 Canada, 1 Germany

PARTNER Study Design



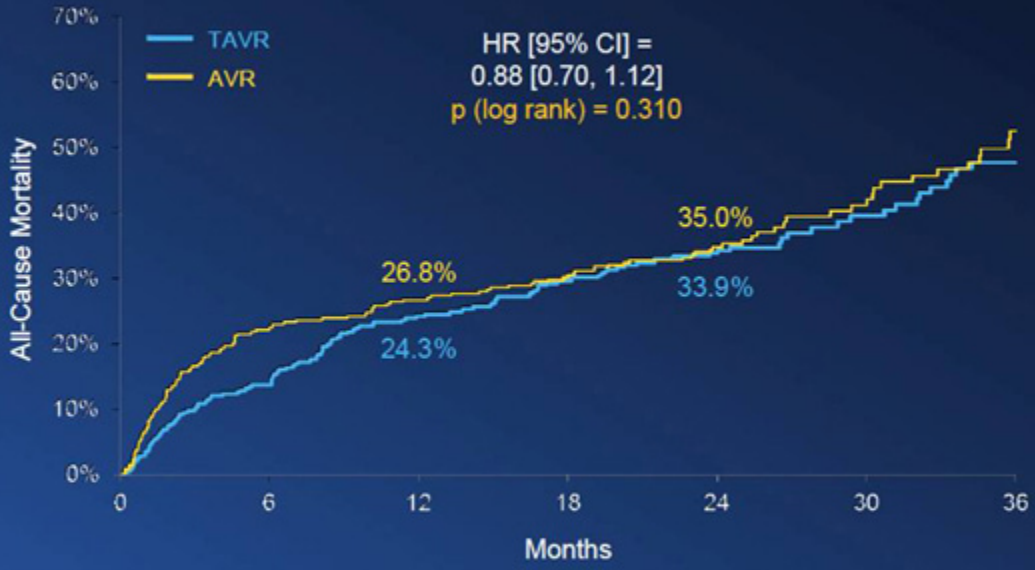
Study Flow

Randomized = 699 patients



*Censored = Patient is alive at last contact but no information available within follow-up window

All-Cause Mortality (ITT)

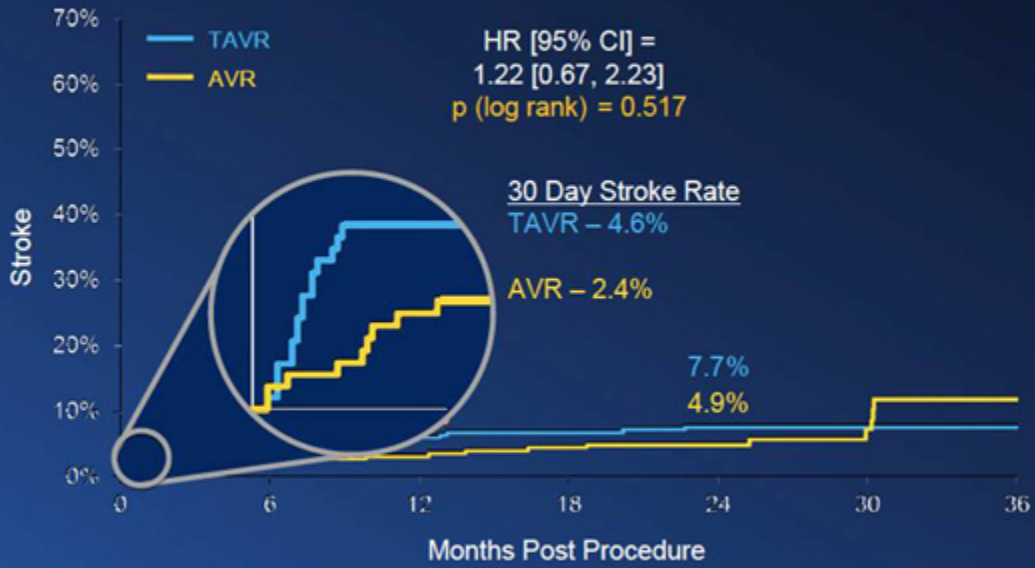


Numbers at Risk

TAVR	348	298	260	234	172	70	31
AVR	351	252	236	217	165	65	32

NYHA Class Survivors (ITT)

Strokes (ITT)



Numbers at Risk

TAVR	348	287	249	224	162	65	28
AVR	351	246	230	211	160	62	31

PARTNER B 2 Year: All CVA (%)

Note: Percents are of patients in the trial (n/179).

	≤ 30 Days	*31 Days – 1 Year*	*1 Year – 2 Years*
All CVA	p = 0.010	p = 0.387	p = 0.028
Ischemic Stroke	p = 0.017	p = 0.155	p = 0.083
Hemorrhagic Stroke	p = 0.316	p = 0.121	p = 0.415

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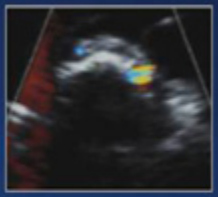
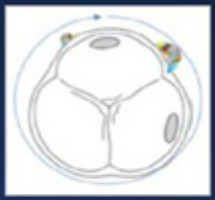
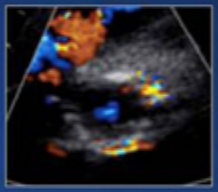
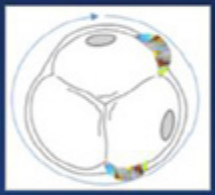
PARTNER Grading Criteria for Paravalvular AR



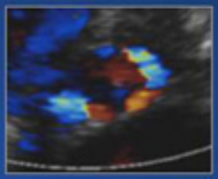


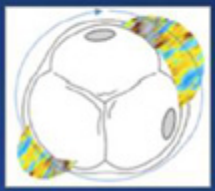
Circumference = 6″
AR = 0.1+0.35 = 0.45″
Ratio = 8%
Severity = Mild (< 10%)





Circumference = 6″
AR = 0.5+0.5 = 1.0″
Ratio = 17%
Severity = Moderate (10 – 20%)
(Trans AR also present)

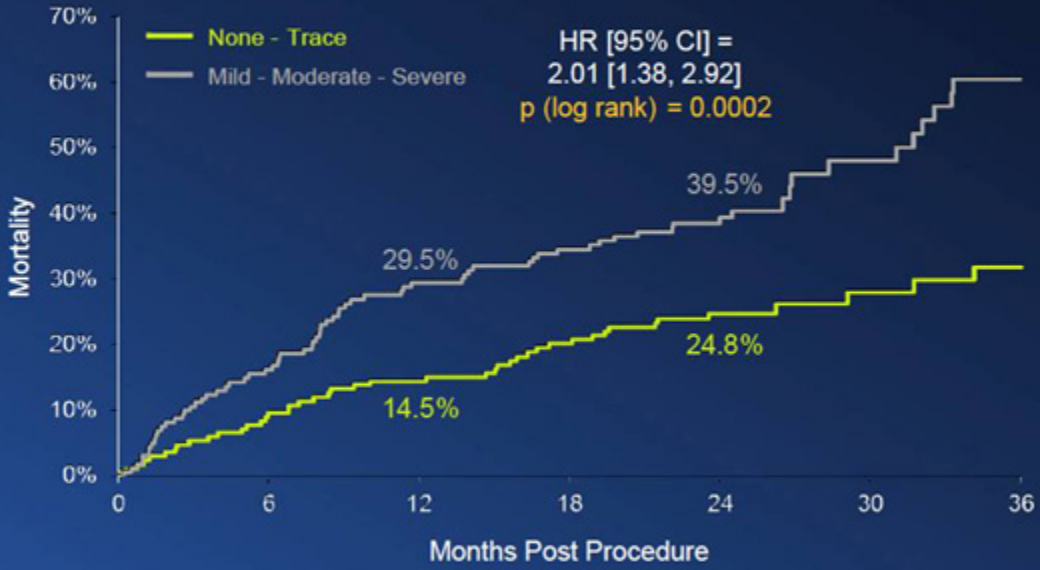




Circumference = 6″
AR = 0.6+1.1 = 1.7″
Ratio = 28%
Severity = Severe (> 20%)

Images courtesy of Pamela Douglas, MD, FASE

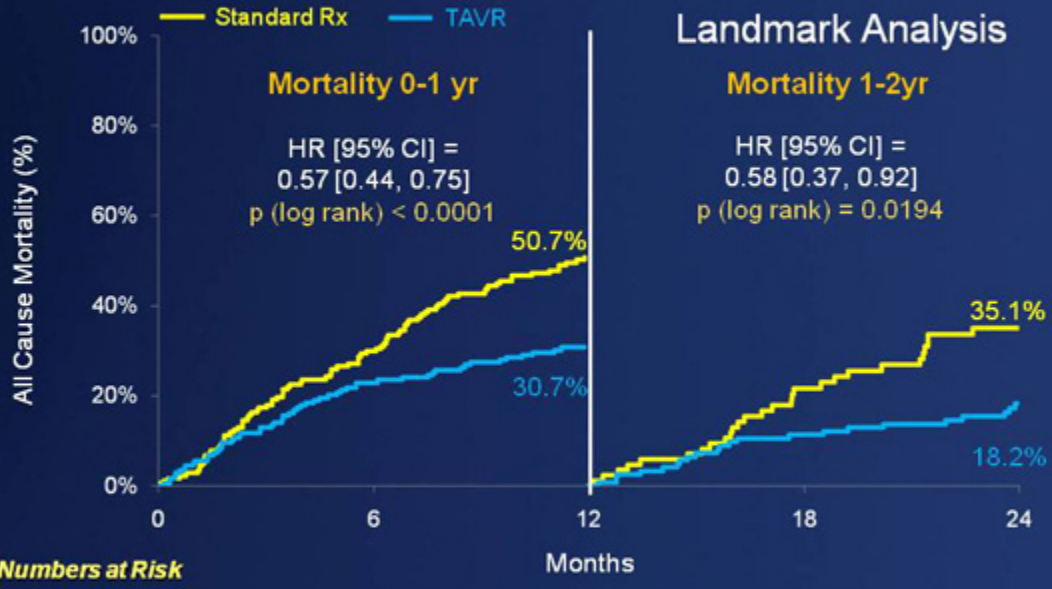
Paravalvular AR and Mortality
TAVR Patients (AT)



Numbers at Risk

None-Tr	167	149	140	126	87	41	16
Mild-Mod-Sev	160	134	112	101	64	26	12

PARTNER B 2 Year: All Cause Mortality (ITT)



Numbers at Risk

TAVR	179	138	124	110	83
Standard Rx	179	121	85	62	42

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CoreValve 18Fr SE Registry: 2 Year Mortality

2-Year Follow-Up of Patients Undergoing Transcatheter Aortic Valve Implantation Using a Self-Expanding Valve Prosthesis

1. Buellesfeld L, et al. *J Am Coll Cardiol.* 2011;57:1650-1657.

CoreValve ADVANCE | Baseline Characteristics

Characteristics	N=1015 %		%
Age (yrs.)	81 ± 6	Prior MI	16.0
Male	49.4	Prior PCI	31.1
Logistic EuroSCORE	19.2 ± 12.4	Permanent Pacemaker	12.8
NYHA		**EuroSCORE Relevant Factors**	
I or II	20.4	Prior CABG	21.4
III or IV	79.6	Cerebrovascular Disease	12.9
Diabetes	30.9	COPD	22.6
CAD	57.6	Pulmonary Hypertension	12.6
PVD	19.5	Prior median sternotomy	17.3
Atrial Fibrillation	32.8	Renal Failure	14.6

CoreValve ADVANCE | Procedural Results

Procedural Parameters N=996	%
Successful vascular access, delivery & deployment of device & successful retrieval of the delivery system	97.8
Correct position of the device in the proper anatomical location	98.7
Mean aortic valve gradient < 20 mmHg	96.2
No severe AR requiring intervention	97.9
Only one valve implanted in the proper anatomical location	96.0

Major Complications; Valve Related N=996	%
Annulus Rupture	0.0
Valve Embolization	0.3
Conversion to open AVR	0.1
Coronary Compromised	0.1

CoreValve ADVANCE | 30-day Outcomes

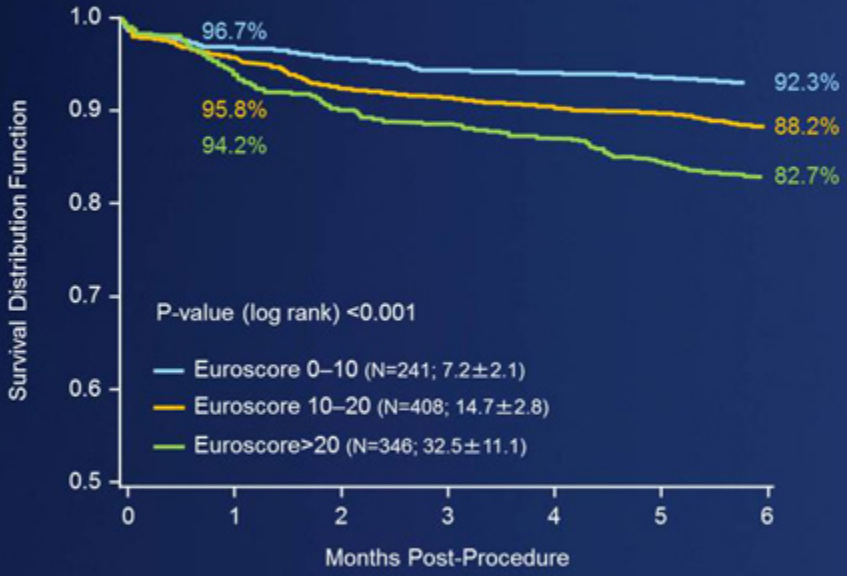
Primary Endpoint N=996	Kaplan-Meier Estimates, %
MACCE	8.3
All-cause Mortality	4.5
Myocardial Infarctions	0.2
Emergent cardiac surgery or percutaneous re-intervention	1.7
Stroke	2.9

Additional VARC Endpoints N=996	Kaplan-Meier Estimates, %
Cardiovascular Mortality	3.4
Major Bleeding	9.7
Life Threatening Bleeding	4.0
Major Vascular Complications	10.7
Acute Kidney Injury - Stage III	0.4

Additional Endpoint N=996	Kaplan-Meier Estimates, %
New Pacemaker Implantation	26.3

CoreValve ADVANCE | 6-month Survival

Kaplan-Meier Estimates of Freedom from **All-cause Mortality** by EuroSCORE group



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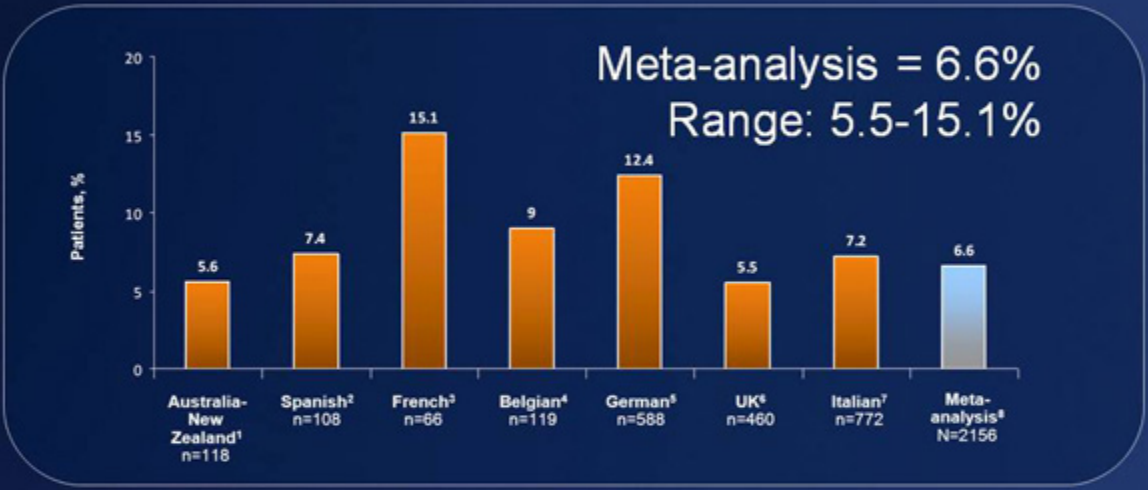
CoreValve Meta-analysis

- N=2156 patients
- 7 national registries
  - Australia-New Zealand, Belgium, France, Germany, Italy, Spain, and UK
- Mean age of the population: 81.6 years
- Male: 47%
- New York Heart Association class III and IV: 77%
- Mean Logistic EuroSCORE: 21.3% (range, 16.0-24.7)
- Mean aortic valve area: 0.63 cm^2
- Mean gradient: 49.7 mm Hg

1. Ruiz CE, et al. Weighted meta-analysis of early and late clinical outcomes after CoreValve® – TAVI in seven national registries. Presented at: EuroPCR; May 17-20, 2011; Paris, France. Analysis sponsored by Medtronic, Inc.

CoreValve 30d Mortality Rate



1. Meredith IT. The Australia-New Zealand Medtronic CoreValve® Registry: outcomes in inoperable and high risk AS patients. Presented at: TCT. 2010.
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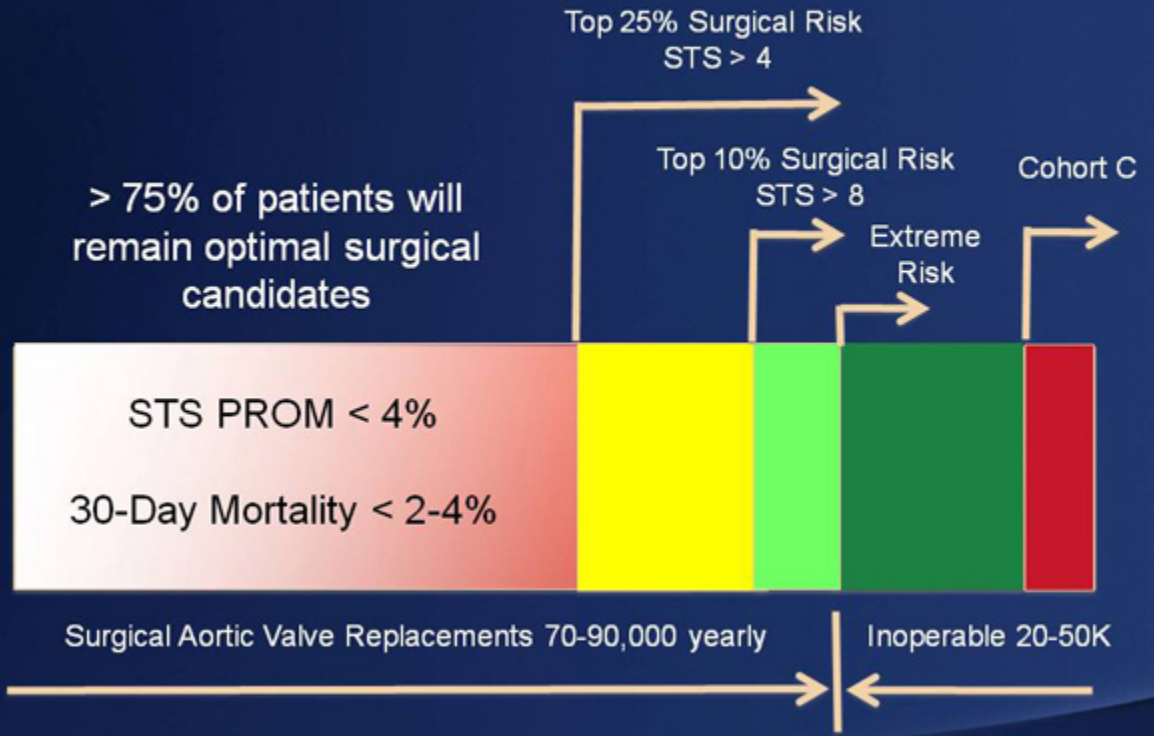
Expanding Into Risk Populations



Better TAVR Outcomes in Lower Risk Patients

Improvements in Transcatheter Aortic Valve Implantation Outcomes in Lower Surgical Risk Patients

A Glimpse Into the Future

Ruediger Lange, MD, PHD, Sabine Bleiziffer, MD, Domenico Mazzitelli, MD, Yacine Elhmidi, MD, Anke Opitz, MD, Marcus Krane, MD, Marcus-Andre Deutsch, MD, Hendrik Ruge, MD, Gernot Brockmann, MD, Bernhard Voss, MD, Christian Schreiber, MD, Peter Tassani, MD, PHD, Nicolo Piazza, MD, PHD

Munich, Germany

N=420 patients (105 per quartile)

	Quartile 1	Quartile 4
Age, years	81.1 years	78.9 years
Logistic Euroscore, %	25.4%	17.8%
STS-PROM, %	7.13%	4.8%
Crude 30 day Mortality, %	11.4%	3.8%

Lange JACC 2012;59:280–7

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- Risk Creep with Commercial TAVR
- Imaging Updates (CTA used preferentially)
- TAVR Complications:
  - Stroke
  - PPM Updates
  - Vascular Access
  - Perivalvular Leaks
  - Early Thrombosis-Restenosis
  - New Onset Atrial fibrillation

CTA For Valve Sizing: We Made the Right Call

Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry

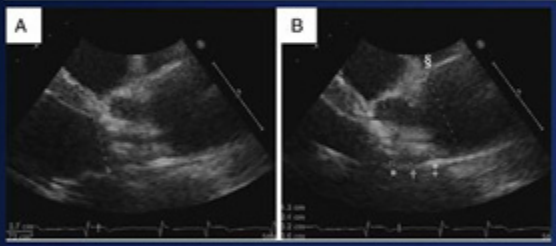
Table 2 Echocardiographic and angiographic characteristics of the study population according to the occurrence of at least moderate post-procedural AR

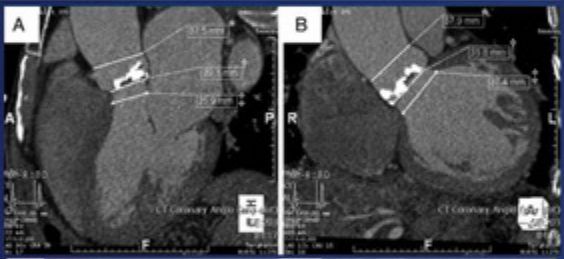
Characteristics	AR≥2/4 (n=119)	AR<2/4 (n=571)	p Value	OR (95% CI)
Aortic valve area (cm^2)	0.6±0.16	0.66±0.18	0.001	–
Mean aortic gradient (mm Hg)	46.8±18.1	48.6±17.3	0.22	–
LVEF (%)	48.6±15.9	52.8±14.8	0.005	–
LVEF≤30%	24 (20)	68 (12)	0.01	1.87 (1.12 to 3.13)
Bicuspid aortic valve	4 (3.4)	8 (1.4)	0.13	2.47 (0.73 to 8.34)
Degree of leaflet calcification				
Mild	9 (7.8)	28 (5)	0.22	1.62 (0.74 to 3.53)
Moderate	44 (38)	188 (33)	0.32	1.23 (0.81 to 1.87)
Severe	62 (54)	346 (62)	0.13	0.73 (0.49 to 1.09)
Aortic annulus diameter (mm)	23.4±2.3	23.5±2.6	0.72	–
Measured with CT	28 (24)	215 (39)	0.002	0.50 (0.32 to 0.79)
Measured with TOE	88 (76)	338 (61)	0.002	2.00 (1.26 to 3.16)

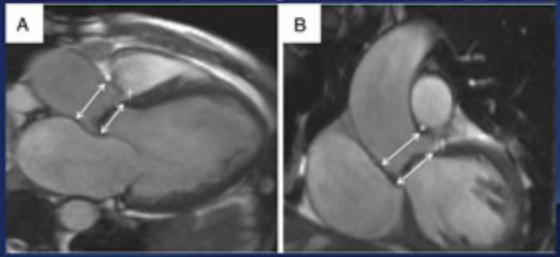
CMR – CTA – TTE Comparisons

Multimodality Imaging in Transcatheter Aortic Valve Implantation and Post-Procedural Aortic Regurgitation

Comparison Among Cardiovascular Magnetic Resonance, Cardiac Computed Tomography, and Echocardiography







Which Gold Standard for Annular Sizing?
N=202

Jabbour JACC 2011; 58:2143–50

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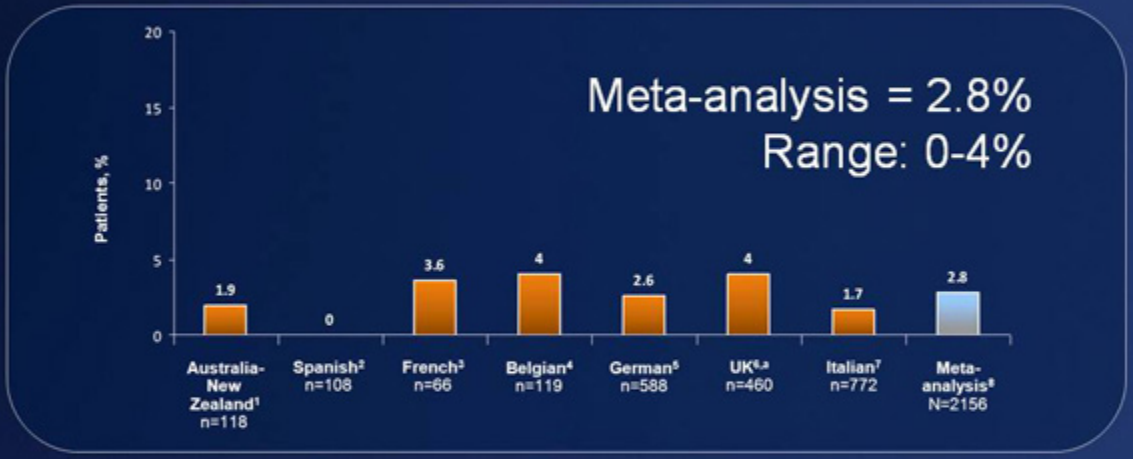
CoreValve Meta-analysis

30d Stroke Rate



Stroke is not defined consistently across all studies.
[a]In-hospital stroke rate reported.

1. Meredith IT. The Australia-New Zealand Medtronic CoreValve® Registry: outcomes in inoperable and high risk AS patients. Presented at: TCT. 2010.
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CoreValve Neurologic Substudy

- Submission of 25% of patients of the CoreValve RCT patients is a requisite of the IDE Submission
- Non participation in the neurologic substudy at this juncture is not really an option
- Neurologic examinations have typically increased the stroke rate
- Comparisons of sAVR and TAVR is more interesting than Extreme Risk Registry or Continued Access
- Essential to link stroke scale to QOL

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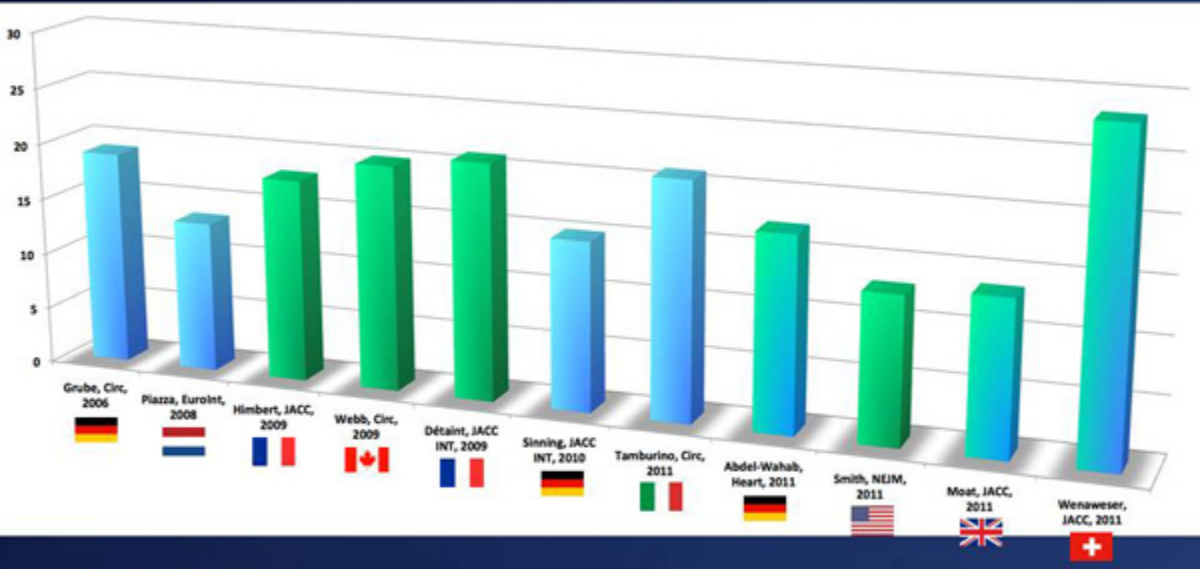
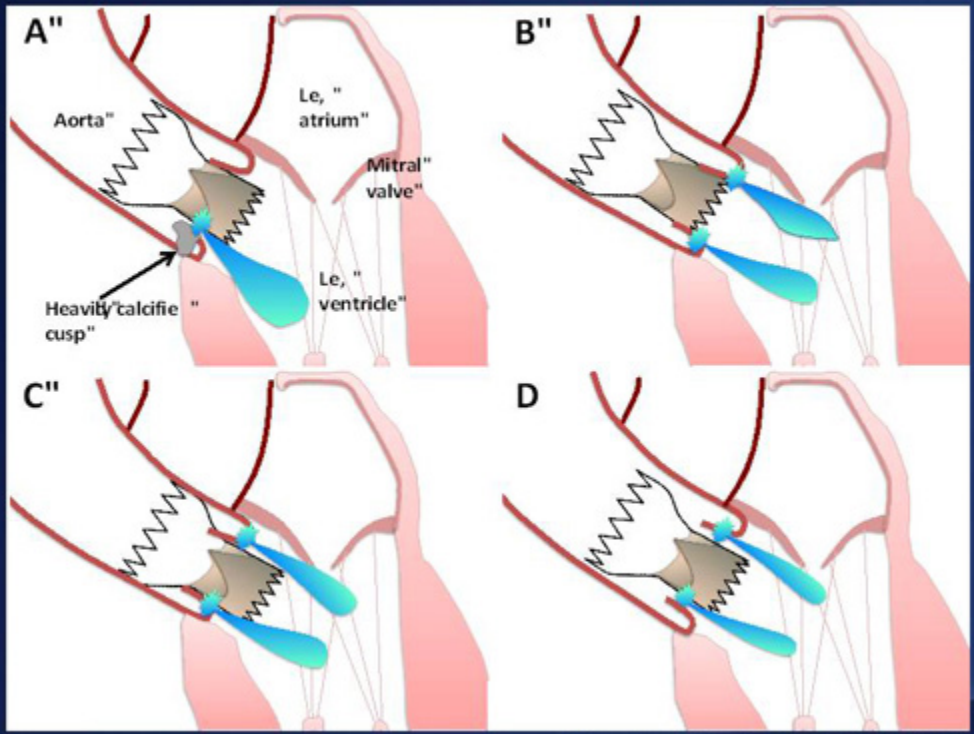
Moderate/severe periprosthetic AR



Blue Medtronic CoreValve
Green: Edwards-SAPIEN

Mechanisms of Peri-prosthetic AR

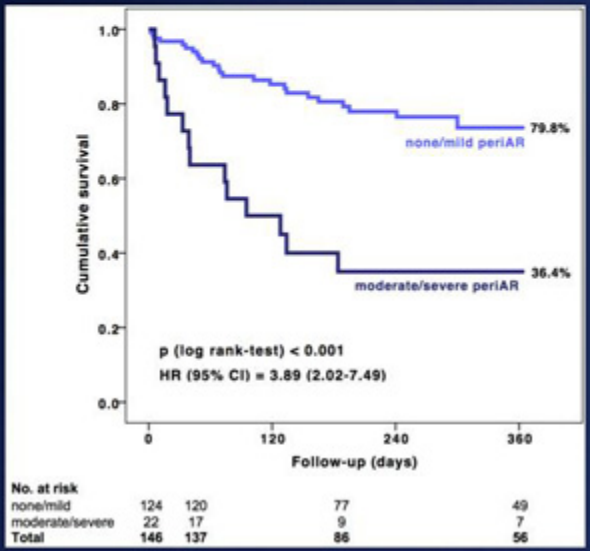


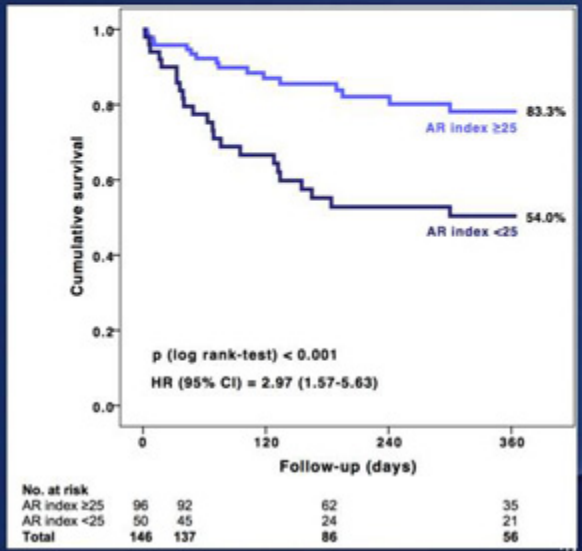
Sinning JM et al., JACC 2012

Significance of Residual AR

Aortic Regurgitation Index Defines Severity of Peri-Prosthetic Regurgitation and Predicts Outcome in Patients After Transcatheter Aortic Valve Implantation

Sinning et al., JACC 2012





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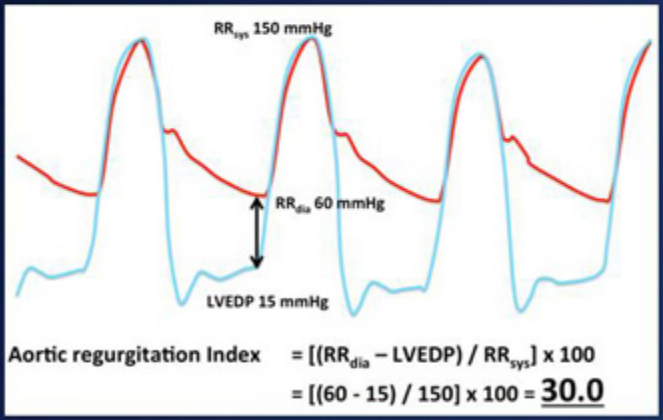
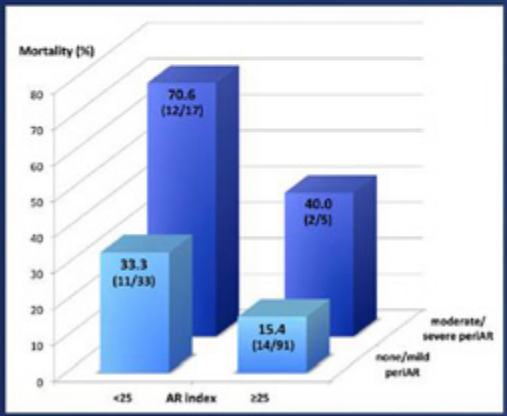
Sinning et al., JACC 2012



Aortic regurgitation Index = $[(RR_{dia} - LVEDP) / RR_{sys}] \times 100$

= $[(60 - 15) / 150] \times 100 =$ **30.0**



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Atrial Fibrillation Post TAVR

Incidence, Predictive Factors, and Prognostic Value of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Implantation

- 138 patients without prior atrial fibrillation
- New onset atrial fibrillation in 31.9% with 72 hours
- Predictive factors of AF were left atrial size (odds ratio [OR]: 1.21 for each increase in 1 mm/m^2) and transapical approach (OR: 4.08, 95% CI: 1.35 to 12.31, p = 0.019).
- Cumulative stroke and stroke/systemic embolism rates at FU in the NOAF group were 13.6% and 15.9% in the NOAF group vs. 3.2% in the no-NOAF group (p = 0.039, adjusted p = 0.037 for stroke; p = 0.020, adjusted p = 0.023 for stroke/systemic embolism).

Amat-Santo J Am Coll Cardiol 2012;59:178–88

CoreValve® System Ongoing Studies

Evaluate procedural best practices

- **ADVANCE Study[3]--- ACC 2012**
  - Designed to evaluate clinical outcomes in "real-world" patients
  - 1017 patients in up to 44 centers followed for up to 10 years
  - Enrollment and data analysis complete
- **ADVANCE-II Study[1]**
  - Designed to characterize current CoreValve® System implantation best practices
  - ->100 patients

Evaluate performance in expanded patient population

- **SURTAVI[1]**

-Randomized controlled trial of TAVI vs SAVR studying broader patient population (intermediate risk)

- **REDO Study[2]**
  - Outcomes in patients with a failing aortic bioprosthesis

SAVR=surgical aortic valve replacement; TAVI=transcatheter aortic valve implantation.

1. Popma J, et al. *Cardiac Interventions Today*. July/August 2010:44-51.
2. Medtronic CoreValve® REDO Study. US National Institutes of Health Web site. http://clinicaltrials.gov/ct2/results?term=NCT01051310. Accessed 7/13/11.