TAVR Clinical Trials

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Disclosure Statement of Financial Interest

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
- Scientific Advisory Board
- Executive Physician Council

Company

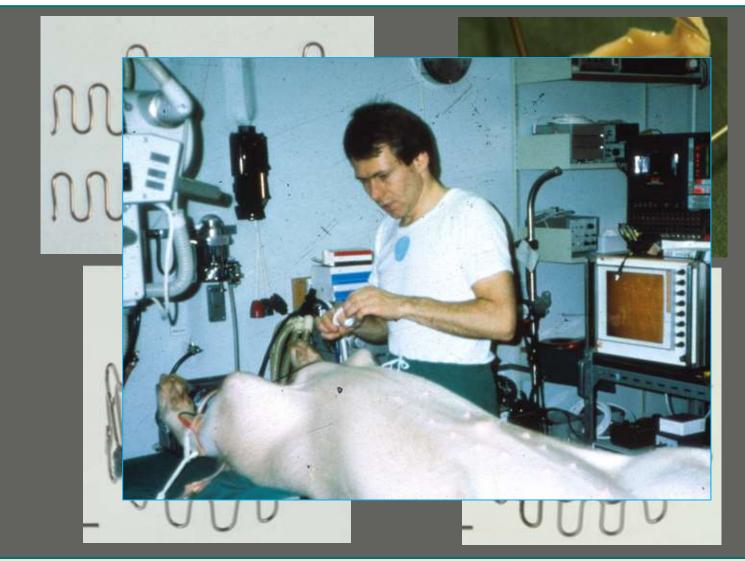
- Edwards Lifesciences, Abbott
- Medtronic, Abbott
- Boston Scientific Corp



TAVR Clinical Evidence in 8 min

- The beginning....
- Clinical Trial Data for benchmarking
- What is hot?

The Andersen Stent-Valve (1989)



2000-2002: The Sheep Era



CERA (Centre d' Experimentation et de Recherche Appliquée) Institut Monsouris, Paris, France

PVT - Cadaver Heart Study at AFIP



Dr. Alain Cribier First-in-Man PIONEER





Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis

First Human Case Description

Alain Cribier, MD; Helene Eltchaninoff, MD; Assaf Bash, PhD; Nicolas Borenstein, MD; Christophe Tron, MD; Fabrice Bauer, MD; Genevieve Derumeaux, MD; Frederic Anselme, MD; François Laborde, MD; Martin B. Leon, MD

Conclusions— Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.

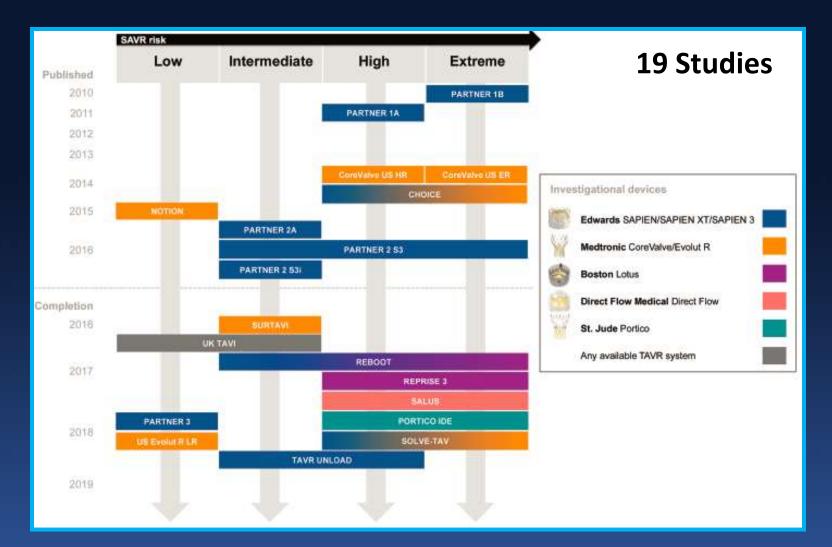
April 16, 2002

TAVR – The Early Skeptics

- Strokes
- Aortic rupture
- Coronary occlusion
- Mitral valve injury
- Valve instability embolization
- Para-valvular regurgitation
- Vascular complications
- Valve durability
- Technical challenges insurmountable

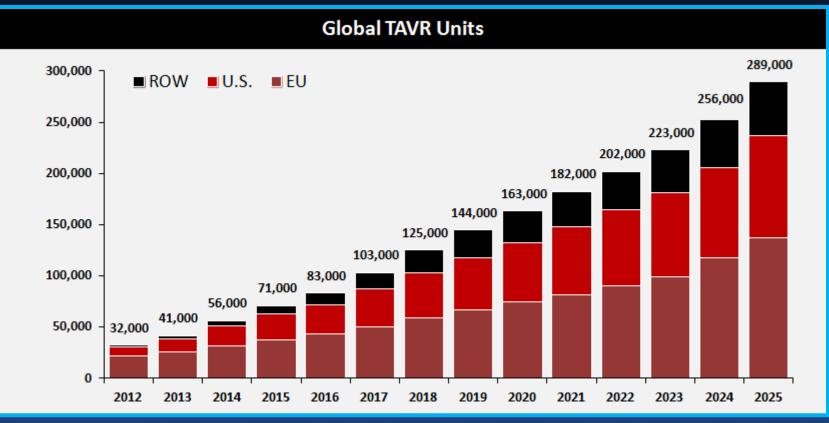
This is a crazy project that will fail!

TAVR Clinical Evidence



Capodanno D and Leon MB. EuroIntervention 2016;12:Y1-Y5.

Estimated Global TAVR Growth



SOURCE: Credit Suisse TAVI Comment –January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW

In the next 10 years, TAVR growth will increase X4!

TVT CHICAGO Transcatheter Valve Therapies (TVT) A Multidisciplinary Heart Team Approach



STS database 2002-2010 (141,905 pts)



Since 2007, in the U.S., >15,000 patients have been enrolled in FDA studies (including 6 RCTs) with multiple generations of two TAVR systems!

PARTNER 5-year FU in Lancet (March, 2015)



5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial

Samir R Kapadia, Martin B Leon, Raj R Makkar, E Murat Tuzcu, Lars G Svensson, Susheel Kodali, John G Webb, Michael J Mack, Pamela S Douglas, Vinod H Thourani, Vasilis C Babaliaros, Howard C Herrmann, Wilson Y Szeto, Augusto D Pichard, Mathew R Williams, Gregory P Fontana, D Craig Miller, William N Anderson, Jodi J Akin*, Michael J Davidson†, Craig R Smith, for the PARTNER trial investigators

5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial

Michael J Mack; Martin B Leon, Craig R Smith, D Craig Miller, Jeffrey W Moses, E Murat Tuzcu, John G Webb, Pamela S Douglas, William N Anderson, Eugene H Blackstone, Susheel K Kodali, Raj R Makkar, Gregory P Fontana, Samir Kapadia, Joseph Bavaria, Rebecca T Hahn, Vinod H Thourani, Vasilis Babaliaros, Augusto Pichard, Howard C Herrmann, David L Brown, Mathew Williams, Jodi Akin*, Michael J Davidson†, Lars G Svensson, for the PARTNER 1 trial investigators

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The risk of all-cause mortality at 5 years was 71.8% in the TAVR group versus 93.6% in the standard treatment group (hazard ratio 0.50, 95% CI 0.39–0.65; p<0.0001).

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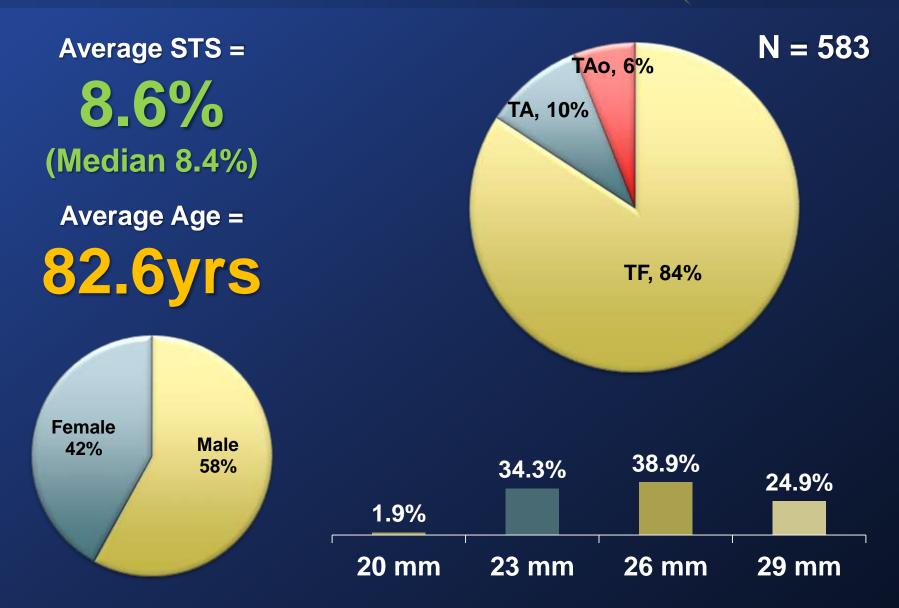
At 5 years, risk of death was 67.8% in the TAVR group compared with 62.4% in the SAVR group (hazard ratio 1.04, 95% CI 0.86-1.24; p=0.76).

Evolution of the Edwards Balloon-Expandable Transcatheter Valves

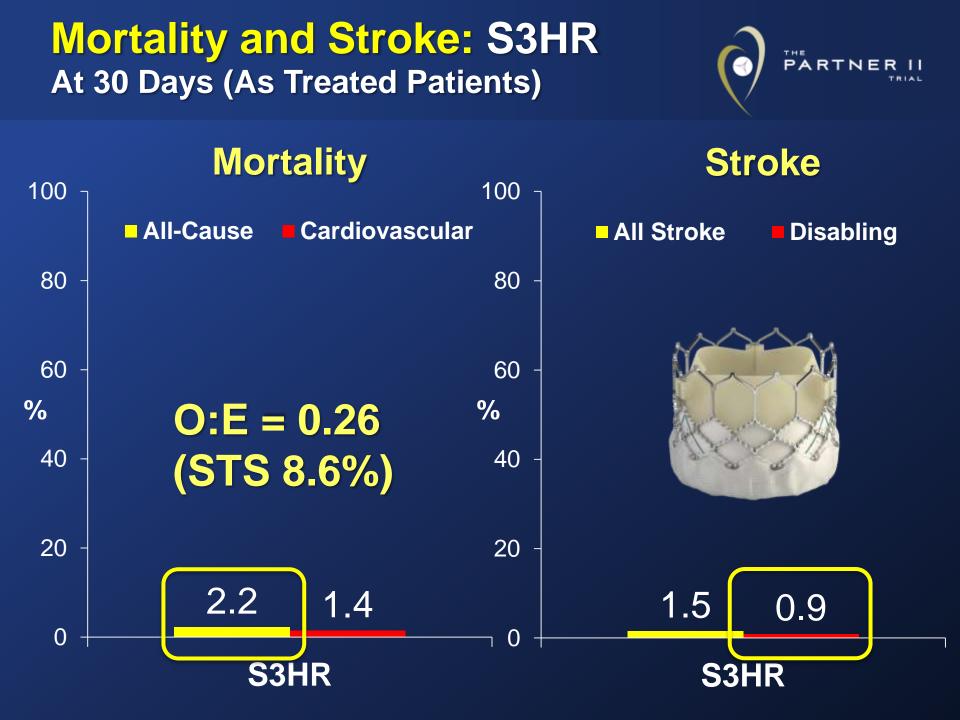




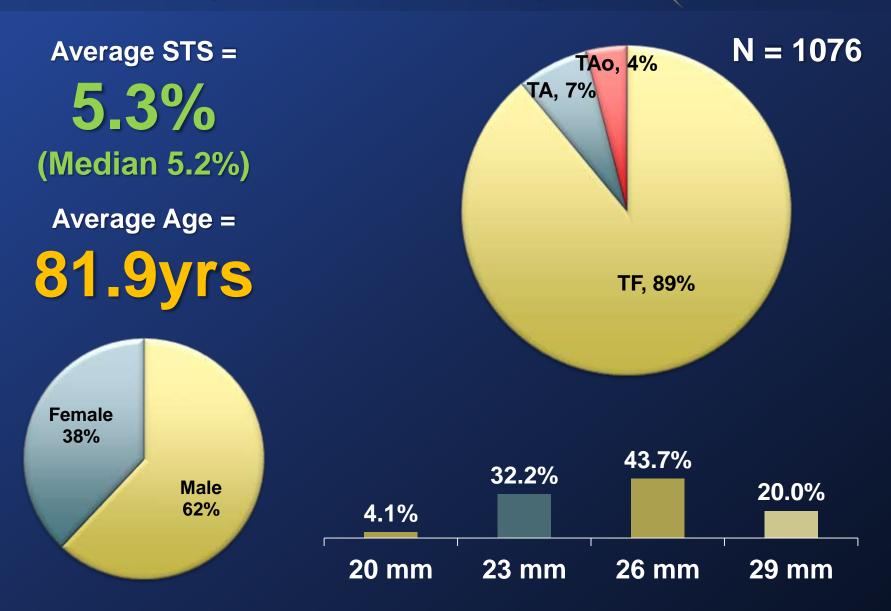
Baseline Patient Characteristics S3HR Patients (n=583 at 29 sites)



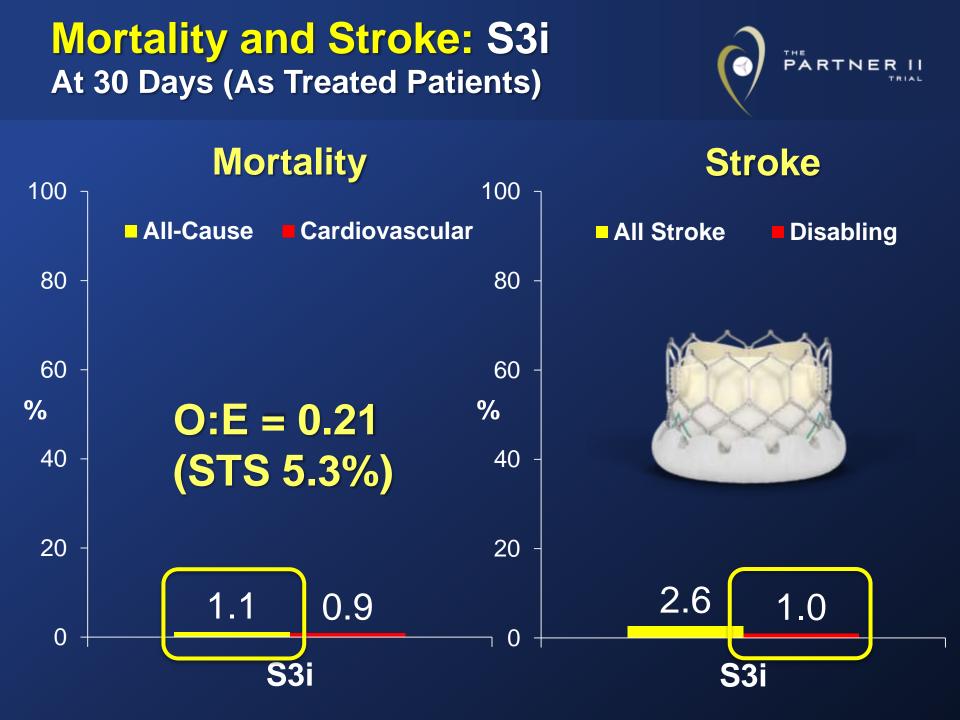
PARTNE



Baseline Patient Characteristics S3i Patients (n=1076 at 51 sites)



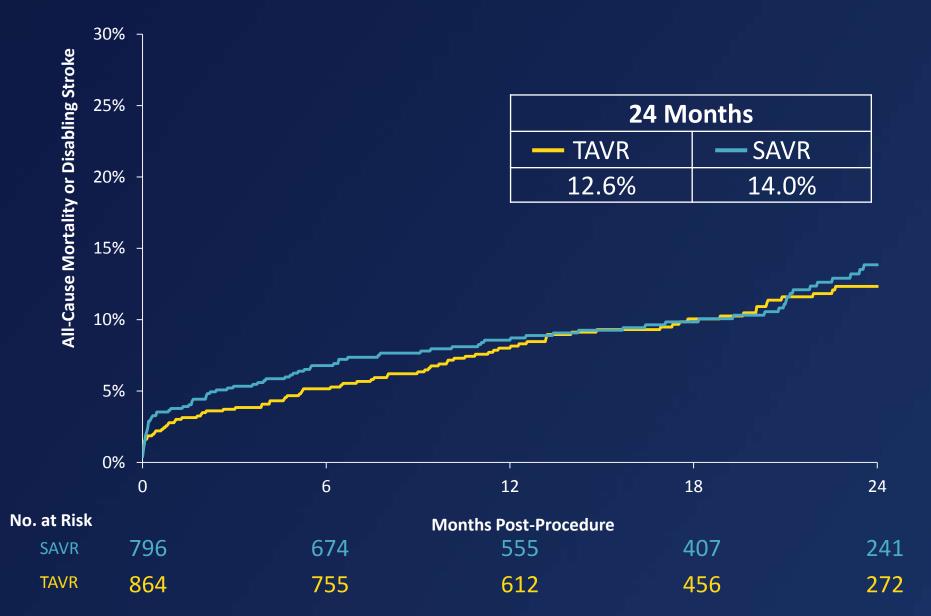
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Transcatheter Aortic Valve Replacement with a Self-Expanding Prosthesis or Surgical Aortic Valve Replacement in Intermediate-Risk Patients: First Results from the SURTAVI Clinical Trial

> Michael J. Reardon, MD For the SURTAVI Investigators

All-Cause Mortality or Disabling Stroke



30-Day Safety and Procedure-related Complications

	TAVR (N=864)	SAVR (N=796)	95% CI for Difference
All-cause mortality or disabling stroke	2.8	3.9	-2.8, 0.7
All-cause mortality	2.2	1.7	-0.9, 1.8
Disabling stroke	1.2	2.5	-2.6, 0.1
All stroke	3.4	5.6	-4.2, -0.2
Overt life-threatening or major bleeding	12.2	9.3	-0.1, 5.9
Transfusion of PRBCs* - n (%)			
0 units	756 (87.5)	469 (58.9)	24.4, 32.5
2 – 4 units	48 (5.6)	136 (17.1)	-14.5, -8.5
≥ 4 units	31 (3.6)	101 (12.7)	-11.7, -6.5
Acute kidney injury, stage 2-3	1.7	4.4	-4.4, -1.0
Major vascular complication	6.0	1.1	3.2, 6.7
Cardiac perforation	1.7	0.9	-0.2, 2.0
Cardiogenic shock	1.1	3.8	-4.2, -1.1
Permanent pacemaker implant	25.9	6.6	15.9, 22.7
Atrial fibrillation	12.9	43.4	-34.7, -26.4

*Percentage rates, all others are Bayesian rates

TAVR Clinical Evidence

Upcoming TAVI trials: rationale, design and impact on clinical practice

Davide Capodanno1*, MD, PhD; Martin B. Leon2, MD

19 Additional Studies!

1. Cardio-Thoracic-Vascular Department, Ferrarotto Hospital, University of Catania, Catania, Italy; 2. Columbia University Medical Center and Cardiovascular Research Foundation, New York, NY, USA

Simplifying TAVR DIRECT EASY TAVI

Expanding Indications

NOTION 2 EARLY TAVR Optimizing Outcomes ACTIVATION REDUCE AKI SENTINEL REFLECT

Capodanno D and Leon MB. EuroIntervention 2016;12:Y1-Y5.

TAVR Clinical Evidence

Upcoming TAVI trials: rationale, design and impact on clinical practice

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Anti-thrombotic Therapy

ARTE POPULAR TAVI AUREA AVATAR GALILEO ATLANTIS Valve Leaflet Thickening/ Thrombosis

RESOLVE SAVORY EVOLUT R Low Risk PARTNER 3 PORTICO IDE

Capodanno D and Leon MB. EuroIntervention 2016;12:Y1-Y5.

PCR

Transcatheter aortic valve implantation for failed surgical aortic bioprostheses using a self-expanding device: early results from the prospective VIVA postmarket study

Prof. Ran Kornowski, Rabin Medical Center, Petah Tikva, Israel

Dr. Didier Tchétché, Clinique Pasteur, Toulouse, France

Prof. Jean-Philippe Verhoye, CHU Rennes, Rennes, France

Dr. Bernard Chevalier, Institut Cardio-vasculaire Paris-Sud, Massy, France

and on behalf of the VIVA Investigators





Baseline Characteristics

Characteristic	All (N=202)
Age (yrs)	79.9 ± 7.2
Men	47.0
Height (cm)	164.3 ± 9.1
Weight (kg)	73.7 ± 16.3
BMI (kg/m²)	27.2 ± 5.4
BSA (m²)	1.8 ± 0.2
LogEuroSCORE (%)	25.0 ± 14.3
STS score (%)	6.6 ± 5.1
Diabetes mellitus	26.2
Peripheral vascular disease	13.9
Chronic renal replacement therapy	1.5
Previous stroke	5.0
NYHA III/IV	70.7
LVEF % (n)	61.0 ± 12.0 (157)

Values are mean ± SD or %.



Devices Utilized

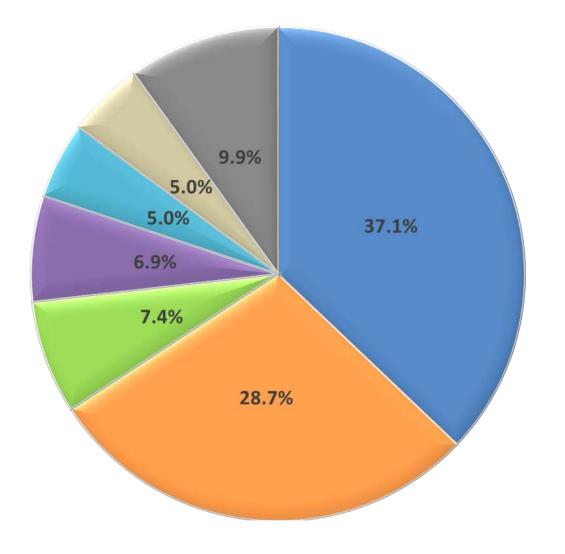




CoreValve Enrolled: n=19 Evolut R Enrolled: n=183



Surgical Valve Types

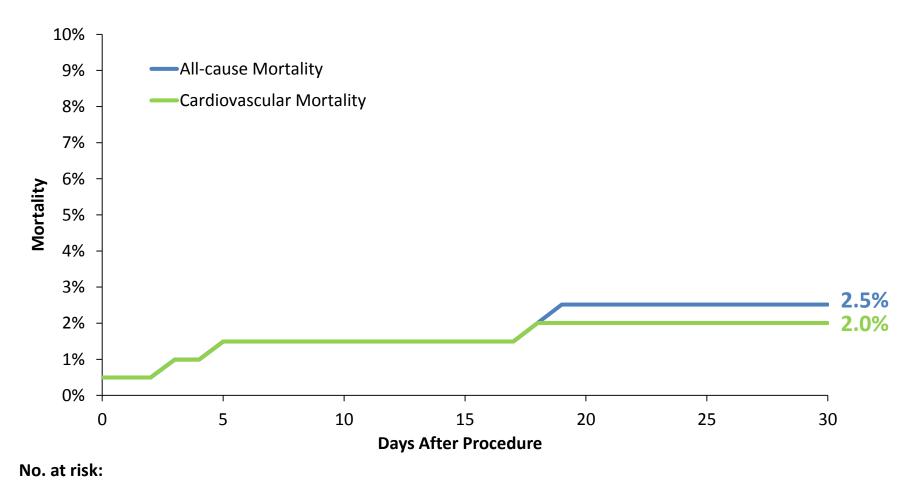


📕 Mitroflow

- 🞽 Perimount/Magna
- Carpentier/Edwards/Porcine
- I Stentless
- Hancock/Hancock II
- 屋 Trifecta
- 🛯 Other



Primary Endpoint: Cardiovascular Mortality at 30 Days



180

202



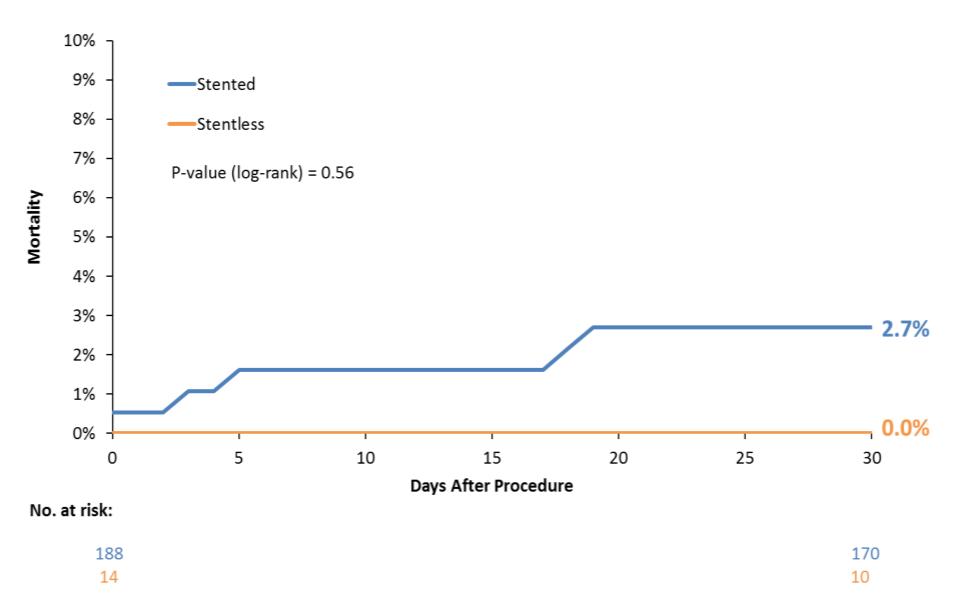
Other Clinical Outcomes at 30 Days

Endpoint	All (N=202)
Duration of hospital stay, days (mean ± SD)	7.4 ± 6.1
All stroke (%)	3.0
Disabling (%)	0.0
Major vascular complication (%)*	6.5
Bleeding (%)*	14.9
Life-threatening	0.0
Major	7.0
Minor	7.9
Acute kidney injury (%)*	0.5
Stage I	0.5
Stage II or III	0.0
Permanent pacemaker implantation (%) [£]	7.0

Kaplan-Meier event rates. *According to the Valve Academic Research Consortium 2 (VARC-2) definition [£]Baseline pacemaker included

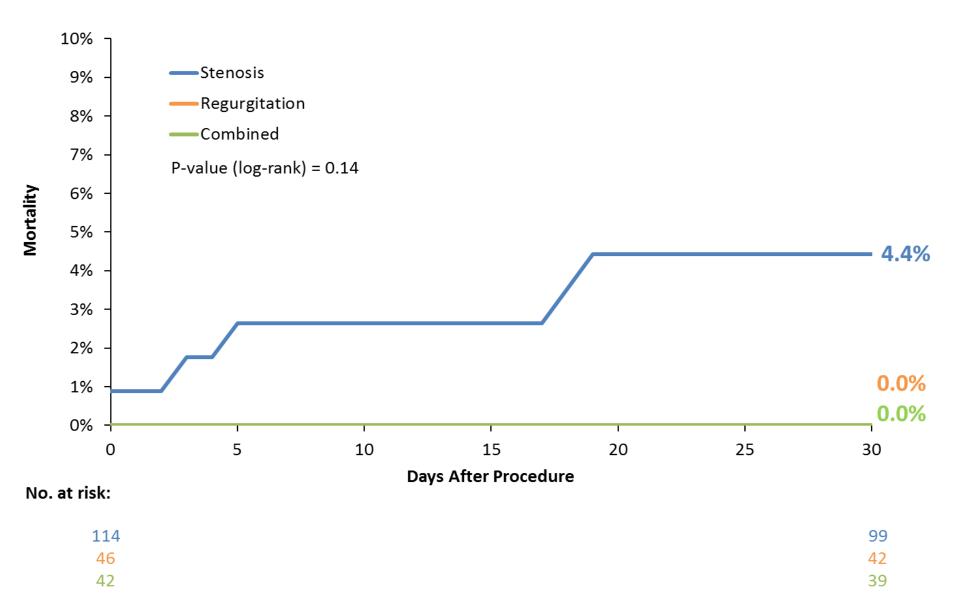


Mortality by Surgical Valve Type



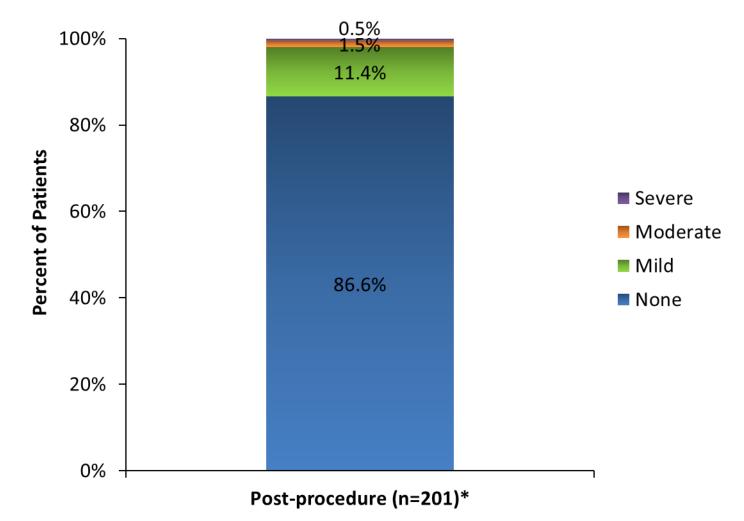


Mortality by Failure Mode

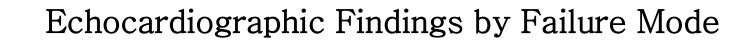


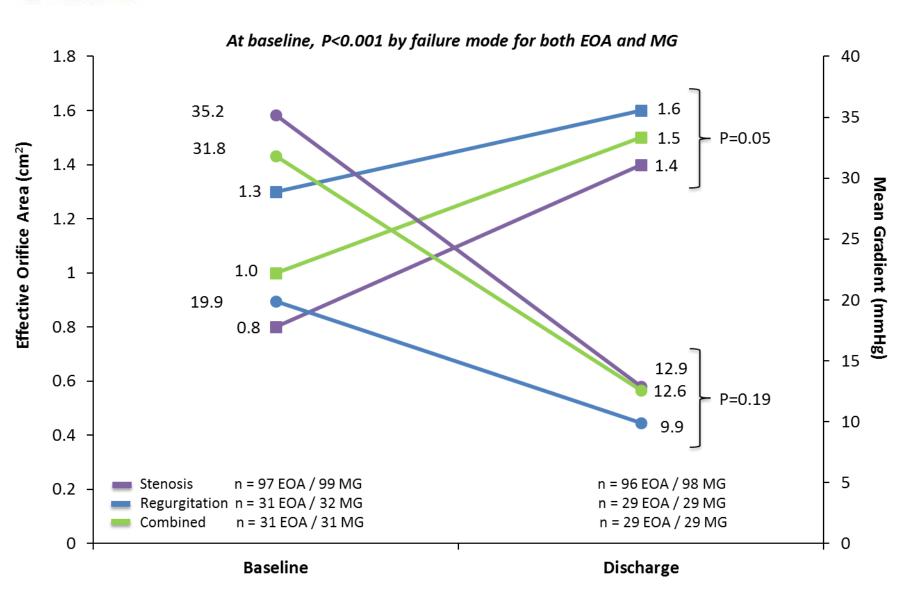


Paravalvular Regurgitation



Official assessments based on site post-procedure aortography data ; core lab data pending *Unable to assess PVL in 1 subject





Echo Core Lab confirmed data

euro

R



The Impact of Bicuspid Aortic Valve Morphology on Outcomes After TAVI

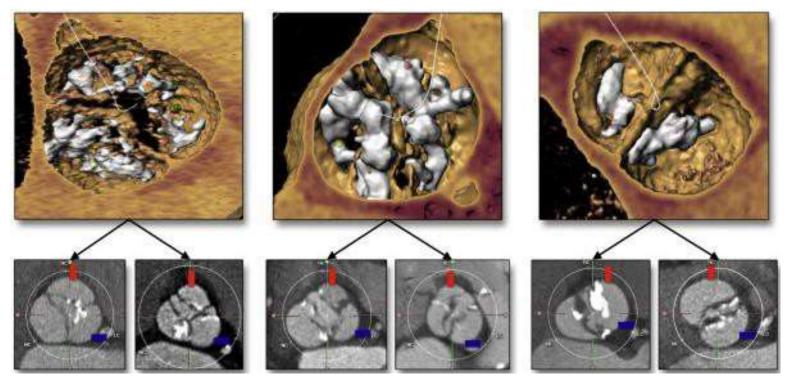
Sung-Han Yoon, MD On Behalf of Bicuspid AS TAVR Registry







Bicuspid AV Morphology

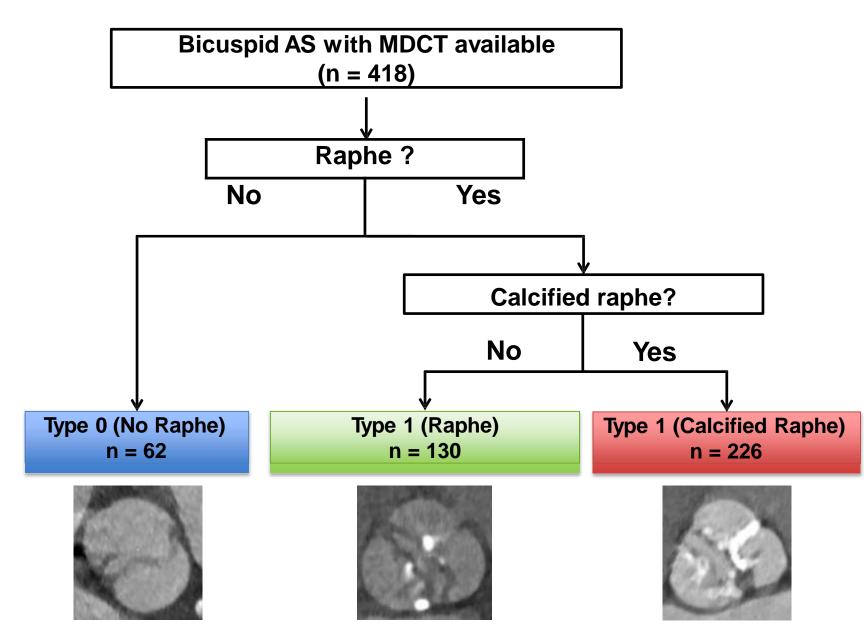


Hasan Jilaihawi et al; JACC: Cardiovascular Imaging, Volume 9, Issue 10, 2016, 1145–1158

We aimed to investigate the association between Bicuspid AS morphology and clinical outcomes after TAVI

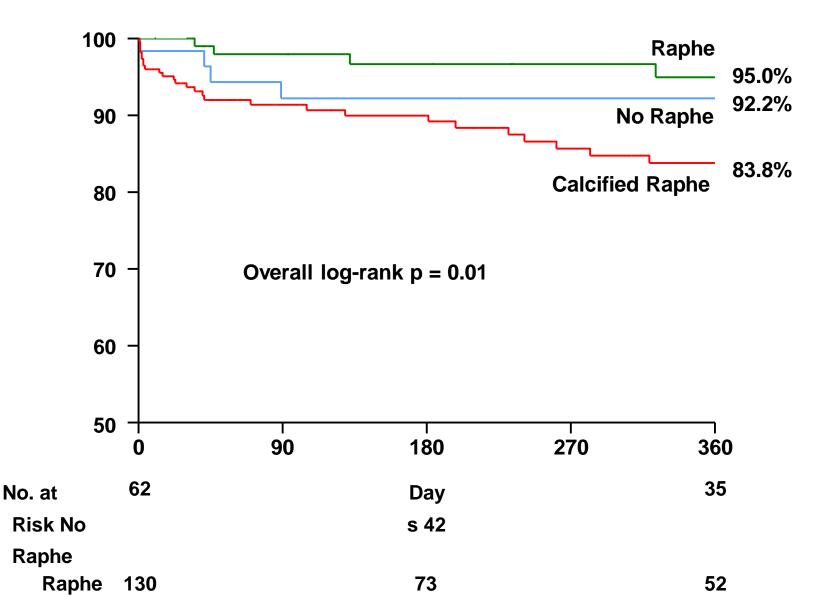


Study Design



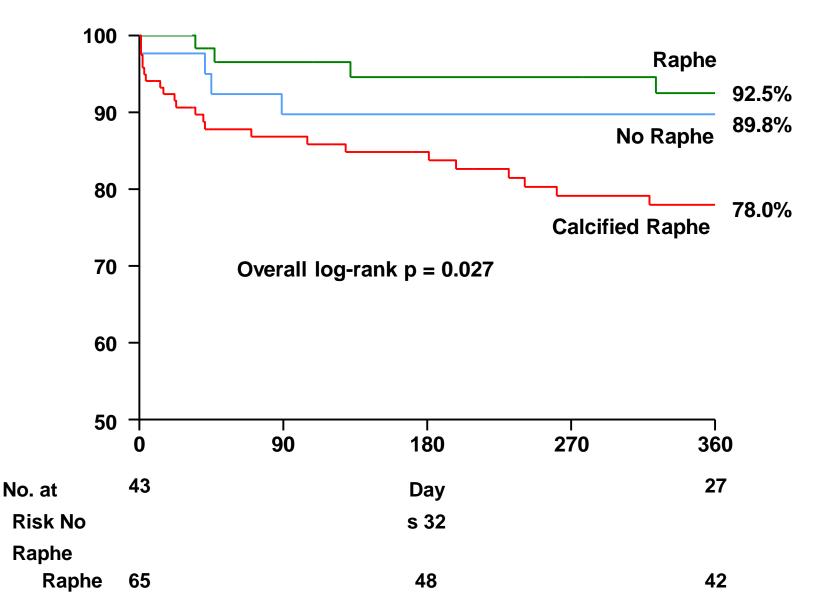


Cumulative Survival at 1 Year Overall Cohort



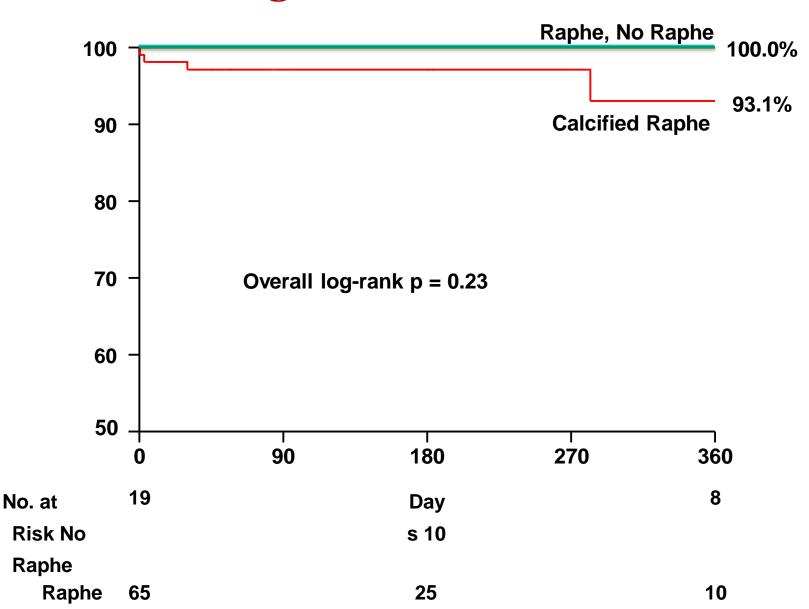


Cumulative Survival at 1 Year Early-generation Devices





Cumulative Survival at 1 Year New-generation Devices



Cerebral Embolic Protection Devices

TriGuard™ Cerebral	Embrella™	Claret Sentinel™
Deflector	Deflector	Dual Filter
Femoral Access	Radial Access	Radial Access
9F Sheath (7F Delivery)	6F Shuttle Sheath	6F Radial Sheath



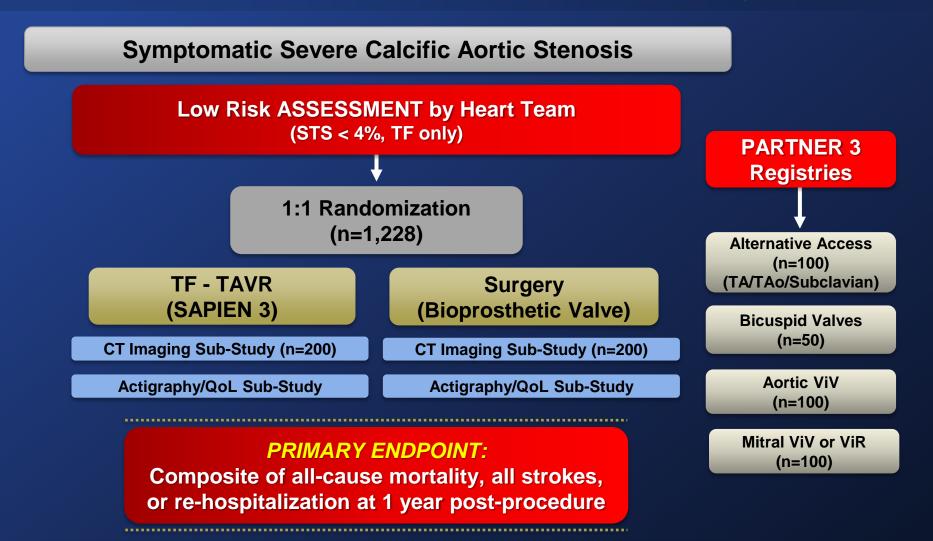
EPD in TAVR: Meta-Analysis

Α				1	0-dav	Stroke		С			Nu	mber	of L	esio	ns pe	er Patient		
~	EPD		Non-EP			Risk Ratio	Risk Ratio	•		EPD		Non	-EPD		Std	Mean Difference	Std. Mean Diff	ference
tudy or Subgroup				-	Weight #	KISK KALIO I-H, Random, 95% CI	M-H, Random, 95% CI	Study or Subgroup	Mean		otal			al We		Random, 95% Cl	IV, Random, S	
Randomized studies	5						1	Randomized studies							-			
Wendt et al 2015	0	14	0	16		Not estimable		Wendt et al 2015	23	12	14	31	1. 1	16 1	5.08 -4	0.71[-1.45, 0.03]		
an Mieghern et al 2016	0	32	2	33	4.2%	0.21 [0.01, 4.13]			- 1 - P	2.56		3.73				0.39 [-1.05, 0.28]		
Lansky et al 2015	2	46	2	39	10.3%	0.85 [0.13, 5.74]		Van Mieghem et al 2015*										
Haussig et al 2016		50	-4		21.3%	1.00 [0.26, 3.78]		Haussig et al 2016				16.67 1				99 [-1.42, -0.56]		
(apadia et al 2016† Subtotal (95% CI)	13	231 373	10		59.9% 95.7%	0.62 [0.28, 1.37] 0.68 [0.36, 1.27]	-	Kapadia et al 2016 Subtotal (95% CI)	5	1177	91 176	5.67				0.11 [-0.40, 0.17] 53 [-1.02, -0.04]	•	
Total events Heterogeneity: Tau ² = 0.00 Test for overall effect: Z =			18 = 3 (P =	0.795) ² = 0%			Heterogeneity: $Tau^2 = 0.18$, Test for overall effect: $2 = 2$		STATE 1210	• 3	7 + 0.00	£; F = 75	3				
Non-randomized co	mparativ	e studie	5					Non-randomized con	ngarati	ve studie	5							
Samim et al 2015	0		0	37		Not estimable		Rodés-Cabau et al 2014	10000			4.67 4	444	6 1	2.4%	0.441-0.44.1.311	-	
Rodés-Cabau et al 2014	2	41	0	11	4 3%	1.43 10.07, 27,781												
Subtotal (95% CI) Total events		56	ò	48	4.3%	1,43 [0.07, 27,78]		Samim et al 2015 Subtotal (95% CI)	0.55	5.926	49	4.67 3		17 1 13 2		0.81 [0.19, 1.43] 0.69 [0.18, 1.19]		•
Heterogeneity: Not applical Test for overall effect: 2 =		0.81)						Heterogeneity: Tau ² = 0.00; Test for overall effect: 2 = 2		2.2.2	19	* 0.491;	f = 0%					
Total (95% CI)		429		296	100.0%	0.70 [0.38, 1.29]	•	Total (95% Cb			225		2	7 10	1.0N -	0.19 -0.71. 0.34	-	
																CONTRACTOR OF A	1	
feterogeneity: Tau ² = 0.00 est for overall effect: Z =	1.14 (P =	0.26)				0.01	0.1 1 20 10 Favours (EPD) Favours (Non-EPD)	Heterogeneity, Tau ¹ = 0.33; Test for overall effect: 2 = 0 Test for subgroup difference	70 P -	0.491							-4 -2 0 Favours (EPO) Fa	ý vours (Non-EPC
Heterogeneity: Tau ² = 0.04 Fest for overall effect: Z = Fest for subgroup difference); Chi ² = 1 1.14 (P =	0.26)	= 4 (P =	= 0.63	31, 1 ⁴ + 0%			Test for overall effect. 2 = 0. Test for subgroup difference	70 P -	= 0.49) = 11.46,	đ =]	(P = 0.0	0071, 1	91.33		per Patien	0.0000000000000000000000000000000000000	ş vaurs (Non-EPC
Heterogeneity: Tau ² = 0.04 Test for overall effect: Z = Test for subgroup difference); Chi ² = 1 1.14 (P =	0,26) 0.23, 0	= 4 (P =	- 0.63 3	31, 1 ⁴ + 0%			Test for overall effect. 2 = 0	70 P -	= 0.49) = 11.46,	đ =]	(∦ = 0.0 Volu	0071, 1	91.33		per Patien Std. Mean Difference	•	
Heterogeneity: Tau ² = 0.00 Fest for overall effect: 2 = Fest for subgroup difference B	0; Chi ² = 1 1 14 (P = tes: Chi ² - EPC Events	0.26) 0.23, 0	= 4 (P = f = 1 (P Non-E	- 0.63 3	31, I ⁴ • 0% 8 0-day	Mortality	Favours [EPD] Favours [Non-EPD]	Test for overal effect. 2 = 0 Test for subgroup difference D Study or Subgroup	.70 (P = 5: Chi ² Mean	= 0.49) = 11.46, To EPD	đ =]	l (P ≈ 0.0 Volu	0071, 1 ⁴ = me of Non-EPO	9133 F Le:	sions		t Std. Mean D	ifference
Heterogeneity, Tau ² = 0.00 Fest for overall effect: Z = Fest for subgroup differenc B Study or Subgroup Randomized studie	0; Chi ² = 1 1 14 (P = tes: Chi ² - EPC Events	0.26) 0.23, 0	= 4 (P = f = 1 (P Non-E	- 0.63 3	31, I ⁴ + 036 6 0-day Weight	Mortality Risk Ratio M-H, Random, 95% Cl	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overal effect 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies	.70 (Ρ 5. Οι ³ Mean	= 0.49) = 11.46, TC EPD 50	d = 1 tal Tota	l (P = 0.0 Volu I Mean	007), i ² - me of Non-EPD SI	91.3 F Le:) Tota	sions I Weight	Std. Mean Difference IV, Random, 95% C	t Std. Mean D 1 IV, Random	ifference
Heterogeneity: Tau ² = 0.00 Fest for overall effect: Z = Fest for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016	0; Chi ² = 1 1.14 (P = tes: Chi ² = Events Is	0.26) 0.23, 0 Total	= 4 (P = f = 1 (P Non-E Events	- 0.63 3 EPD Total 50	31, 1 ² + 03; 60-day Weight 10, 8%	Mortality Risk Ratio M-H, Random, 95% Cl 0.33 (0.01, 7.99) —	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overall effect 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015	.70 (Ρ - 5 Ch ² Mean	0.49) = 11.46, EPD 50 60	f = 1 tal Tota	1 (P = 0.0 Volu d <u>Mean</u> 4 168	0071, 1 ² - me of Non-EPO SI 21	91.33 F Le: 0 Tota 7 1	sions I Weight 6 7.1%	Std. Mean Difference IV, Random, 95% C -0.47 (-1.20, 0.25	t Std. Mean D I IV, Random	ifference
Heterogeneity: Tau ² = 0.00 Fest for overall effect: 2 = Test for subgroup differenc B Study or Subgroup Randomized studie Haussig et al 2016 Lansky et al 2015	0; Chi ² = 1 1.14 (P = tes: Chi ² - Events ts 0	0.26) 0.23, c Total 50 46	= 4 (P = f = 1 (P Non-E	= 0.63 3 700 70tal 50 39	31, 1 ² + 03; O-day Weight 10, 85; 19, 53;	Mortality Risk Ratio M-H, Random, 95% Cl	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overall effect 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Wieghem et al 2016	70 (P - 5 Ch ² Mean 88 120.67	= 0.49) = 11.46, EPD = 50 60 182.96	f = 1 tal Tota 1 2	1 (P = 0.0 Volu 1 Mean 4 168 2 272 33	007), I ⁴ = me of Kon-EPO SI 21 318.5	91.33 F Le: 7 10 7 11 2 11	sions 4 Weight 6 7.1X 5 8.4X	Std. Mean Difference IV, Random, 95% C -0.47 (-1.20, 0.25 -0.60 (-1.27, 0.07	t Std. Mean D I IV, Random	ifference
feterogeneity: Tau ² = 0.00 fest for overall effect: 2 = fest for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016 Lansky et al 2015 Van Mieghem et al 2015	0; Chi ² = 1 1.14 (P = tes: Chi ² - EP(Events 15 0 1 1	0.26) 0.23, 0 Total 50 46	= 4 (P = f = 1 (P Non-E Events 1 2	= 0.63 3 PD Total 50 39 33	31, 1 ⁴ + 03; O-day Weight 10, 8% 19, 5%	Mortality Risk Ratio M-H, Random, 95% Cl 0.33 (0.01, 7.99) 0.42 (0.04, 4.50)	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overall effect: 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Wieghent et al 2016	70 (P - 5 Chi ³ Mean 88 120 67 466	0,49) = 11.46, EPD 50 182.96 652.99	ff = 1 tal Tota 1 2 4	1 (P = 0.0 Volu 1 Mean 4 168 2 272 33 9 800	0071, 1 ⁴ = me of Si Si Si Si Si Si Si Si Si Si Si Si Si	9133 F Le: 7 10 2 11 3 40	sions 8 Weight 6 7.1% 5 8.4% 5 22.8%	Std. Mean Difference Nr, Random, 95N C -0.47 (-1.20, 0.25 -0.60 (-1.27, 0.07 -0.30 (-0.70, 0.11	t Std. Mean D I IV, Random	ifference
teterogeneity: Tau ² = 0.00 est for overall effect: Z = fest for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016 Lansky et al 2016 Van Mieghem et al 2016	0; Chi ² = 1 1.14 (P = tes: Chi ² - EP(Events 15 0 1 1	0.26) 0.23, 0 Total 50 46 32	= 4 (P = f = 1 (P Non-E Events 1 2 3	= 0.63 3 PD Total 50 39 33 111	31, 1 ² • 03; 0-day Weight 10.8% 19.5% 22.3%	Mortality Risk Ratio M-H, Random, 95% Cl 0.33 (0.01, 7.99) 0.42 (0.04, 4.50) 0.34 (0.04, 3.13)	Favours (EPD) Favours (Non-EPD) Risk Ratio	³ Test for overall effect: 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Weghem et al 2016 Haussg et al 2016 Kapada et al 2016	70 (P - 5 Chi ³ Mean 88 120 67 466	= 0.49) = 11.46, EPD = 50 60 182.96	f = 1 tal Tetu 1 2 4 9	1 (P = 0.0 Volu 4 168 2 272.33 9 800 1 424.97	007), I ⁴ = me of Kon-EPO SI 21 318.5	9133 FLes 7 10 2 12 3 45 1 9	sions 8 Weight 5 8.4% 5 22.8% 8 46.3%	Std. Mean Difference N. Random, 95% C -0.47 (-1.20, 0.25 -0.60 (-1.27, 0.07 -0.30 (-0.70, 0.11 -0.08 (-0.36, 0.21	t Sid. Kean D I N, Random	ifference
feterogeneity: Tau ² = 0.00 fest for overall effect: 2 = fest for subgroup difference B Randomized studie Haussig et al 2016 Lansky et al 2016 Jan Mieghem et al 2016 Kapadia et al 2016 Subtotal (95% CI) Total events	5; Chi ² = : 114 (P = tes: Chi ² - EP(Events 15 0 1 1 3 5	0.26) 0.23, (Total 50 46 32 234 362	= 4 (P = f = 1 (P Non-E Events 1 2 3 2 8	- 0.63 3 FPD Total 50 39 33 111 233	31, 4 = 05 O-day Weight 10,8% 19,5% 22,3% 34,5% 87,0%	Mortality Risk Ratio M-H, Random, 95% Cl 0.33 (0.01, 7.99) - 0.42 (0.04, 4.50) 0.34 (0.04, 3.13) 0.71 (0.12, 4.20)	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overall effect: 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Wieghent et al 2016	70 (P - 5 Chi ³ Mean 88 120 67 466	0,49) = 11.46, EPD 50 182.96 652.99	ff = 1 tal Tota 1 2 4	1 (P = 0.0 Volu 4 168 2 272.33 9 800 1 424.97	0071, 1 ⁴ = me of Si Si Si Si Si Si Si Si Si Si Si Si Si	9133 FLes 7 10 2 12 3 45 1 9	sions 8 Weight 5 8.4% 5 22.8% 8 46.3%	Std. Mean Difference Nr, Random, 95N C -0.47 (-1.20, 0.25 -0.60 (-1.27, 0.07 -0.30 (-0.70, 0.11	t Sid. Kean D I N, Random	ifference
Heterogeneity: Tau ² = 0.00 Fest for overall effect: Z = Test for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016 Lansky et al 2016 Kapadia et al 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0	0; Chi ² = 1 1 14 (P = res: Chi ² - EP(Events 1 1 3 5 0; Chi ² =	0.26) 0.23, 0 Total 50 46 32 234 362 0.34, d	= 4 (P = f = 1 (P Non-E Events 1 2 3 2 8	- 0.63 3 FPD Total 50 39 33 111 233	31, 4 = 05 O-day Weight 10,8% 19,5% 22,3% 34,5% 87,0%	Mortality Risk Ratio M-H, Random, 95% Cl 0.33 (0.01, 7.99) - 0.42 (0.04, 4.50) 0.34 (0.04, 3.13) 0.71 (0.12, 4.20)	Favours (EPD) Favours (Non-EPD) Risk Ratio	³ Test for overall effect: 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Weghem et al 2016 Haussg et al 2016 Kapada et al 2016	(0) (P = 5 Ch ² 88 120,67 466 383.2	• 0.49) = 11.46, FC EPD • 50 182.96 652.99 540.26 2.84, cf +	ff =] tal Tota 2 4 9 17	1 (P = 0.0 Volu 4 168 2 272 33 9 800 1 424 97 6	0071, 1 ⁴ - me of Si 21 318.5 1,466.5 567.4	9133 FLes 7 10 2 12 3 45 1 9	sions 8 Weight 5 8.4% 5 22.8% 8 46.3%	Std. Mean Difference N. Random, 95% C -0.47 (-1.20, 0.25 -0.60 (-1.27, 0.07 -0.30 (-0.70, 0.11 -0.08 (-0.36, 0.21	t Sid. Kean D I N, Random	ifference
Heterogeneity: Tau ² = 0.00 Fest for overall effect: Z = Fest for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016 Lansky et al 2016 Kapadia et al 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0	0; Chi ² = 1 1 14 (P = tes: Chi ² + EPR Events 1 1 3 5 0; Chi ² + 1.29 (P -	0.26) • 0.23, o Total 50 46 32 234 362 0.34, d • 0.20)	= 4 (P = f = 1 (P Non-E Events 1 2 3 2 2 8 = 3 (P	- 0.63 3 FPD Total 50 39 33 111 233	31, 4 = 05 O-day Weight 10,8% 19,5% 22,3% 34,5% 87,0%	Mortality Risk Ratio M-H, Random, 95% Cl 0.33 (0.01, 7.99) - 0.42 (0.04, 4.50) 0.34 (0.04, 3.13) 0.71 (0.12, 4.20)	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overall effect: 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Wieghent est al 2016 Kapasta et al 2016 Subtotal (95% CI) Heterogenethy Taz ² = 0.00 Test for overall effect: 2 = 2	170 (P - es Chi ² Mean 88 120,67 456 383.2 (Chi ² = 104 (P -	• 0.49) = 11.46, EPD • 50 • 60 182.96 • 652.99 540.26 • 540.26 • 0.04)	ff =] tal Tota 2 4 9 17	1 (P = 0.0 Volu 4 168 2 272 33 9 800 1 424 97 6	0071, 1 ⁴ - me of Si 21 318.5 1,466.5 567.4	9133 FLes 7 10 2 12 3 45 1 9	sions 8 Weight 5 8.4% 5 22.8% 8 46.3%	Std. Mean Difference N. Random, 95% C -0.47 (-1.20, 0.25 -0.60 (-1.27, 0.07 -0.30 (-0.70, 0.11 -0.08 (-0.36, 0.21	t Sid. Kean D I N, Random	ifference
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Heterogeneity Tau ² = 0.00 Fest for overall effect: 2 = Fest for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016 Lansky et al 2016 Lansky et al 2015 Subtotal (95% CI) Total events Heterogeneity Tau ² = 0.0 Test for overall effect: 2 = Non-randomized of Sanim et al 2015 Sanim et al 2015 Rode's-Canau et al 2014	0; Chi ² = 1 1 14 (P = ces: Chi ² + EPC Events 1 1 3 5 0; Chi ² + 1, 29 (P + omparati	0.26) • 0.23, c Total 50 46 32 234 362 0.34, d • 0.25 we studi 15	= 4 (P = f = 1 (P Non-E Events 1 2 3 2 2 8 = 3 (P es	- 0.63 3 50 39 33 111 233 - 0.95	31, 1 ² = 05 O-day Weight 10, 8% 19, 5% 22, 3% 34, 5% 87,0% 13, 0%	Mortality Risk Rafio M-H, Random, 95% Cl 0.33 (0.01, 7.99) 0.42 (0.04, 4.50) 0.34 (0.04, 3.13) 0.71 (0.12, 4.20) 0.48 (0.16, 1.46)	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overall effect: 2 = 0 Test for subgroup difference D Study of Subgroup Randomized studies Wendt et al 2015 Van Weghem et al 2016 Haussig et al 2016 Subtotal (95% CI) Heterogenethy, Taa ² = 0.00 Test for overall effect: 2 = 2 Non-caedomized con Rodér-Cabau et al 2014	70 φ ss Chi ² 88 120.67 466 383.2 (Chi ² + 104 φ mparati 365	• 0, 49] = 11 46, Fo EPD • 60 182 96 652 99 540 26 2 84, df + • 0.04) ve studies 392 593	ff = 1 tal Totu 1 2 4 9 17 3 (P	1 (P = 0.0 Volu 4 168 2 272 33 9 800 1 424 97 6 • 0 421 P 4 456 67	007[1 ² = me of Kon-EPO 51 31855 1,4665 567.4 + 0% 770.3	913 f Le: f Le: f 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9	sions 4 Weight 5 7 1% 5 8 4% 5 8 4% 5 8 4% 6 5.0%	Sod. Mean Ofference N, Random, 95% C -0.47 [-120, 025 -0.60[-127, 007 -0.30 [-0.70, 011 -0.06 [-0.36, 021 -0.22 [-0.43, -0.01 -0.22 [-0.43, -0.01	t Sid. Kean D I N, Random	ifference
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = Test for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016 Lansky et al 2015 Van Mieghem et al 2016 Kapadia et al 2015 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Non-randomized o Samim et al 2015 Rodés-Canaou et al 2014 Subtotal (95% CI)	0; Chi ² = : 114 (P = res: Chi ² + EPC Events is 0 1 1 3 5 0; Chi ² = : 129 (P - 0 mparati 0 3	0.26) • 0.23, c Total 50 46 32 234 362 0.34, d • 0.20 we studi 15	= 4 (P = f = 1 (P Non-E Events 1 2 3 2 3 2 8 = 3 (P *	- 0.63 3 50 39 33 111 233 - 0.95 37	31, 1 ² = 05 O-day Weight 10, 8% 19, 5% 22, 3% 34, 5% 87,0% 13, 0%	Mortality Risk Ratio M-H, Random, 95% CI 0.33 [0.01, 7.99] - 0.42 [0.04, 4.50] 0.34 [0.04, 3.13] 0.71 [0.12, 4.20] 0.48 [0.16, 1.46] Not estimable	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overall effect: 2 = 0 Test for subgroup difference D Study of Subgroup Randomized studies Wendt et al 2015 Van Weghem et al 2016 Haussig et al 2016 Subtotal (95% CI) Heterogenethy, Taa ² = 0.00 Test for overall effect: 2 = 2 Non-caedomized con Rodér-Cabau et al 2014	70 φ ss Chi ² 88 120.67 466 383.2 (Chi ² + 104 φ mparati 365	• 0.49) = 11.46, EPD • 50 182.96 652.99 540.26 2.84, cf. • • 0.04) ve studies	ff = 1 tal Totu 1 2 4 9 17 3 (P	1 (P = 0.0 Volu 4 168 2 272 33 9 800 1 424 97 5 = 0.421 P 4 458 67 5 179.8	007L H = me of Kon-EPO 51 318.5 1,466.5 567.4 = 0%	913 f Ler f Ler f 1 2 2 2 2 3 4 1 3 17 17 7 1 9 3	sions 4 Weight 5 7 1% 5 84% 5 84% 5 84% 6 5.0% 7 10.4%	Sod. Mean Ofference N, Random, 95% C -0.60[-127, 0.07 -0.30[-0.70, 0.11 -0.08[-0.36, 0.21 -0.22[-0.48, -0.01	t Std. Mean D IN, Random	ifference
tetarogeneity. Tau ² = 0.00 test for overall effect: Z = Test for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016 (ansky et al 2016 (ansky et al 2016 Subtotal (95% CI) Total events Heterogeneity. Tau ² = 0.0 Test for overall effect Z = Non-randomized o Santim et al 2015 Subtotal (95% CI) Total events Heterogeneity. Not applicat	0; Chi ² = 1 1 14 (P = res: Chi ² + EPC Events 1 1 1 3 5 0; Chi ² + 1 29 (P - 0 3 sble	0.26) 0.23, c 7 Total 50 46 32 234 362 0.34, d 0.20) 15 41 56	= 4 (P = f = 1 (P Non-E Events 1 2 3 2 3 2 8 = 3 (P *	- 0.63 3 50 39 33 111 233 - 0.95 37 11	31, 1 ² = 05 O-day Weight 10, 8% 19, 5% 22, 3% 34, 5% 87,0% 13, 0%	Mortality Risk Ratio M-H, Random, 95% CI 0.32 (0.01, 7.99) 0.42 (0.04, 4.50) 0.34 (0.04, 4.50) 0.34 (0.04, 3.13] 0.71 (0.12, 4.20) 0.48 (0.16, 1.46) Not estimable 2.00 (0.11, 36.09)	Favours (EPD) Favours (Non-EPD) Risk Ratio	Test for overal effect. 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Weghen et al 2015 Haussig et al 2016 Kapača et al 2016 Subtatal (95% CI) Heterogenety, Tau ² = 0.00 Test for overal effect. 2 = 2 Non-randomized con Rodes-Cabas et al 2014 Samm et al 2015	70 (P - Mean 88 5 Chi ² 88 5 20 - 466 383 2 120 - 57 120 - 23 120 - 23 120 - 23 120 - 23 120 - 23	 0.49] 11.46, EPO 50 60 182.96 62.99 540.25 2.84, st = 0.04, st = 88.222 0.04, st = 	ff = 1 tal Totu 1 2 4 9 17 3 (P - 3 4 3 4	1 (P = 0.0 Volu 4 168 2 272 33 9 800 1 424 97 6 0 421 (P 4 458.67 5 179.8 9	007[1 ² - me of Kon-EPO 3185 1,4665 567 4 - 0% 770.3 225 1	913 f Ler f Ler f 1 2 2 2 2 3 4 1 3 17 17 7 1 9 3	sions 4 Weight 5 7 1% 5 84% 5 84% 5 84% 6 5.0% 7 10.4%	Sid. Mean Difference N, Random, 95% C -0.47 [-1.20, 0.25 -0.60 [-1.27, 0.07 -0.30 [-0.70, 011 -0.36 [-0.35, 0.22 -0.22 [-0.43, -0.01 -0.20 [-1.06, 0.67 -0.30 [-0.90, 0.30	t Std. Mean D IN, Random	ifference
Haussig et al 2016 Lansky et al 2015 Van Mieghem et al 2016 Kapadia et al 2016 Subtotal (95% CI) Total events Heterogeneity Tau ² = 0.0 Text for overall effect 2 =	0; Chi ² = 1 1 14 (P = res: Chi ² + EPC Events 1 1 1 3 5 0; Chi ² + 1 29 (P - 0 3 sble	0.26) 0.23, c 7 Total 50 46 32 234 362 0.34, d 0.20) 15 41 56	= 4 (P = f = 1 (P Non-E Events 1 2 3 2 3 2 8 = 3 (P *	= 0.65 3 PD Total 50 39 33 111 233 = 0.95 37 11 48	31, 1 ² = 05 O-day Weight 10, 8% 19, 5% 22, 3% 34, 5% 87,0% 13, 0%	Mortality Risk Ratio M-H, Random, 95% CI 0.32 (0.01, 7.99) 0.42 (0.04, 4.50) 0.34 (0.04, 4.50) 0.34 (0.04, 3.13] 0.71 (0.12, 4.20) 0.48 (0.16, 1.46) Not estimable 2.00 (0.11, 36.09)	Favours (EPD) Favours (Non-EPD) Risk Ratio	³ Test for overall effect: 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Weghem et al 2016 Haussig et al 2016 Subtotal (95% CI) Heterogeneity: Taa ² = 0.00 Test for overall effect: 2 = 2 Non-candomized con Rudér-Cabau et al 2014 Savite et al 2015 Subtotal (95% CI) Heterogeneity: Taa ² = 0.00 Test for overall effect: 2 = 1	70 (P - Mean 88 5 Chi ² 88 5 20 - 466 383 2 120 - 57 120 - 23 120 - 23 120 - 23 120 - 23 120 - 23	 0.49] 11.46, EPO 50 60 182.96 62.99 540.25 2.84, st = 0.04, st = 88.222 0.04, st = 	d = 1 tal 1 2 4 9 17 3 (P - 4 1 (P)	(P = 0.0 Volu 4 168 2 272 33 9 800 1 424 97 6 • 0 421 P • 4 458.67 5 179.8 9 = 0.853 P	007[1 ² - me of Kon-EPO 3185 1,4665 567 4 - 0% 770.3 225 1	9133 f Le: 0 Tota 7 10 2 12 3 40 17 17 7 1 17 7 1 9 3 4	sions 8 Weight 6 7.1% 5 8.4% 5 2.2% 8 46.3% 4 84.6% 7 10.4% 8 15.4%	Sod. Mean Difference N, Random, 95% C -0.47 [-120, 025 -0.30 [-127, 007 -0.30 [-0.70, 011 -0.06 [-0.56, 021 -0.22 [-0.43, -0.01 -0.22 [-0.43, -0.01 -0.30 [-0.50, 0.30 -0.26 [-0.76, 0.23	t Sid. Kean D I N, Random	ifference
Heterogeneity: Tau ² = 0.00 Fest for overall effect: Z = Test for subgroup difference B Study or Subgroup Randomized studie Haussig et al 2016 (Lansky et al 2016 (Lansky et al 2016) Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Non-randomized of Samim et al 2015 Rodés-Cabau et al 2015 Rodés-Cabau et al 2015 Heterogeneity: Not applica Test for overall effect: Z =	0; Ch ² = 1.14 (# = EPC Ch ² + EVEnts 5 0 0 1 1 1.29 (# - 0 0 J 2 (# - 0 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	0.26) 0.23, c 7 Total 50 46 32 234 362 0.34, d 0.20) 0.20) 0.20, 15 41 56 c 0.64) 418	= 4 (P = 1	= 0.63 3 FPD Total 50 39 311 213 = 0.95 37 11 48 281	$\frac{1}{100.0\%}$	Mortality Risk Ratio M-H, Random, 95% CI 0.33 [0.01, 7.99] 0.42 [0.04, 4.50] 0.34 [0.04, 3.13] 0.71 [0.12, 4.20] 0.48 [0.16, 1.46] Not estimable 2.00 [0.11, 36.09] 2.00 [0.11, 36.09]	Favours (EPD) Favours (Non-EPD) Risk Ratio	³ Test for overall effect: 2 = 0 Test for subgroup difference D Study or Subgroup Randomized studies Wendt et al 2015 Van Mieghen et al 2016 Kapasia et al 2016 Kapasia et al 2016 Subtotal (95% CI) Heterogenetry Taz ² = 0.00, Test for overall effect: 2 = 2 Non-candomized con Robin-Cabasa et al 2014 Sarbitet al 2015 Subtotal (95% CI) Heterogenetry Taz ² = 0.00, Heterogenetry Taz ² = 0.00, Heterogenetry Taz ² = 0.00, Heterogenetry Taz ² = 0.00, Heterogenetry Taz ² = 0.00, Heterogenetry Taz ² = 0	70 (P + 5 Ch ² 88 120,67 466 383 2 120,67 466 383 2 120,67 466 120,67 120,23 120,23 120,23 120,7	0.49) = 11.46, Fro 50 60 182.94 652.99 540.26 0.04, 0.04	f = 1 tal Tota 2 4 9 17 3 7 7 3 7 7 2 7 22	E (P = 0.0 Volu 4 168 2 272.33 9 500 1 424.97 6 0.421 P 4 458.67 5 179.8 9 9 5	0071 P - me of Kon-EPO SI 211 3125.5 567.4 - 0% 770.3 225.1 - 0%	9133 f Le: 0 Tota 7 10 2 12 3 40 17 17 7 1 17 7 1 9 3 4	sions 8 Weight 6 7.1% 5 8.4% 5 2.2% 8 46.3% 4 84.6% 7 10.4% 8 15.4%	Sid. Mean Difference N, Random, 95% C -0.47 [-1.20, 0.25 -0.60 [-1.27, 0.07 -0.30 [-0.70, 011 -0.36 [-0.35, 0.22 -0.22 [-0.43, -0.01 -0.20 [-1.06, 0.67 -0.30 [-0.90, 0.30	t Sid. Kean D I N, Random	ifference

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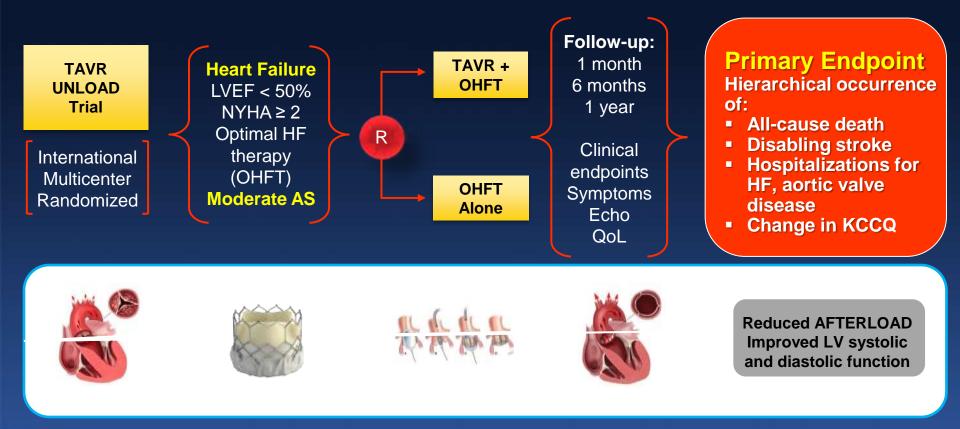
The PARTNER 3 Trial Study Design





Follow-up: 30 days, 6 mos, 1 year and annually through 10 years

TAVR UNLOAD Trial Study Design (600 patients, 1:1 Randomized)



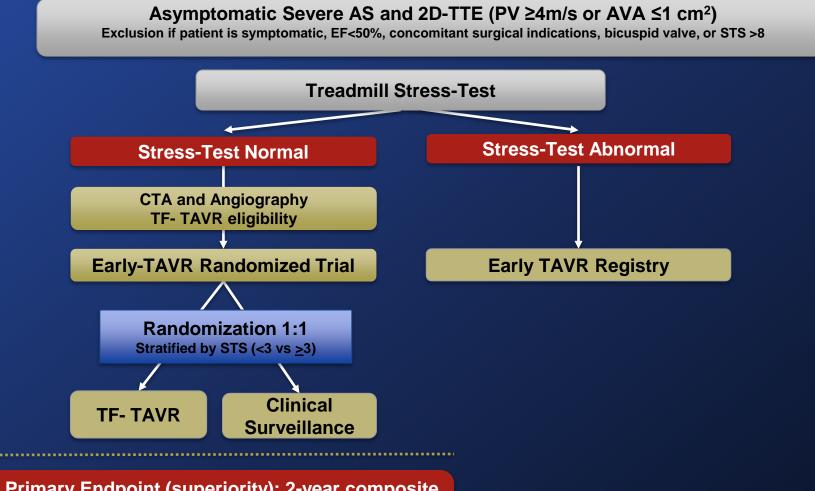
COLUMBIA UNIVERSITY MEDICAL CENTER

- NewYork-Presbyterian



EARLY TAVR Trial Study Flow





Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)