Evolving Trends in Complications after TAVR

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Physician Name	Company/Relationship
Eberhard Grube, MD	Medtronic, CoreValve: C, SB, AB, OF LivaNova: C, SB, AB Mitralign: AB, SB, E Boston Scientific: C, SB, AB Millipede: SB, C, AB Kona: AB, E Abbott Vascular: AB InSeal Medical: AB, E, Valtech: E, SB, Claret: SB Keystone: AB Shockwave: E, AB

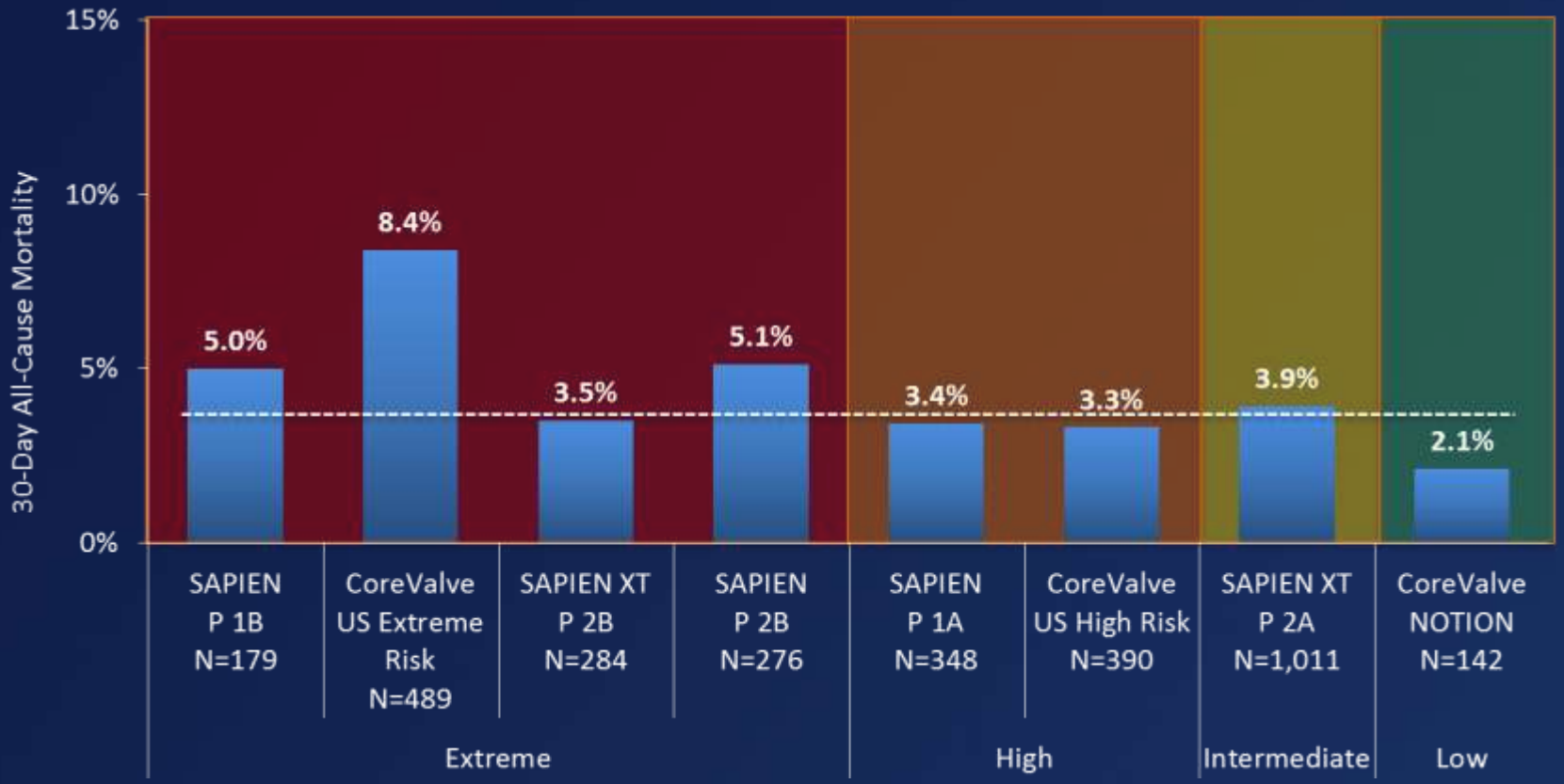
Key

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 '

30-Day All-Cause Mortality

Across the Spectrum of Risk

- *TAVR has been rigorously studied to octogenarians at varying levels of surgical risk since 2007.*
- *Early all-cause mortality has generally stayed under 5%, which demonstrates that overall, this is a relatively safe procedure.*

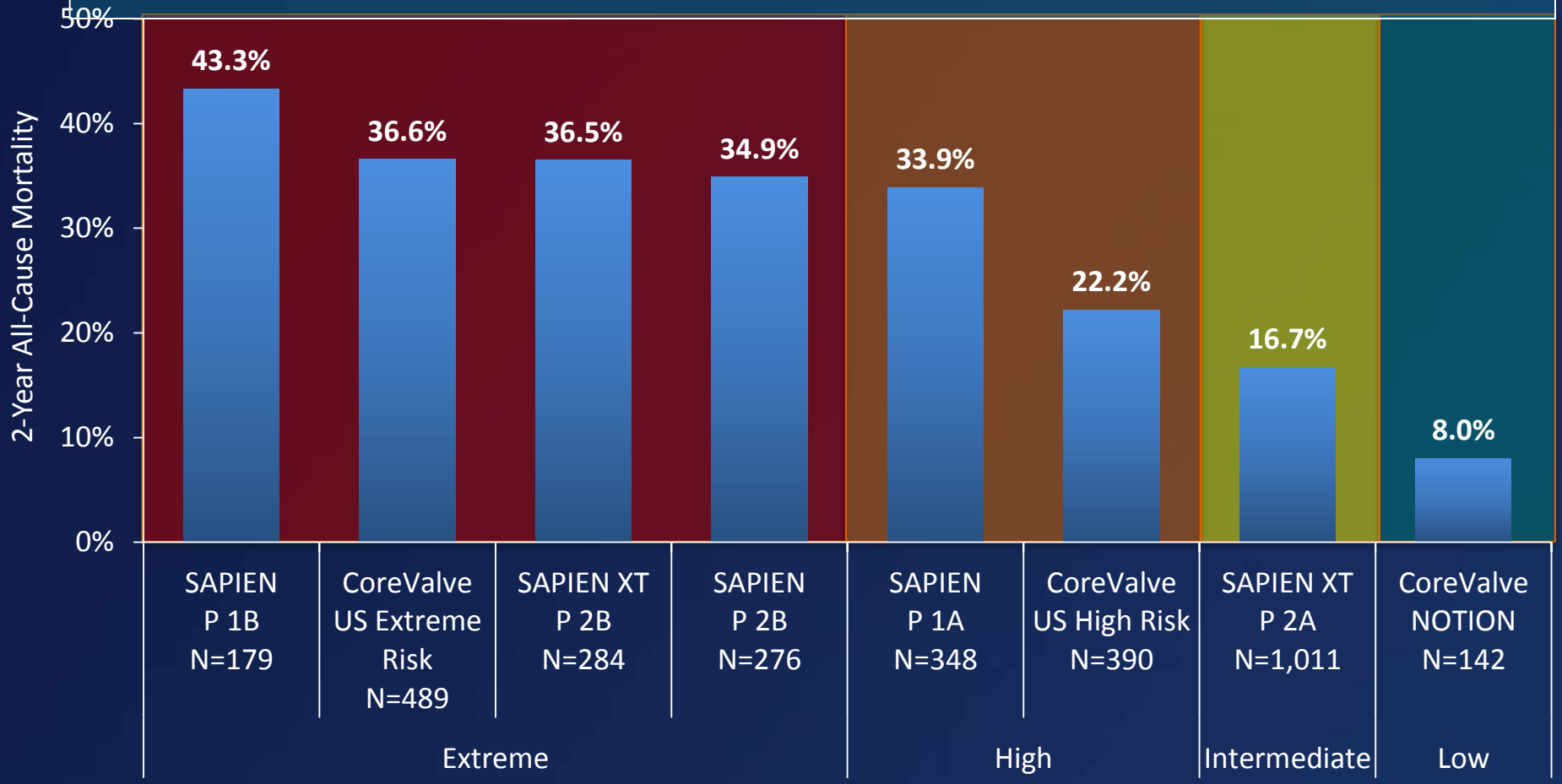


[1]Leon, et al., *N Engl J Med* 2010;363:1597-1607; [2]Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; [3]Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; [4]Smith, et al., *N Engl J Med* 2011;364:2187-98; [5]Adams, et al., *N Engl J Med* 2014;370:1790-8; [6]Leon, et al., *N Engl J Med* 2016;374:1609-20; [7]Thyregod, et al., *J Am Coll Cardiol* 2015;65:2184-94

2-Year All-Cause Mortality

Across the Spectrum of Risk

- *At later time points, all-cause mortality begins to stratify according to risk status*
- *The better the condition of the patient at baseline, the better the longer-term survival will be*

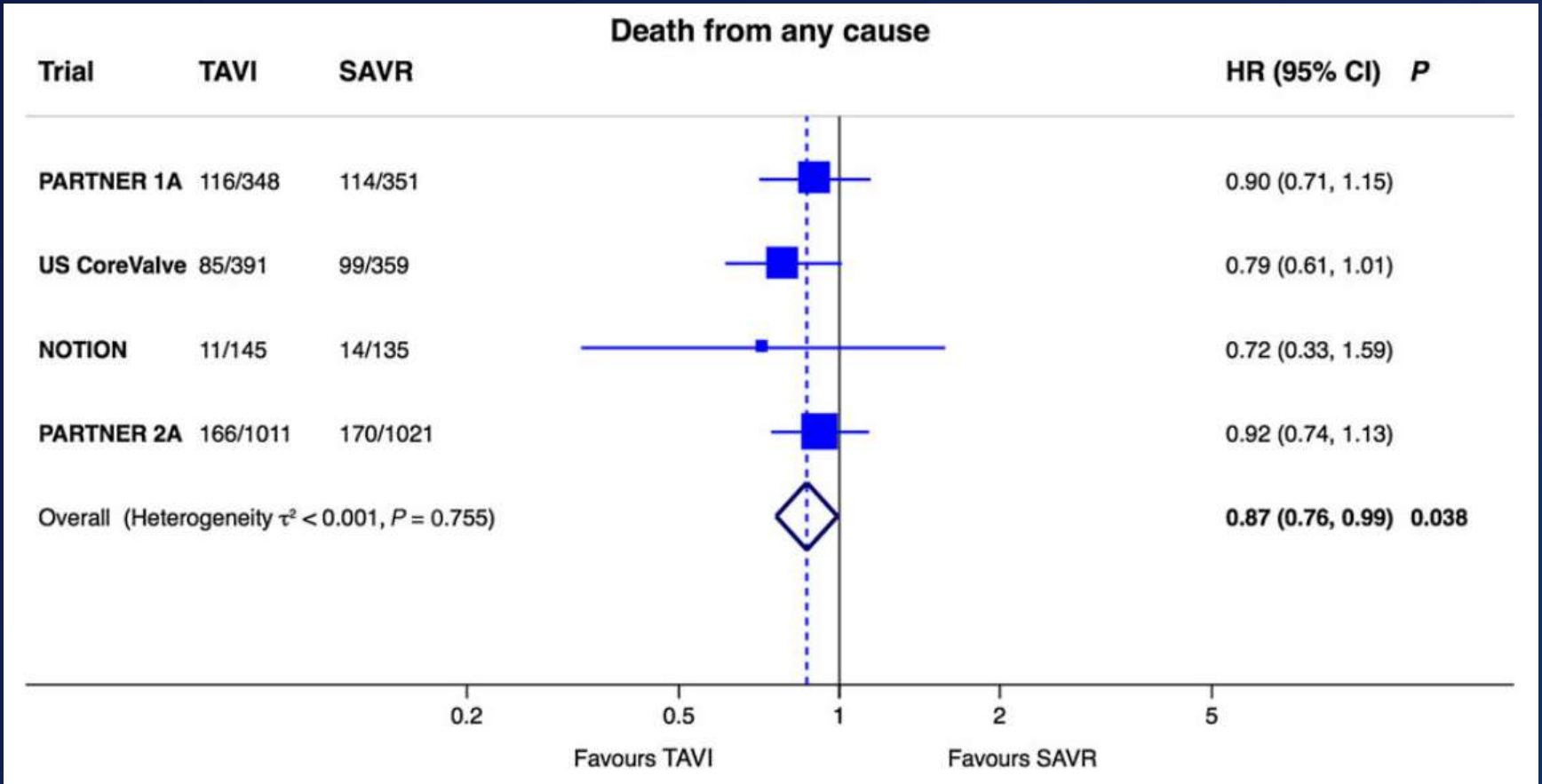


[1]Leon, et al., *N Engl J Med* 2010;363:1597-1607; [2]Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; [3]Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; [4]Smith, et al., *N Engl J Med* 2011;364:2187-98; [5]Adams, et al., *N Engl J Med* 2014;370:1790-8; [6]Leon, et al., *N Engl J Med* 2016;374:1609-20; [7]Thyregod, et al., *J Am Coll Cardiol* 2015;65:2184-94

TAVR vs. SAVR

Meta-Analysis

- *A recently published meta-analysis of randomized trials comparing TAVR with SAPIEN, SAPIEN XT, or CoreValve to SAVR shows an astonishing finding*
- *TAVR provides a statistically significant 13% relative risk reduction of death from any cause compared to SAVR in octogenarian patients*



[1]Siontis, et al., *Eur Hear J* 2016; doi:10.1093/eurheartj/ehw225

TAVR Complications

Comparison of Old Outcomes to New

CLINICAL RESEARCH — Valvular Medicine

Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation Clinical Trials

A Consensus Report From the Valve Academic Research Consortium

EXPEDITED REVIEW — Heart Valve Disease

Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation

The Valve Academic Research Consortium-2 Consensus Document†

- TAVR is now a highly attractive treatment strategy for younger, lower-risk patients.
- Medical device companies have worked to iterate their TAVR devices or introduce new technology to mitigate key complications :

Neurological Injury	Need for Permanent Pacemakers
Vascular Complications	Paravalvular Leak

- Using standardized endpoint definitions, the goal of this presentation is to compare complication rates with foundation devices to those with contemporary devices and show the progress being made

[1]Leon, et al., *J Am Coll Cardiol* 2011;57:253-69; [2]Kappetein, et al., *J Am Coll Cardiol* 2012;60:1438-54

Prevention of TAVI Complications

- TAVI-related complications can occur at any time, from the time of the procedure to years post implant.
- An individual patient may be at increased risk for certain complications due to comorbidities or anatomical features.
- Furthermore, the risk of a given complication may differ by valve type.
- For these reasons, it is critically important to engage the heart team for case planning and assess each patient individually.
- Prosthesis type, size, and access route should be determined on a case-by-case basis.

Some Caveats….

- TAVR data is often collected from observational studies and registries.
- Selection bias may be at play. The local heart team and operator select the prosthesis type, size, and access route on a case-by-case basis using clinical judgment.
- This selection bias and potential variability in patient baseline characteristics must be kept in mind as independent data sets are compared.

Transfemoral TAVR Devices

Iterative Device Design

For the purposes of this presentation, the devices are categorized in the following way

Foundation Devices

SAPIEN

CoreValve

SAPIEN XT

Contemporary Devices

Portico

Direct Flow

Lotus

SAPIEN 3

Evolut R

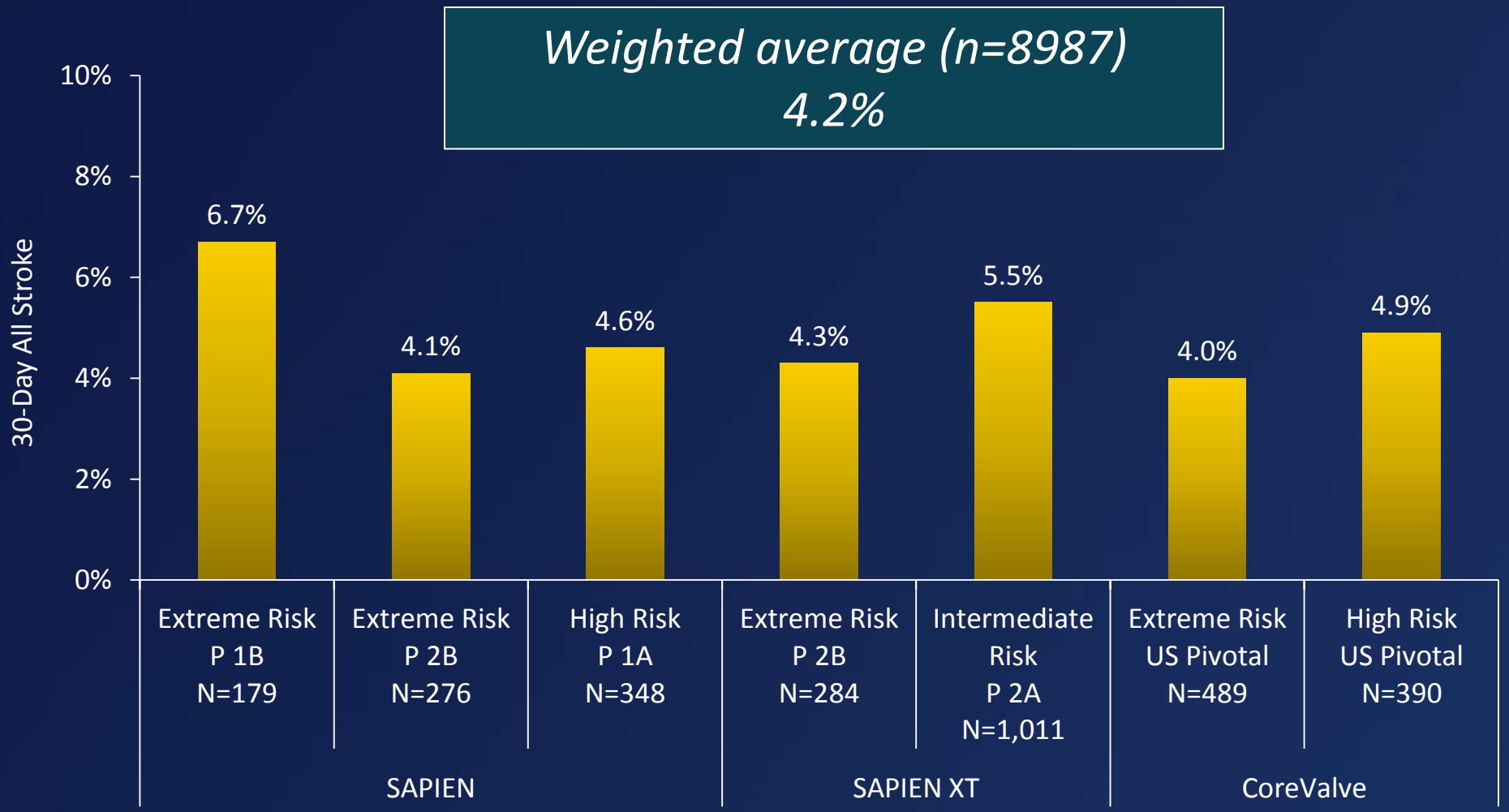
Symetis ACURATE neo TF

The Complications

Neurologic Injury

Neurological Injury

Incidence with Foundation Devices

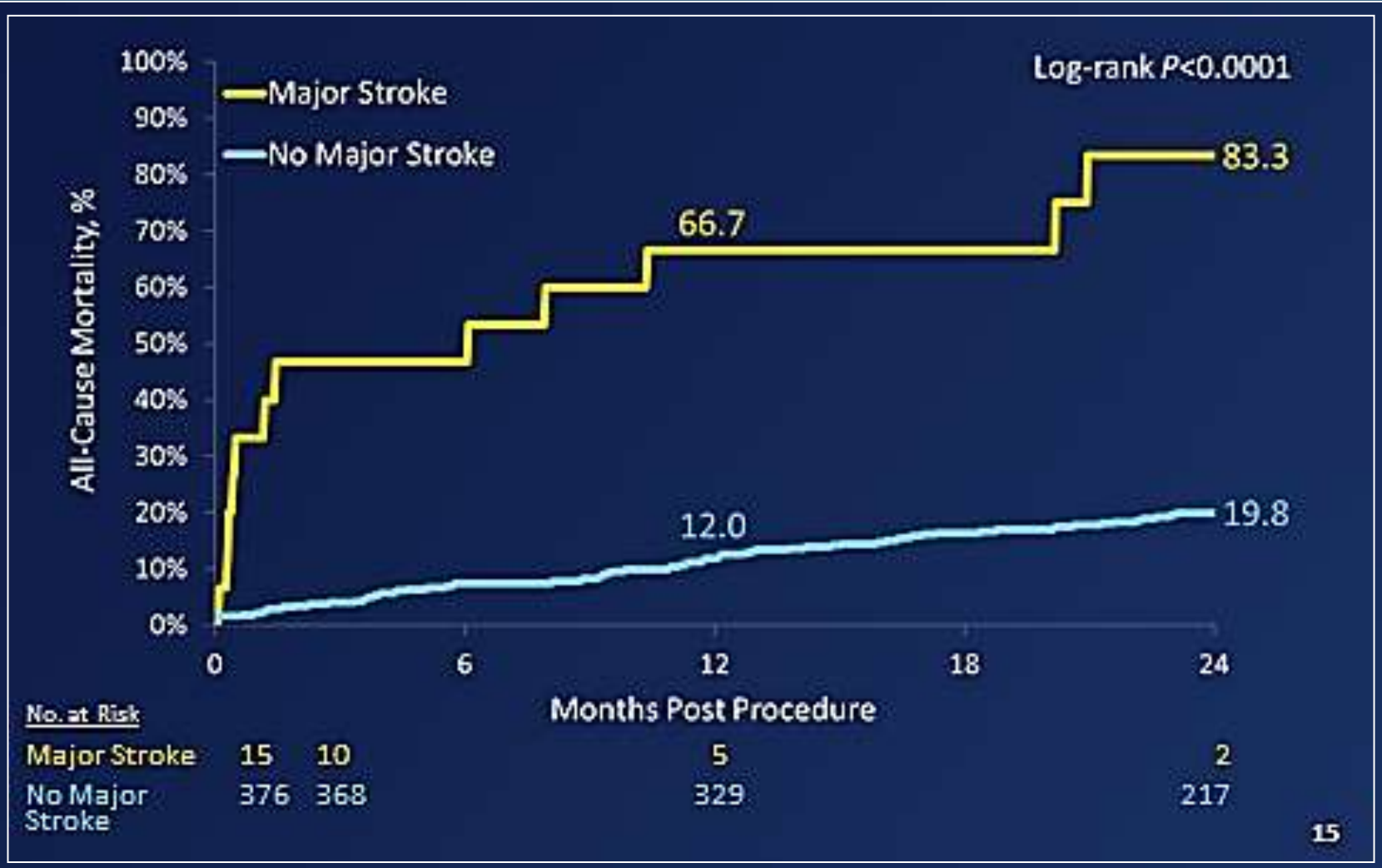


[1]Leon, et al., *N Engl J Med* 2010;363:1597-1607; [2]Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; [3]Smith, et al., *N Engl J Med* 2011;364:2187-98; [4]Leon, et al., *N Engl J Med* 2016;374:1609-20; [5]Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; [6]Adams, et al., *N Engl J Med* 2014;370:1790-8;;

Neurological Injury

Why Does it Matter?

Patients experiencing a VARC-1 major stroke in the CoreValve US Pivotal Trial had an 67% probability of death by 1 year post-procedure, increasing to 83% by 2 years



[1]Gleason, et al., presented at AATS 2015

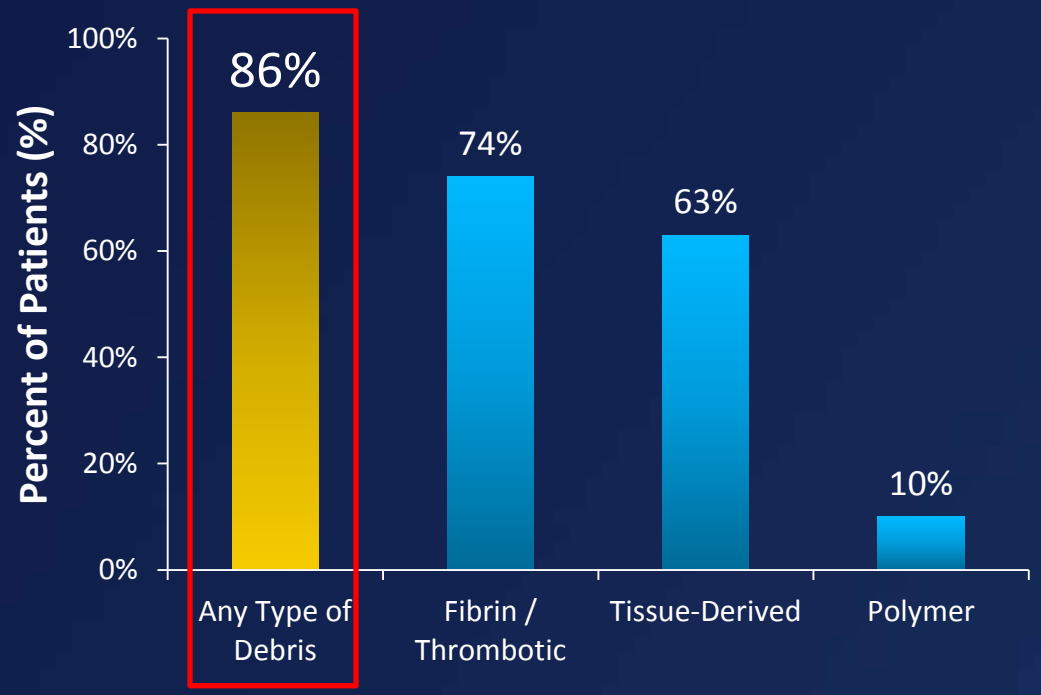
Neurological Injury

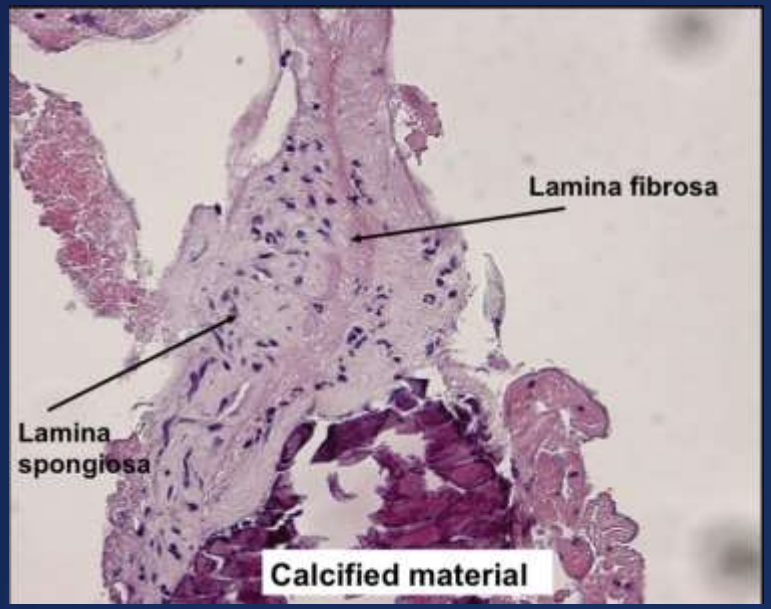
How Does it Happen?

Van Mieghem, et al., placed Claret Montage filters into the brachiocephalic and left common carotid arteries during TAVI, and examined the contents after the procedure.

The key findings:

- *Macroscopic debris was released into the circulation in ~90% of TAVI procedures*
- *The debris was composed of thrombotic material, fragments of valve leaflet, calcified particles, myocardial tissue, and plastic fragments from interventional tools*



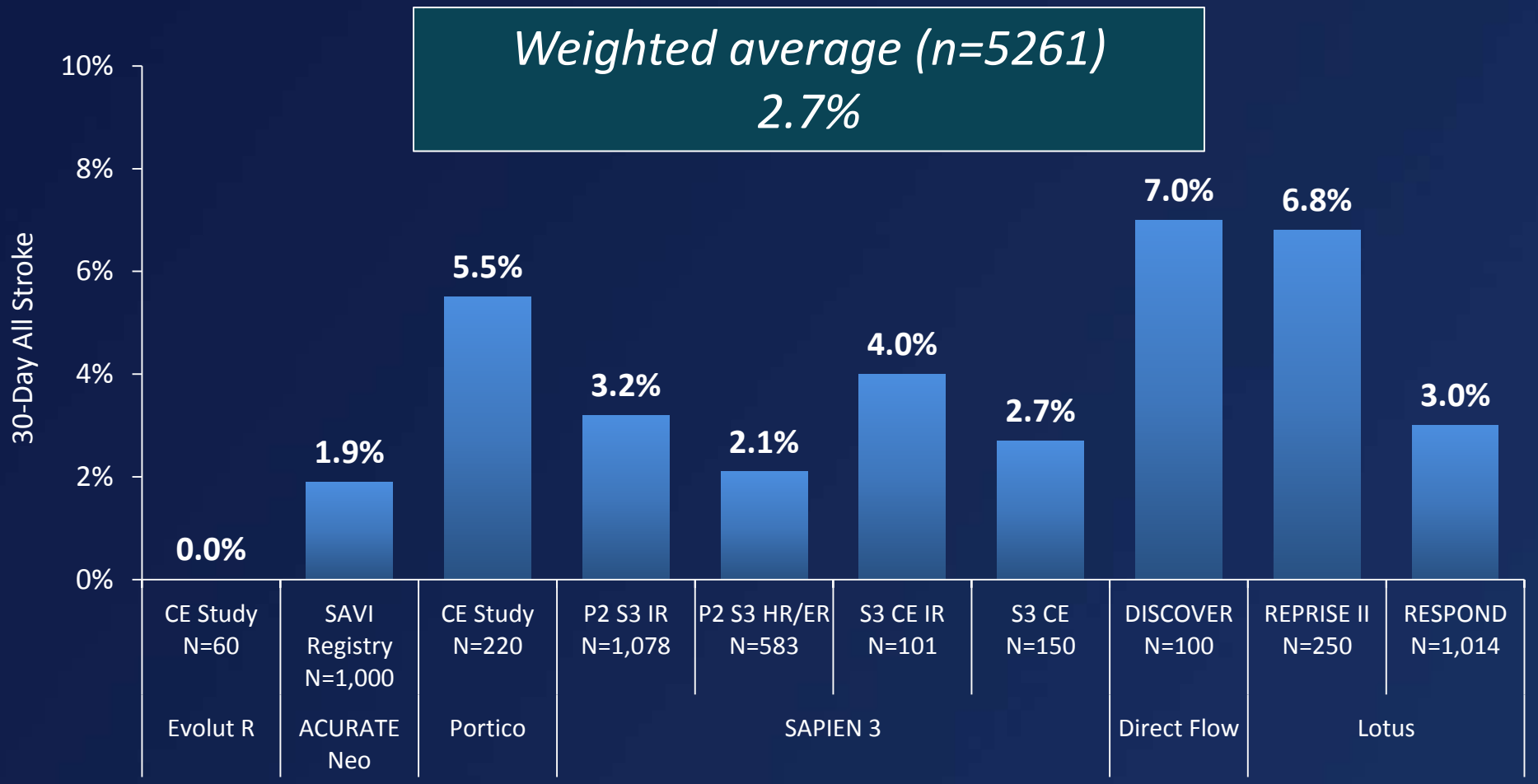


Fragments of aortic valve leaflet

[1]Van Mieghem, et al., *J Am Coll Cardiol Intv* 2015; 8: 718-24

Neurological Injury

Incidence with Contemporary Devices

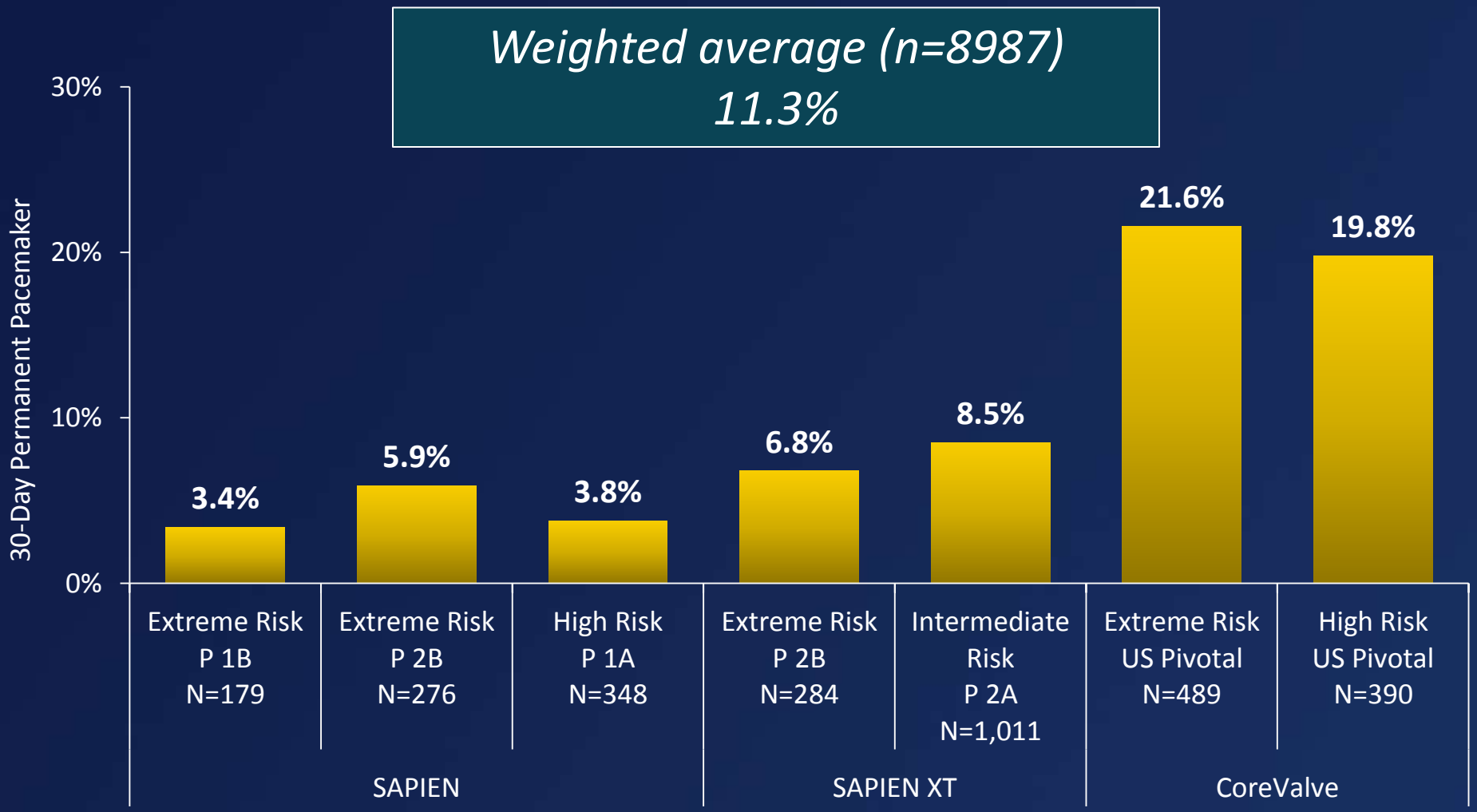


[1]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [2]Moellman, et al., presented at PCR London Valves 2015; [3]Linke, et al., presented at PCR London Valves 2015; [4]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [5]Vahanian, et al., presented at EuroPCR 2015; [6]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [7]DeMarco, et al, presented at TCT 2015; [8]Lefevre, et al., *J Am Coll Cardiol Intv* 2016; 9: 68-75; [9]Meredith, et al., presented at PCR London Valves 2015; [10]Falk, et al., presented at EuroPCR 2016

Need for Permanent Pacemakers

Permanent Pacemakers

Incidence with Foundation Devices



[1]Leon, et al., *N Engl J Med* 2010;363:1597-1607; [2]Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; [3]Smith, et al., *N Engl J Med* 2011;364:2187-98; [4]Leon, et al., *N Engl J Med* 2016;374:1609-20; [5]Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; [6]Adams, et al., *N Engl J Med* 2014;370:1790-8;;

Permanent Pacemakers

Why Do They Matter?

Studies out to 3 years have not demonstrated an impact on mortality

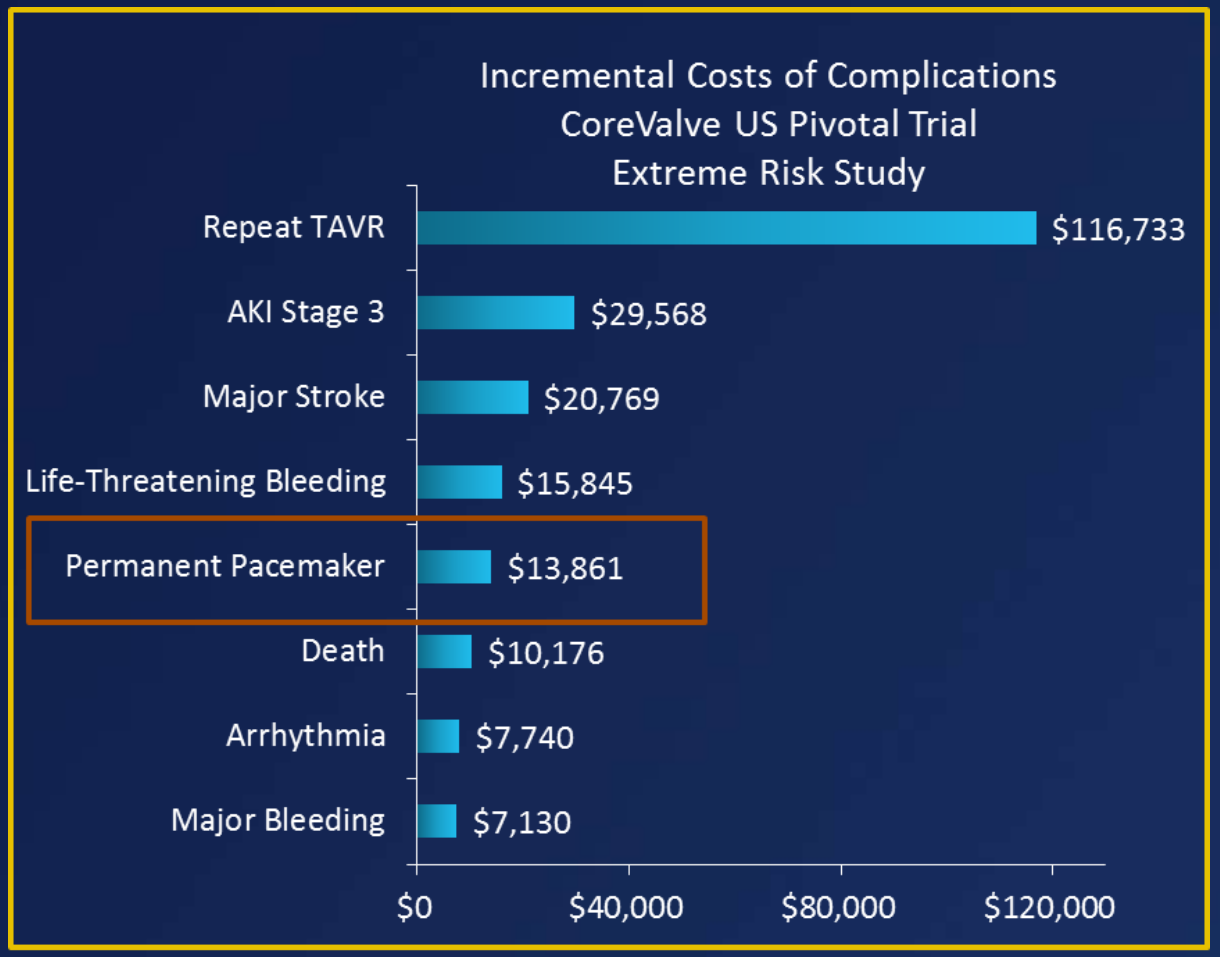
Study	Valve Type (n)	30 Day PPM Rate	Follow-up	Mortality impact
De Carlo[1]	CoreValve (n=275)	25.5%	1 year	None (p=0.90)
Buellesfeld[2]	CoreValve (n=319) Edwards (n=34)	27.8%	1 year	None (p=0.77)
Pereira[3]	CoreValve (n=65)	32.8%	1 year	None (p=0.11)
Nazif[8]	SAPIEN (n=1973)	8.8%	1 year	None (p=0.08)
CoreValve ANZ[4]	CoreValve (n=476)	31.1%	2 years	None (p=0.32)
Extreme Risk US Trial[5]	CoreValve (n=489)	21.6%	3 years	None (p=0.62)
ADVANCE[7]	CoreValve (n=1015)	26.3%	3 years	None (p=0.70)
Urena[6]	CoreValve (n=698) Edwards (n=858)	15.4%	3 years	None (p=0.15)

[1]De Carlo M, et al., *Am Heart J* 2012; 163: 492-9; [2]Buellesfeld L, et al., *J Am Coll Cardiol* 2012; 60(6): 493-501; [3]Pereira E, et al., *PACE* 2013; 36(5): 559-69; [4]Muller D, et al., presented at EuroPCR 2013; [5]Popma J, et al., *J Am Coll Cardiol* 2014; 63(10): 1972-81; [6]Urena M, et al., *Circulation* 2014; 129: 1233-1243; [7]Piazza N, et al., presented at TVT 2015; 8Nazif T, et al., *J Am Coll Cardiol Intv* 2015; 8: 60-9

Permanent Pacemakers

Why Do They Matter?

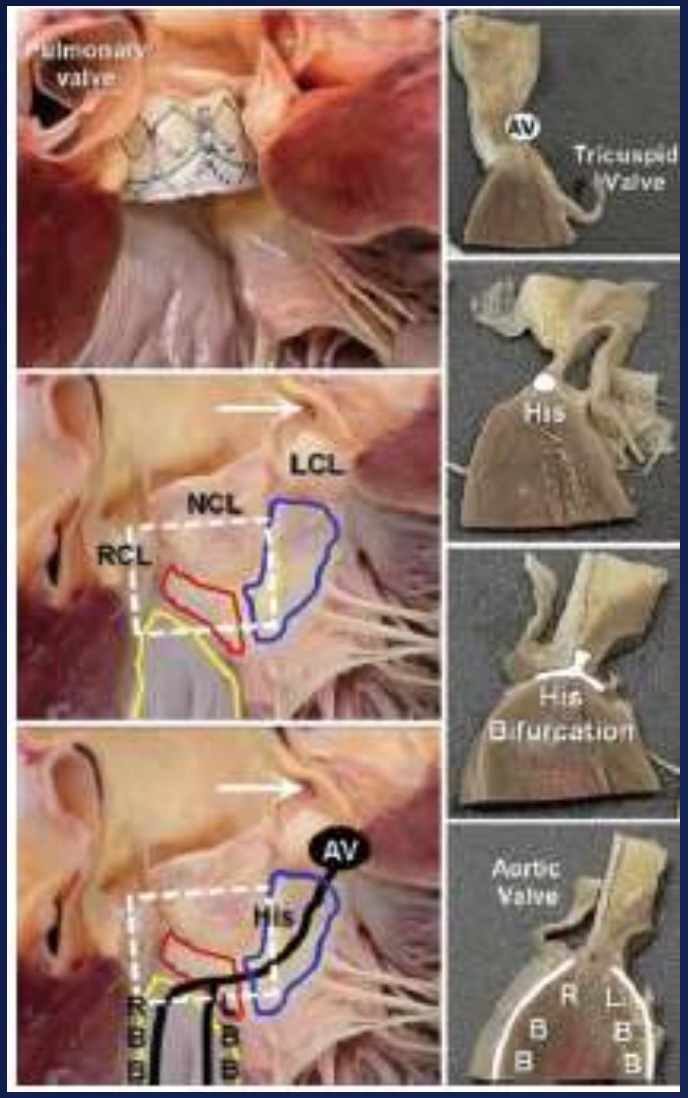
- *Pacemakers do add cost to the procedure, both in terms of the device and length of hospital stay*
- *Infections or other complications can result*



[1]Baron, et al., presented at TCT 2014

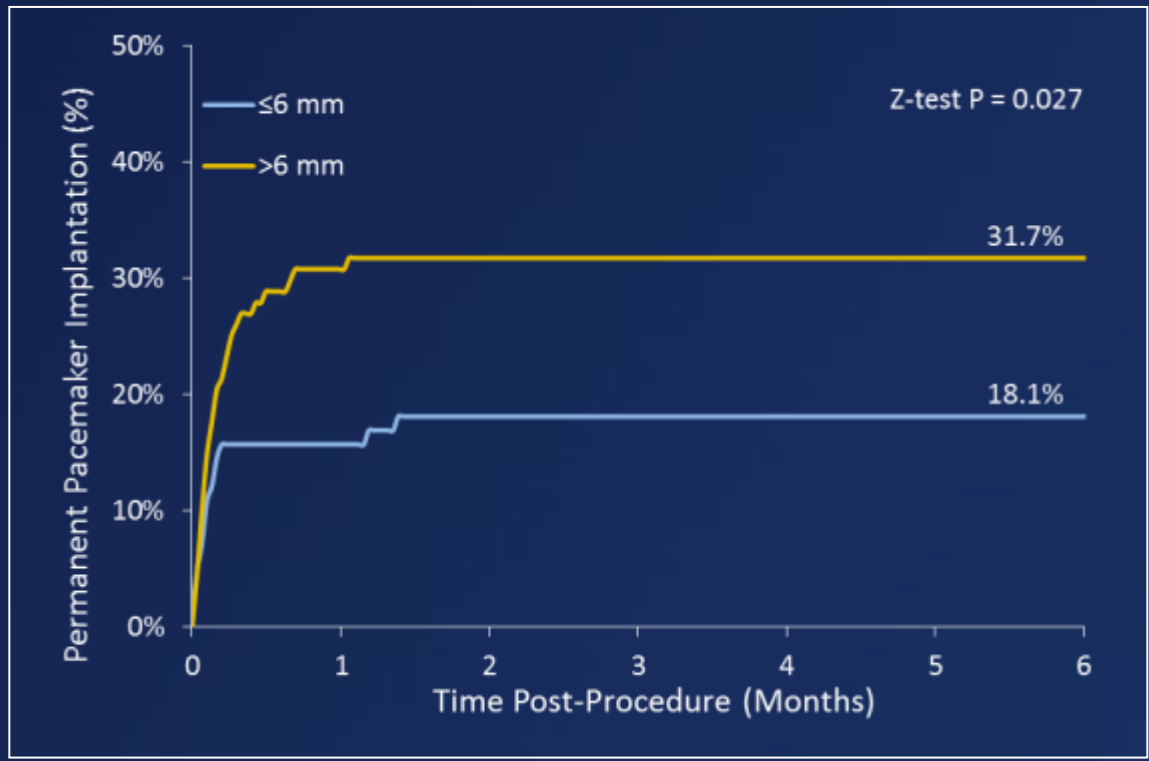
Permanent Pacemakers

Why Do They Happen?



White box represents location of the valve

- *Arrhythmias may result when the valve comes in close or direct contact with the conduction system.*
- *Studies with CoreValve have shown that maintaining shallow implant depth is the best avoidance strategy.*



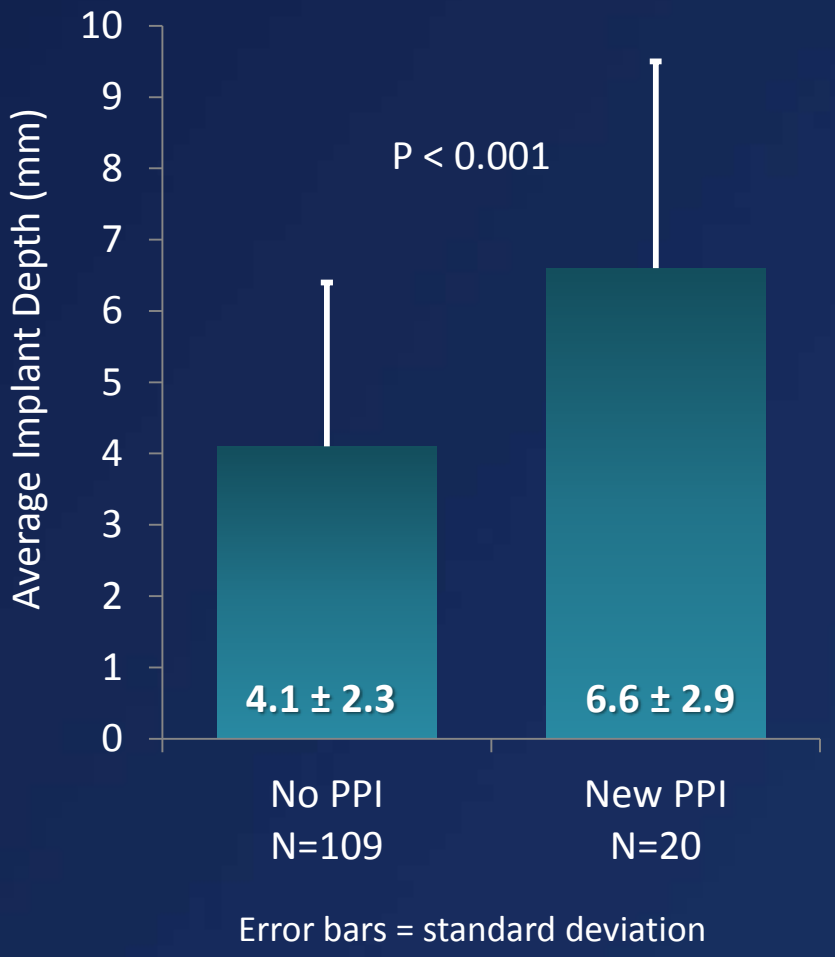
[1]Bax, et al., *Eur Heart J* 2014; 35:2639-54; [2]Petronio, et al., presented at EuroPCR 2014

Predictors of Permanent Pacemakers

Evolut R

- A Medtronic-sponsored sub-analysis was performed to find predictors of permanent pacemakers in a cohort of 151 Evolut R patients
- 22 patients with a pacemaker at baseline were excluded
- Of the remaining 129 patients, 20 required a new pacemaker
- The implants were significantly deeper in these patients

New Permanent Pacemaker Rate at 30 Days: 15.6% (n=20)



[1]Meredith, et al., presented at EuroPCR 2016

Predictors of Permanent Pacemakers

Evolut R

- Cox-regression showed that depth greater than 5 mm increased the risk of a new permanent pacemaker by 7x
- Calcification and oversizing were not important factors

	UNIVARIABLES		MULTIVARIABLES	
Variable	Hazard Ratio [95% CI]	P Value	Hazard Ratio [95% CI]	P Value
Average implant depth (>5 mm)	4.67 [1.77, 12.31]	0.002	6.9 [2.4, 19.6]	0.0003
Presence of RBBB	3.42 [1.36, 8.57]	0.009	6.1 [2.3, 15.9]	0.0003
26 mm valve	0.56 [0.21, 1.55]	0.266		
Oversizing > 20%	1.34 [0.56, 3.22]	0.515		
Overall root calcification (>480 mm^3)	1.33 [0.51, 3.50]	0.561		
Overall LVOT calcification (>4 mm^3)	1.97 [0.73, 5.34]	0.181		
Overall total calcification (>510 mm^3)	1.03 [0.40, 2.66]	0.959		

CI = confidence interval; RBBB = right bundle branch block.

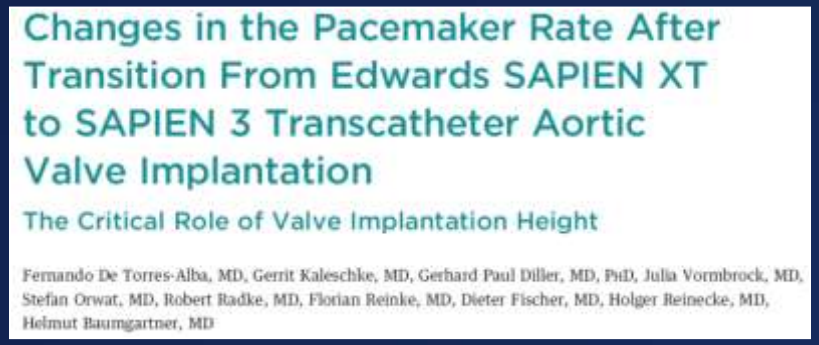
[1]Meredith, et al., presented at EuroPCR 2016

Predictors of Permanent Pacemakers

SAPIEN 3

Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve

Oliver Husser, MD,[a] Costanza Pellegrini, MD,[a] Thorsten Kessler, MD,[a] Christof Burgdorf, MD,[a] Hannah Thaller,[a] N. Patrick Mayr, MD,[b] Albert M. Kasel, MD,[a] Adnan Kastrati, MD,[a,c] Heribert Schunkert, MD,[a,c] Christian Hengstenberg, MD[a,c]



Changes in the Pacemaker Rate After Transition From Edwards SAPIEN XT to SAPIEN 3 Transcatheter Aortic Valve Implantation

The Critical Role of Valve Implantation Height

Fernando De Torres-Alba, MD, Gerrit Kaleschke, MD, Gerhard Paul Diller, MD, PhD, Julia Vormbrock, MD, Stefan Orwat, MD, Robert Radke, MD, Florian Reinke, MD, Dieter Fischer, MD, Holger Reinecke, MD, Helmut Baumgartner, MD

Implant depth
(OR 1.06, 1.02-1.11, p=0.006

Implant depth
(OR 0.94, 0.90-0.99, p=0.006)

Prosthesis oversizing
(OR 3.50, 1.24-9.85, p=0.018)

QRS duration (pre-procedural)
(OR 1.03 per msec, 1.01-1.06, p=0.003)

[1]Husser, et al., *J Am Coll Cardiol Intv* 2016; 9:244-54; [2]De Torres-Alba, et al., *J Am Coll Cardiol Intv* 2016; 9: 805-13

Predictors of Permanent Pacemakers

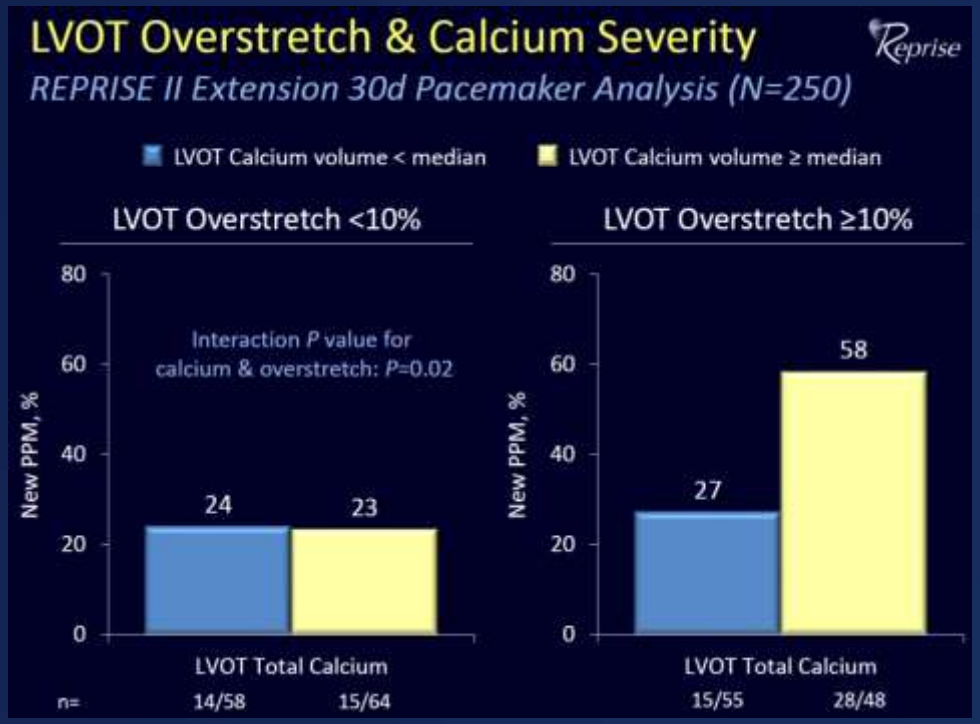
Lotus

Baseline RBBB
(OR 12.79, 4.45-36.22, p<0.001)

LVOT area overstretch > 10%
(OR 3.42, 1.74-6.74, p<0.001)

1st degree AV block
(OR 2.49, 1.13-5.47, p=0.02)

LVOT total calcium
(OR 1.80, 1.03-3.14, p=0.04)



[1]Dumonteil, et al., presented at ACC 2015

Predictors of Permanent Pacemakers

Portico

- *A sub-analysis from the Portico CE trial indicates while implant depth does not matter for Portico, post-dilatation is the strongest modifiable factor leading to permanent pacemaker*

Portico and Pacing at 30D

- 10 patients (9.7%) received a PPM of those:
  - 4 patients with intra-operative rhythm disturbances had heart block which led to PPM at discharge
    - all 4 patients were free of rhythm disturbances during wire placement and valvuloplasty
  - 6 patients received PPM prior to discharge unrelated to intra-operative rhythm, caused by sinus arrest(1), sick sinus(1) or heart block (4)
  - Depth of implant was not statistically significant between those who did and did not receive a PPM after TAVI valve implantation

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

Portico and Pacing at 30D

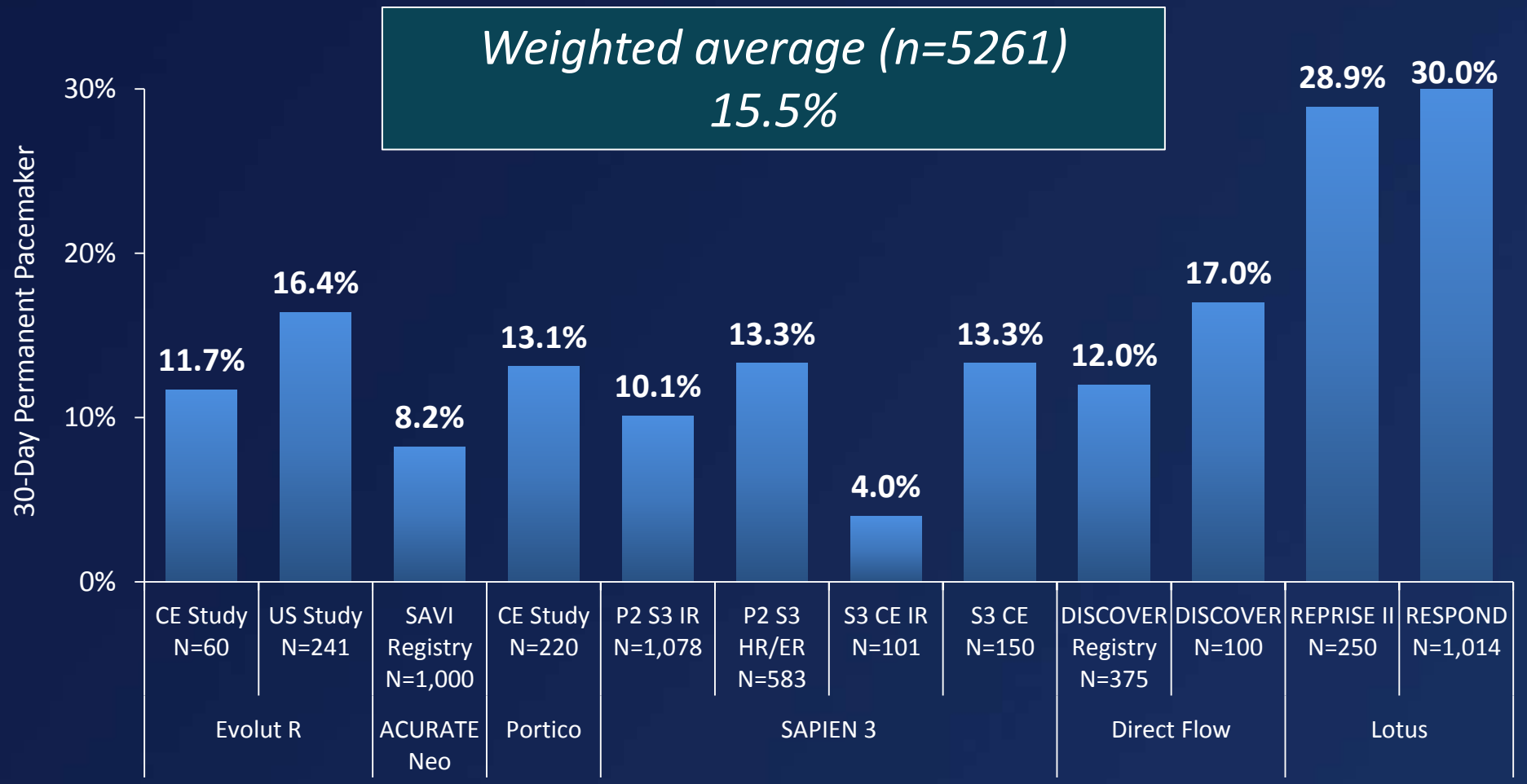
- 10 patients (9.7%) received a PPM of those:
  - Not related to new LBBB but pe-existence of RBBB (n=10) appears to increase risk (n=4)
  - Post dilatation appears to increase risk (50% of patients had post-dilatation)
  - Resheathing/repositioning does not appear to increase risk (n=3)

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

[1]Manoharan, et al., presented at TVT 2015

Permanent Pacemakers

Incidence with Contemporary Devices

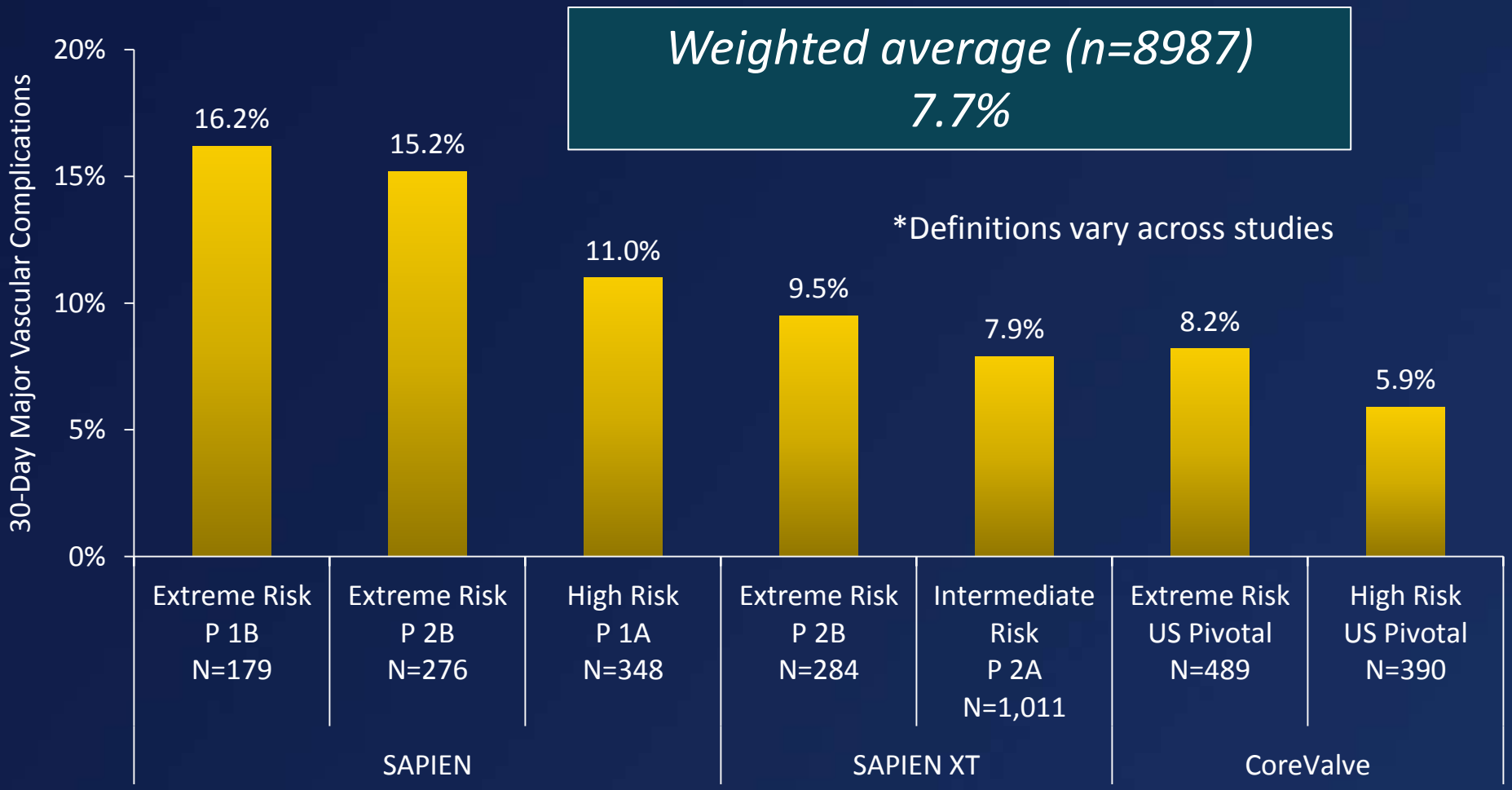


[1]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [2]Williams, et al., presented at ACC 2016; [3]Moellman, et al., presented at EuroPCR 2016; [4]Linke, et al., presented at PCR London Valves 2015; [5]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [6]Vahanian, et al., presented at EuroPCR 2015; [7]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [8]DeMarco, et al, presented at TCT 2015; [9]Lefevre, et al., *J Am Coll Cardiol Intv* 2016; 9: 68-75; [10]Meredith, et al., presented at PCR London Valves 2015; [11]Falk, et al., presented at EuroPCR 2016

Vascular Complications

Vascular Complications

Incidence with Foundation Devices



Minimum Vessel Diameter (mm)	8.0/7.0	7.0	8.0/7.0	7.0	6.0/6.5	6.0

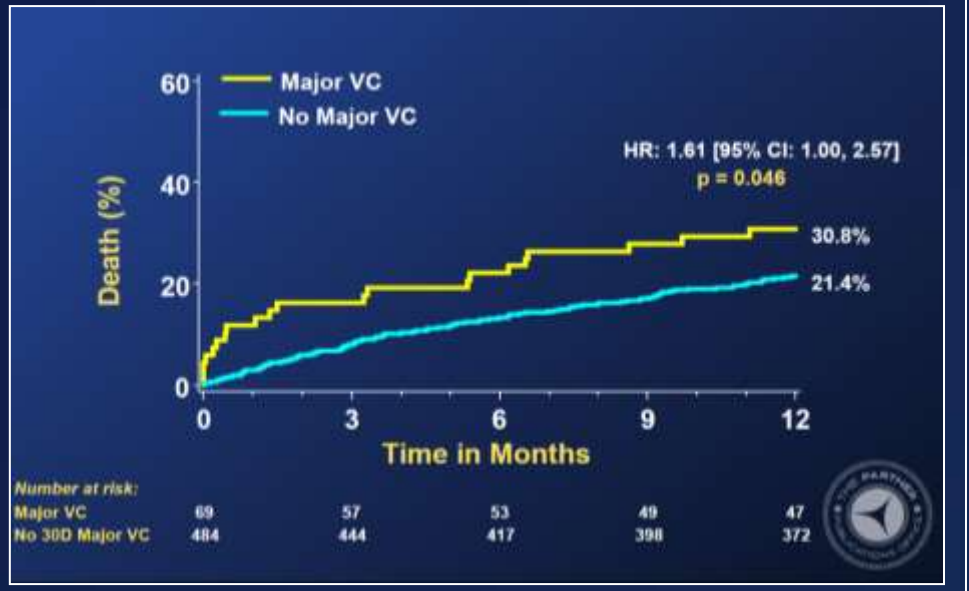
[1]Leon, et al., *N Engl J Med* 2010;363:1597-1607; [2]Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; [3]Smith, et al., *N Engl J Med* 2011;364:2187-98; [4]Leon, et al., *N Engl J Med* 2016;374:1609-20; [5]Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; [6]Adams, et al., *N Engl J Med* 2014;370:1790-8;;

Vascular Complications

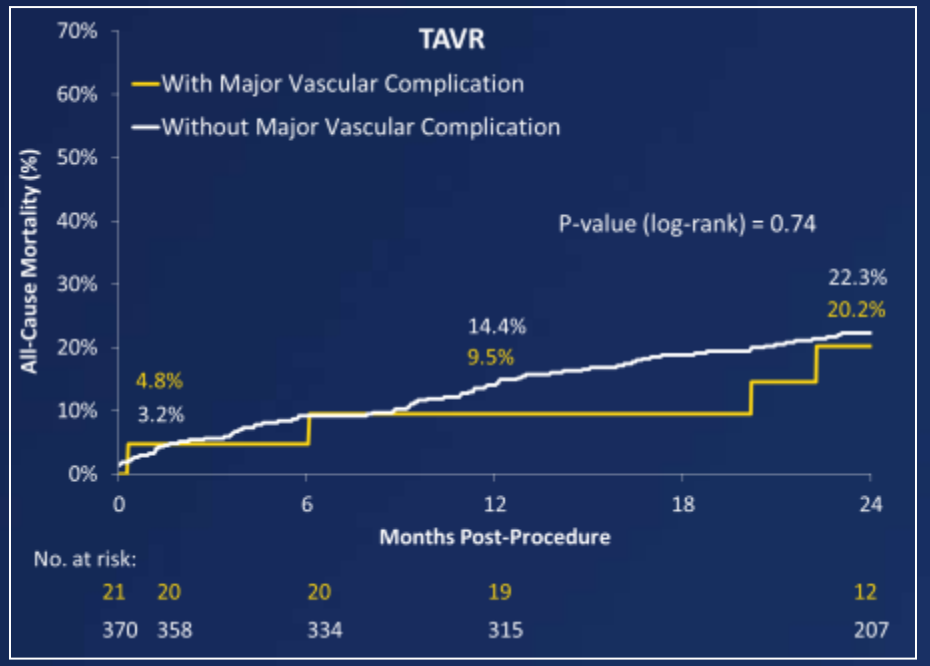
Why Do They Matter?

- *Patients experiencing a major vascular complication with SAPIEN or SAPIEN XT in PARTNER 2B had a significantly higher risk of death by 1 year compared to patients without a complication*
- *This was not the case in the CoreValve US Pivotal Trial. Vascular complications did not impact mortality.*
- *The smaller delivery systems with expandable and collapsible sheaths may lessen the severity of the complications, but supportive data is needed.*

PARTNER 2B



CoreValve US Pivotal Trial

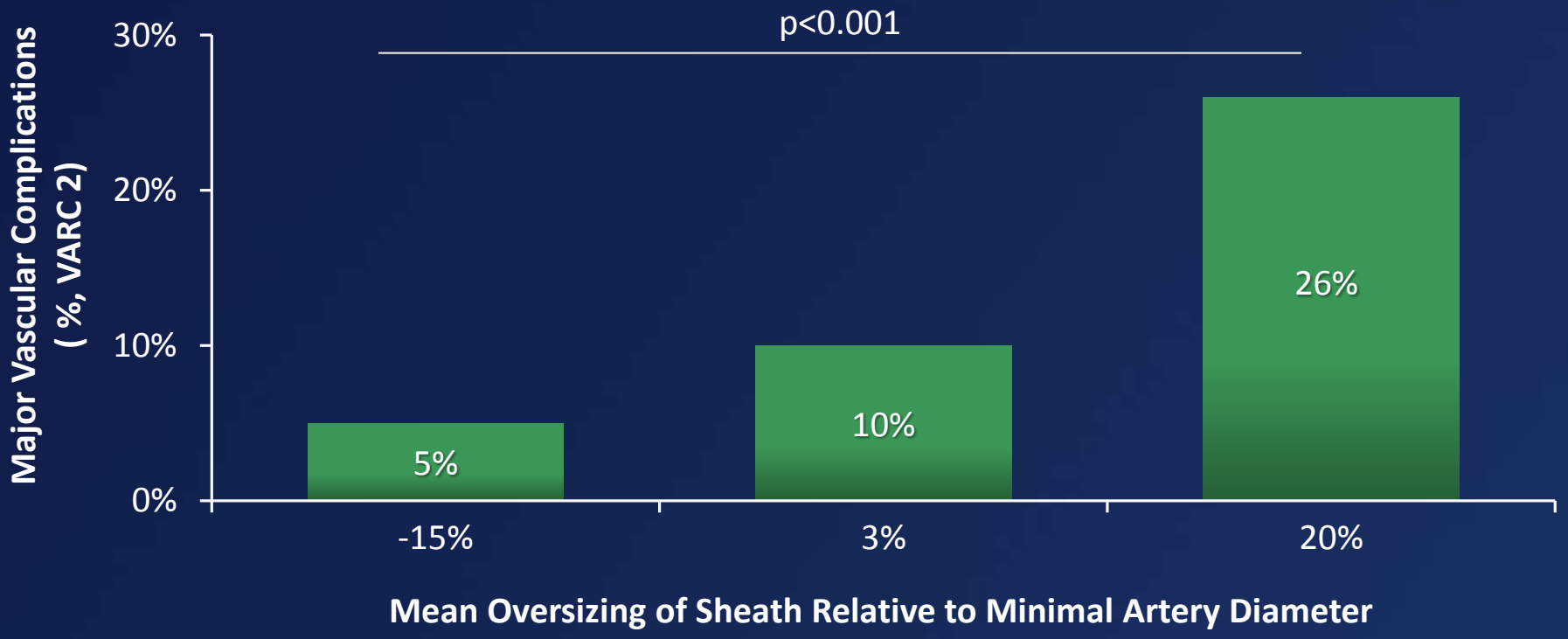


[1]Leon, et al., presented at ACC 2013; [2]Conte, et al., presented at WTSA 2016

Vascular Complications

Why Do They Happen?

- *High sheath to femoral artery ratio (SFAR)*
- *The University of Pennsylvania showed a linear relationship between major vascular complications and the degree to which the sheath is oversized relative to the minimal artery diameter.*

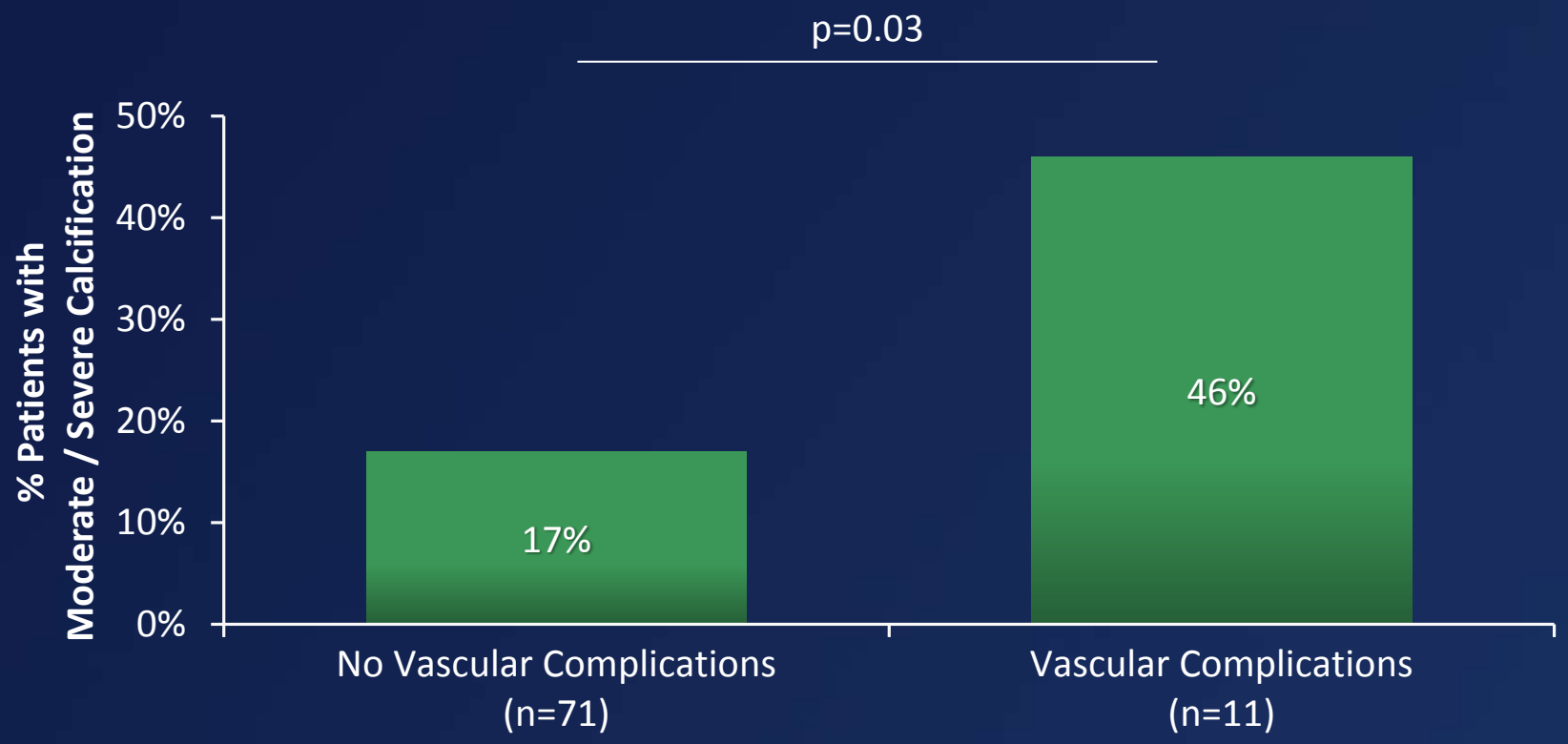


[1]Hayashida, et al., *J Am Coll Cardiol Cardiovasc Int* 2011; 4(8): 851-8; [2]Krishnaswamy, et al., *Catheter Cardiovasc Interv* 2014,[E-pub ahead of print], http://dx.doi.org/10.1002.ccd.25488; [3] Kadakia, et al., *Circ Cardiovasc Interv* 2014,[E-pub ahead of print], http://dx.doi.org/10.1161/circinterventions.113.001030

Vascular Complications

Why Do They Happen?

- *Calcification*
- *Toggweiler, et al[4]., showed that moderate / severe calcification is more common in patients that experience vascular complications.*

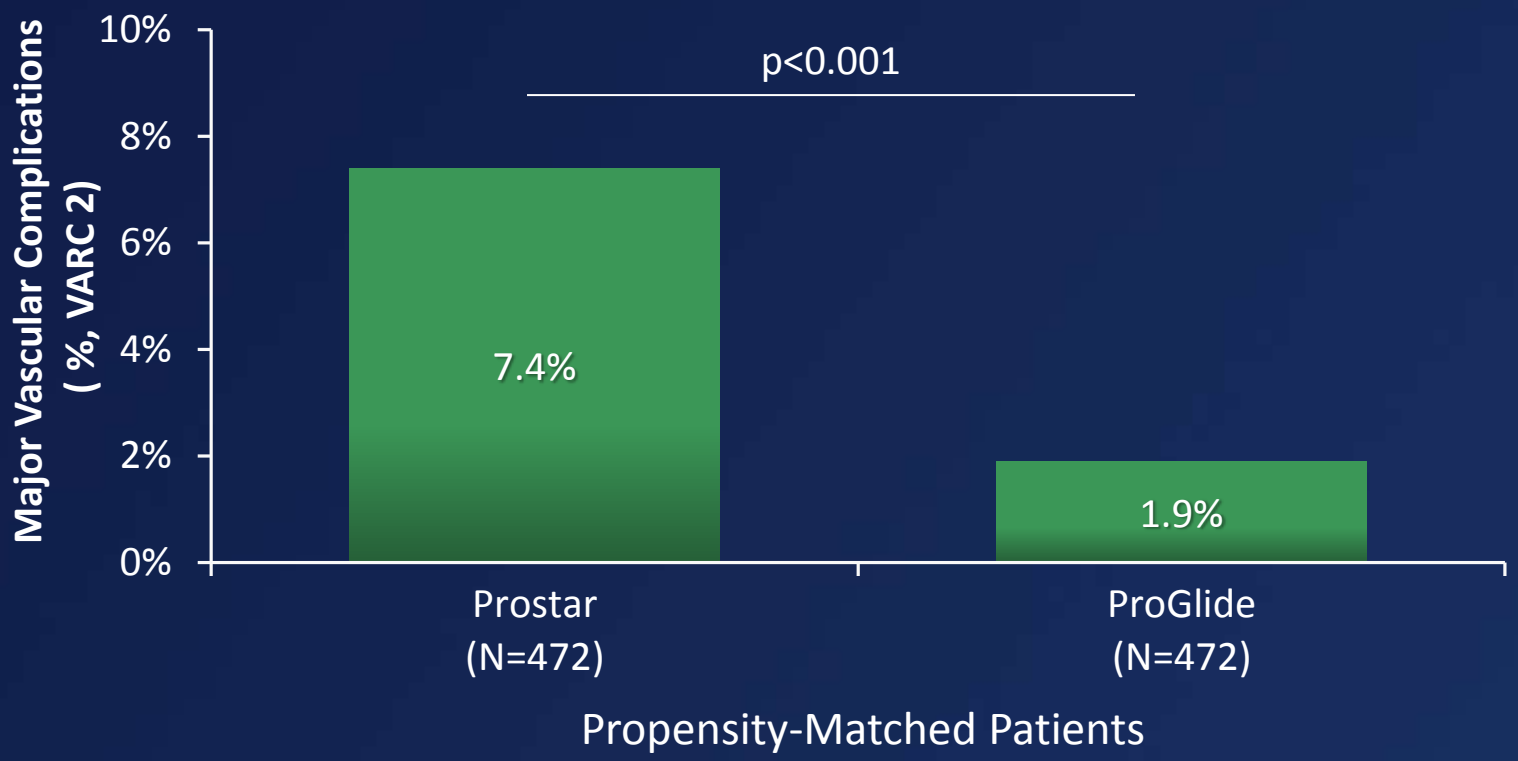


[1]Hayashida, et al., *J Am Coll Cardiol Cardiovasc Int* 2011; 4(8): 851-8; [2]Vavuranakis, et al. *Cardiovasc Ther* 2013; epub; [3]Krishnaswamy, et al., *Catheter Cardiovasc Interv* 2014,[E-pub ahead of print], http://dx.doi.org/10.1002.ccd.25488; [4]Toggweiler, *J Am Coll Cardiol* 2012; 59(2): 113-8

Vascular Complications

Why Do They Happen?

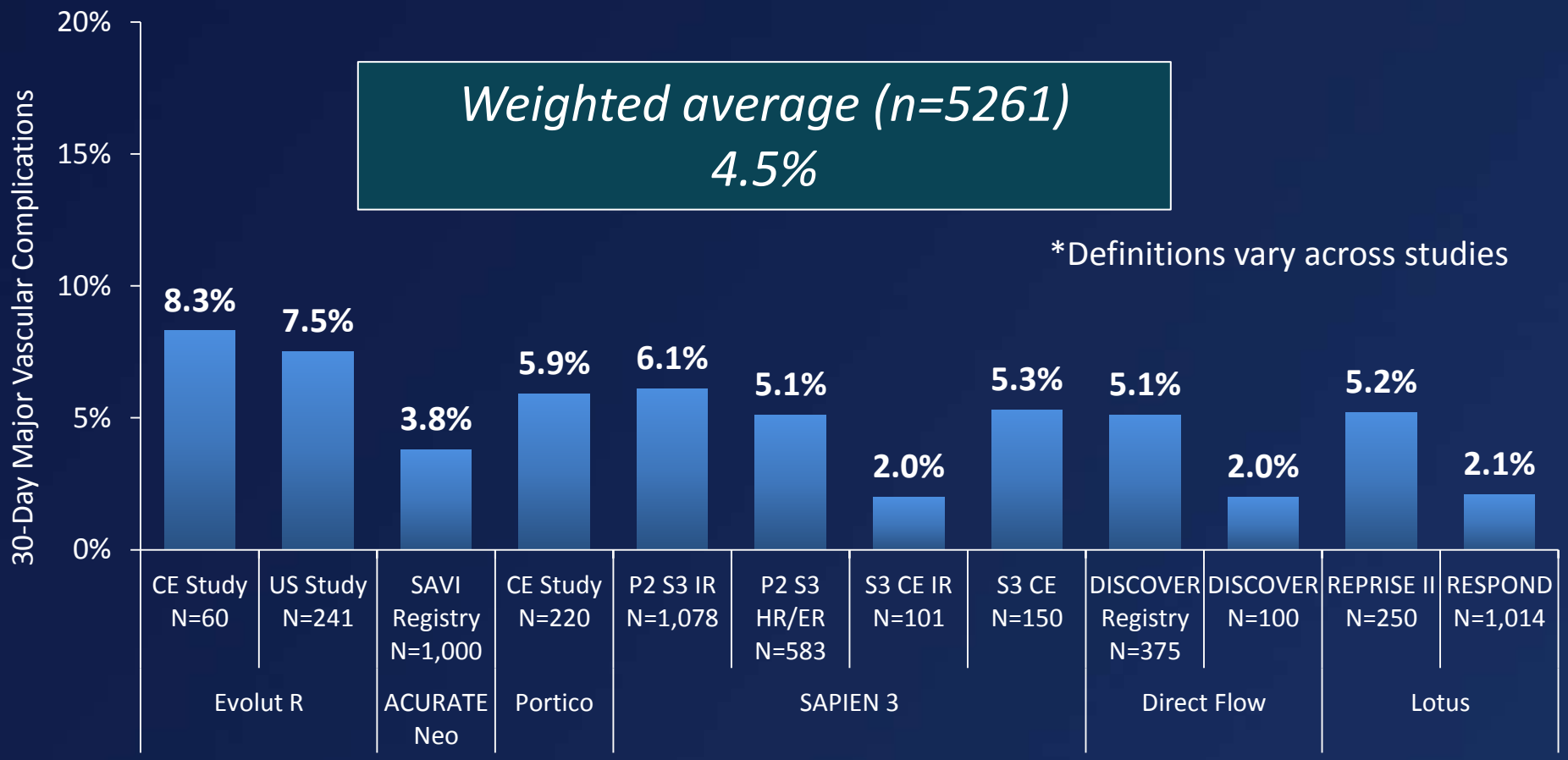
- *Closure device failure*
- *The randomized CONTROL Study demonstrated that major vascular complications due to closure device failure are significantly less common with ProGlide compared to Prostar*[2]



[1]Pichard, et al., presented at ACC 2014; [2]Barbash, et al., *Eur Heart J* 2015; epub ahead of print

Vascular Complications

Incidence with Contemporary Devices



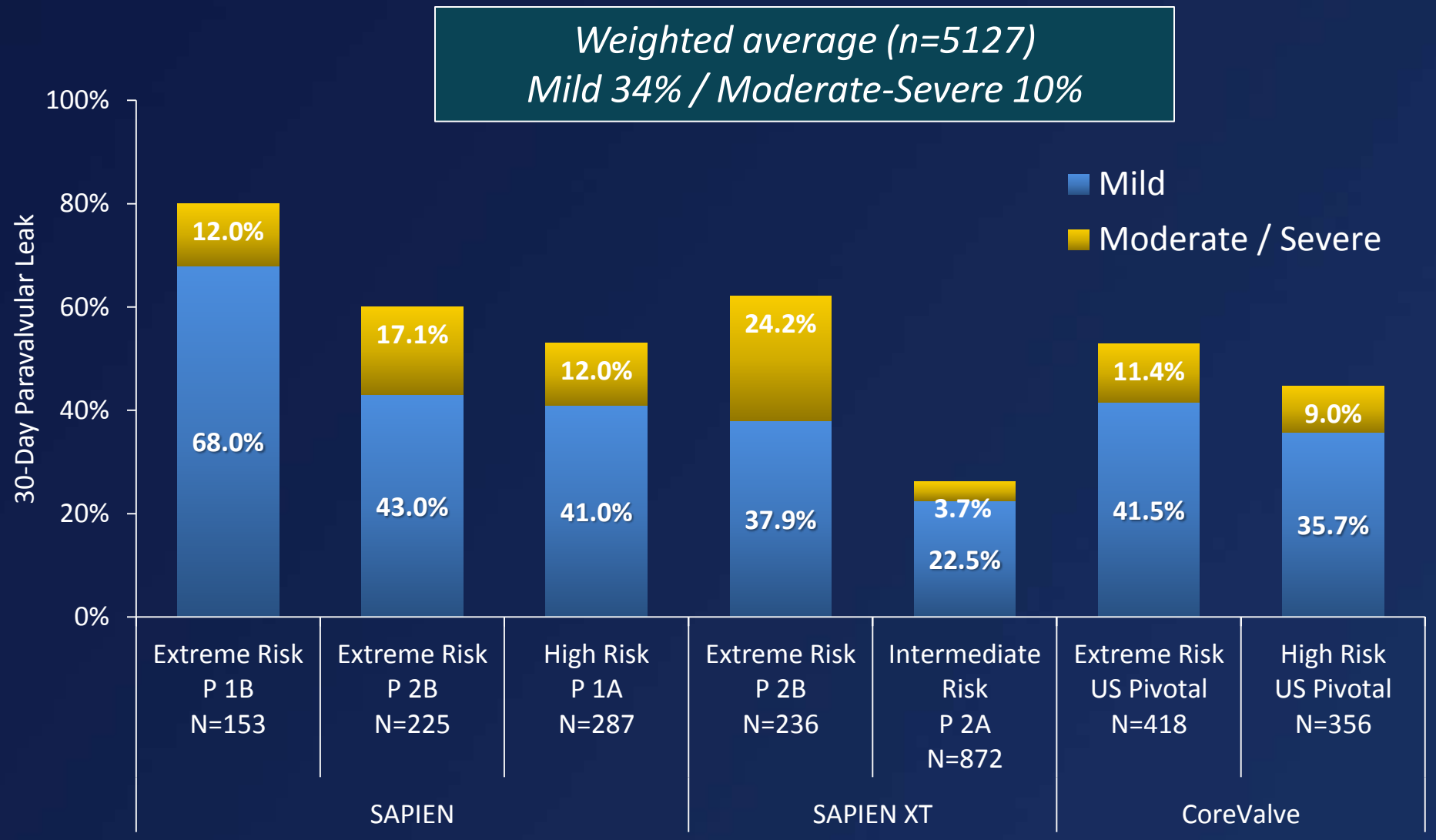
Minimum Vessel Diameter (mm)	5.0	6.0	6.0	5.5/6.0	6.0	6.0

[1]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [2]Williams, et al., presented at ACC 2016; [3]Moellman, et al., presented at EuroPCR 2016; [4]Linke, et al., presented at PCR London Valves 2015; [5]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [6]Vahanian, et al., presented at EuroPCR 2015; [7]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [8]DeMarco, et al, presented at TCT 2015; [9]Lefevre, et al., *J Am Coll Cardiol Intv* 2016; 9: 68-75; [10]Meredith, et al., presented at PCR London Valves 2015; [11]Falk, et al., presented at EuroPCR 2016

Paravalvular Leak

Paravalvular Leak

Incidence with Foundation Devices



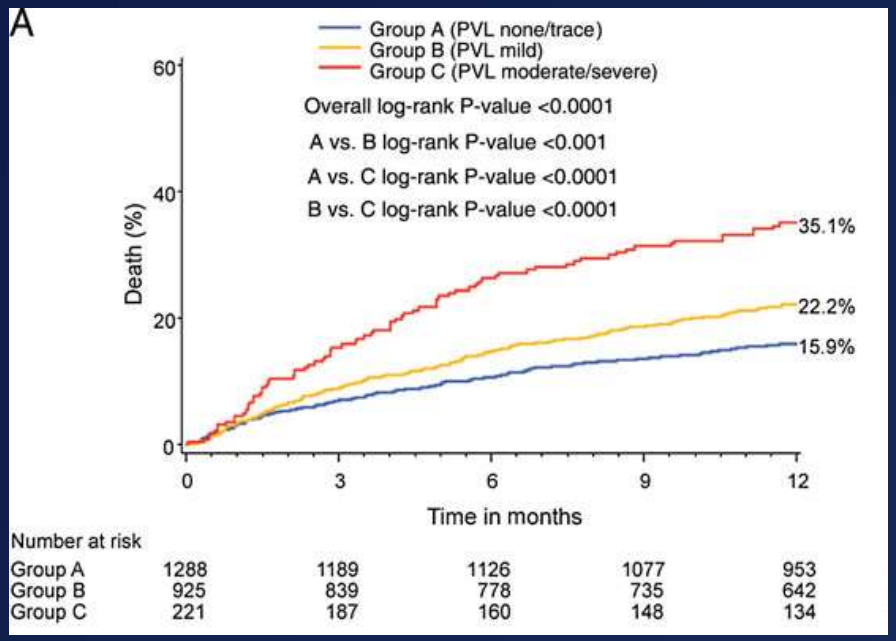
[1]Leon, et al., *N Engl J Med* 2010;363:1597-1607; [2]Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; [3]Smith, et al., *N Engl J Med* 2011;364:2187-98; [4]Leon, et al., *N Engl J Med* 2016;374:1609-20; [5]Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; [6]Adams, et al., *N Engl J Med* 2014;370:1790-8;;

Paravalvular Leak

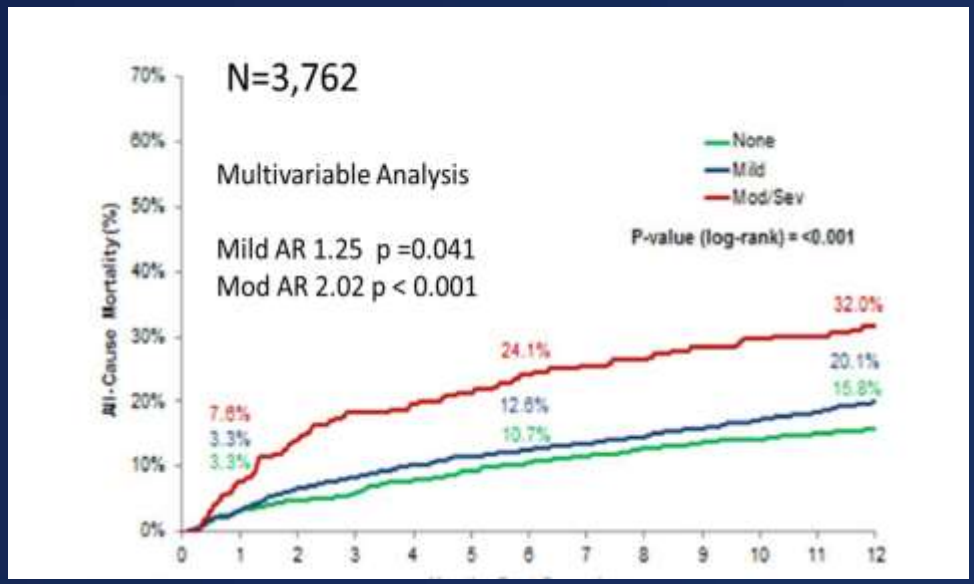
Why Does it Matter?

- *Moderate / severe PVL is a multivariable predictor of all-cause mortality across multiple studies, increasing the risk by approximately 2x.*
- *Mild PVL impacted 1-year mortality in both PARTNER and the CoreValve US Pivotal Trial, but to a lesser extent*

PARTNER



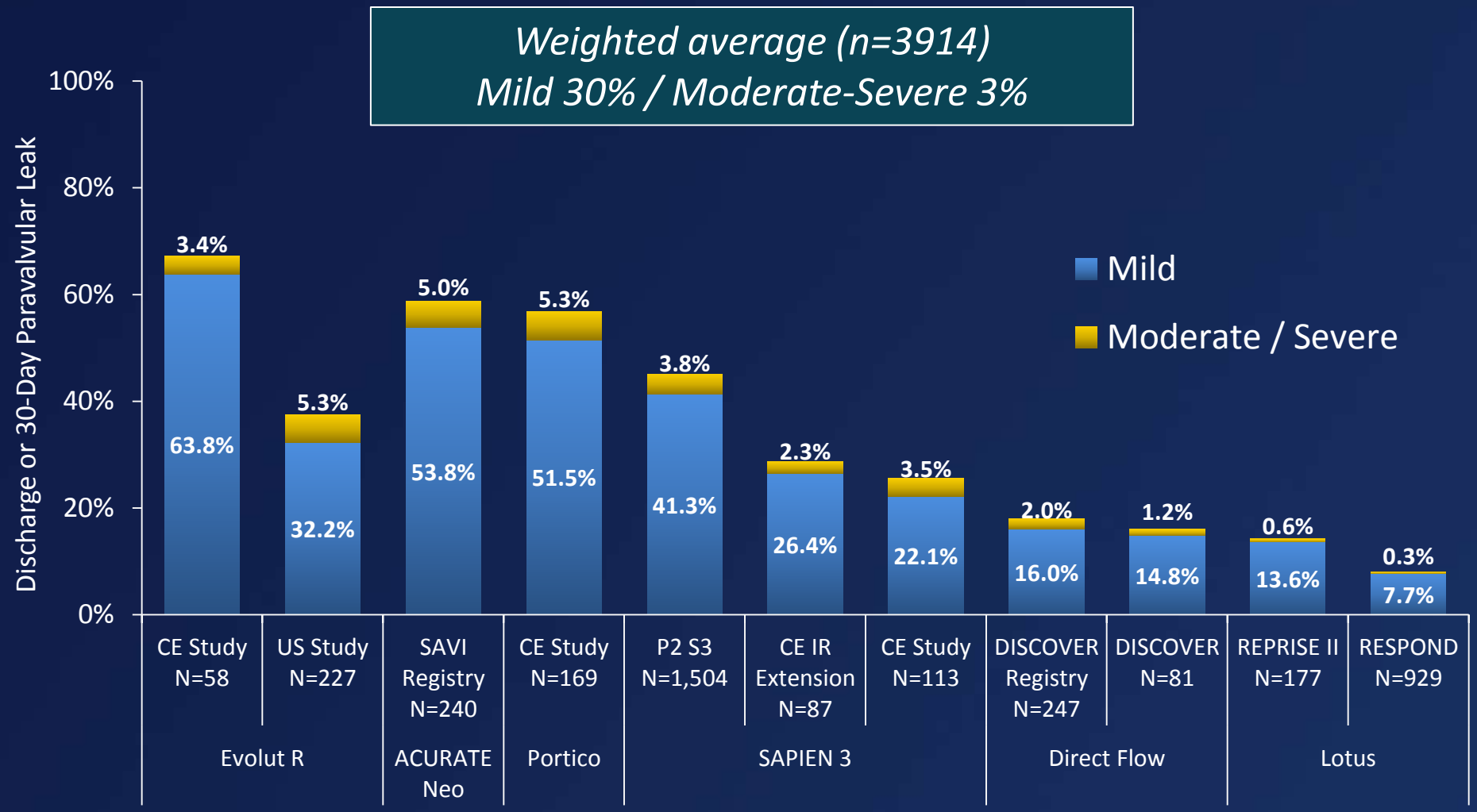
CoreValve US Pivotal Trial



[1]Kodali S, et al., *Eur Heart J* 2015; 36: 449-456; [2]Popma, et al., presented at TVT 2016

Paravalvular Leak

Incidence with Contemporary Devices

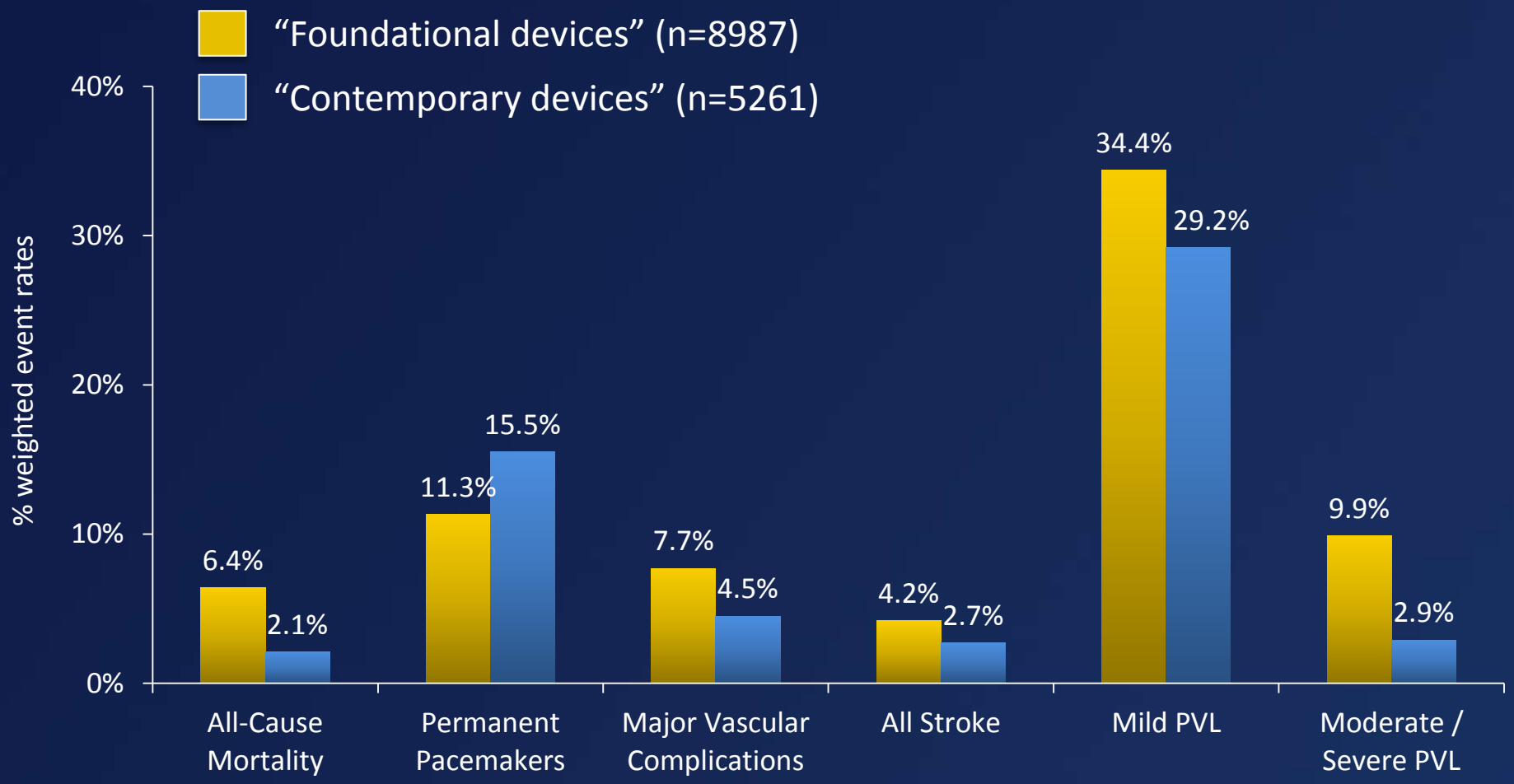


[1]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [2]Williams, et al., presented at ACC 2016; [3]Moellman, et al., presented at PCR London Valves 2015; [4]Linke, et al., presented at PCR London Valves 2015; [5]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [6]Vahanian, et al., presented at EuroPCR 2015; [7]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [8]DeMarco, et al, presented at TCT 2015; [9]Lefevre, et al., *J Am Coll Cardiol Intv* 2016; 9: 68-75; [10]Meredith, et al., presented at PCR London Valves 2015; [11]Falk, et al., presented at EuroPCR 2016

Overall, How Did We Do?

Summary

Weighted Event Rates



Foundational devices include CoreValve, Edwards SAPIEN, SAPIEN XT and contemporary devices include Evolut R, SAPIEN 3, Acurate Neo, Portico, Direct Flow, LOTUS

Thank you for your kind attention!

Final Thoughts

- Compared with foundation devices, contemporary TAVR devices are designed with lower delivery profile and features to reduce PVL.
- These design goals seem to have been realized:
  - Transfemoral access can be achieved in approximately 90% of TAVR patients without any increase in vascular complication rate.
  - The rate of moderate / severe PVL is approaching zero!
  - Stroke has decreased slightly, which may be a result of the smaller delivery systems
- Still the overall rate of mild PVL is unchanged at approximately 30%, and this may be prognostically important.
- Some new devices have brought the overall rate of permanent pacemaker implantation up, and this needs to be addressed.
- Continued device and procedural evolution will be necessary in the future.