Monitoring Conduction Disturbance and Avoiding Permanent Pacemaker

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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

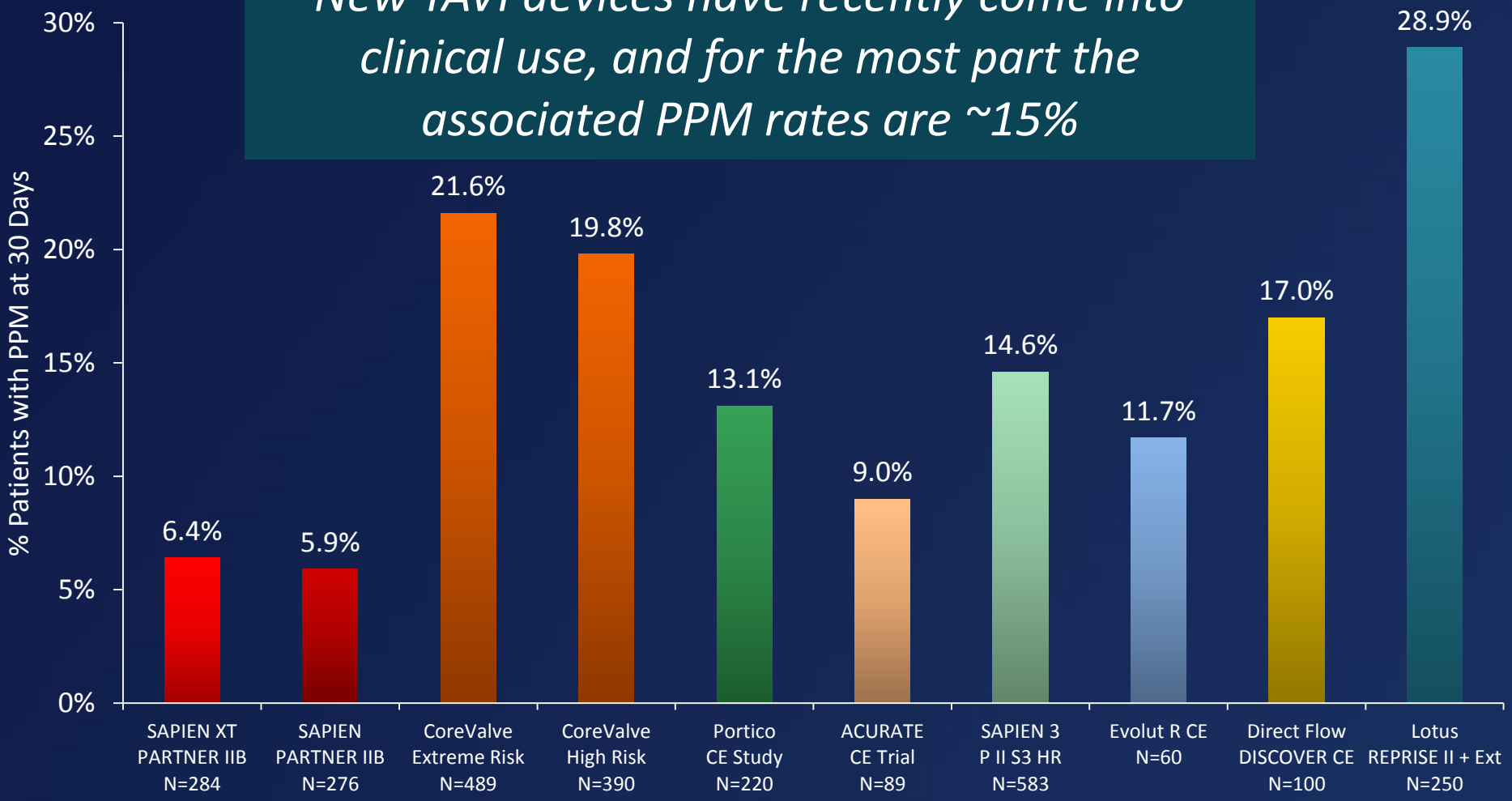
G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board
C – Consulting fees, Honoraria R – Royalty Income I – Intellectual Property Rights
SB – Speaker' s Bureau O – Ownership OF – Other Financial Benefits '

Incidence of new permanent pacemakers after TAVI

Permanent Pacemakers

Rate at 30 Days

New TAVI devices have recently come into clinical use, and for the most part the associated PPM rates are ~15%

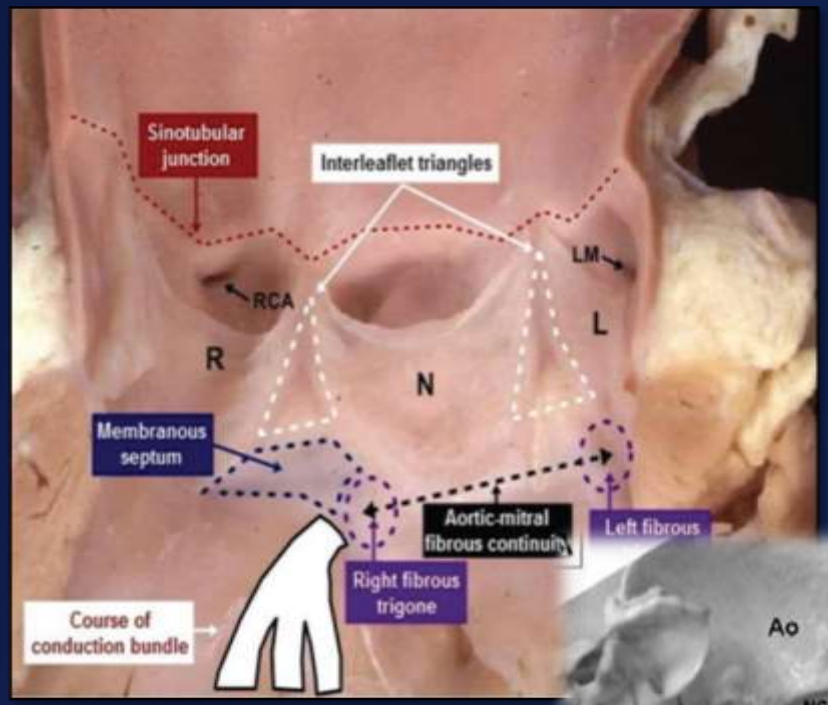


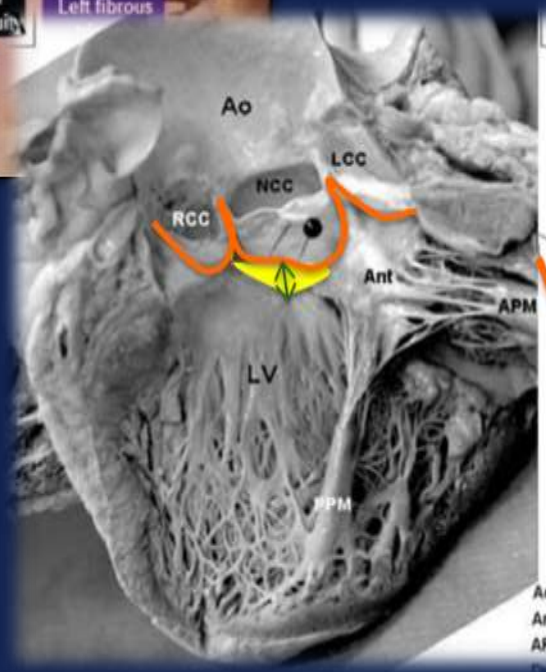
[1]Leon, et. al. presented at ACC 2013; [2]Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; [3]Adams, et al., *N Engl J Med* 2014; 370: 1790-8; [4]Linke, et. al. presented at PCR London Valves 2015; [5]Abizaid, et al., presented at CRT 2015; [6]Kodali, et al., presented at ACC 2015; [7]Manoharan, et al., presented at TCT 2015; [8]Naber, et al., presented at EuroPCR 2015; [9]Vahanian, et al., presented at EuroPCR 2015; [10]Schofer, et al., *J Am Coll Cardiol* 2014; 63: 763-8; [11]Meredith, et al., presented at PCR London Valves 2014

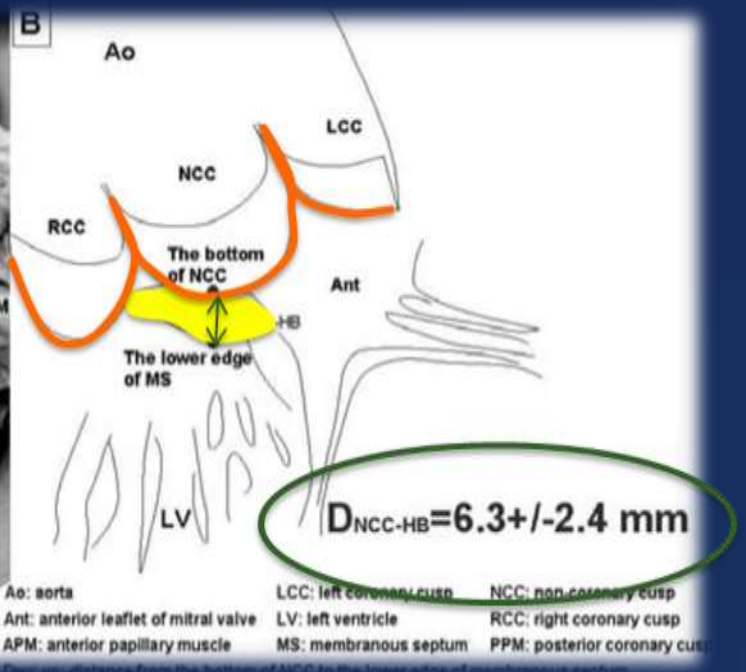
Driving Factors

Anatomy

- *Close proximity of the aortic valve to the cardiac conduction system[1]*
- *Distance between non-coronary cusp and His-bundle: on average, 6.3 mm*
- *Distance varies among individuals, but is usually <10 mm*







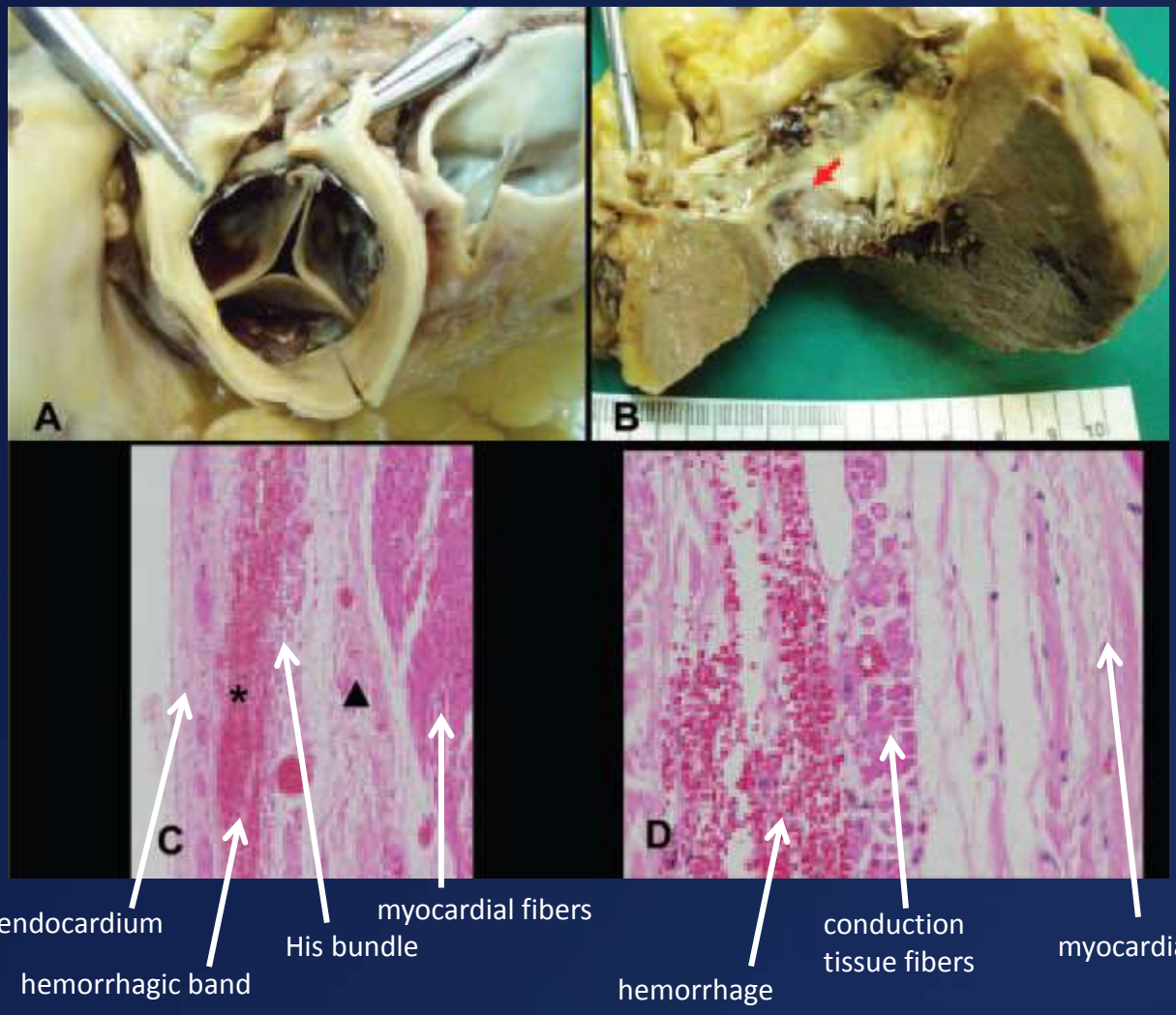
[1] Igawa O., et al., *Circ J* 2009; 73 Suppl I: 257.

Anatomy

- *Prosthetic valves may contact the conduction system, causing injury (inflammation, or in this case, hemorrhage)*[1]

Appropriately implanted **Edwards Sapien** valve:

Following removal of prosthetic valve, hemorrhagic lesions observed



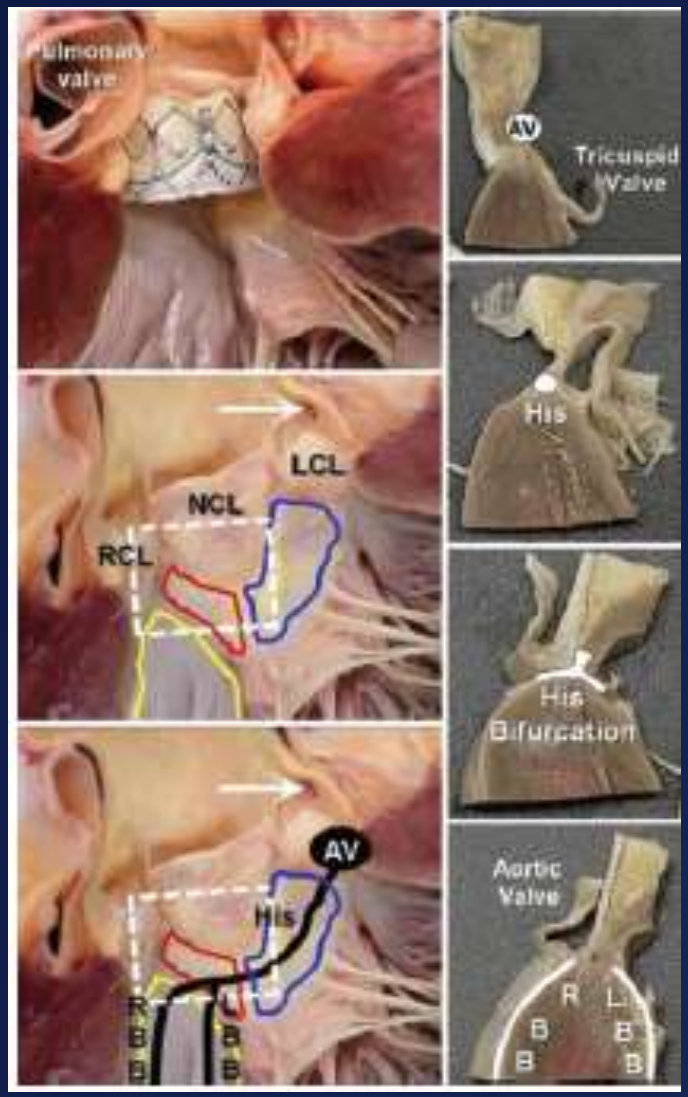
Hematoxylin and eosin, x10

Hematoxylin and eosin, x40

[1] Moreno R., et al., *Circ ulation* 2009; 120: e29-30.

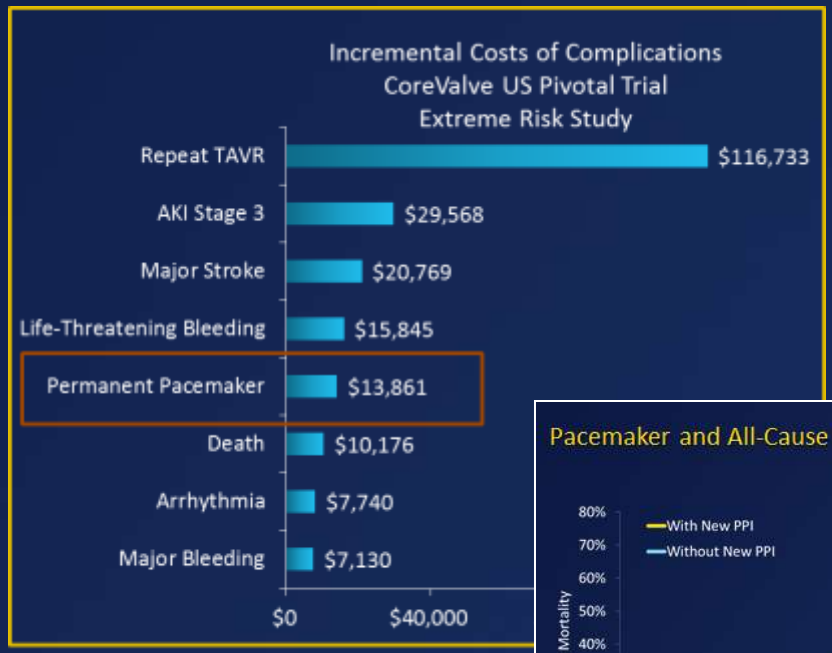
Permanent Pacemakers

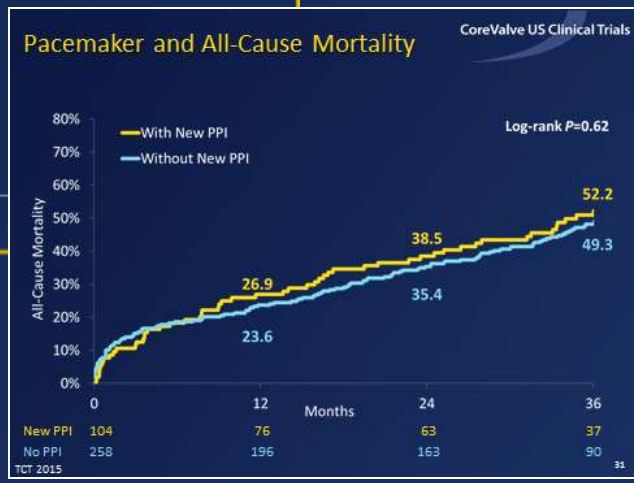
Anatomical Connection



White box represents location of the valve

- *New pacemakers do not impact mortality out to 3 years post TAVR, but they do add procedural costs.*





[1]Bax, et al., *Eur Heart J* 2014; [2]Baron, et al., presented at TCT 2014

Reducing PPI| Impact of Learning Curve

Effect of learning curve: the rate of Permanent Pacemaker Implantation in the CoreValve Australia-New Zealand Study decreased over time as operators gained experience

PPM rates in 6-mo blocks of pt enrollment, except most recent is 8-mo.

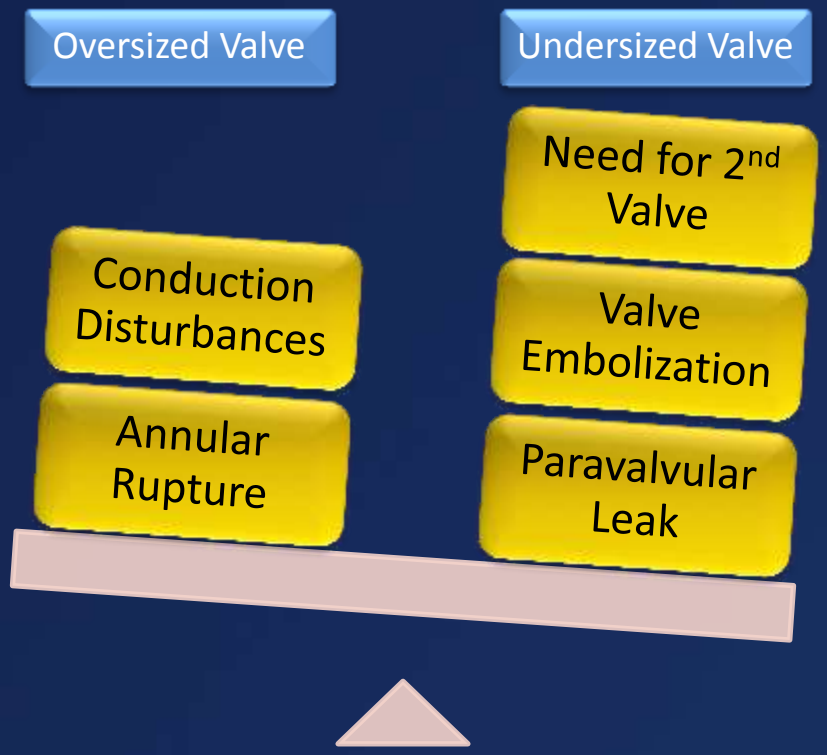
[1]Muller, et al. Presented at EuroPCR 2013

Valve Selection

A Patient-Centered Approach

MSCT is the gold-standard tool for pre-TAVI assessment of aortic root anatomy. It should be used in all indicated cases.

- *Assess annulus geometry*
- *Identify adverse features which may precipitate PVL, annular rupture, or coronary occlusion*
- *Select an appropriate bioprosthesis type and size.*
    - *In cases where the valve is on the borderline between two sizes, the relative complication risks should be considered for the individual patient*



[1]Dvir, et al., *Catheter Cardiovasc Interv* 2015;86:508-15

Historical Predictors

- *Well over 40 studies have been published on predictors of post-TAVI conduction disturbances and permanent pacemaker implant*
- *Studies varied in size, rigor, and the univariable characteristics which were considered, but some central themes emerged:*

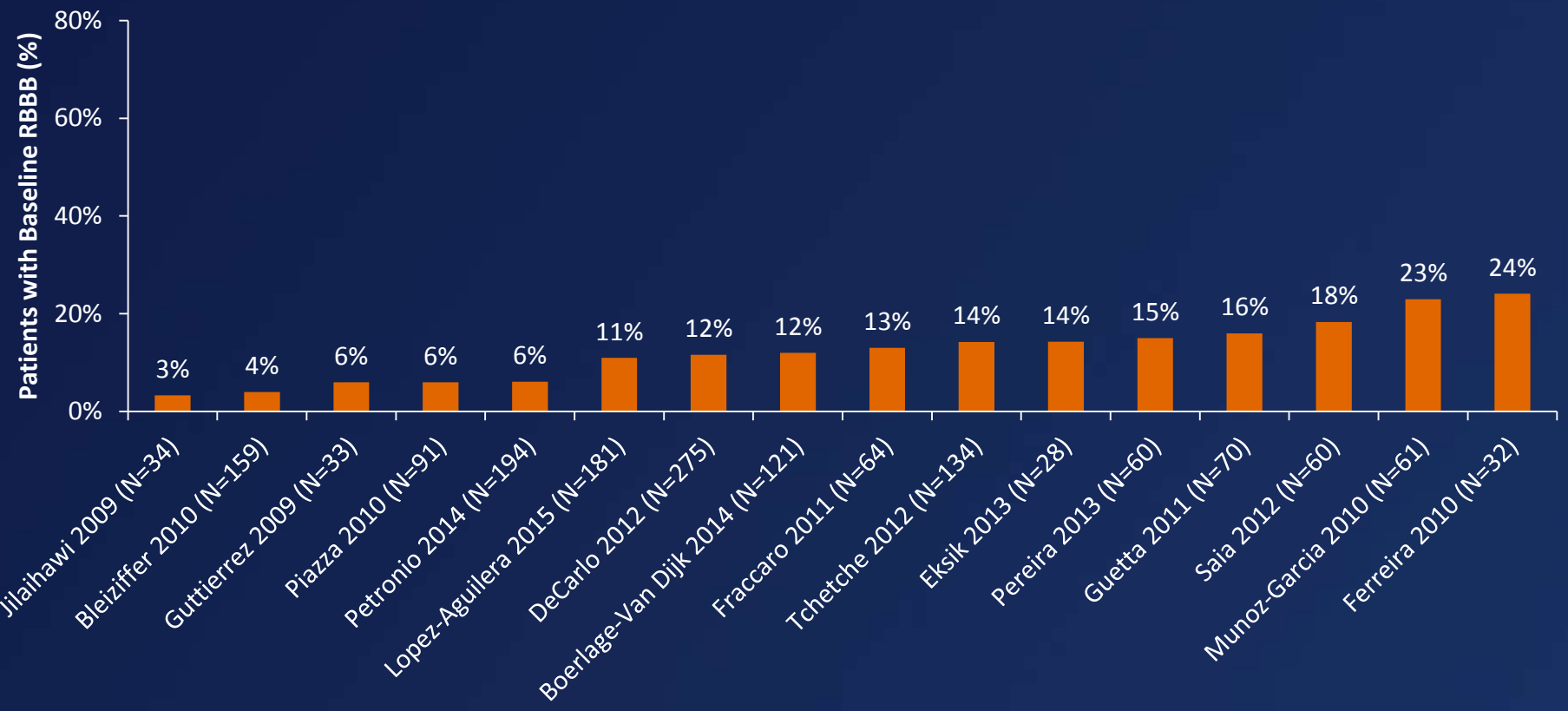
Clinical	Anatomical	Procedure and Operator-Related
• Male gender[3]	• Variations in location of LBBB exit point[1]	• Radial force of the prosthesis[3]
• Age > 75 years[9]	• Septum thickness[1,6]	• Implant Depth[2,3,7,12]
• Previous MI[3]	• Thickness of the non-coronary cusp[1]	• Balloon Aortic Valvuloplasty[8]
• Right Bundle Branch Block (RBBB)[2,3,4,5,7]		• Application of PPI guidelines[10]
• Other pre-existing conduction disturbances[3,4,8,9]		• Learning Curve[11]

[1]Jilaihawi, et al. Am Heart J 2009; [2]Munoz-Garcıa, et. al. JACC CV 2012; [3]Piazza et. al. EuroIntervention 2010; [4]De Carlo , et. al. Am Heart J 2012; [5]Calvi, et. al. JICE 2011; [6]Saia, et. al. Cath Card Intv 2012; [7]Fraccarao, et. al. Am J Card 2011; [8]Khawaja, et. al. Circ 2011; [9]Schroeter et. al. EuroPACE 2011; [10]Wenaweser, et. al. presented at EuroPCR 2013; [11]Meredith, et. al. presented at TCT 2012. 12Petronio, et al., J Am Coll Cardiol Intv 2015; 8: 837-46,

Predictor of Permanent Pacemaker

Right Bundle Branch Block at Baseline

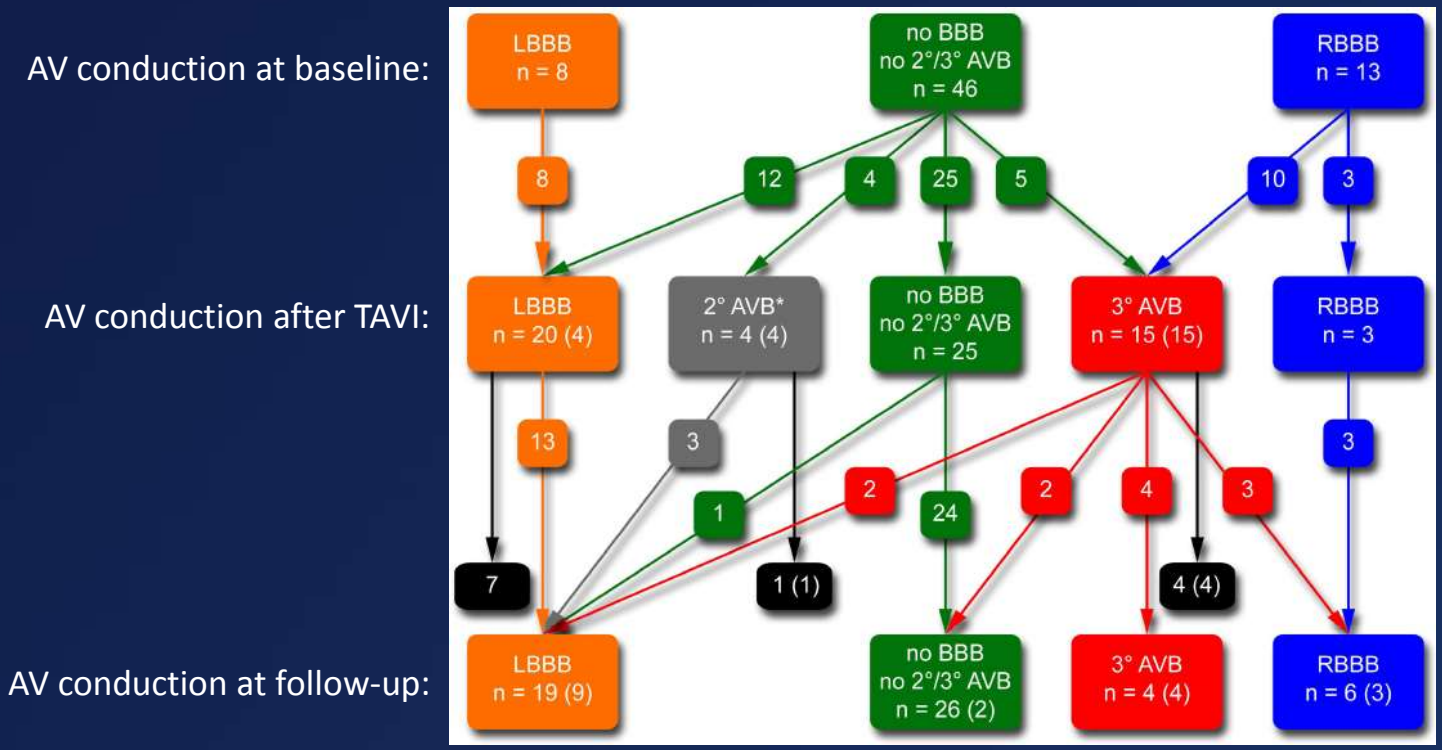
- *Right bundle branch block at baseline is one of the strongest predictors of complete AV block and permanent pacemaker implantation*
- *The incidence is known to vary by cohort, but can reach 24%*



Predictor of Permanent Pacemaker

Right Bundle Branch Block at Baseline

- *This chart demonstrates how pre-existing RBBB can contribute to the formation of 3°AV block if the patient develops LBBB during TAVI*



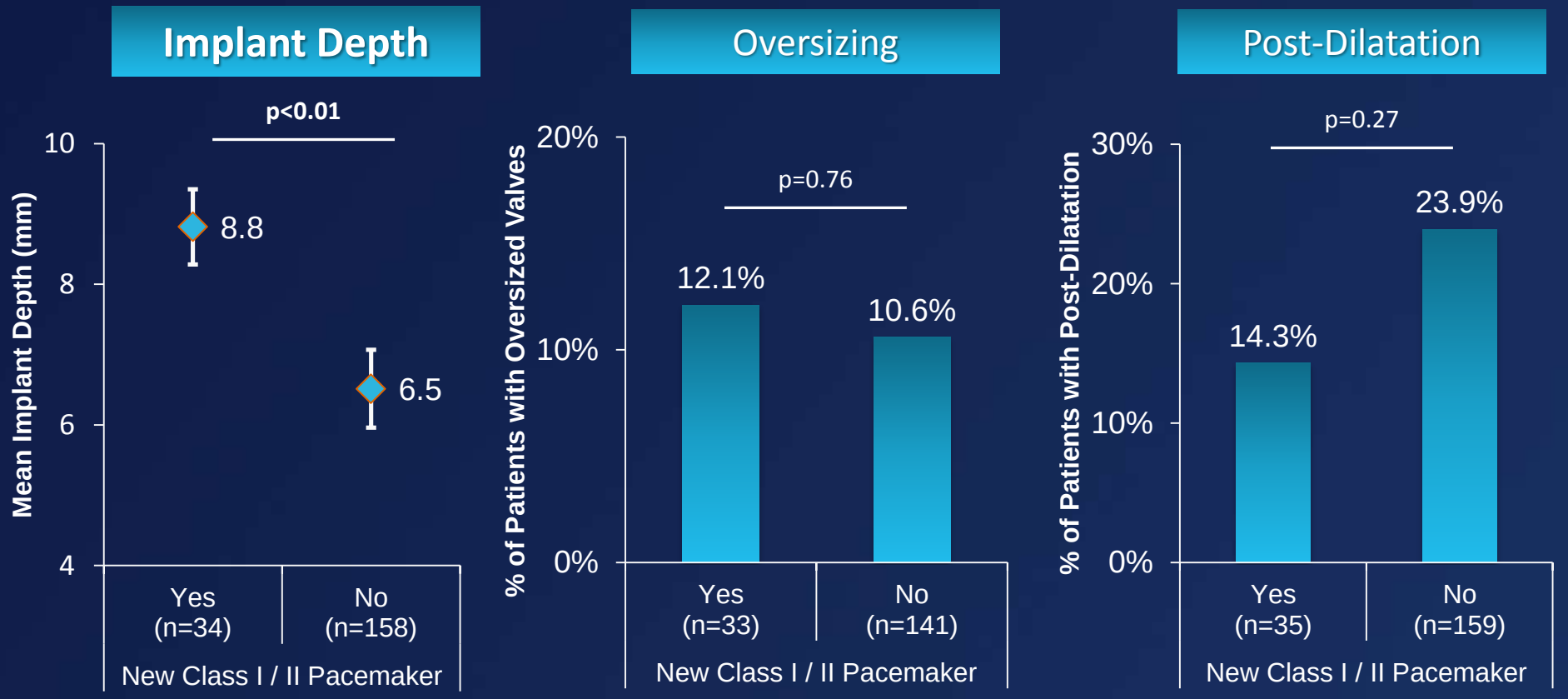
- Black boxes = pts w/o follow-up , ▪ # in parentheses = pts with PPI

Roten et. al., Am J Card 2010

Predictors of Permanent Pacemaker for CoreValve

Implant Depth

- *The ADVANCE II study showed that implant depth is the strongest modifiable factor which predicts PPM with CoreValve. Note that oversizing and Post Dilatation does not lead to PPM with this valve.*



Error bars are standard error

Implant depth defined as the distance from the lower edge of the non-coronary leaflet to the ventricular edge of the frame

*Oversizing occurs when a valve is implanted in an annulus that is smaller than the range defined by the CoreValve sizing guide

% Oversizing = 100 x ([Perimeter of CoreValve– CT Derived Perimeter of the Annulus] / CT Derived Perimeter of the Annulus)

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

Predictors of Permanent Pacemaker for Lotus

- *A sub-analysis from REPRISE II indicates that overstretching is the strongest modifiable predictor of permanent pacemakers for the Lotus valve, especially in calcified anatomies.*

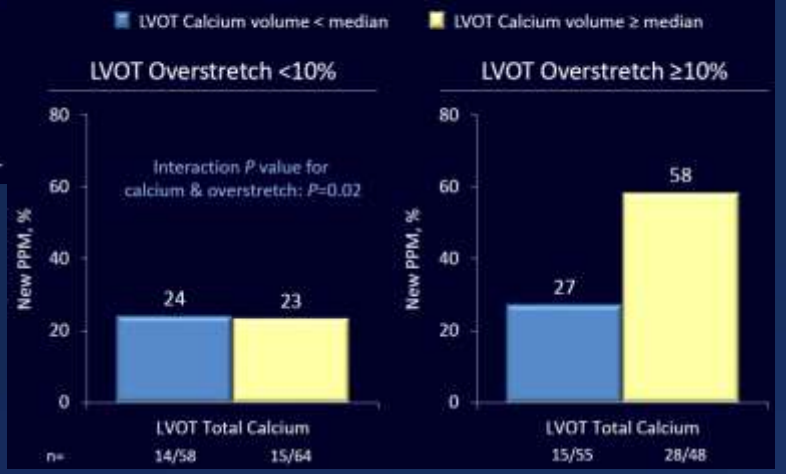
Significant Multivariate Predictors

REPRISE II Extension 30d Pacemaker Analysis (N=250)

Variable	Odds Ratio	95% CI	*P* value
Baseline RBBB	12.70	4.45, 36.22	<0.001
LVOT area overstretch ≥10%	3.42	1.74, 6.74	<0.001
1st degree AV block	2.49	1.13, 5.47	0.02
LVOT total calcium volume, per 100 mm^3 increase	1.80	1.03, 3.14	0.04

LVOT Overstretch & Calcium Severity

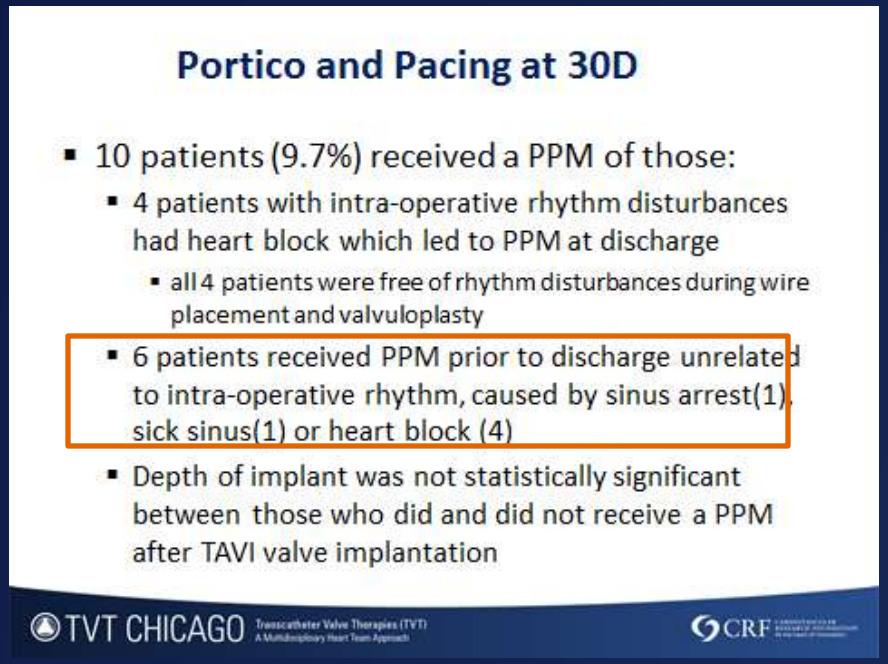
REPRISE II Extension 30d Pacemaker Analysis (N=250)

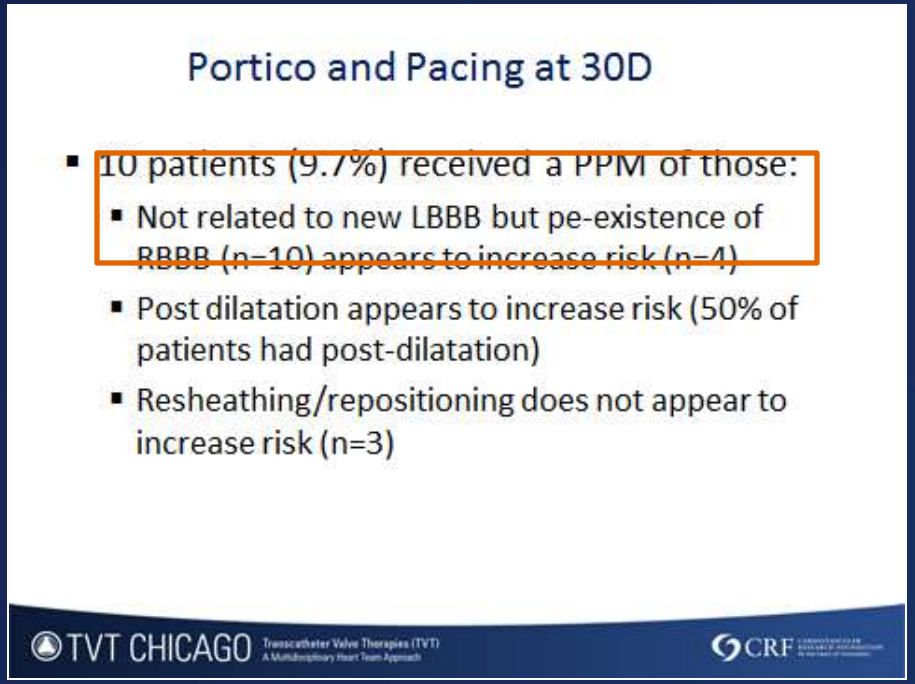


[1]Dumonteil, et al., presented at ACC 2015

Predictors of Permanent Pacemaker for 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*





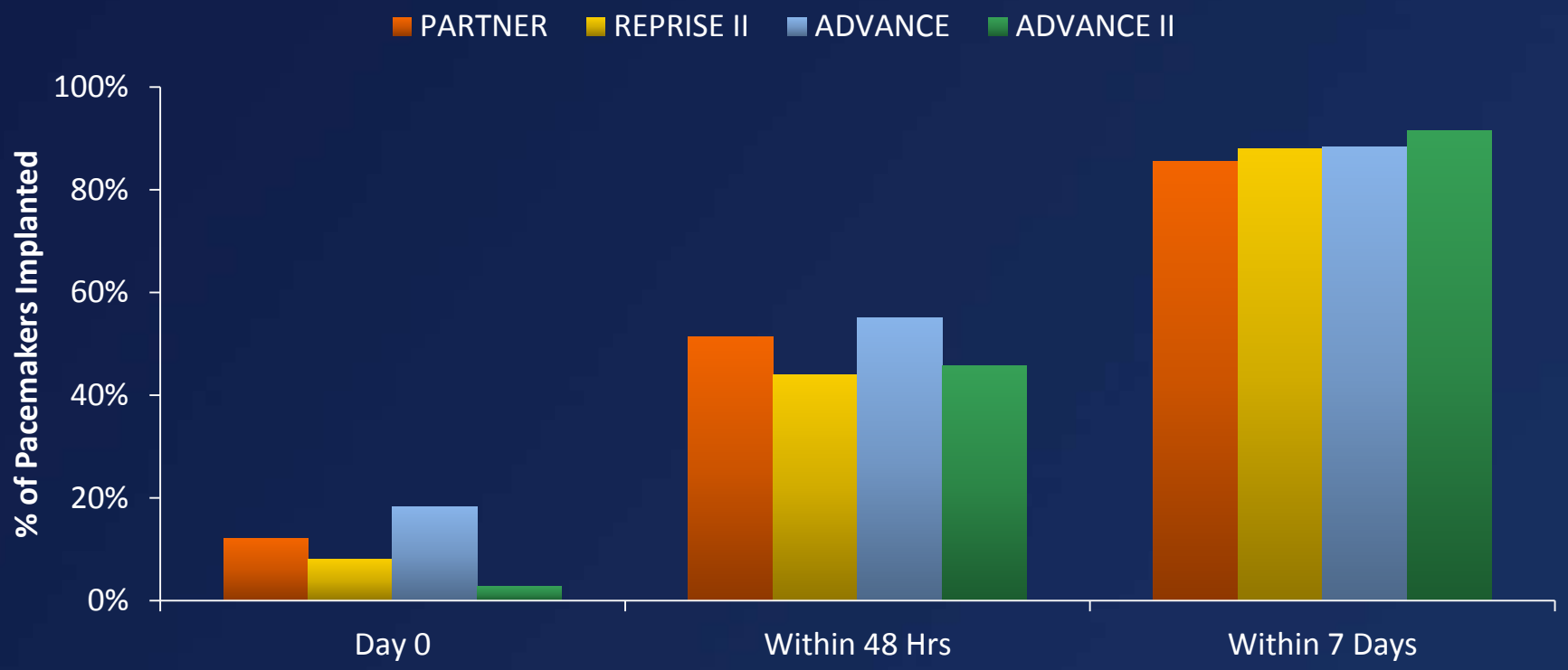
[1]Manoharan, et al., presented at TVT 2015

Timing of Permanent Pacemaker Implantation

Permanent Pacemaker Implantation

Time Course

- *The time course of permanent pacemaker implantation was similar across 4 different clinical trials using 3 different valve types (SAPIEN, Lotus, and CoreValve)*
- *50% of the pacemakers were implanted within 48 hours of TAVI, while 90% were implanted within 7 days.*



[1]Nazif T, et al., *J Am Coll Cardiol Intv* 2015; 8:60-9; [2]Medtronic Data on File; [3]Petronio, et al., presented at EuroPCR 2014; [4]Dumonteil, et al., presented at ACC 2015

Clinical Impact of Permanent Pacemaker Implantation

Clinical Impact of New PPM

All-Cause Mortality

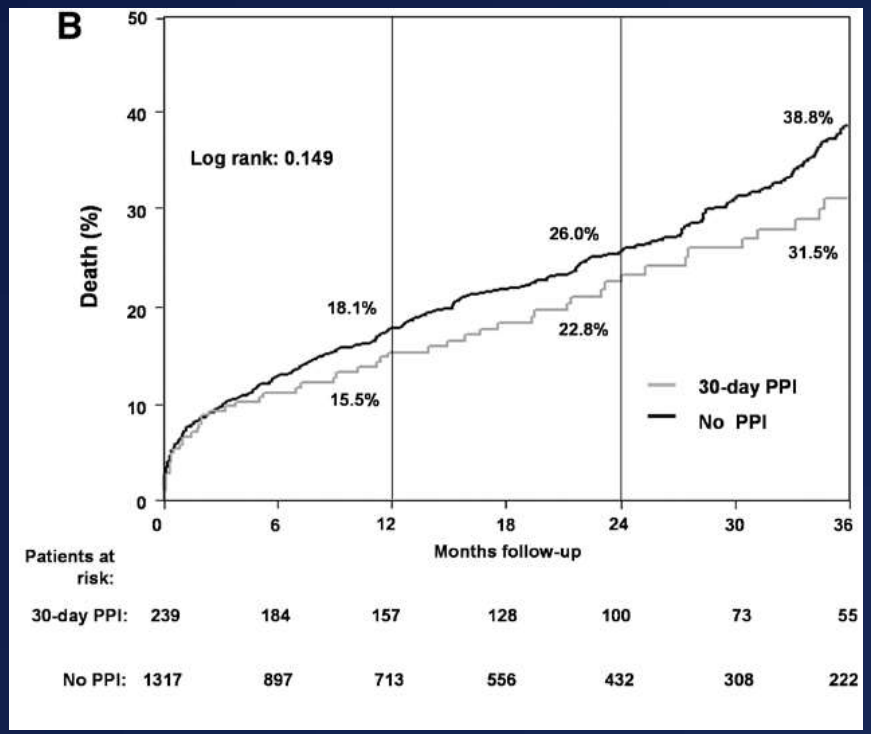
Studies out to 3 years have shown no negative impact of PPM on all-cause mortality

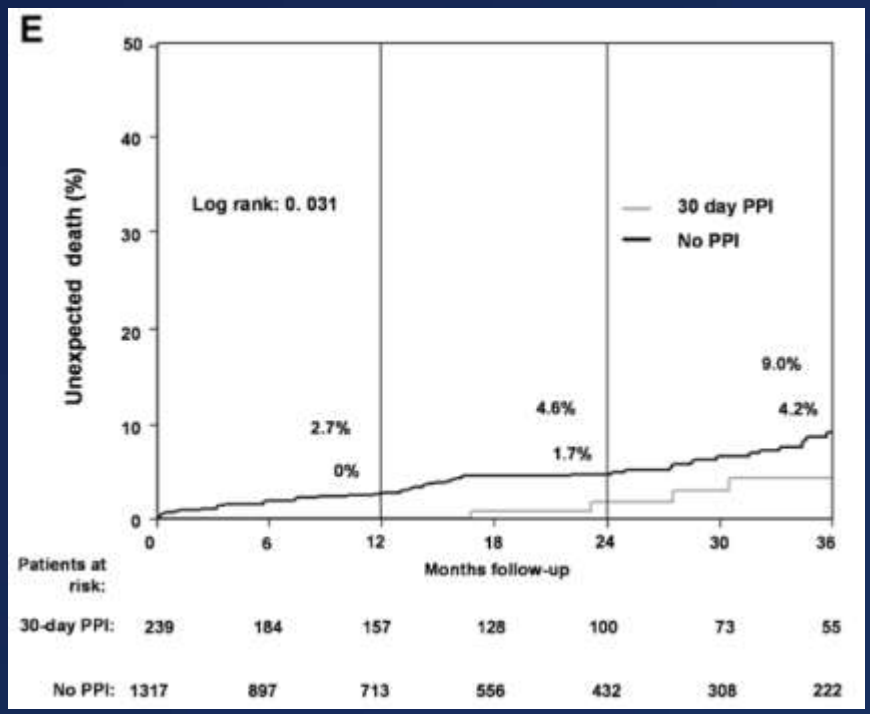
Study	Valve Type, N	30 Day PPM Rate	% of PPMs Implanted for HD or complete AVB	Follow-up	Pacing at Follow-up	Impact of PPM on All-cause Mortality
De Carlo[1]	CoreValve N=275	25.5%	73.5%	1 year	NR	None (p=0.90)
Buellesfeld[2]	CoreValve N=319 Edwards N=34	27.8%	62.2%	1 year	NR	None (p=0.77)
Pereira[3]	CoreValve N=65	32.8%	84.2%	1 year	Mean ventricular pacing 49.5%	None (p=0.111)
Nazif[8]	SAPIEN N=1973	8.8%	79%	1 year	Ventricular pacing in 50.5%	None (p=0.08)
CoreValve ANZ[4]	CoreValve N=476	31.1%	NR	2 years	NR	None (p=0.32)
US Pivotal Trial (Extreme Risk)[5]	CoreValve N=489	21.6%	78.8%	3 years	NR	None (p=0.62)
ADVANCE[7]	CoreValve N=1015	26.3%	NR	3 years	NR	None (p=0.699)
Urena[6]	CoreValve N=698 Edwards N=858	15.4%	75.3%	3 years	Paced rhythm detected in 66.9%	None (p=0.149)

Clinical Impact of New PPM

All-Cause Mortality

One study has shown a protective effect of pacemakers against sudden death





[1]Urena M, et al., *Circulation* 2014; 129: 1233-1243

Resolution of Pacemaker Indications

Resolution of Indications for PPM

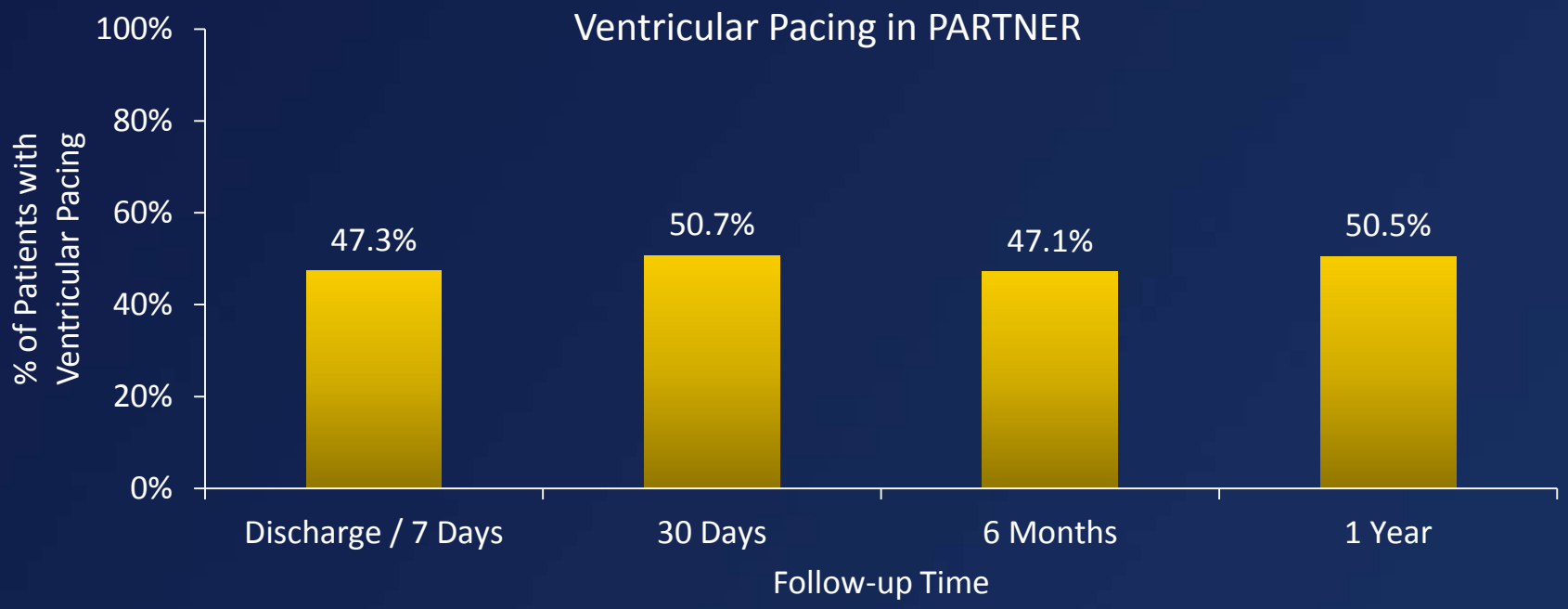
- *Resolution of TAVI-induced high degree AV block occurs in a substantial proportion of patients*
- *Predictors for resolution and the time frame for its occurrence are not well studied.*

Study	Valve Type, N	Total Pacemakers Implanted (n)	PPMs Implanted for HD/Complete AVB (n)	Follow-up	Patients with HD/Complete AVB at Follow-up*
Roten[2]	CoreValve N=41 SAPIEN N=26	23	19 (82.6%)	74 days (median)	28.6% (4 / 14)
Guetta[5]	CoreValve N=70	28	25 (89.3%)	3 months	40% (10 / 25)
Fraccaro[4]	CoreValve N=70	25	22 (88%)	6 months (mean)	29.4% (5 / 17)
Munoz-Garcia[1]	CoreValve N=61	21	21 (100%)	7.1 months (mean)	85.7% (18 / 21)
Simms[7]	CoreValve N=100	17	14 (82.4%)	7.7 months (mean)	33.3% (4 / 12)
Pereira[8]	CoreValve N=65	19	16 (84.2%)	10.3 months (mean)	18.8% (3 / 16)
Van der Boon[6]	CoreValve N=167	36	28 (77.8%)	11.5 months (median)	50% (14 / 28)
Thygesen[9]	CoreValve N=234	64	46 (71.9%)	12.2 months (mean)	40.6% (13 / 32)
Rubin[3]	CoreValve N=50	22	20 (90.1%)	14.3 months (median)	86.7% (13 / 15)
Renilla[10]	CoreValve N=95	36	32 (88.9%)	35 months (median)	52.6% (10/19)

Permanent Pacemakers

The Limitation

- *In PARTNER, only half of the patients implanted with a new pacemaker still had a paced rhythm at hospital discharge*
  - ➢ *For many patients, the need for pacing support is only temporary*
  - ➢ *But for how long? Days? Weeks? This is patient-specific*

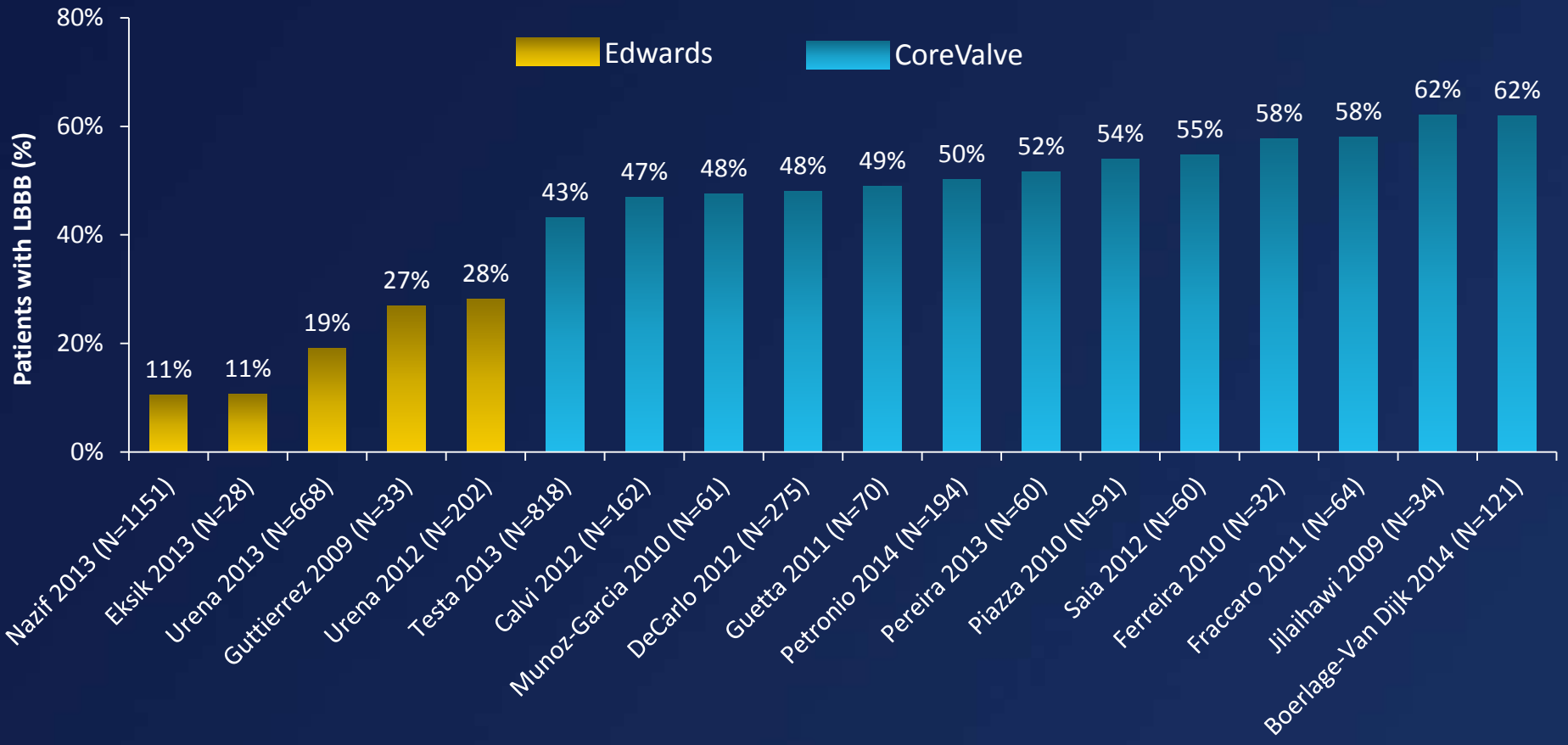


[1]Nazif T, et al., *J Am Coll Cardiol Intv* 2015; 8:60-9; [2]Arnold S, et al., *Circ Cardiovasc Interv* 2014; 7:829-36

New-onset Left Bundle Branch Block

Incidence of LBBB

Post-TAVI or Hospital Discharge



[1]Boerlage-Van Dijk K, et al., *PACE* 2014; 37: 1520-1529; [2]De Carlo M, et al., *Am Heart J* 2012; 163: 492-9; [3]Ferreira N, et al., PACE 2010; 33: 1364-1372; [4]Fraccaro C, et al., *Am J Cardiol* 2011; 107: 747-754; [5]Guetta V, et al., *Am J Cardiol* 2011; 108: 1600-1605; [6]Munoz-Garcia A, et al., *Rev Esp Cardiol* 2010; 63(12): 1444-51; [7]Piazza N, et al., *EuroIntervention* 2010; 6(4): 475-84; [8]Saia F, et al., *Catheter Cardiovasc Interv* 2012; 79(5): 7712-9; [9]Jilaihawi H, et al., *Am Heart J* 2009; 157: 860-6; [10]Calvi V, et al., *J Interv Card Electrophysiol* 2012; 34: 189-95; [11]Pereira E, et al., PACE 2013; 36(5): 559-69; [12]Petronio AS, et al., presented at EuroPCR 2014; [13]Testa L, et al., *Circulation* 2013; 127: 1300-1307; [14]Eksik A, et al., *J Invasive Cardiol* 2013; 25(6): 305-309; [15]Nazif T, et al., *Eur Heart J* 2013; epub ahead of print; [16]Urena M, et al., *J Am Coll Cardiol Intv* 2014; 7(2): 128-36; [17]Urena M, et al., *J Am Coll Cardiol* 2012; 60(18): 1743-52; [18]Gutierrez M, et al., *Am Heart J* 2009; 158: 302-8.

Clinical Impact of New LBBB

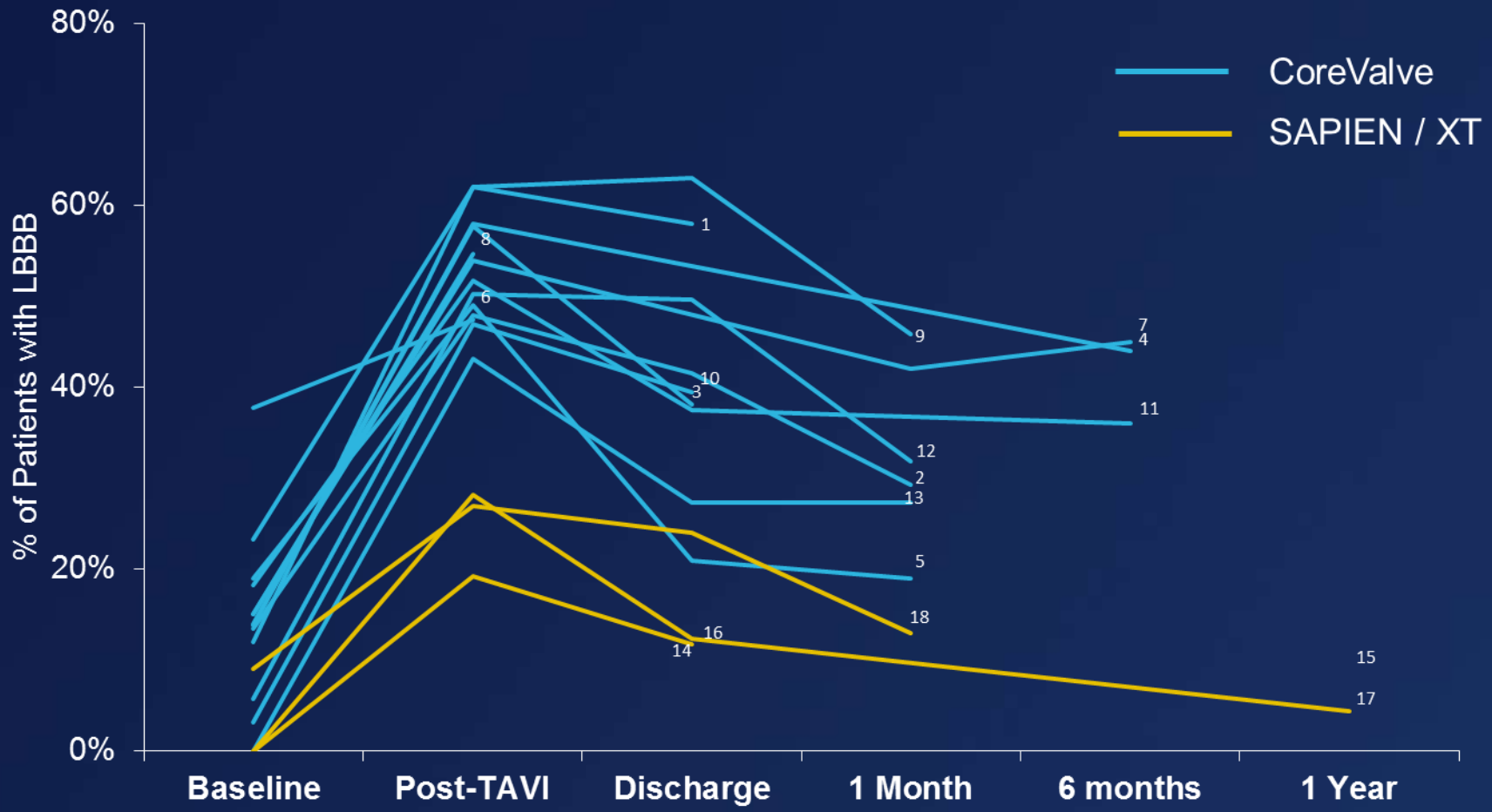
Possible Reasons for Inconclusive Results:

- Competing comorbidities which dominate the clinical course for these patients
- LBBB resolves with time and is no longer a risk factor
- Patients are being treated with pacemakers

LBBB Resolution

Time Course

Across studies there is extreme variability in the extent and time course of resolution

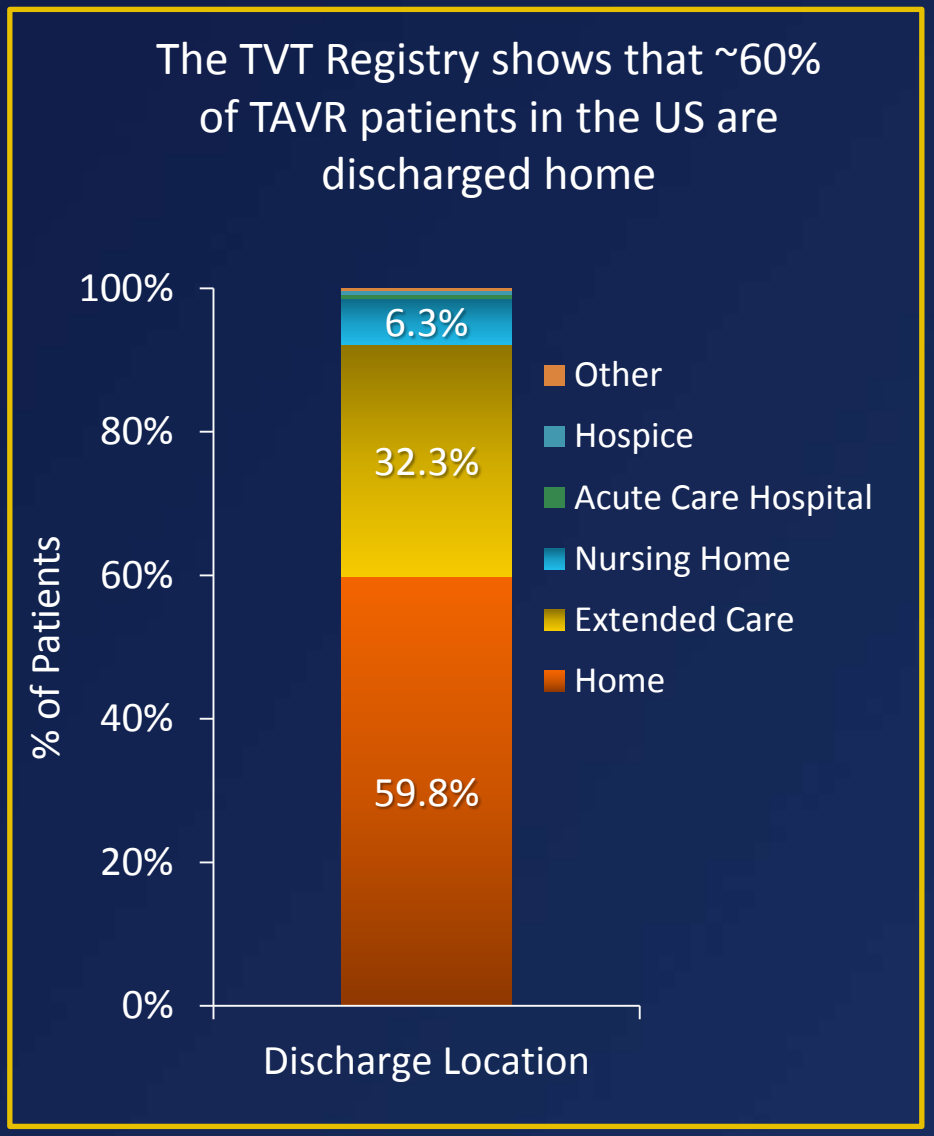


[1]Boerlage-Van Dijk K, et al., *PACE* 2014; 37: 1520-1529; [2]De Carlo M, et al., *Am Heart J* 2012; 163: 492-9; [3]Ferreira N, et al., PACE 2010; 33: 1364-1372; [4]Fraccaro C, et al., *Am J Cardiol* 2011; 107: 747-754; [5]Guetta V, et al., *Am J Cardiol* 2011; 108: 1600-1605; [6]Munoz-Garcia A, et al., *Rev Esp Cardiol* 2010; 63(12): 1444-51; [7]Piazza N, et al., *EuroIntervention* 2010; 6(4): 475-84; [8]Saia F, et al., *Catheter Cardiovasc Interv* 2012; 79(5): 7712-9; [9]Jilaihawi H, et al., *Am Heart J* 2009; 157: 860-6; [10]Calvi V, et al., *J Interv Card Electrophysiol* 2012; 34: 189-95; [11]Pereira E, et al., PACE 2013; 36(5): 559-69; [12]Petronio AS, et al., presented at EuroPCR 2014; [13]Testa L, et al., *Circulation* 2013; 127: 1300-1307; [14]Eksik A, et al., *J Invasive Cardiol* 2013; 25(6): 305-309; [15]Nazif T, et al., *Eur Heart J* 2013; epub ahead of print; [16]Urena M, et al., *J Am Coll Cardiol Intv* 2014; 7(2): 128-36; [17]Urena M, et al., *J Am Coll Cardiol* 2012; 60(18): 1743-52; [18]Gutierrez M, et al., *Am Heart J* 2009; 158: 302-8.

Post-Discharge Monitoring

Post-Discharge Monitoring

The Limitation



[1]Holmes, et al., *JAMA* 2015; 313: 1019-28

Post-Discharge Monitoring

The Need

- Clinical follow-up is typically accomplished through scheduled visits at the outpatient clinic, or by telephone
- Patients at home may not realize their condition is deteriorating until the situation becomes serious
- Implantable or wearable monitoring systems could allow physicians to remotely track their patients and potentially intervene sooner, before hospitalization is necessary

Permanent Pacemakers

A Better Solution?

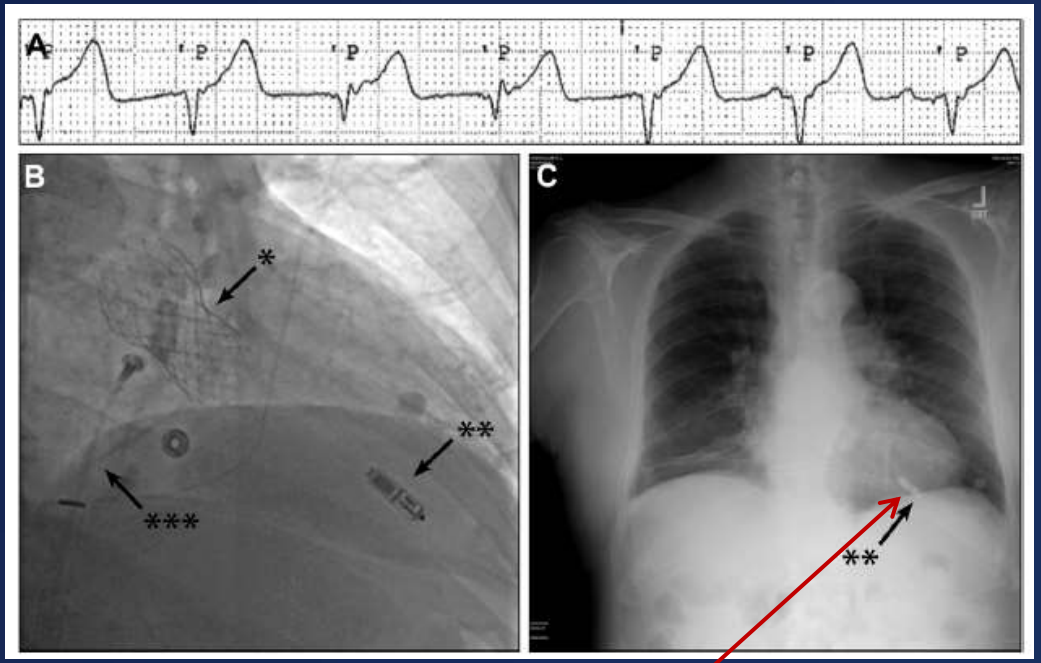
Early implantation of a *COST EFFECTIVE*, leadless pacemaker could:

- ✓ Encourage earlier mobility
- ✓ Reduce complications such as pocket infection
- ✓ Decrease length of stay
- ✓ Provide VVIR pacing as a bridge to a dual chamber device, if the pacing indication persists

Transcatheter Leadless Pacemaker Implantation for Complete Heart Block Following CoreValve Transcatheter Aortic Valve Replacement

MARAT FUDIM, M.D., JOSEPH L. FREDI, M.D., STEPHEN K. BALL, M.D., and CHRISTOPHER R. ELLIS, M.D.

From the Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, Tennessee, USA



Final Position of the Micra

[1]Fudim, et al., *J Cardiovasc Electrophysiol* 2016;27:125-6

Post-Discharge Monitoring

Medtronic SEEQ Mobile Cardiac Telemetry

SEEQ is an external patch monitor that patients could wear for the first month at home

Patch-based ECG monitoring

- Up to 30 days of continuous monitoring[1]
- Automatic and patient marked events recorder

Wireless Communication

- Automatic transmission of data to Medtronic Monitoring Center

Medtronic Monitoring Center

- Attended 24/7 by trained cardiographic technicians
- Proactive assessment of data and patient compliance
- Customizable physician reporting

Post-Discharge Monitoring

Medtronic Reveal LINQ Insertable Cardiac Monitor

LINQ is a small subcutaneous ECG monitor which lasts 3 years

Device

Insertion

CareLink Network

Follow-up

Home Monitor

Patient Assistant

Alerts

Reports

Take Home Messages

- Contemporary studies show that permanent pacemakers are implanted in ~15% of patients following TAVI
- One predictor that is common to all valve types is the presence of RBBB at baseline. Otherwise, relevant predictors are specific to valve type.
- New-onset LBBB is a common finding after TAVI, regardless of valve type
- There is conflicting data as to the impact of new LBBB on mortality.
- The data suggest that it's reasonable to implant pacemakers in patients with new persistent LBBB, for example those that also have QRS >160 msec
- The vast majority of pacemakers are implanted during the index hospitalization. Only ~10% occur after discharge.
- Pacemakers have not been shown to negatively impact mortality

Thank you very much for your Attention