Eberhard Grube, MD

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 Direct Flow: C, SB, AB Mitralign: AB, SB, E Boston Scientific: C, SB, AB Biosensors: E, SB, C, AB Cordis: AB Abbott Vascular: AB InSeal Medical: AB, E, Valtech: E, SB, Claret: SB Keystone: AB

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'

Europe

- Europe holds the largest collective TAVI experience in the world.
- Key results from national registries and company-sponsored studies have laid the foundation for what we know about TAVI in clinical practice.
- In the last year, important short- and long-term TAVI data has been released from Europe. This presentation provides a short overview of key findings.

Clinical Evidence

- Over 27,000 patients have been treated with CoreValve and SAPIEN / XT in Europe.

	CoreValve	SAPIEN / XT
CoreValve ADVANCE	1,015	NA
FRANCE 2 Registry	1,298	2,635
GARY	3,627	4,814
UK Registry	1,932	2,051
Italian Registry	1,334	0
Belgian Registry	408	473
Spanish Registry	108	0
Milan Registry	89	132
Ibero-American	1,220	0
Swiss Registry	336	317
Swedish Registry	311	255
SOURCE Registry	NA	2,307
SOURCE XT Registry	NA	2,706
Total Patients	**11,678**	**15,690**

Europe

- Important New 30-day Results
  - ADVANCE II
  - CHOICE

CoreValve ADVANCE II

- The CoreValve ADVANCE II Study is a prospective, non-randomized study which was performed to investigate ***conduction abnormalities and new permanent pacemaker*** implantation after TAVI, following best implantation practices and ESC guidelines for conduction disturbances.

- 200 patients were enrolled in 6 countries in European countries.

- Special attributes of ADVANCE II:
  - 100% of patients were monitored
  - Events were adjudicated by an independent clinical events committee to VARC-2 definitions
  - All data was analyzed by an independent core lab: echo, angio, MSCT, EKG, pacemaker interrogation

- 30-day outcomes were presented at EuroPCR 2014[1]

[1]Petronio, et al., presented at EuroPCR 2014

CoreValve ADVANCE II

- The CoreValve ADVANCE II Study showed exceptional VARC-2 safety outcomes at 30-days[1]

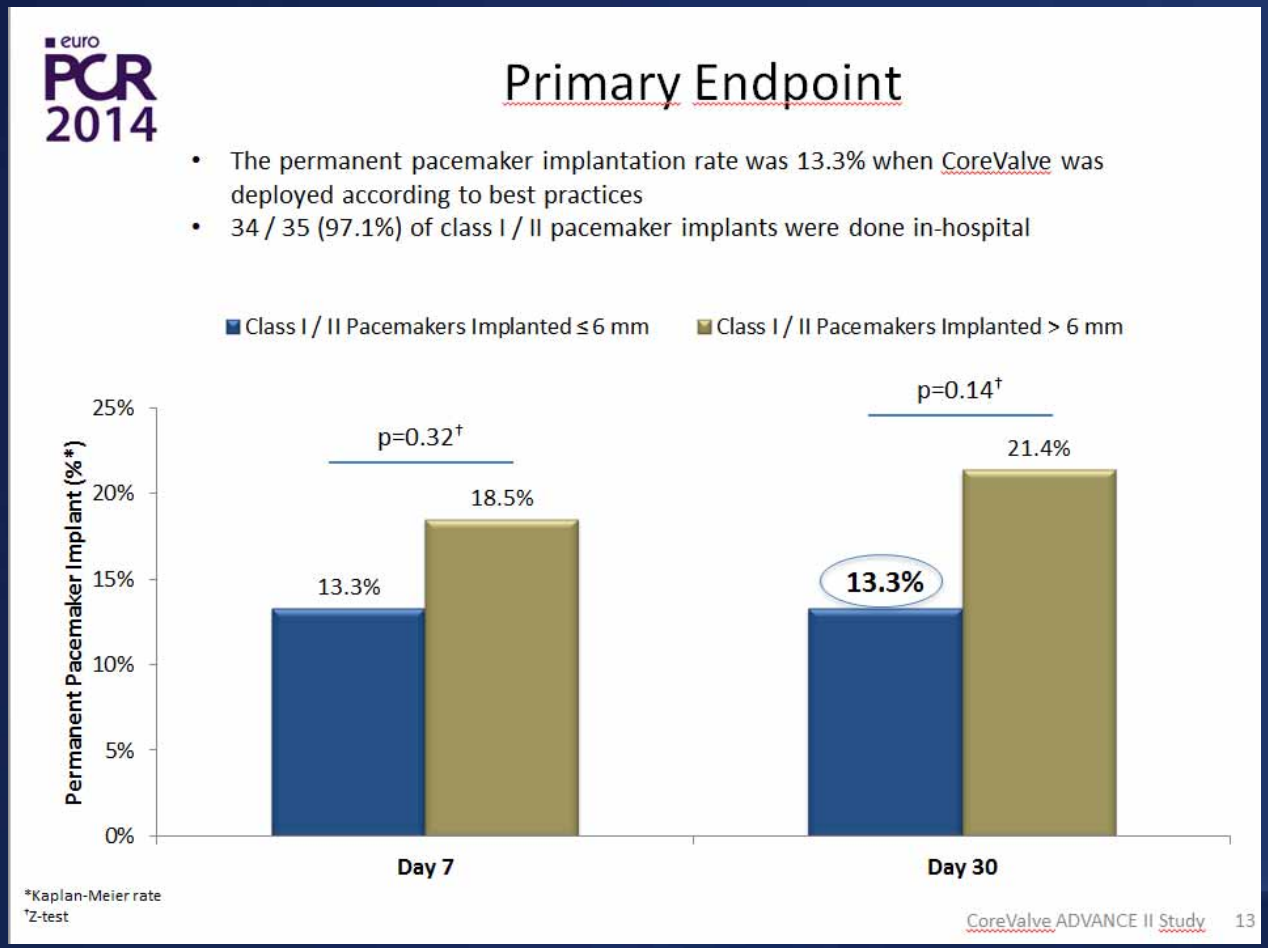
ADVANCE II 30-Day VARC-2 Outcomes[1]

	Kaplan-Meier Event Rates (n=194)
All-cause mortality	1.6
Cardiovascular mortality	1.6
Stroke	2.1
Life-threatening or disabling bleeding	4.1
Major vascular complications	11.9
Minor vascular complications	12.4
Myocardial infarction	0.5
Acute kidney injury, stage III	0.5

[1]Petronio, et al., presented at EuroPCR 2014

CoreValve ADVANCE II

- When CoreValve was implanted at a depth of 6 mm or less, and pacemakers were implanted only for class I / II indications, the 30-day pacemaker implantation rate was 13.3%[1].
- This is among the lowest permanent pacemaker implantation rates reported with CoreValve, and demonstrates the critical importance of shallow implant depth.



TAVI Summit 2014

[1]Petronio, et al., presented at EuroPCR 2014

CHOICE

- CHOICE is an investigator-initiated, multicenter trial in Germany which randomized 241 patients to transfemoral TAVI with CoreValve or SAPIEN XT[1].
- The primary endpoint of VARC device success favored SAPIEN XT, however there were no differences in 30-day VARC safety outcomes.

CHOICE 30-Day VARC Outcomes[1]

	CoreValve (n=120)	SAPIEN XT (n=121)	p
Mean STS Score	6.2%	5.6%	0.17
Device Success	77.5%	95.9%	<0.001
All-cause Mortality	5.1%	4.1%	0.77
Cardiovascular Mortality	4.3%	4.1%	0.99
Stroke	2.6%	5.8%	0.33
Myocardial Infarction	0%	0.8%	0.99
Life Threatening Bleeding	12.0%	8.3%	0.35
Major Vascular Complications	11.1%	9.9%	0.76

[1]Abdel-Wahab, et al., *JAMA* 2014; 311(15): 1503-14

Europe

- Important New 1-Year Outcomes
  - GARY

GARY

- The German Aortic Valve Registry (GARY) is a prospective, controlled, multicenter registry aimed at comparing outcomes of catheter-based procedures to SAVR.
- 1- year outcomes from 13,860 patients enrolled from Jan 2011 – Dec 2011 were presented at TCT 2013[1].
- Patients undergoing TAVI were significantly older and had more comorbidities, driving higher 1-year mortality.

	GARY[1]	
	SAVR (n=6523)	Transvascular TAVI (n=2694)
Age	68.3 ±11.3	81.1 ±6.2
CAD	18.6%	53.6%
Prior Cardiac Surgery	9.4%	17.7%
NYHA Class IV	*5.1%*	*12.5%*
30-Day Mortality	*2.4%*	*5.6%*
1-Year Mortality	*6.7%*	*20.7%*

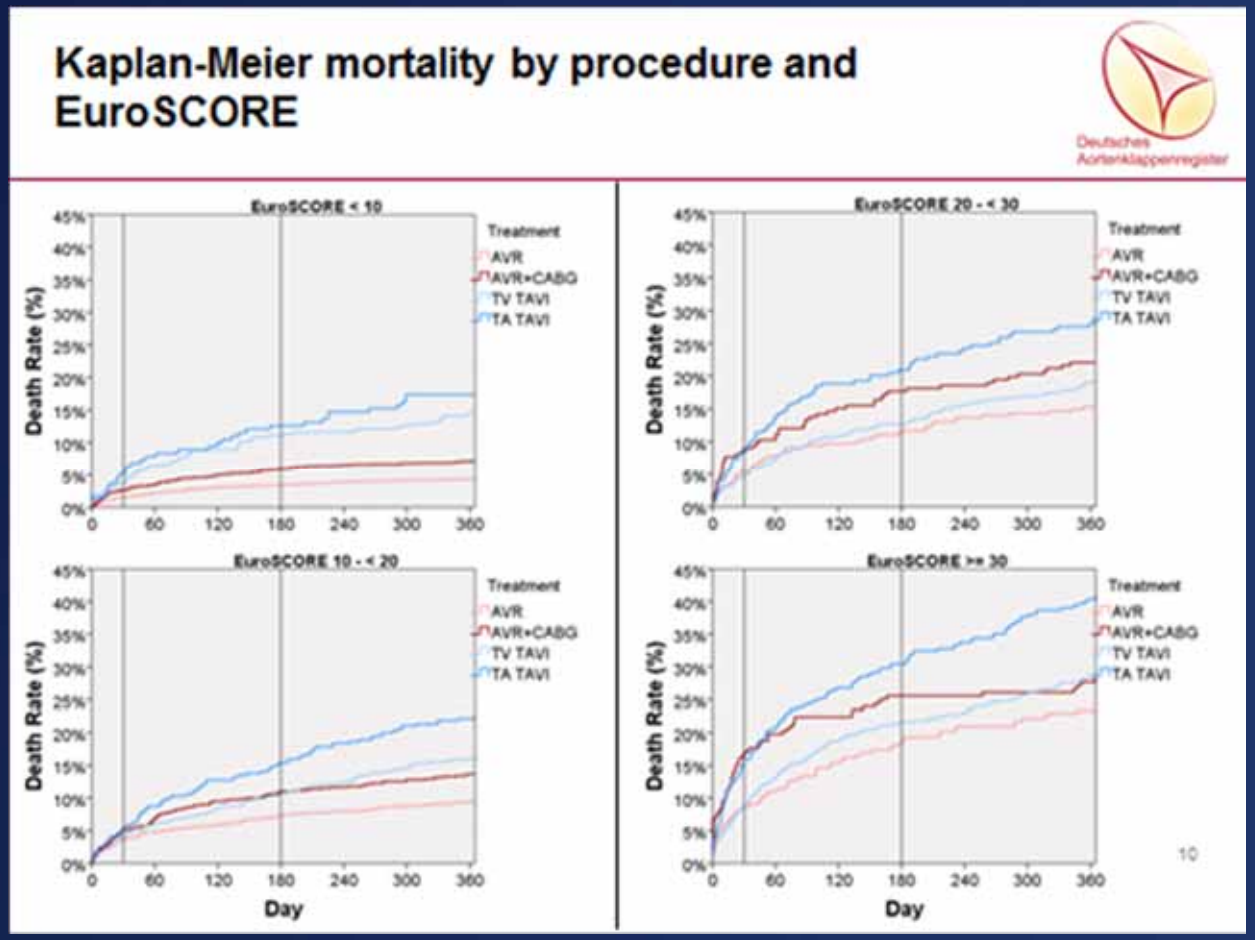
[1]Figulla, et al., presented at TCT 2013

GARY

- GARY demonstrated the trend of increasing 1-year mortality with increasing log EuroSCORE, independent of the intervention (TAVI or SAVR).

Log EuroSCORE (< 10)

Log EuroSCORE (20, ≤ 30)



Log EuroSCORE (10, ≤ 20)

Log EuroSCORE (> 30)

[1]Figulla, et al., presented at TCT 2013

Europe

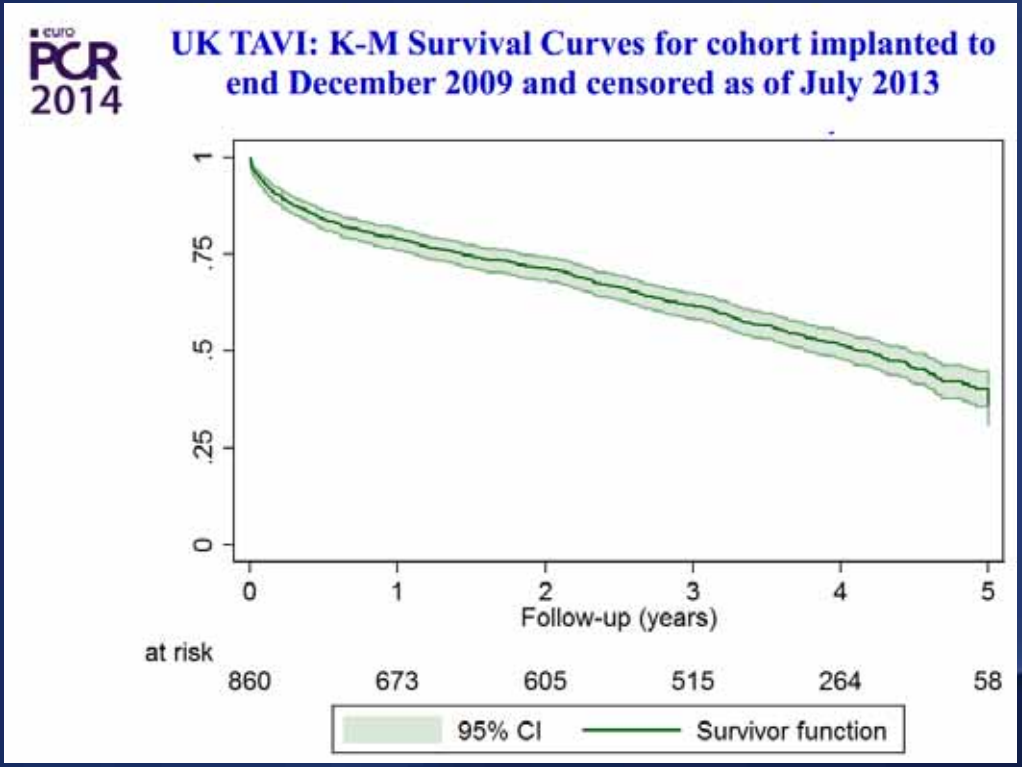
- Important Longer-Term Data
  - UK TAVI Registry
  - ADVANCE 2-year data
  - SOURCE XT 2-year data
  - CoreValve CE Mark Trial 4-year data

UK TAVI Registry

- The UK TAVI Registry is the longest-running TAVI registry in Europe with over 4,500 TAVI patients enrolled.
- At EuroPCR 2014, late clinical outcomes from this registry were reported for the first time.
- Analysis focused on 870 patients enrolled from January 2007 – December 2009
- 410 SAPIEN, 452 CoreValve, 8 not classified
- Follow-up: ranged from 3.5 – 6.4 years

UK TAVI Registry[1]

	Alive	Survival
3 Years	536 / 870	61.6%
5 Years	NR	48.4%



[1]Duncan, et al., presented at EuroPCR 2014

UK TAVI Registry

- Multivariable analysis was performed to learn what factors drive long-term mortality in TAVI patients.
- Diabetes, AF, respiratory disease, and renal impairment were significant predictors

euro PCR 2014

Baseline Demographics
Predictors of Mortality at 3-year Follow-Up

Variable	Alive (n=536)	Dead (n=334)	Univariate Model (HR: 95%CI)	P value	Multivariate Model (HR: 95%CI)	P value
Age (years)	81.5±7.4	82.6±6.6	1.01 (1.00-1.03)	0.082		
Male Gender (n)	269/535 **50.2%**	187/334 **56.0%**	1.23 (0.99-1.53)	0.064		
Diabetes (n)	107/527 **20.3%**	89/334 **26.7%**	1.32 (1.03-1.68)	0.027	1.11 (0.99-1.25)	0.08
AF (n)	**111/532 20.9%**	**95/332 28.6%**	**1.39 (1.09 -1.76)**	**0.008**	**1.35 (1.05 – 1.72)**	**0.018**
COPD (n)	**130/515 25.2%**	**109/319 34.2%**	**1.42 (1.12-1.79)**	**0.004**	**1.30 (1.02-1.65)**	**0.034**
Cr>200µg/mmol (n)	**22/523 4.2%**	**35/330 10.6%**	**2.08 (1.46-2.95)**	**<0.0001**	**1.69 (1.15-2.48)**	**0.008**
Euroscore ≥ 18.5 (n)	**243/536 45.3%**	**192/334 57.5%**	**1.45 (1.17-1.81)**	**0.001**	**1.24 (1.05-1.47)**	**0.012**
CAD (n)	234/514 **45.5%**	160/314 **51.0%**	1.25 (0.99-1.56)	0.056		
Prev Cardiac Sx (n)	164/523 **31.4%**	95/330 **28.8%**	0.92 (0.72-1.17)	0.50		
PVD (n)	138/509 **27.1%**	103/323 **31.9%**	1.18 (0.93-1.80)	0.18		
NYHA Class						
I/II (n)	131/533 **24.6%**	68/333 **20.4%**	1.00			
III/IV(n)	402/533 **75.4%**	265/333 **79.6%**	1.21 (0.93-1.59)	0.16		
Ao peak grad (mmHg)	81.3±26.9	80.1±27.9	0.998 (0.994-1.002)	0.32		

[1]Duncan, et al., presented at EuroPCR 2014

UK TAVI Registry

- Importantly, TAVI factors such as device type, route of delivery, and complications did NOT drive long-term mortality.

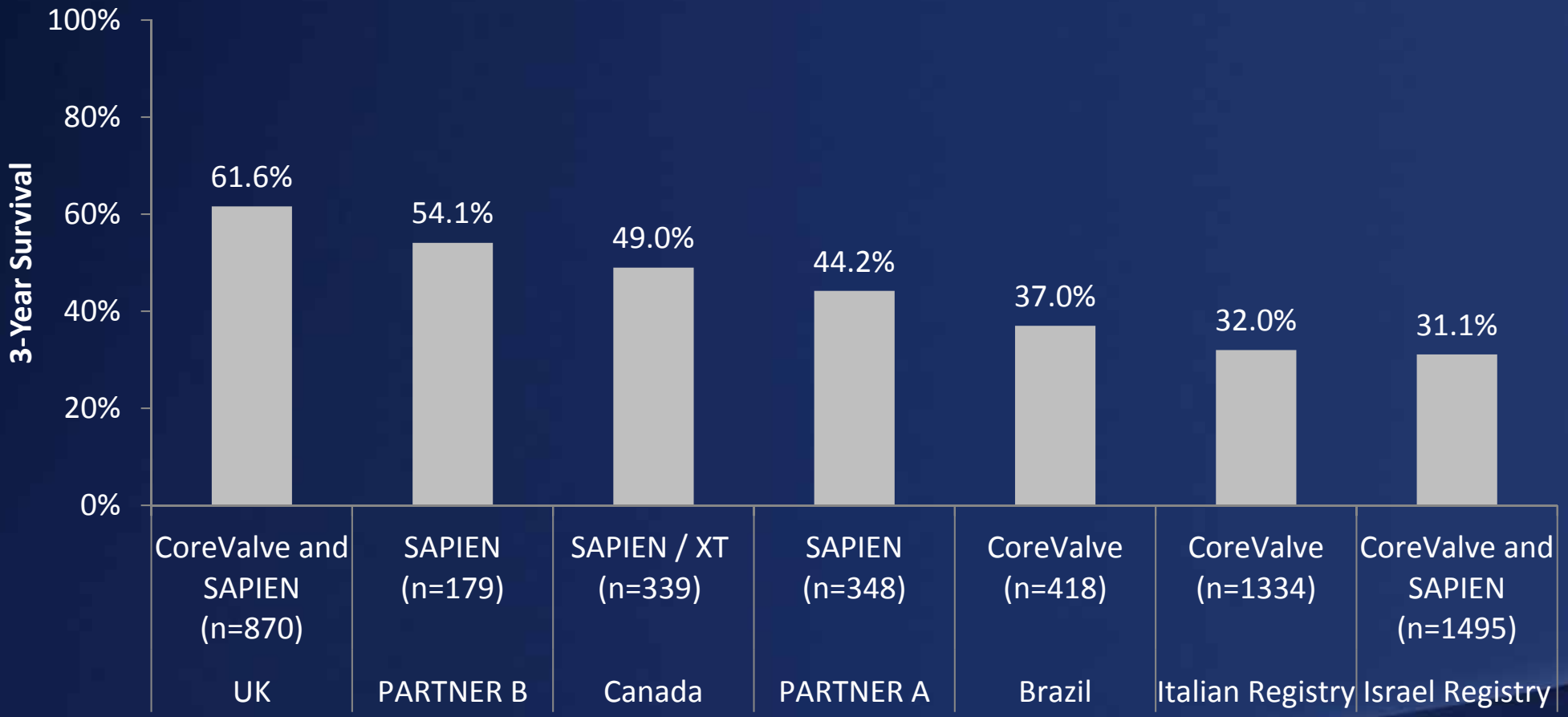
Device / Access / Procedural Complications as Predictors of Mortality at 3-year Follow-Up

Variable	Alive (n=536)	Dead (n=334)	Univariate Model (HR – 95%CI)	P value	Multivariate (HR – 95%CI)	P value
Valve Type						
Edwards Sapien (n)	243/410 **59.3%**	167/410 **40.7%**	1.00	0.078		
Medtronic CoreValve (n)	292/452 **64.6%**	160/452 **35.4%**	0.82 (0.66-1.02)			
Route						
Transfemoral (n)	385/599 **64.3%**	214/599 **35.7%**	0.76 (0.60-0.95)	0.017	0.81 (0.64-1.03)	0.09
Non-transfemoral (n)	151/271 **55.7%**	120/271 **44.3%**	1.00		1.00	
Procedural Complications						
AR (mod / severe) (n)	67/527 **12.7%**	48/322 **14.9%**	1.21 (0.89-1.65)	0.22		
Permanent Pacemaker (n)	87/535 **16.2%**	64/332 **19.3%**	1.01 (0.78-1.36)	0.92		
Major vasc comp (n)	29/535 **5.4%**	26/333 **7.8%**	1.39 (0.92-2.11)	0.11		

[1]Duncan, et al., presented at EuroPCR 2014

UK TAVI Registry in Comparison

- Several studies and registries around the world have previously reported data out to 3 years, and survival rates varied from 30-60%.
- As shown by the UK multivariable analysis, this may be explained by baseline differences in patient comorbidities / risk.



[1]Duncan, et al., presented at EuroPCR 2014; [2]Kapadia, et al., presented at TCT 2012; [3]Webb, et al., presented at TCT 2013; [4]Leon, et al., presented at TCT 2013; [5]Brito, et al., presented at SOLACI 2013; [6]Petronio, et al., presented at TCT 2012; [7]Danenberg, et al., presented at EuroPCR 2013

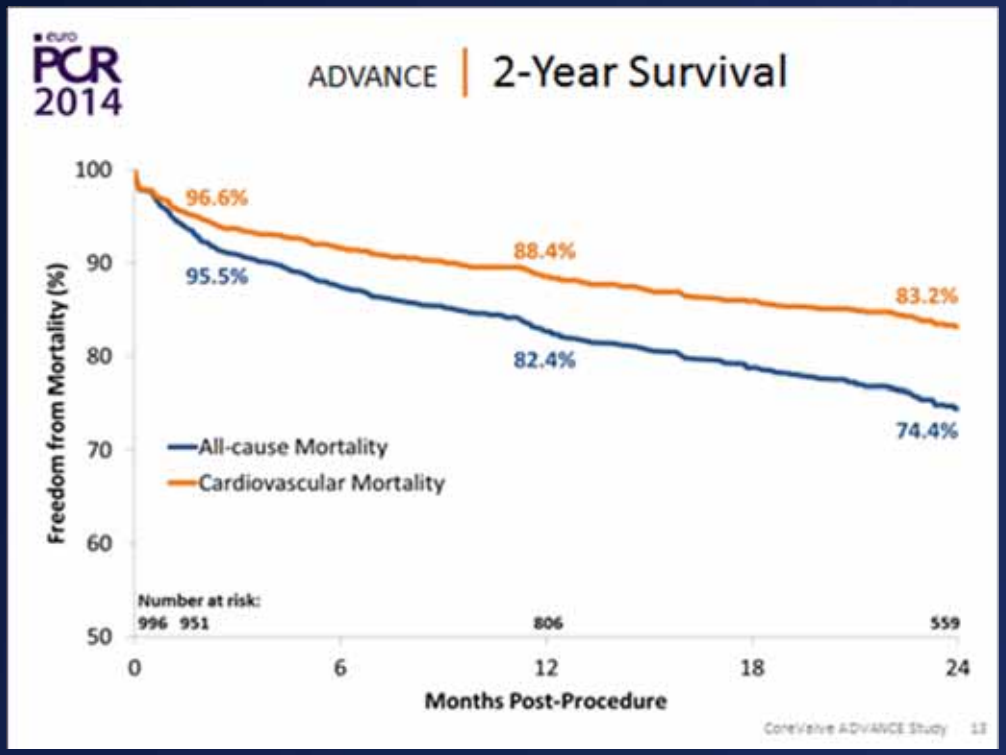
CoreValve ADVANCE

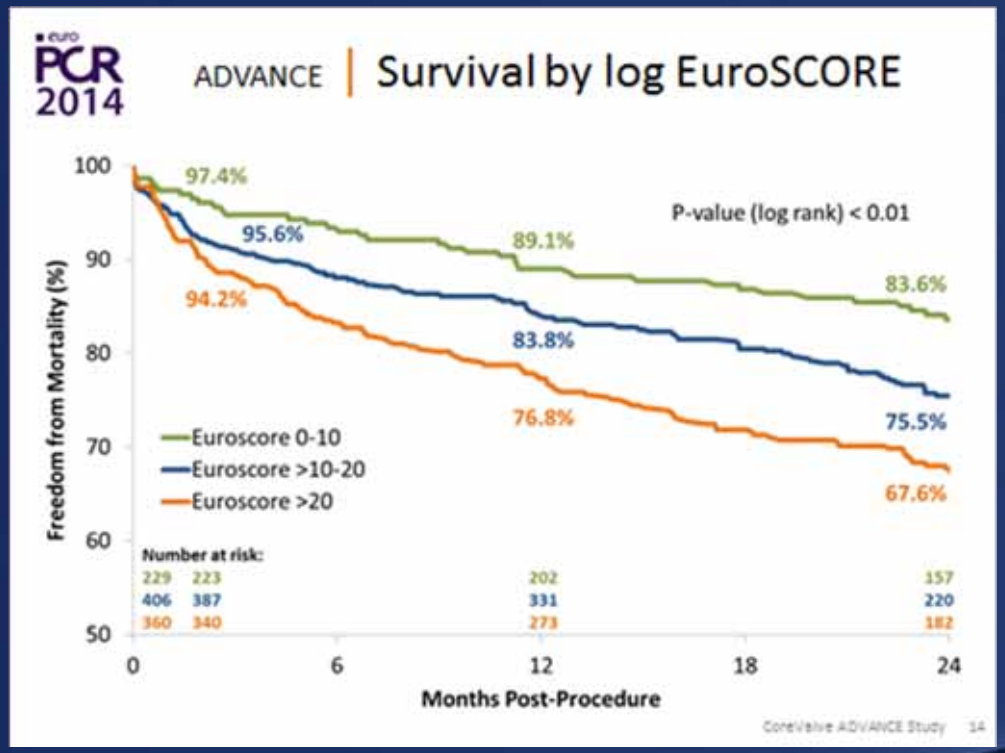
- The CoreValve ADVANCE Study is one of the largest “real world” TAVI trials
- 1,015 patients were enrolled in 12 countries in western Europe, Asia, and South America.
- Special attributes of ADVANCE:
  - 100% of patients are monitored
  - Events are adjudicated by an independent clinical events committee to VARC-1 definitions
  - Represents “real-world” experience with CoreValve
- 2-year outcomes were presented at EuroPCR 2014[1]

[1]Linke, et al., presented at EuroPCR 2014

CoreValve ADVANCE

- The CoreValve ADVANCE Study demonstrated excellent survival (74.4%) in the whole cohort.
- Categorization according to log EuroSCORE demonstrated that patients in better health at baseline had better survival over time.





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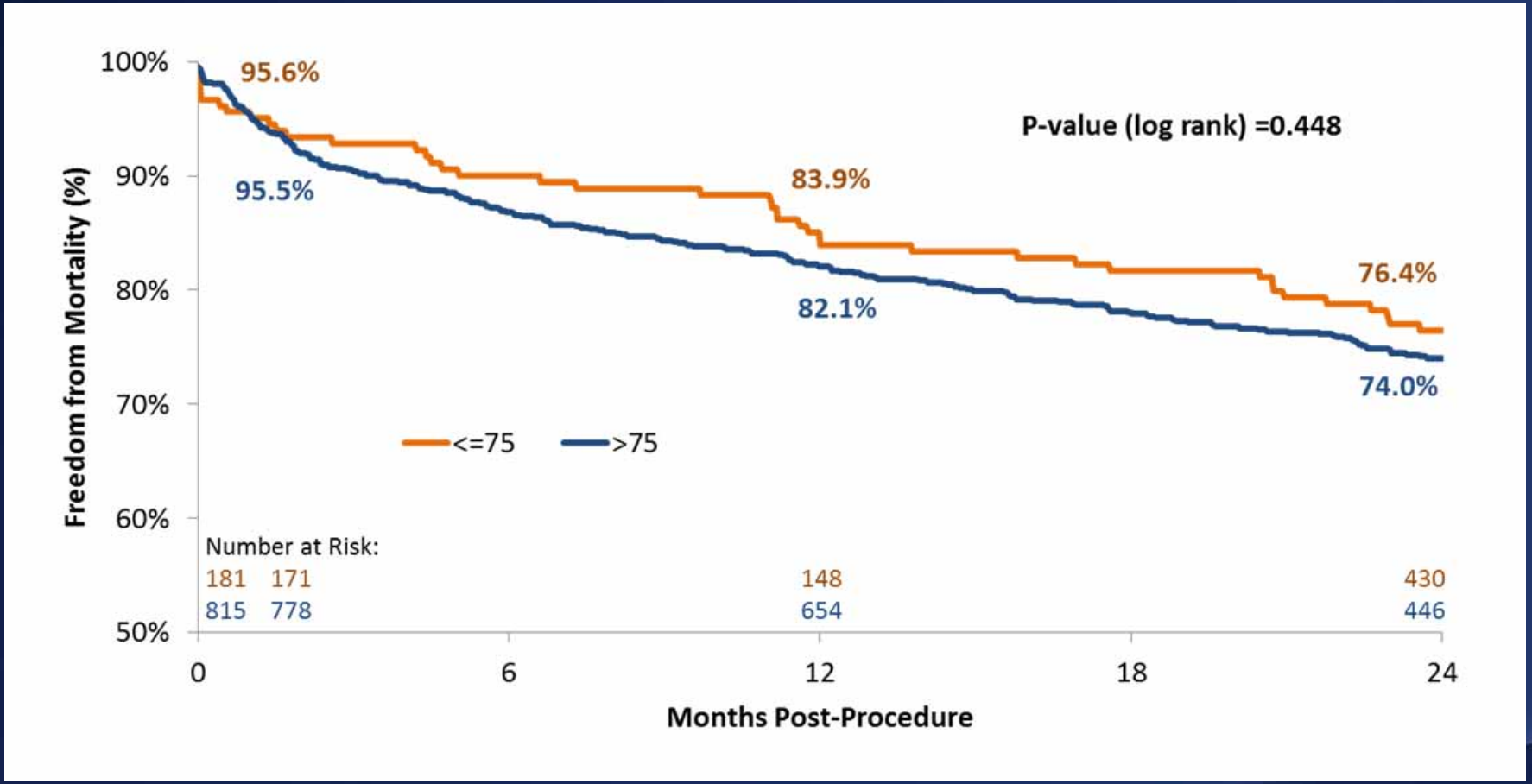
[1]Linke, et al., presented at EuroPCR 2014

CoreValve ADVANCE

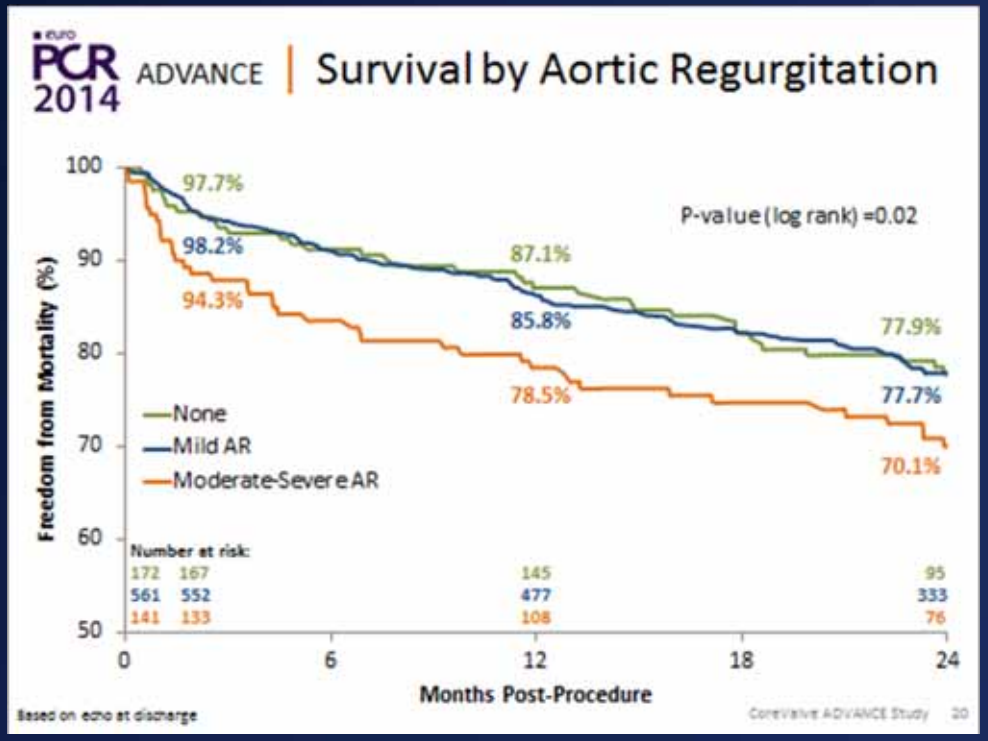
- Despite the significant differences in baseline comorbidities, patients ≤ 75 years of age and those > 75 had similar rates of all-cause mortality out to 2 years[1]
- Take-home message: age itself is not a significant driver of mortality in TAVI patients.

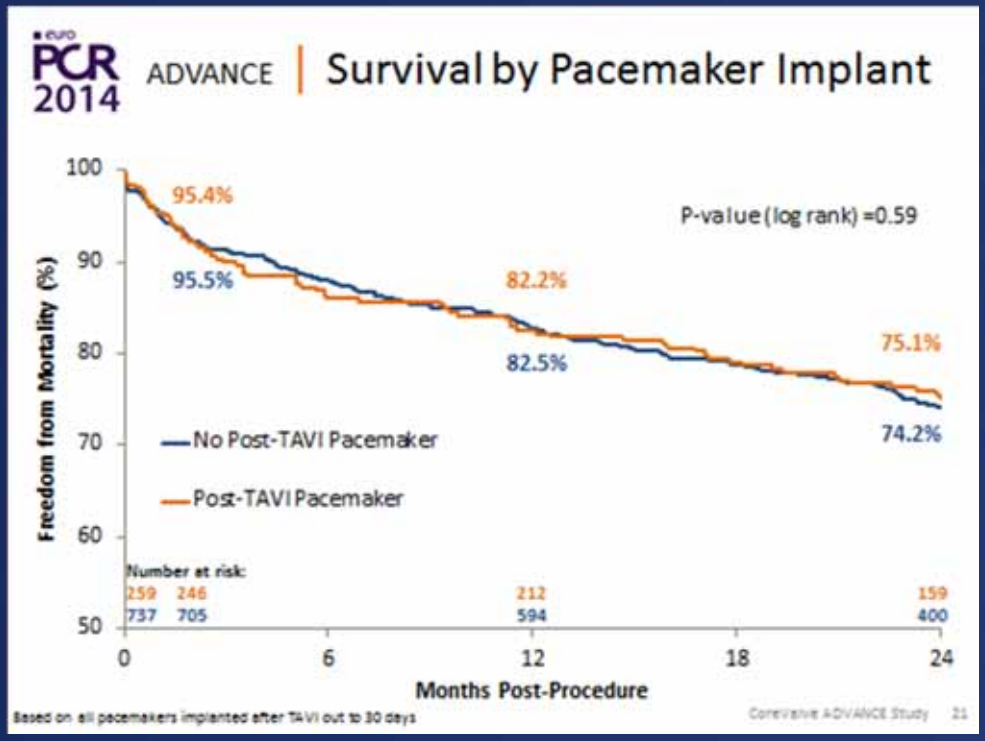


[1]Grube, et al., presented at EuroPCR 2014

CoreValve ADVANCE

- Importantly, the CoreValve ADVANCE study continued to demonstrate that mild aortic regurgitation and pacemaker implantation did not determine survival at 2 years.





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[1]Linke, et al., presented at EuroPCR 2014

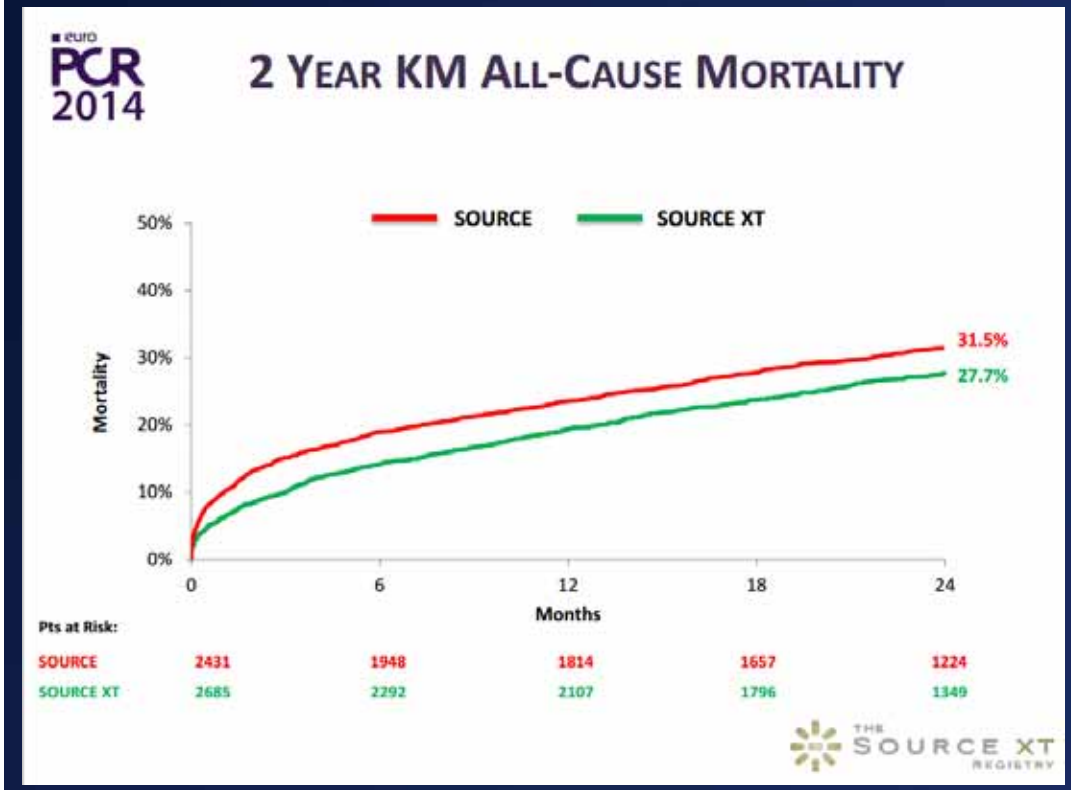
SOURCE XT

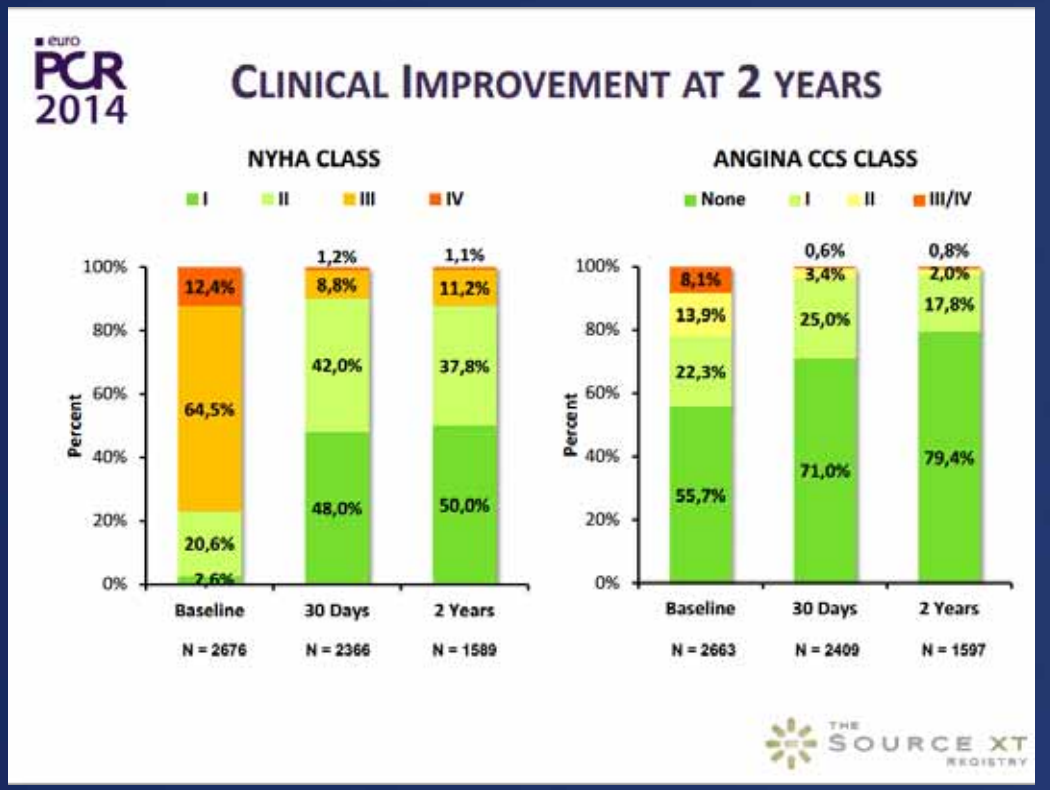
- SOURCE XT is a multicenter, prospective, observational post-approval study of the SAPIEN XT valve.
- 2,706 patients were enrolled in 17 countries in Europe, Asia, and Africa.
- Special attributes of SOURCE XT:
  - Events are adjudicated by an independent clinical events committee to VARC-1 definitions.
  - Represents “real-world” experience with SAPIEN XT
- 2-year outcomes were presented at EuroPCR 2014[1]

[1]Windecker, et al., presented at EuroPCR 2014

SOURCE XT

- Two-year outcomes from SOURCE XT show a large treatment effect in terms of symptom relief and improved quality of life[1].
- 2-Year Survival: 72.3%



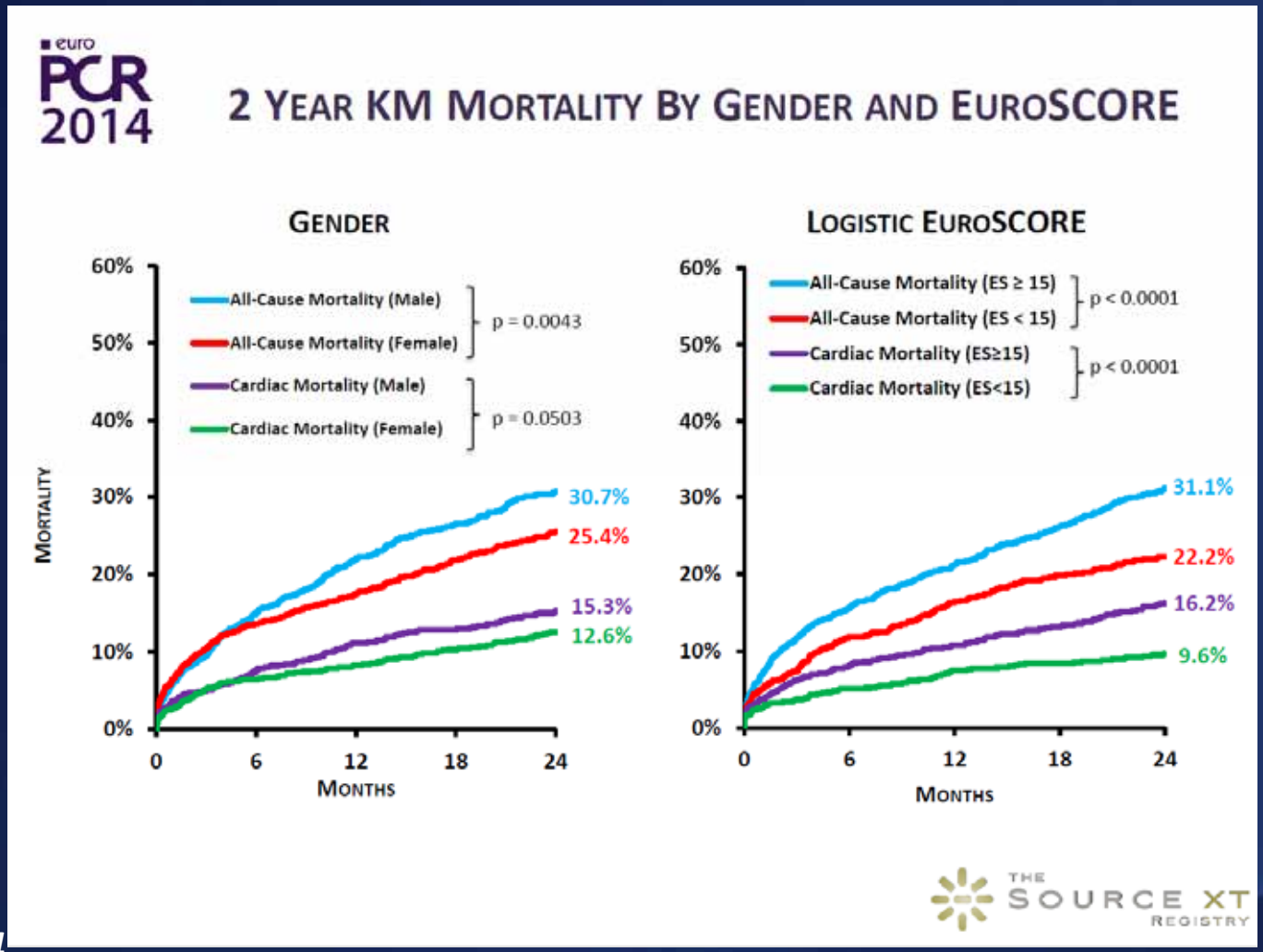


TAVI Summit 2014

[1]Windecker, et al., presented at EuroPCR 2014

SOURCE XT

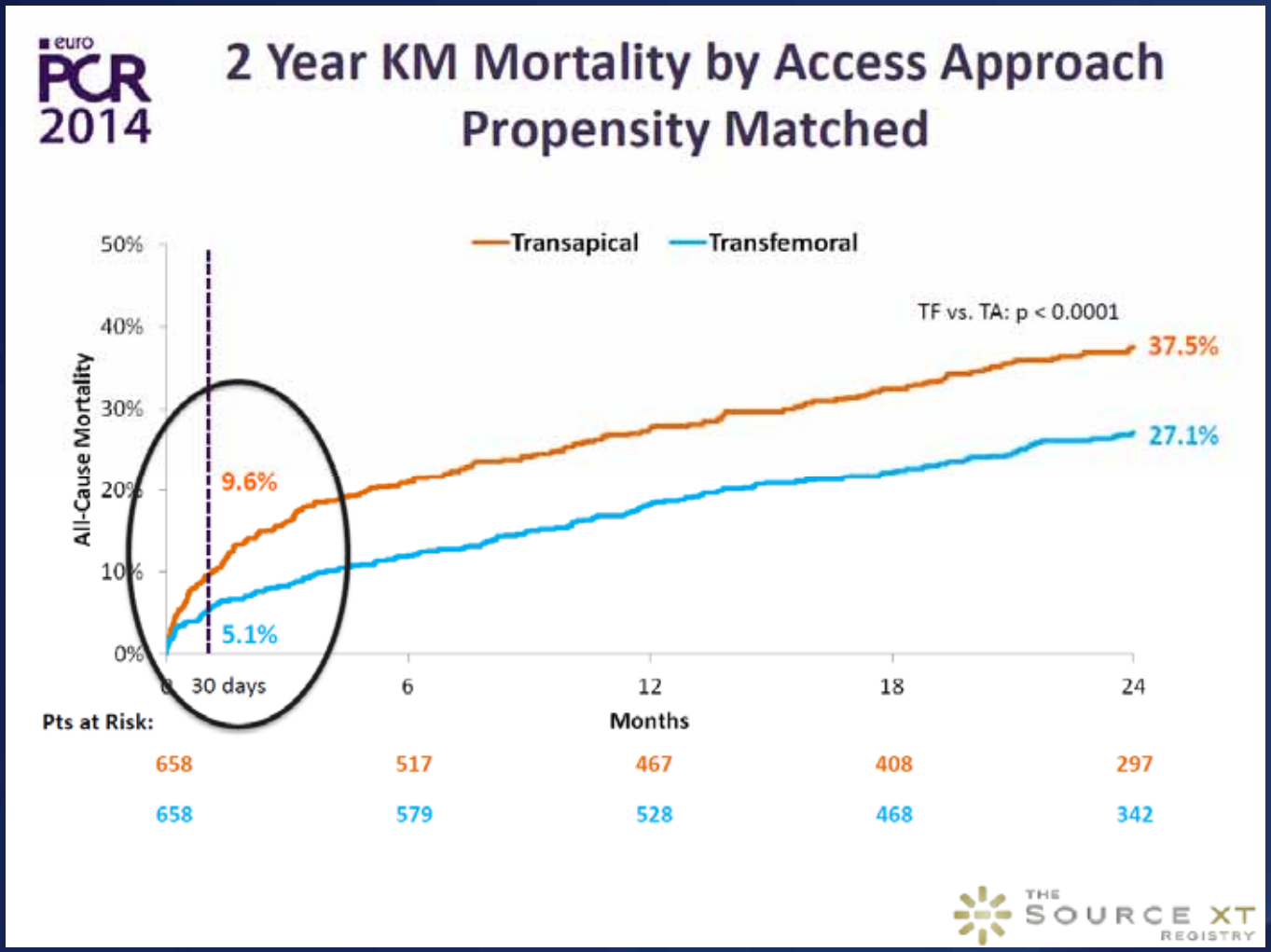
- Females had a lower 2-year mortality rate compared to males (25.4% vs. 30.7%, p=0.0043)
- As expected, mortality increased with increasing log EuroSCORE



[1]Windecker, et al., presented at EuroPCR 2014

SOURCE XT

- Comparison of transfemoral and transapical cohorts with propensity-matched baseline characteristics showed that patients in the transfemoral group had a survival advantage at 2-years[1].

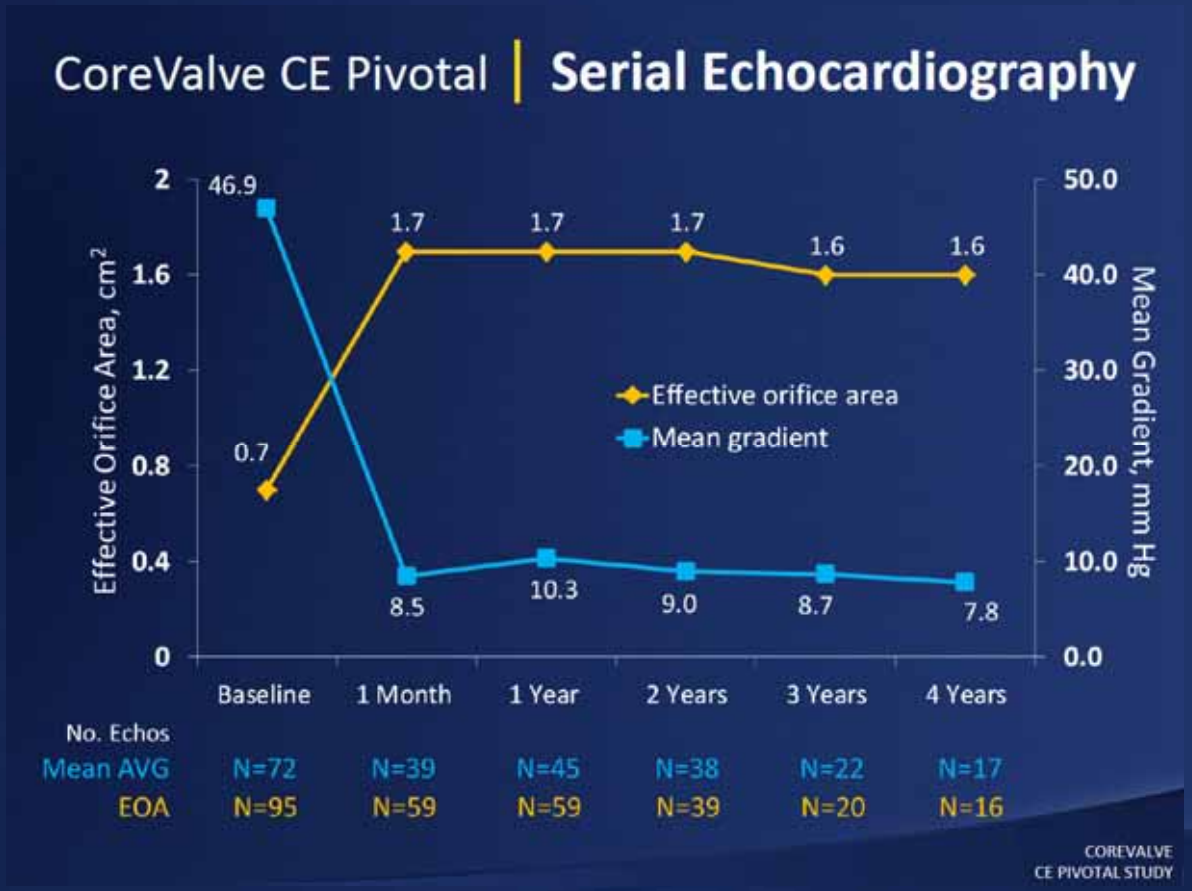


TAVI Summit 2014

[1]Walther, et al., presented at EuroPCR 2014

CoreValve CE-Mark Pivotal Trial

- 4-year data from the CoreValve CE-Mark Pivotal Trial were presented at ACC 2014[1].
- 126 patients were enrolled at 9 centers in Europe and Canada.
- An echo core lab was used to assess long-term valve performance.
- Results demonstrated stable hemodynamics over time and no structural valve deterioration.



[1]Kovac, et al., presented at ACC 2014

Conclusions

- Over 27,000 patients have been treated with CoreValve and SAPIEN / XT in Europe.
- Longer-term data is becoming available from the European TAVI registries, and a key theme has emerged:
  - ***mortality at ≥ 2 years is primarily driven by intrinsic patient factors.***
- Importantly, TAVI "side effects" do not seem to strongly influence long term mortality. ***However:***
  - The relative influence of aortic regurgitation on mortality remains a clinical concern, and therefore must be aggressively managed at the time of the procedure.