Medical Device Development in a Large Multinational Company

Stanton Rowe
Corporate Vice President
Chief Scientific Officer

An Amazing Job

- **What is it like to develop a life-saving device and meet some of patients whom have benefitted?**

What is it like…?

- It takes talent and time and a medical problem to solve that you really understand
- It takes resources; money, capabilities, testing, quality & regulatory talent
- It is highly regulated and the processes and requirements are understood
- Innovation (not iteration) in a large or small company means about a 25-40% success rate

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What does success look like?

- **You develop something proprietary- patents matter!**
- **You develop something that has sustainable competitive advantage**
- **You develop something that proves clinical benefit in clinical trials**
- **You develop something that payors, CMS or patients value and will pay for**
- **You develop something that is sold into the market and helps patients live better lives**

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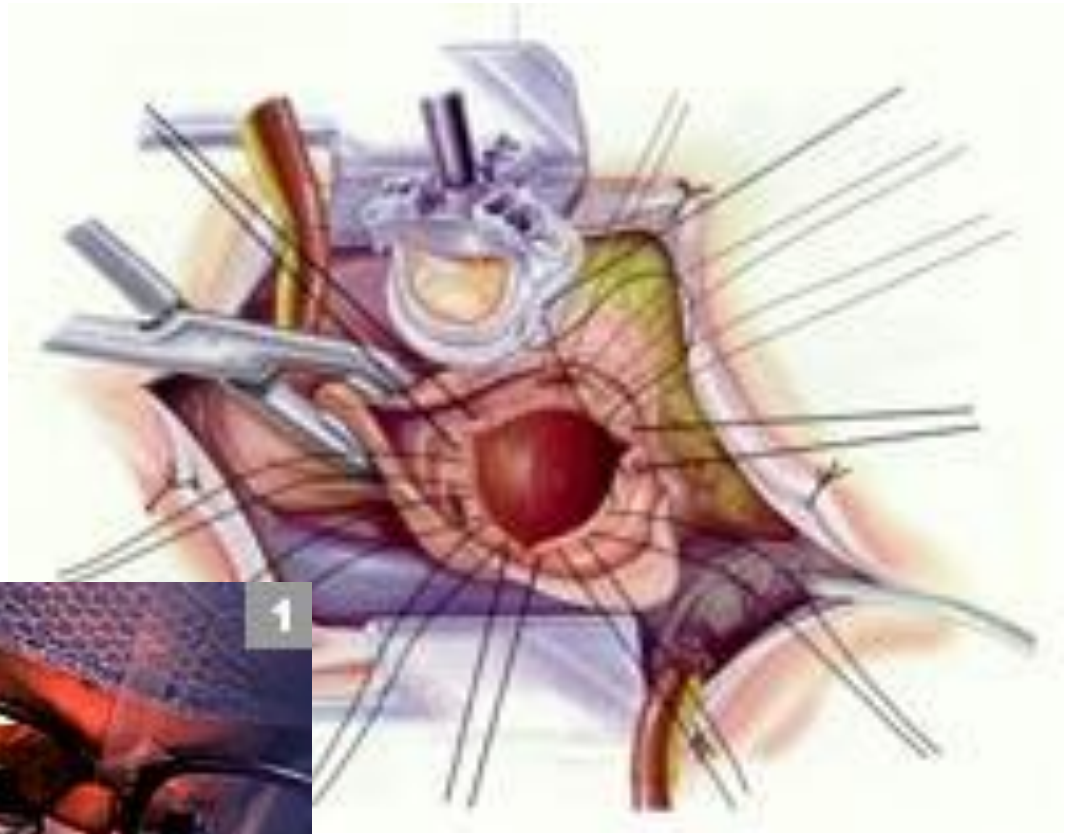
Current Therapy- Open Heart Surgery



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Cardiac Cath Procedure

Percutaneous Valve Technologies, Inc. (PVT)

- **1999 Incorporated- Founding Partners**
  - **Dr. Alain Cribier**
  - **Dr. Martin Leon**
  - **Stanley Rabinovich**
  - **Stanton Rowe**
- **May-2000**
  - **Angels, founders and Aran funded 9 months $740k at $2M valuation**

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Engineering questions

- What compressive forces must the frame (stent) resist?
- How strong must we make the frame to form a circular valve?
- How can new manufacture a frame that large; no tubing that large?
- What material is preferred for the frame?
- How do we attach a fixed diameter valve to an expandable and collapsible frame?
- How do you make the attachment durable?
- How can we seal around the valve and prevent PVL? Without increasing profile?
- What is the optimal valve design for hemodynamics/profile/tissue damage? Unicuspid, bicuspid, tricuspid or quadracuspid?
- What is the optimal valve material? Polymers, co-polymers, tissue?

What surgeons said about THVs… (to VC's)

- Don't touch the pericardial tissue, it's fragile and cannot withstand crimping to a smaller profile
- The native calcified aortic valve cannot be stented open
- If you tried to stent open the calcified native valve, you will cause strokes by embolizing the calcium and debris
- The THV cannot/will not be retained and will embolize itself
- THVs will have smaller valve areas and therefore be inferior to surgical valves in performance
- The THV cannot be made durable
- The THV will have perivalvular leaks which will cause endocarditis
- Cardiologists know nothing about Aortic Stenosis and should not treat these patients

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Percutaneous Valve Technologies

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Heroic Therapy

L'actualité
- A la "Une"
- France-Monde
- Sports
- Normandie
- Eure
- Seine-Maritime
- Yvelines

Zoom
- Présidentielle 2002
- Star Academy : le concours
- Concours de l'entreprise innovante
- Des Bugatti en Normandie
- En route pour

Normandie

Eugène à cœur vaillant.

Première mondiale au CHU de Rouen : le professeur Alain Cribier et son équipe ont posé une valve cardiaque artificielle sans chirurgie. Inopérable hier, Eugène, 57 ans, récupère.

Une première mondiale, aboutissement de quinze années de recherches, ça se raconte et ça se fête. Hier au CHU de Rouen, le professeur Alain Cribier, chef du service de cardiologie, s'est retrouvé au centre de toutes les sollicitations.
Alors il a expliqué, détaillé, partagé sa réussite en racontant l'aventure scientifique et humaine qui a permis d'obtenir un tel résultat. Car la technique d'implantation sans chirurgie d'une valve aortique, inventée sous son impulsion, a permis mardi dernier de sauver la vie d'un homme de 57 ans, inopérable et condamné à très brève échéance.

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PARTNER Manuscripts in NEJM (October, 2010 – May, 2012)

THE PARTNER TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2010 VOL. 363 NO. 17

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela S. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2011 VOL. 364 NO. 23

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis

Raj R. Makkar, M.D., Gregory P. Fontana, M.D., Hasan Jilaihawi, M.D., Samir Kapadia, M.D., Augusto D. Pichard, M.D., Pamela S. Douglas, M.D., Vinod H. Thourani, M.D., Vasilis C. Babaliaros, M.D., John G. Webb, M.D., Howard C. Herrmann, M.D., Joseph E. Bavaria, M.D., Susheel Kodali, M.D., David L. Brown, M.D., Bruce Bowers, M.D., Todd M. Dewey, M.D., Lars G. Svensson, M.D., Ph.D., Murat Tuzcu, M.D., Jeffrey W. Moses, M.D., Matthew R. Williams, M.D., Robert J. Siegel, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Stuart Pocock, Ph.D., Craig R. Smith, M.D., and Martin B. Leon, M.D., for the PARTNER Trial Investigators*

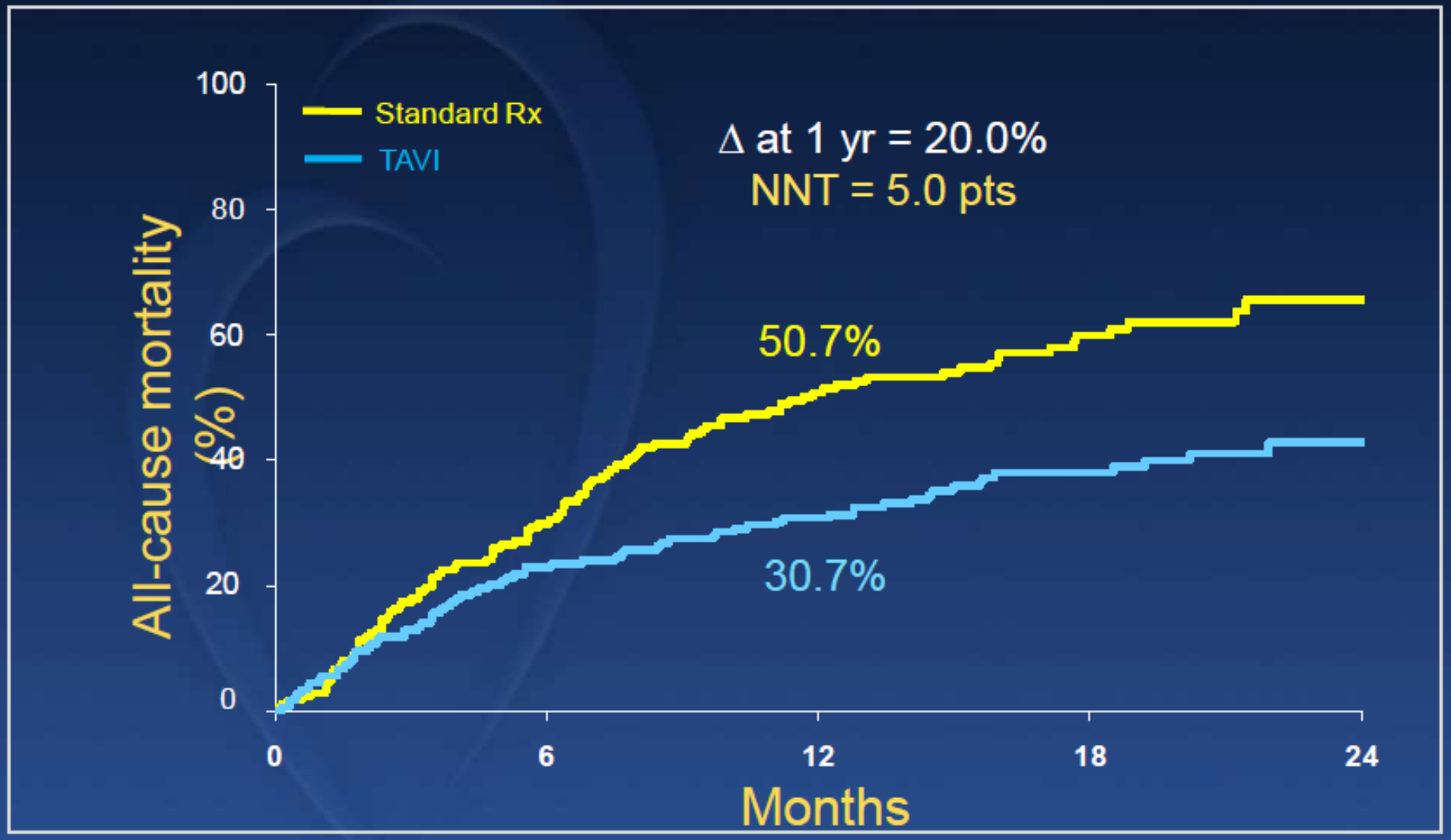
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement

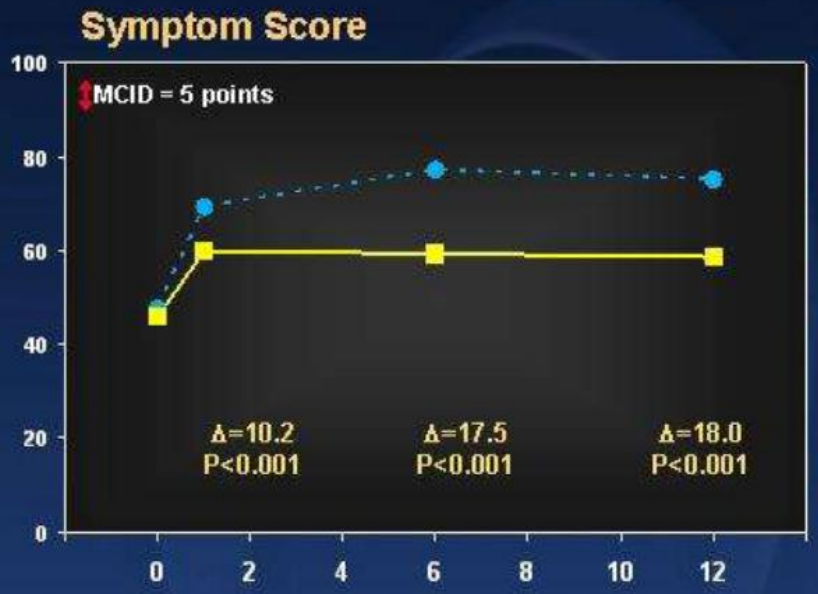
Susheel K. Kodali, M.D., Mathew R. Williams, M.D., Craig R. Smith, M.D., Lars G. Svensson, M.D., Ph.D., John G. Webb, M.D., Raj R. Makkar, M.D., Gregory P. Fontana, M.D., Todd M. Dewey, M.D., Vinod H. Thourani, M.D., Augusto D. Pichard, M.D., Michael Fischbein, M.D., Wilson Y. Szeto, M.D., Scott Lim, M.D., Kevin L. Greason, M.D., Paul S. Teirstein, M.D., S. Chris Malaisrie, M.D., Pamela S. Douglas, M.D., Rebecca T. Hahn, M.D., Brian Whisenant, M.D., Alan Zajarias, M.D., Duolao Wang, Ph.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., and Martin B. Leon, M.D., for the PARTNER Trial Investigators*

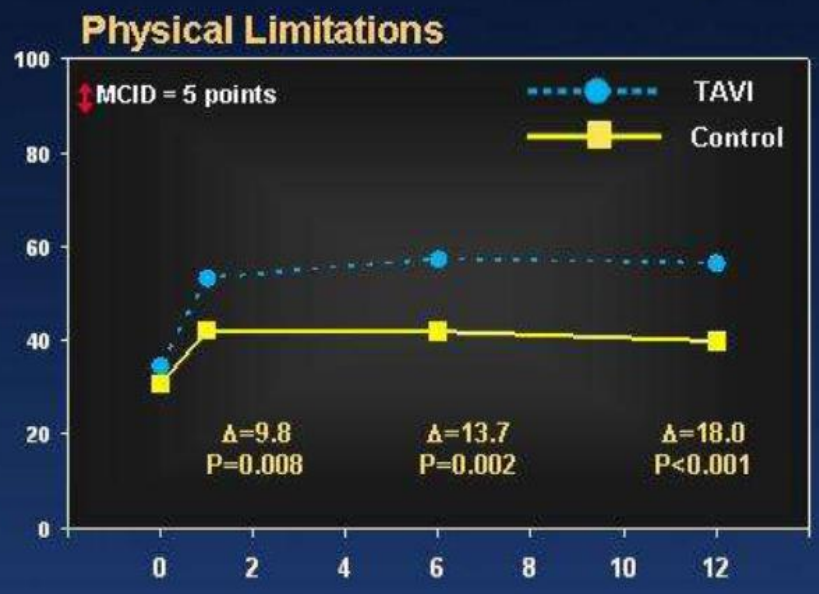
All Cause Mortality

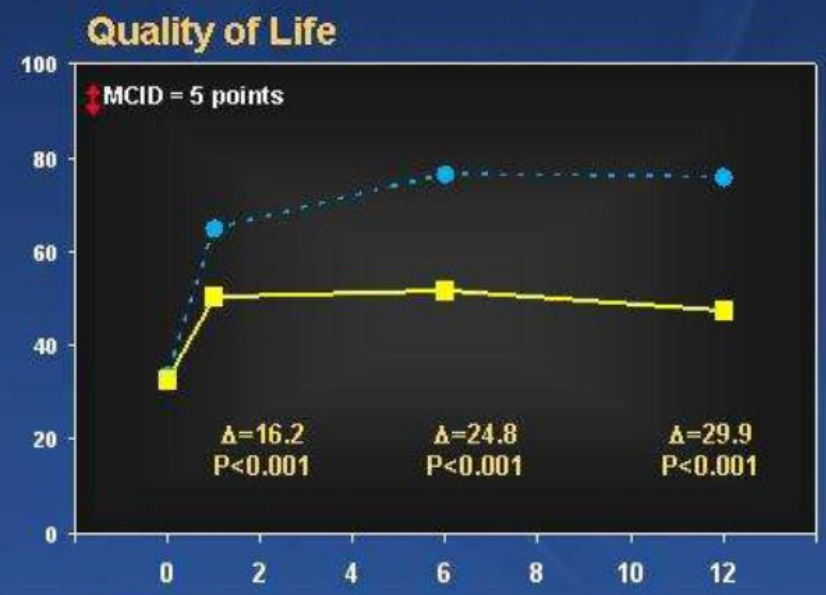


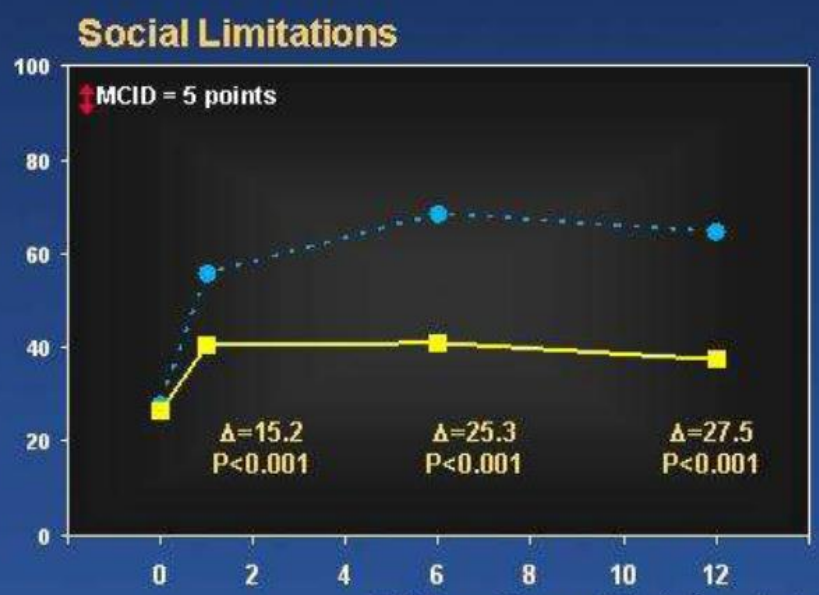
Numbers at Risk					
TAVI	179	138	122	67	26
Standard Rx	179	121	83	41	12

Change in QOL (KCCQ): TAVR vs Standard Rx



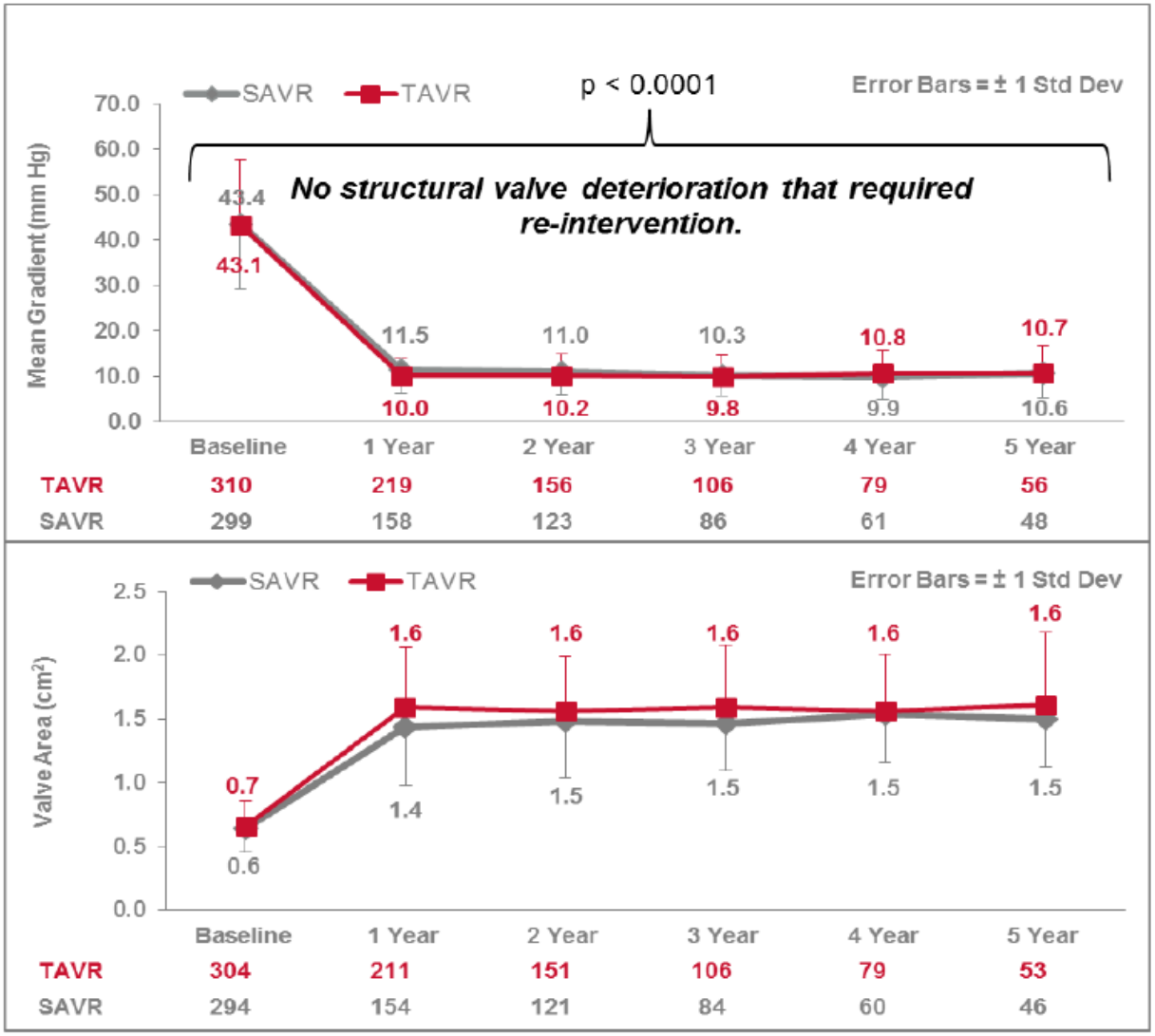






Cohen et al TCT 2010

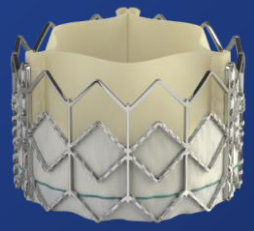
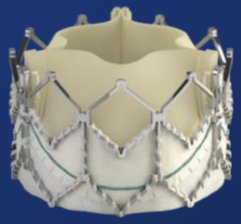
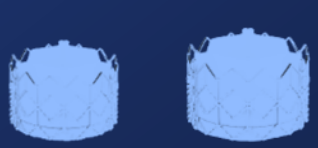
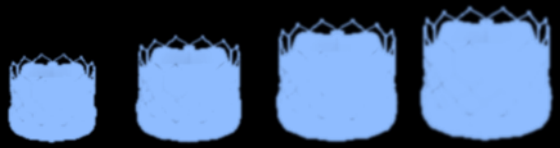
MCID = minimum clinically important difference



***Mack M et al. Lancet* 2015;6736(15)60308-7**

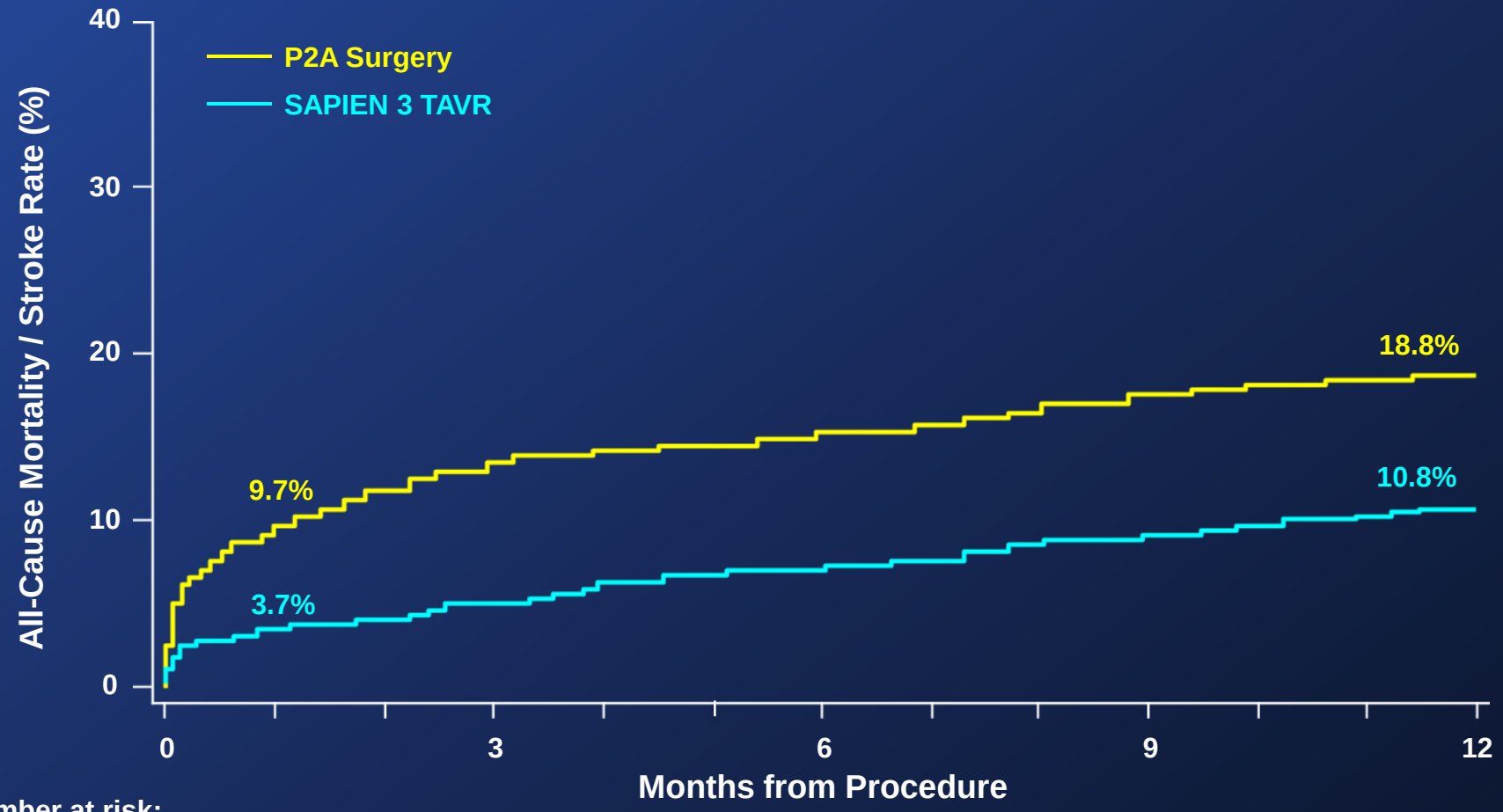
SAPIEN Platforms in PARTNER
Device Evolution

THE PARTNER II TRIAL

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes	 23 mm, 26 mm	 23 mm, 26 mm, 29 mm	 20 mm, 23 mm, 26 mm, 29 mm

Unadjusted Time-to-Event Analysis
All-Cause Mortality and All Stroke (AT)

THE PARTNER II TRIAL

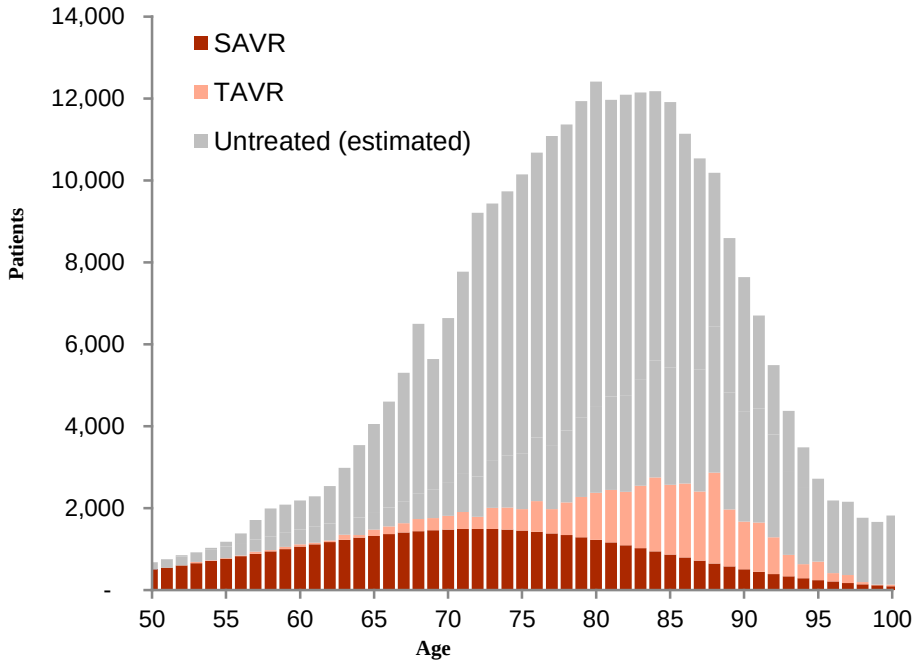


Number at risk:

P2A Surgery	944	805	786	757	743
S3 TAVR	1077	1012	987	962	930

TAVR Experience Has Changed Our Understanding of Aortic Stenosis

2015 Severe Symptomatic AS Patients in the U.S.[1]



Observations
For Severe, Symptomatic AS Patients

- **Advanced age is a barrier not only to treatment but diagnosis**
  - A safe interventional procedure has the potential to reduce these barriers
- **Historically, patient treatment rates decreased with age**
  - Opportunity for TAVR to lift treatment rates in older age groups

(1) Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007, Freed 2010, Iung 2007, Pellikka 2005, Brown 2008, Thourani 2015, internal estimates.

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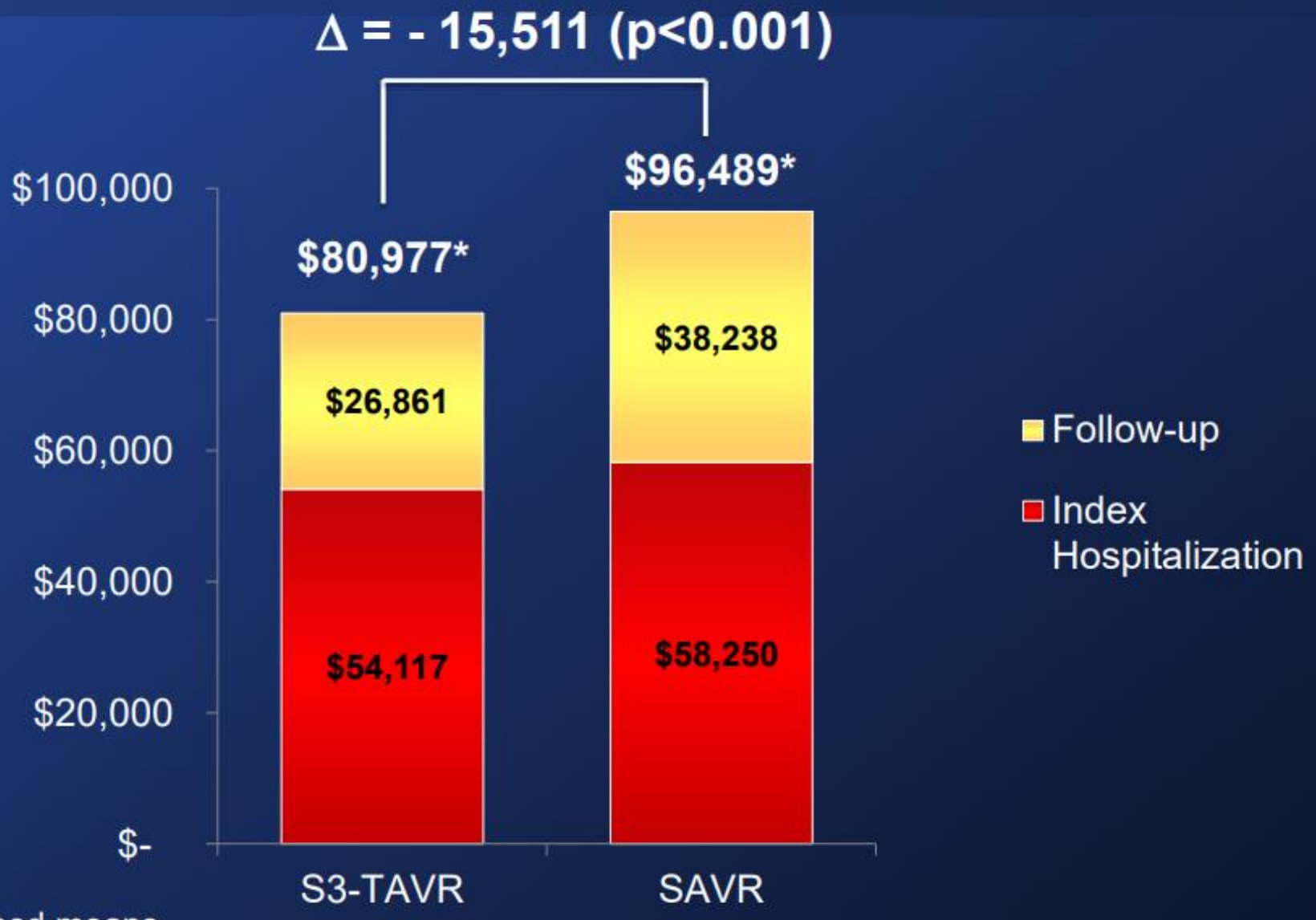
Total 1-Year Costs



* Trimmed means

Conclusions

THE PARTNER II TRIAL

- For patients with severe AS and intermediate surgical risk similar to those enrolled in the PARTNER 2A and S3i trials, TAVR should be the preferred strategy based on both clinical and economic considerations

On the basis of these findings, we conclude…

It's About Patients!

Total US VC Investment to CA[**]

2017 California Digital Health VC Investment by Category

Source: Rock Health Digital Health Funding Database.

California Life Sciences Wages by Sector

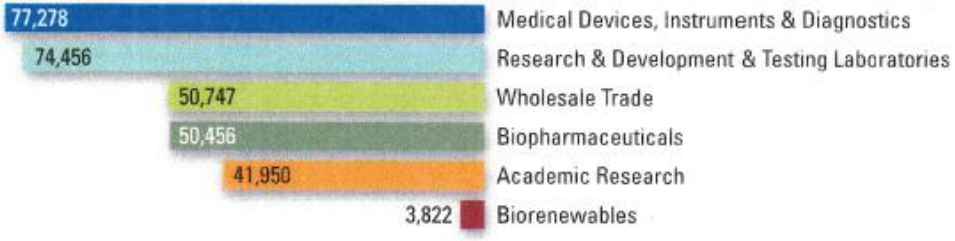
in California, 2016

	Average Wage	Total Wages
Academic Research	$73,007	$3.1B
Biopharmaceuticals	$152,703	$7.7B
Biorenewables	$72,696	$278M
Medical Devices, Instruments and Diagnostics	$94,528	$7.3B
Research & Development and Testing Laboratories	$140,574	$10.5B
Wholesale Trade	$101,261	$5.1B
Total	**$113,674**	**$34.0B**

Source: Bureau of Labor Statistics Quarterly Census of Employment and Wages; 2012 Economic Census.

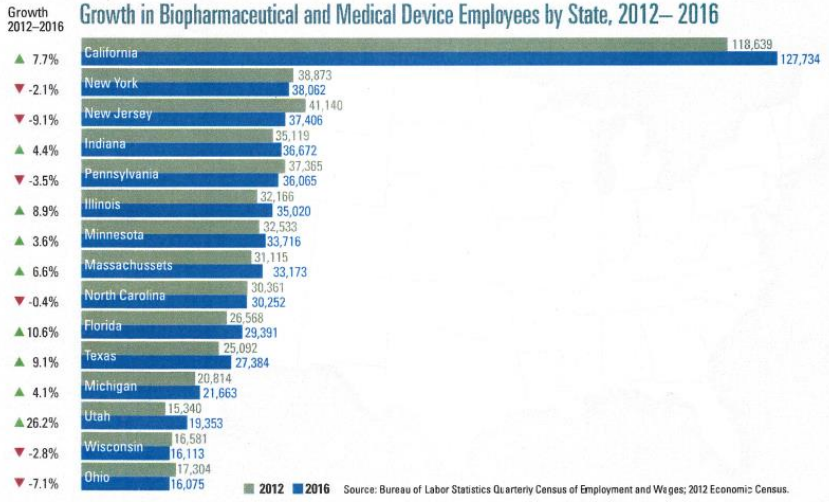
Total Life Sciences Employees by Sector

in California, 2016



Source: Bureau of Labor Statistics Quarterly Census of Employment and Wages; 2012 Economic Census.

Growth in Biopharmaceutical and Medical Device Employees by State, 2012– 2016



Edwards

Helping Patients is Our Life's Work, and

life is now