Advances in Percutaneous Valve Interventions

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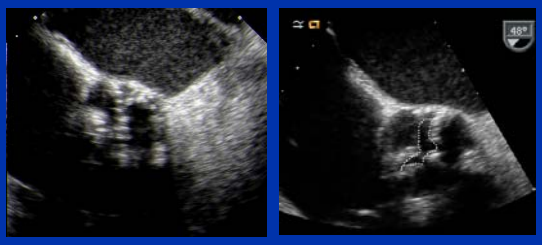
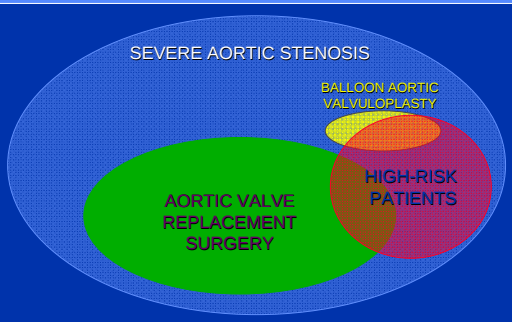
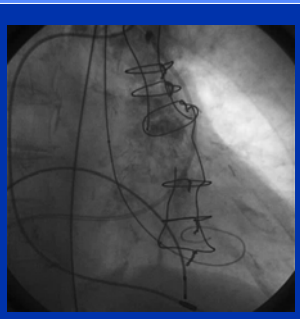
Severe Aortic Stenosis

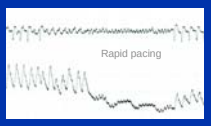


Severe Aortic Stenosis: Therapy



Procedure: Retrograde Aortic Valvuloplasty

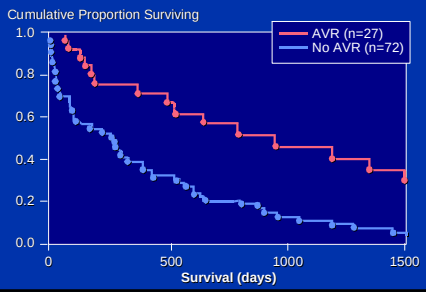




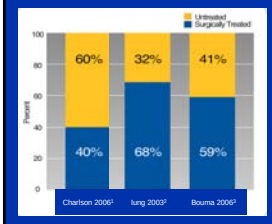
Procedure: Antegrade Aortic Valvuloplasty

Survival of Severe Aortic Stenosis Patients

Balloon Valvuloplasty with and without Aortic Valve Replacement



Need For AS Treatment Options



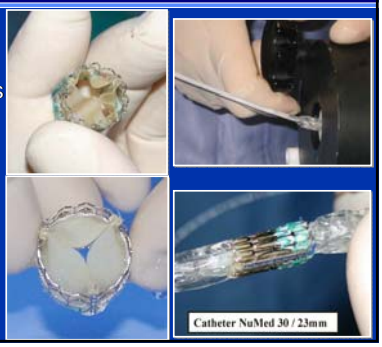
1. Charlson E et al. J Heart Valve Dis 2006;15:312-321
2. Iung B et al. European Heart Journal 2003;24:1231-1243
3. Bouma B J et al. Heart 1999;82:143-148

Percutaneous AVR

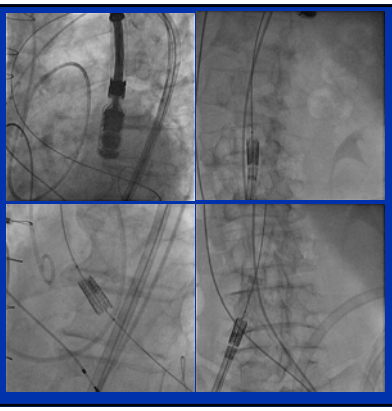
Edward-Sapien Aortic Valve

Tricuspid Bio-prothesis

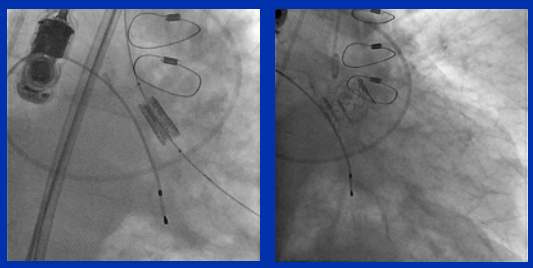
- Highly resistant stent
- Bovine pericardium
- Balloon expandable
- 14-16 mm



Retrograde Approach

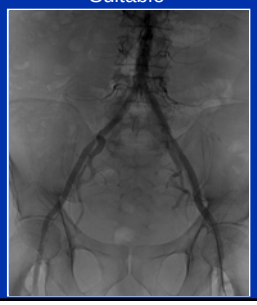


Retrograde Approach

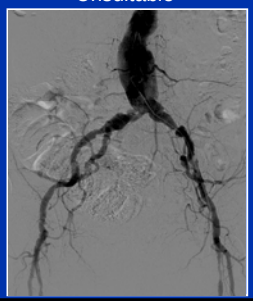


Delivery of Transcatheter Valves

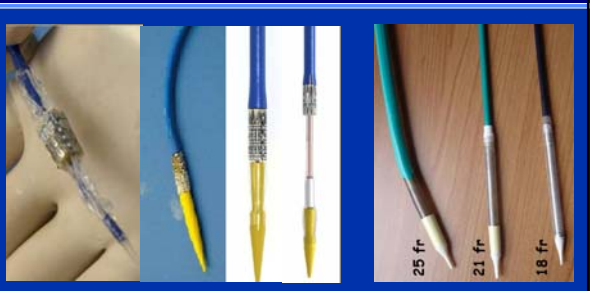
Suitable



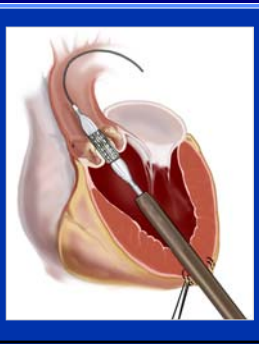
Unsuitable



Advancements in Delivery Sheath



Transapical Aortic Valve Replacement

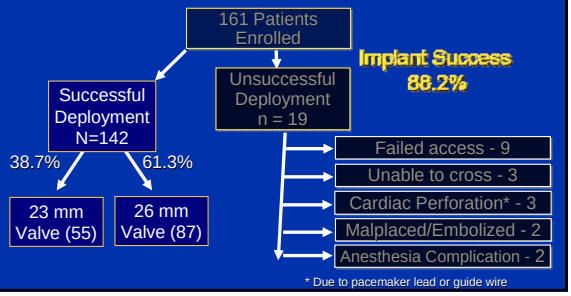


Edward-Sapien Experience

First-in-Man	Feasibility	Randomized Control	Post-market
Procedural success in humans	Demonstrate "reasonable" safety & effectiveness	Effectiveness vs Control (AVR & medical therapy)	Evaluate transition to commercial use Procedural success & clinical outcomes
RECAST REVIVE REVIVE I REVIVAL I	REVIVE II REVIVAL II IDE TRAVERCE PARTNER EU	PARTNER IDE	SOURCE

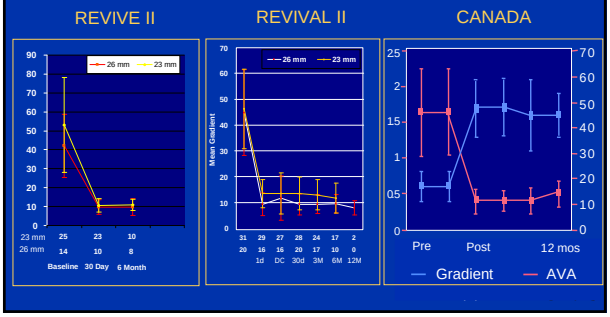
REVIVE II & REVIVAL II (Transfemoral)

Procedural Results



* Due to pacemaker lead or guide wire

Change in Mean Gradient After PAVR



REVIVE & REVIVAL II
Mortality and Morbidity

	≤ 30 days	> 30 days *	Total
MACCE	29 (18.6%)	26 (16.8%)	52 (32.3%)
Death	18 (11.2%)	26 (16.1%)	44 (27.3%)
MI	5 (3.1%) **	1 (0.6%) **	6 (3.7%) **
Stroke	7 (4.3%)	3 (1.9%)	10 (6.2%)
Major	4 (2.5%)	3 (1.9%)	7 (4.3%)
Minor	3 (1.9%)	0	3 (1.9%)
Urgent Cardiac Surgery	2 (1.2%)	0	2 (1.2%)

* F/U – (mean 9.8 months, median 11.9 months, max. 27.3 months)
** MI= CK-MB or Trop > 3 times normal + ECG changes or symptoms

REVIVE & REVIVAL II

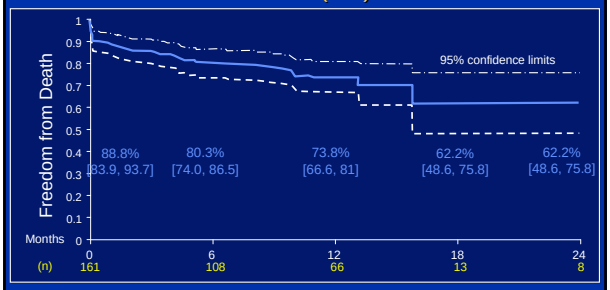
Complications within 30 days

Vascular Complications	25 (15.5%)
Renal Failure req. Dialysis	2 (1.2%) *
Permanent Pacemaker	8 (4.9%)

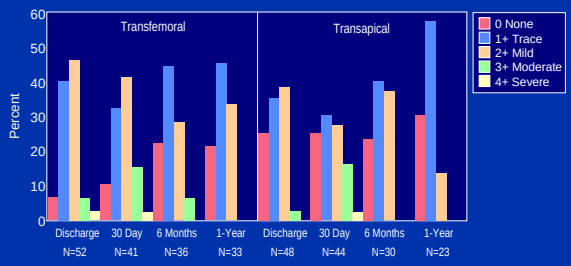
* One patient on CVVHD prior to valve implantation

REVIVE & REVIVAL II

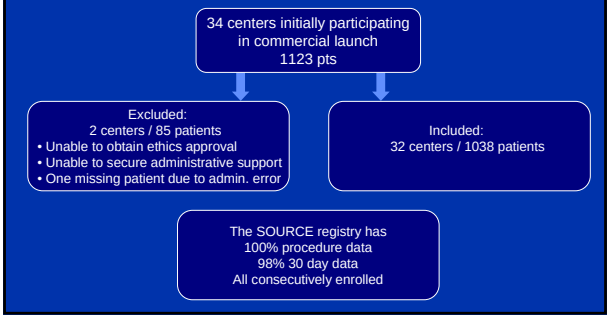
Survival (KM)



Paravalvular Leak



SOURCE Registry



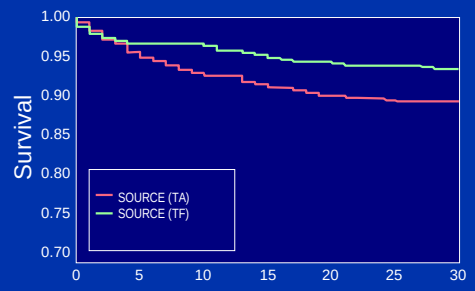
SOURCE Registry

	TF (n=463)	TA (n=575)	P-value
Age (yrs)	81.7	80.7	NS
Female	55.2%	56%	NS
Pulmonary disease	25.4%	29.4%	NS
Renal dysfunction	26.3%	32.9%	0.024
Logistic EuroSCORE	25.7	29.2	<0.005
Peripheral Vascular Disease	10.9%	27.5%	<0.001
Carotid Artery Stenosis (>50%)	7.6%	17.1%	<0.001
Incidence of CAD	47.4%	56.0%	<0.006
Porcelain Aorta	4.6%	11.5%	<0.001
Prior CABG	17.6%	26.9%	<0.001
Mitral Valve Disease	16.1%	32.8%	<0.001

SOURCE Registry: 30 Day Complications

	TF (n=463)	TA (n=575)	Total (n=1038)
Death	29 (6.3%)	59 (10.3%)	88 (8.5)
Stroke	11 (2.4%)	16 (2.6%)	27 (2.5%)
Renal failure requiring dialysis	23 (5.0%)	69 (11.7%)	92 (8.7%)
Permanent pacemaker	31 (6.7%)	42 (7.3%)	73 (7.0%)

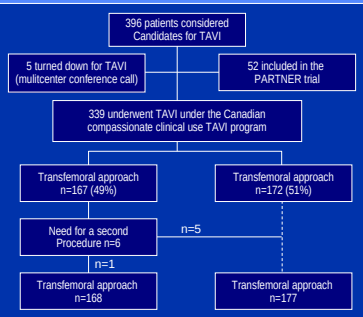
30 Day Mortality : TA – TF in SOURCE Registry



SOURCE Registry: Vascular Complications

Vascular Complications	None	All	Major	P-value
Survival transfemoral	94.1%	92.2%	88.6%	NS
Survival transapical	90.7%	72.7%	61.1%	<0.001

Canadian Experience



J. Rodes-Cabau,TCT 2009

Canadian Experience: Baseline Characteristics

Variable	All patients (n=339)	Transfemoral (n=167)	Transapical (n=172)	P value
Age (years)	81±8	83±8	80±8	0.009
Male sex	152 (45)	91 (55)	61 (35)	<0.001
BMI (kg/m^2)	26±5	25.6±4.9	25.6±4.7	0.93
Diabetes	79 (23)	37 (22)	42 (24)	0.89
Hypertension	252 (74)	102 (61)	150 (87)	<0.001
NYHA Functional Class				
I-II	30 (9)	12 (7)	18 (10)	0.33
III-IV	309 (91)	155 (93)	154 (90)	
Chronic artial fibrillation/flutter	115 (34)	66 (40)	49 (28)	0.01
Coronary artery disease	234 (69)	110 (66)	124 (72)	0.72
Previous myocardial infarction	173 (51)	82 (49)	91 (53)	0.91
Previous PCI	99 (29)	47 (28)	52 (30)	1.00
Prior coronary artery bypass grafting	116 (34)	49 (29)	67 (39)	0.17

J. Rodes-Cabau, TCT 2009

Canadian Experience: Baseline Characteristics

Variable	All patients (n=339)	Transfemoral (n=167)	Transapical (n=172)	P value
Cerebrovascular disease	77 (23)	27 (16)	50 (29)	0.01
Peripheral vascular disease	120 (36)	31 (19)	89 (52)	<0.001
COPD	100 (29)	45 (27)	55 (32)	0.55
Creatinine (µmol/l)	119±83	124±85	113±81	0.23
eGFR<60ml/min	191 (56)	86 (51)	104 (60)	0.33
STS-PROM score (%)	9.8±6.4	9.0±5.8	10.5±6.9	0.03
Porcelain aorta	61 (18)	28 (17)	33 (19)	0.78
Frailty	85 (25)	42 (25)	43 (25)	0.80
Pulmonary hypertension	84 (25)	35 (21)	49 (28)	0.26
Severe mitral regurgitation	27 (8)	18 (11)	9 (5)	0.04
Mean aortic gradient (mmHg)	46±17	48±18	44±17	0.08
Aortic valve area (cm^2)	0.63±0.17	0.63±0.16	0.63±0.18	0.93
LVEF (%)	55±14	55±14	56±14	0.72
LVEF <40%	55 (16)	26 (16)	28(16)	1.00

J. Rodes-Cabau, TCT 2009

Canadian Experience: 30 Day Outcomes

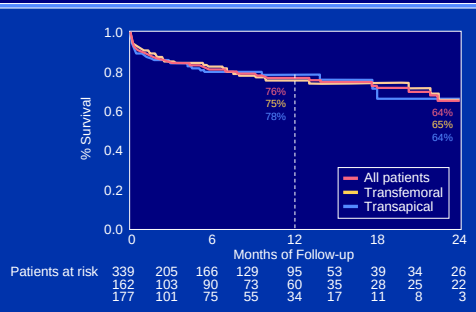
	All patients (n=345)	TF (n=168)	TA (n=177)	P value
Successful procedure	322 (93.3)	152 (90.5)	170 (96.0)	0.051
Procedural death	6 (1.7)	3 (1.8)	3 (1.7)	1.00
Valve embolization	7 (2.0)	5 (3.0)	2 (1.1)	0.27
Need for a second valve	9 (2.6)	4 (2.4)	5 (2.8)	1.00
Conversion to open heart surgery	6 (1.7)	2 (1.2)	4 (2.3)	0.69
Need for hemodynamic support	14 (4.1)	7 (4.2)	7 (4.0)	1.00
Major access site complications	45 (13.0)	22 (13.1)	23 (13.0)	1.00
Life threatening arrhythmias	28 (8.1)	12 (7.1)	16 (9.0)	0.56

Canadian Experience: 30 Day Outcomes

	All patients (n=345)	TF (n=168)	TA (n=177)	P value
Myocardial infarction	4 (1.2)	1 (0.6)	3 (1.7)	0.62
Stroke	8 (2.3)	5 (3.0)	3 (1.7)	0.49
Sepsis	10 (2.9)	5 (3.0)	5 (2.8)	1.00
Need for hemodialysis	9 (2.6)	3 (1.8)	6 (3.4)	0.50
Need for pacemaker	17(4.9)	6 (3.6)	11 (6.2)	0.32
30-day mortality	36 (10.4)	16 (9.5)	20 (11.3)	0.60

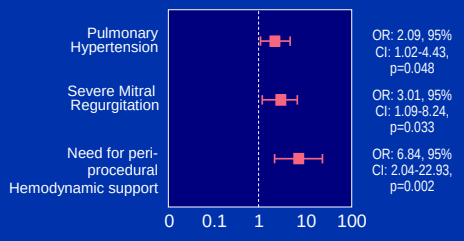
J. Rodes-Cabau, TCT 2009

Canadian Experience: 30 Day Outcomes



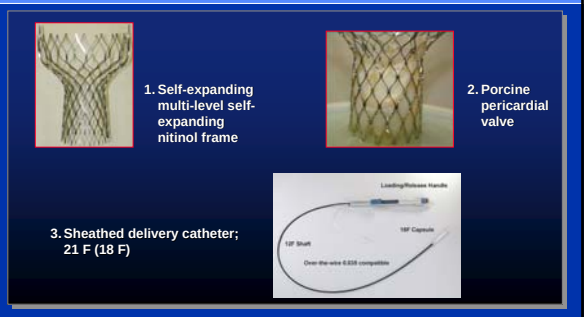
J. Rodes-Cabau, TCT 2009

Canadian Experience: Predictors

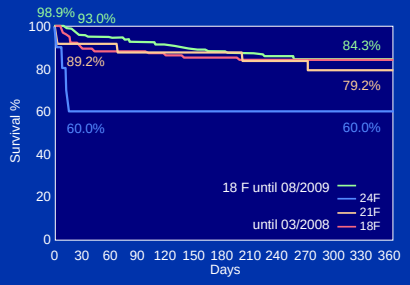


J. Rodes-Cabau, TCT 2009

Core Valve



CoreValve: Survival Curves



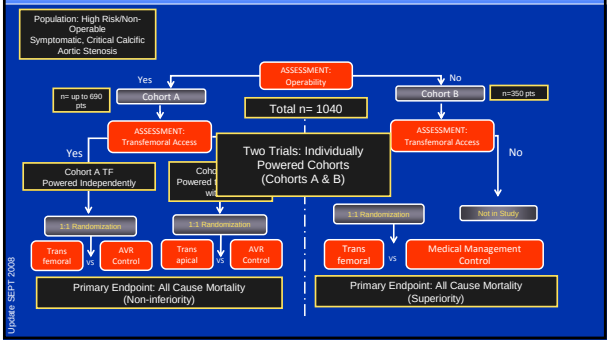
Grube E, Circ Cardiovasc Intervent 2008:1:167-175

CoreValve: In Hospital Outcomes

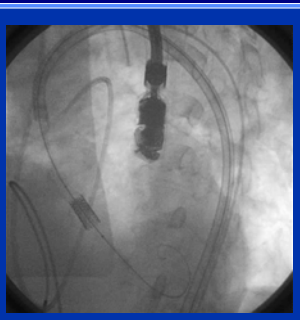
	25F	21F	18F Initially	18F 2008	18F 2009
Patient, n	10	24	102	187	130
Death, n (%)	4 (40.0)	2 (8.3)	10 (9.8)	11 (5.8)	4 (3.0)
Stoke, n (%)	1 (10.0)	2 (8.3)	3 (2.9)	4 (2.1)	2 (1.5)
Major, n (%)	1 (10.0)	0	1 (1.0)	3 (1.6)	1 (0.8)
Minor, n (%)	0	2 (8.3)	2 (2.0)	1 (0.5)	1 (0.8)
Myocardial Infarction, n (%)	0	(4.2)	2 (2.0)	0	0
Pacemaker requiring, n (%)	1 (10)	3 (13)	30 (33)	70 (37)	51 (39)

Grube E, Circ Cardiovasc Intervent 2008:1:167-175

The PARTNER IDE Trial

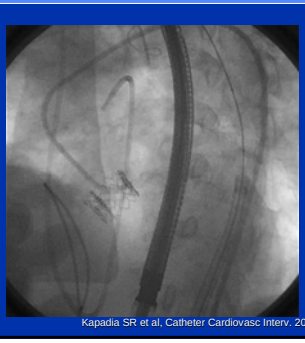


Percutaneous Aortic Valve Replacement



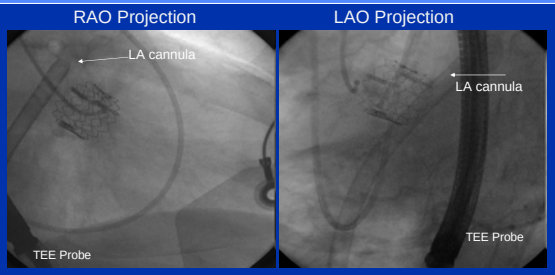
Kapadia SR et al, Catheter Cardiovasc Interv. 2009 Jun 1;73(7):966-72

LMT Obstruction



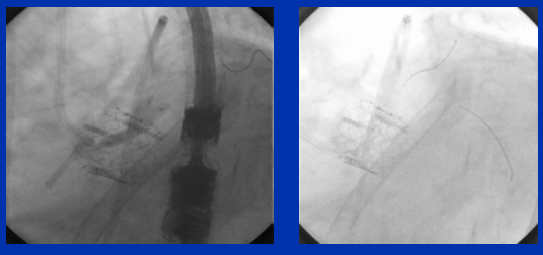
Kapadia SR et al, Catheter Cardiovasc Interv. 2009 Jun 1;73(7):966-72

TandemHeart Inserted



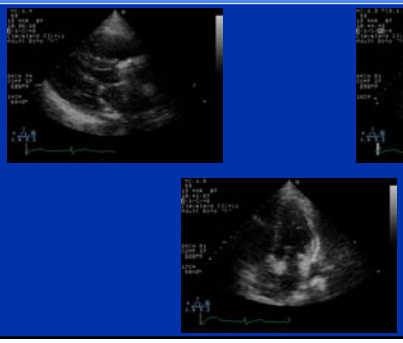
Kapadia SR et al, Catheter Cardiovasc Interv. 2009 Jun 1;73(7):966-72

Final Result: Stents in the Left Main



Kapadia SR et al, Catheter Cardiovasc Interv. 2009 Jun 1;73(7):966-72

36 Month Follow Up



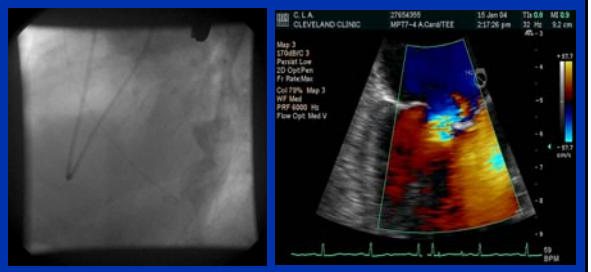
Transcatheter Aortic Valve Implantation

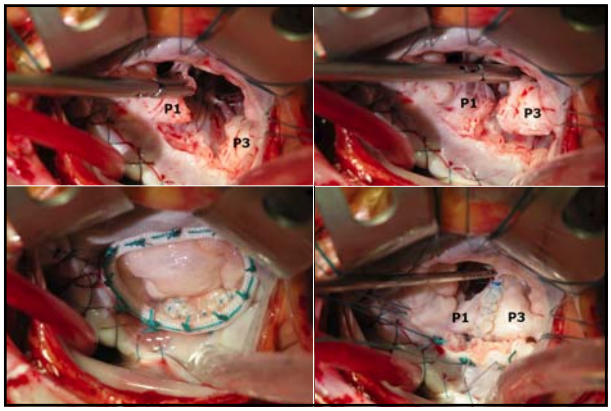
Where do we stand?

- Unmet clinical need
  - Untreated patients
    - High risk
    - Not surgical candidate
- TAVR can be implanted
  - Safely
  - With precision
  - Predictability improved but not optimal
- TAVR Function
  - Excellent hemodynamic results
  - Encouraging clinical outcomes

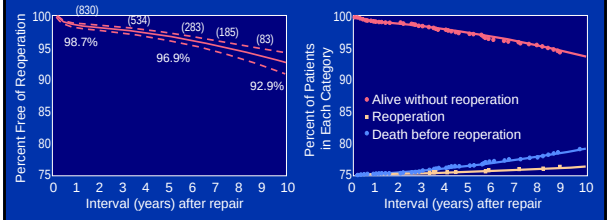
- Caring for very sick patients
  - Fixing the heart is not enough
  - Neither purely medical nor surgical
  - Preplanning
  - Anticipating complications
- Team work is *sine qua non*
  - Cardiovascular interventionalist
  - Imaging (echo/ct)
  - CV anesthesiology, critical care
- Training
  - Who should do these procedures?
  - How to train?
- How to evaluate?

Mitral Regurgitation



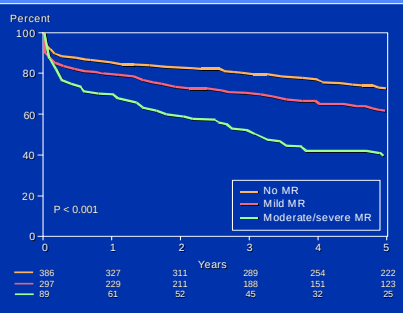


Degenerative Mitral Valve Disease: 10 year Outcome



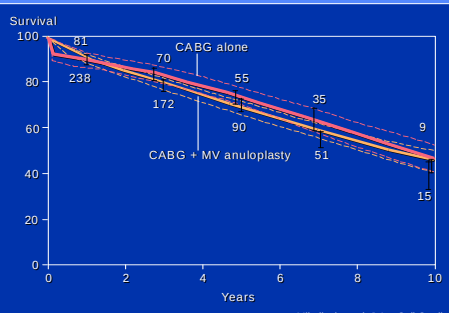
Gillinov et al, The Journal of Thoracic and Cardiovascular Surgery, 1998

Mortality : Functional MR after MI



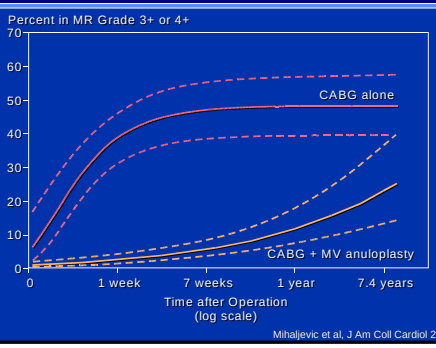
Bursi, F. et al. Circulation 2005; 111:295-301

Repair of Functional MR With Surgery



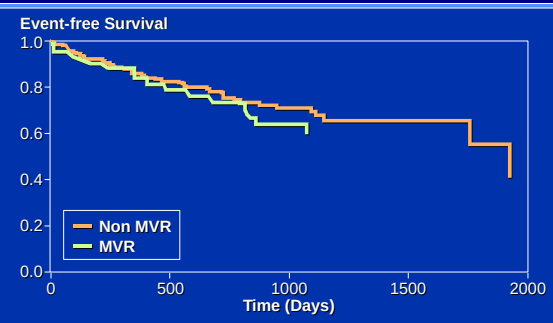
Mihaljevic et al, J Am Coll Cardiol 2007;49:2191–201

Recurrence of MR After Repair



Mihaljevic et al, J Am Coll Cardiol 2007;49:2191–201

Annuloplasty for Dilated Cardiomyopathy



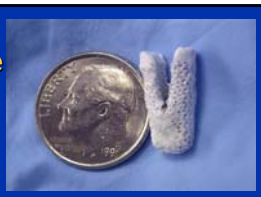
Wu, A. H. et al. J Am Coll Cardiol 2005;45:381-387

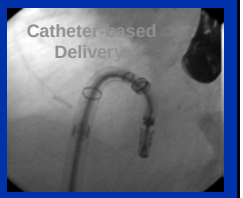
Percutaneous Mitral Valve Repair Devices

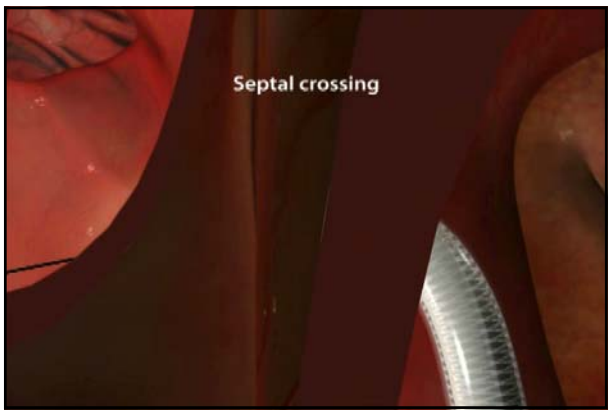
Approach	Device (Company)	Description	Testing Phase
Edge-Edge	Mitraclip (Evalve)	Clip for e-e repair	EVEREST
	Mobius (Edwards)	Suture based e-e repair	Phase I
	St Jude	Edge-edge repair	Preclinical
Coronary Sinus	Carillon(CarDimension)	Anchor, cinching	Phase I
	Monarch (Edwards)	Anchor, tensioning	Phase I
	PTMA (Viacor)	Reversible, adjustable	Phase I
Other	Coapsys (Myocor)	Epicardial remodeling	Phase I
	Mitralign	CS guided suture	Phase I
	PS3	Septal to CS anchoring	Phase I

Modified from Gillinov et al. Semin Thorac Cardiovasc Surg 2006;18:155-121

E-Valve

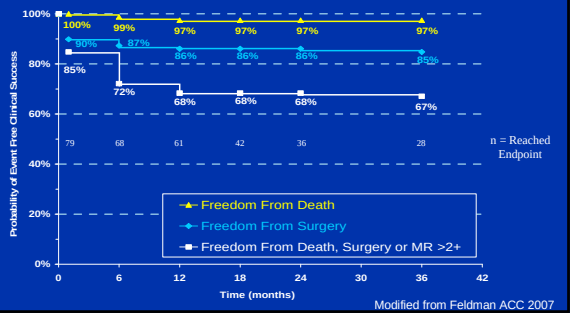






Event Free Clinical Success Kaplan-Meier

Patients with Acute Procedural Success, n = 79

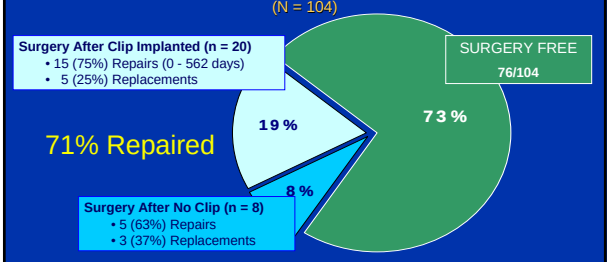


Modified from Feldman ACC 2007

Surgical Options Preserved

Surgery Following Clip Procedure

(N = 104)

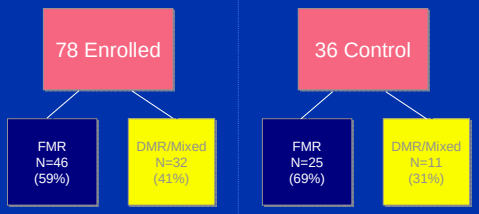


Courtesy of Feldman ACC 2007

EVEREST I & II Enrollment

Enrollment	Population	n
EVEREST I	Registry patients	55
Feasibility (completed)		
EVEREST II	Roll-in	60
Randomized n=279	Randomized Clip	184
(100% enrolled)	Randomized Surgery	95
EVEREST II	High Risk Registry	78
(100% enrolled)		
EVEREST II REALISM	Registry patients	41
Continued Access Registry (enrolling)	(non HRR and HRR)	
Total enrolled		513

HRR vs. Retrospective Control



Control patients identified and consented for 12 month follow-up to determine survival in a group of patients with significant MR treated by standard of care

HRR: Baseline Co-morbidities

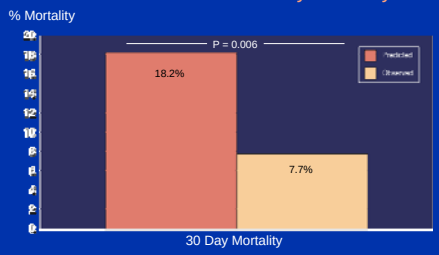
Significant Co-morbidities in HRR and Control Cohorts

Baseline Co-Morbidities	HRR N=78	Control N=36	Euro Heart Survey*	
			Not Operated, N=193	Operated, N=203
Age (mean)	77	77	69	63
NYHA Class III or IV	90%	84%	70%	65%
History CAD	85%	71%	60%	38%
Hypertension	90%	85%	53%	47%
Diabetes Mellitus	41%	42%	21%	10%
COPD / Chronic Lung Disease	35%	33%	21%	11%
Moderate to Severe Renal Failure	23%	31%	n/a	n/a
Prior Cardiac Surgery	59%	50%	7%	3%
Etiology: DMR	41%	31%	n/a	n/a
Etiology: FMR	59%	69%	n/a	n/a
Predicted Mortality	18.2%	17.4%	n/a	n/a

* Mirabel et al. European Heart Journal, 2007

HRR: Primary Safety Endpoint

Actual vs. Predicted 30 day Mortality*

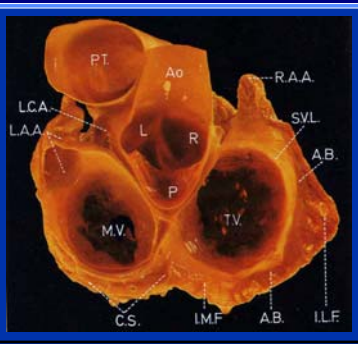


*Based on STS Risk Calculator, or Surgeon Estimate (required specific co-morbidities, 12% risk used if score not provided by surgeon)

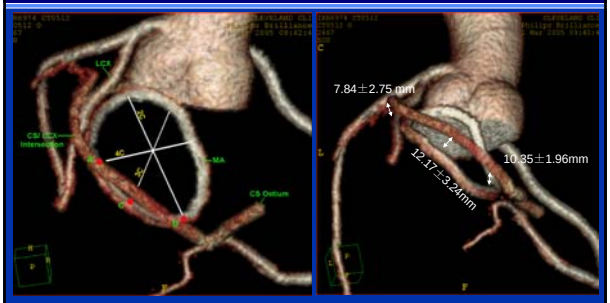
EVEREST II High Risk Registry: Outcomes

- The MitraClip was implanted very safely (96%)
- Clinical benefit was sustained to 12 months
- Re-hospitalization for CHF decreased
- LV Function was improved through 12 months
  - Decrease in LV End Diastolic and Systolic Volumes
  - Increase in Forward Stroke Volume
  - Decrease in Septo-lateral Annular Dimensions

Mitral Valve : Relation to the CS



Mitral Annulus - Coronary Sinus Relationship



Choure et al. JACC 2006;48:1938-1945

Vertical distance between CS and MA at different sites.

- Variable p<0.001
- Shorter near to commisures

CS - MA Relationship in CHF and MR

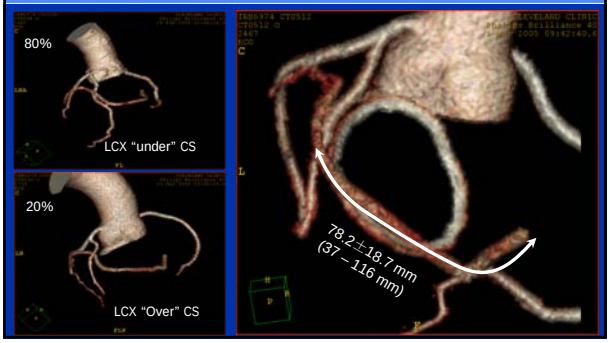
		Without MR (n=25)	With MR (n=11)	p
Minimal distance between CS and MA (mm)	4 - Chamber	7.8 ± 2.8	11.2 ± 4.5	0.01
	2 - Chamber	10.4 ± 1.9	8.2 ± 4.1	0.04
	3 - Chamber	12.2 ± 3.2	12.7 ± 3.4	0.64

Choure et al. JACC 2006;48:1938-45

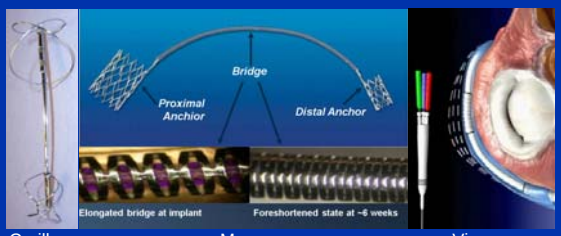
		Without MR (n=90)	With MR (n=15)	p
Distance between CS and MA (mm)	MVA Level	4.8 ± 2.5	7.3 ± 3.9	0.005
	Prox CS	8.1 ± 2.4	9.3 ± 1.9	0.019
	Distal CS	8.3 ± 3.1	12.1 ± 3.6	< 0.001

Tops et al. Circ 2007;115:1426-32

Coronary Sinus - Circumflex Relationship



Coronary Sinus Devices



Carillon Monarc Viacor

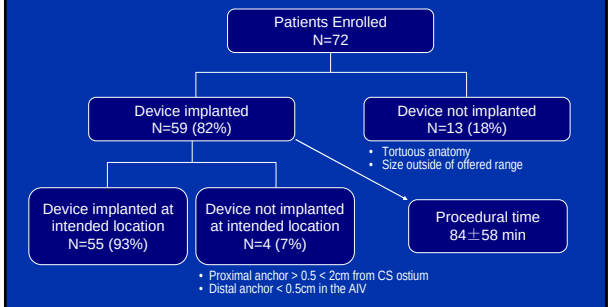
EVOLUTION

(Clinical EValuation Of the Edwards Lifesciences PercUTaneous MItral AnnulOplasty System for the treatment of Mitral RegurgitatioN)

- Prospective, multi-center feasibility study
- Functional mitral regurgitation
- Primary objective - acute safety (30d,90d)
- Secondary objective - Reduction in MR by at least one grade at 90 days

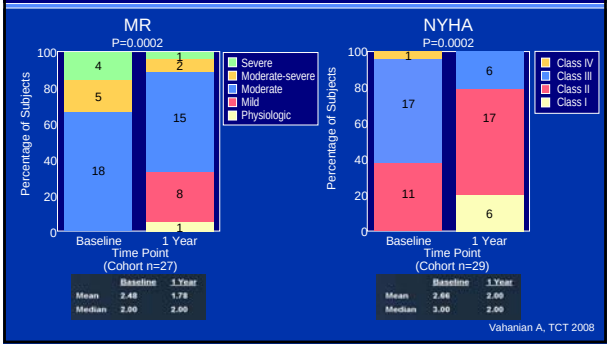
Vahanian A, TCT 2008

EVOLUTION: Procedural Data



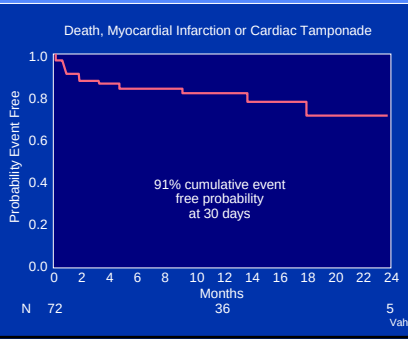
Vahanian A, TCT 2008

EVOLUTION: MR and NYHA Class



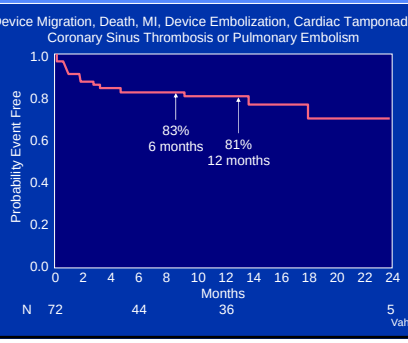
Vahanian A, TCT 2008

EVOLUTION: Patient Outcome



Vahanian A, TCT 2008

EVOLUTION: Patient Outcome



Vahanian A, TCT 2008

EVOLUTION: Cumulative MACE

Tamponade (2)	
Day 1	**Probable cause: Use of non-J-Tip Guidewire***
Day 6	**Probable cause: Use of non-J-Tip Guidewire***
MI (3)	
Day 16	**Distal anchor positioned at first diagonal branch***
Day 19	**LCx occlusion, pre-existing disease***
Day 551	**OM1 Occlusion***
Death (10)	
Day 22	**Arrhythmia**
Day 24	**Heart Failure**
Day 51	**Bacterial infection**
Day 52	**Fall leading to cranial hemorrhage**
Day 61	**Pulmonary embolism**
Day 96	**Multi-organ system failure - post MV surgery**
Day 141	**Heart Failure**
Day 280	**Worsening for cardiopulmonary disease**
Day 421	**Worsening CHF and acute renal failure**
Day 552	**Left heart failure due to MI**

Vahanian A, TCT 2008

CARILLON™ : *The AMADEUS™ Trial*

- Prospective, single-arm, Six month, multi-center trial
- Primary Endpoint
  Thirty day rate of Major Adverse Events
- Secondary Endpoints
  - •Long-term safety
  - •Hemodynamic and functional changes
  - •NYHA Class
  - •Exercise (6 minute walk test; Maximum Exercise Time)
  - •QOL (KCCQ)
  - •MR Reduction

Schofer et al, Circulation. 2009 Jul 28;120(4):272-4.

CARILLON™ Studies

- AMEDEUS
  - Prospective, single-arm, multi-center trial
  - Evaluate patients with HF and FMR @ 1 & 6 months (CARILLON®XE implant)
- TITAN
  - Prospective, single-arm, multi-center trial
  - Evaluate patients with HF and FMR @ 1, 6, 12, 18 & 24 months (CARILLON®XE2 implant)

Schofer et al, Circulation. 2009 Jul 28;120(4):272-4.

CARILLON™ Studies

- Inclusion Criteria
  - Dilated ischemic or non-ischemic cardiomyopathy (LVEDD>55mm)
  - NYHA Class II-IV / FMR 2+ to 4+ / EF < 40%
  - 6 MWT distance between 150m & 450m
  - Stable on heart failure meds
- Primary End Point
  - 30-day major adverse events
- Secondary End Points
  - NYHA class / MR reduction / QOL (KCCQ)
  - 6-minute walk test / maximum exercise time

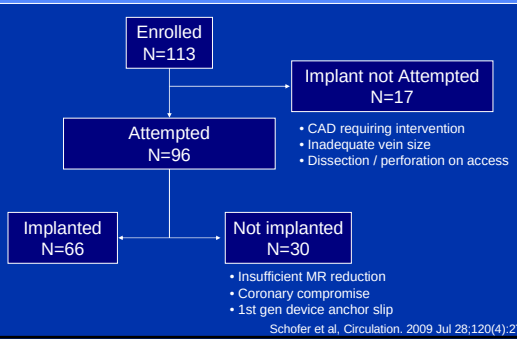
Schofer et al, Circulation. 2009 Jul 28;120(4):272-4.

Baseline Characteristics

	AMADEUS Trial (n=48)	TITAN Trial (n=53)
Age (yrs)	64.4 (25-81 yrs)	62.0 (24-79)
Gender	M = 83% (40) F = 17% (8)	M = 77% (41) F = 23% (12)
History of CAD	73%	63%
NYHA Class	II-9 III-37 IV-2	II-1 III-50 IV-2
EF	29.3% (10-39)	28.4% (9-39)
MR (Core Lab Baseline)	2+=16 3+=17 4+=15	2+=16 3+=29 4+=8
LVEDD (mm)	66.8 (50-92)	69.9 (55-81)

Schofer et al, Circulation. 2009 Jul 28;120(4):272-4.

Procedural Outcome



Schofer et al, Circulation. 2009 Jul 28;120(4):272-4.

Complications

AMADEUS™
Modified intention to treat analysis

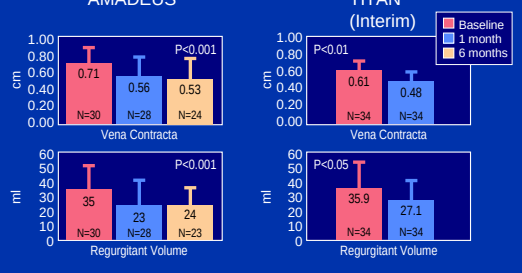
Event	Incidence
Death	2.2% (1/46)
Myocardial infarction	6.5% (3/46)
Cardiac perforation • Clinically significant • Pericardial tamponade requiring percutaneous intervention	6.5% (3/46) 6.5% (3/46) 2.2% (1/46)
Device embolization	0.0% (0/46)
Surgery or PCI related to device	0.0% (0/46)
MAE rate	13.0% (6/46)

TITAN™
Modified intention to treat analysis

Event	Incidence
Death	1.9% (1/53)
Myocardial infarction	0.0% (0/53)
Cardiac perforation • Clinically significant • Pericardial tamponade requiring percutaneous intervention	0.0% (0/53) 0.0% (0/53) 0.0% (0/53)
Device embolization	0.0% (0/53)
Surgery or PCI related to device	0.0% (0/53)
MAE rate	1.9% (1/53)

Schofer et al, Circulation. 2009 Jul 28;120(4):272-4.

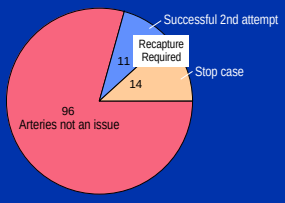
MR Reduction



Schofer et al, Circulation. 2009 Jul 28;120(4):272-4.

Coronary Artery Compromise

Patients attempted - AMADEUS™ & TITAN™



- Arteries crossed in 73% (70/96) of patients
- All 25 cases of coronary compromise successfully "recaptured"
- In 11 cases, a 2nd device was successfully placed more proximally
- Coronary compromise prevents implant in only 15% of patients

Challenges of Percutaneous Mitral Valve Interventions

Aortic Stenosis

- Severity
  - Gradients, AVA
  - Not load dependent
- Mechanism
  - Calcific
- Outcome
  - Mortality
  - Durability (gradient)

Mitral Regurgitation

- Severity
  - 1-4+
  - Load dependent
- Mechanism
  - annulus, leaflet, ventricular
- Outcome
  - Severity
  - Functional improvement
  - Mortality
  - Durability (severity of MR)