

20th Anniversary of TAVR

From Concept to Human Application

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Statement of Financial Interest

I have the following potential disclosure to report

- Edwards LifeSciences: Past Consultant
- Cardiawave: Scientific Advisory Board
- Meril LifeSciences: Scientific Advisory Board

**Rouen, France, May 21st 2022:
*Celebration of the 20th Anniversary of TAVR***



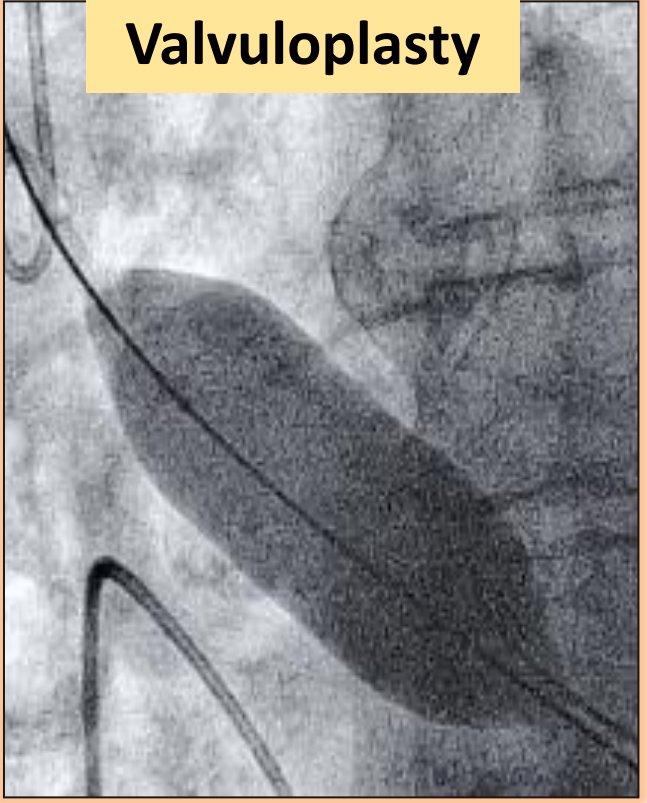
Rouen: Over the last 40 years, development of cardiac catheterization techniques for treating degenerative aortic stenosis

Aortic Stenosis (Season 1...)

Rational

Aortic Stenosis (Season 2...)

1985
Balloon Aortic Valvuloplasty



F.I.M. Lancet, 1986

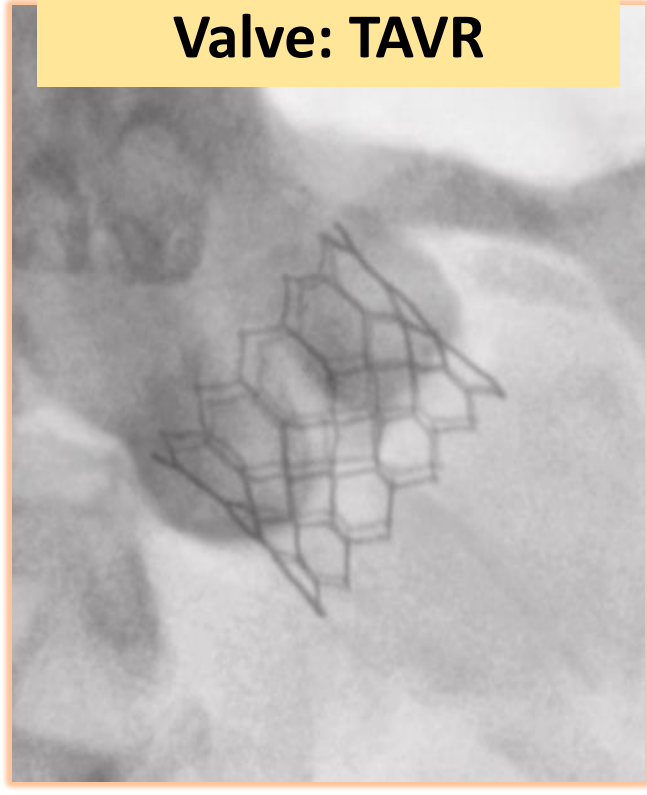
A single goal for these two linked innovations:

To provide a live saving therapeutic option for patients with symptomatic AS and declined for surgical valve replacement

**Without SAVR (1/3 of pts):
Mortality # 80% at 2 years**

**In the 1980s,
SAVR was also declined
in all patients older than 70-y
(50% of Pts turned down)**

2002
Transcatheter Aortic Valve: TAVR



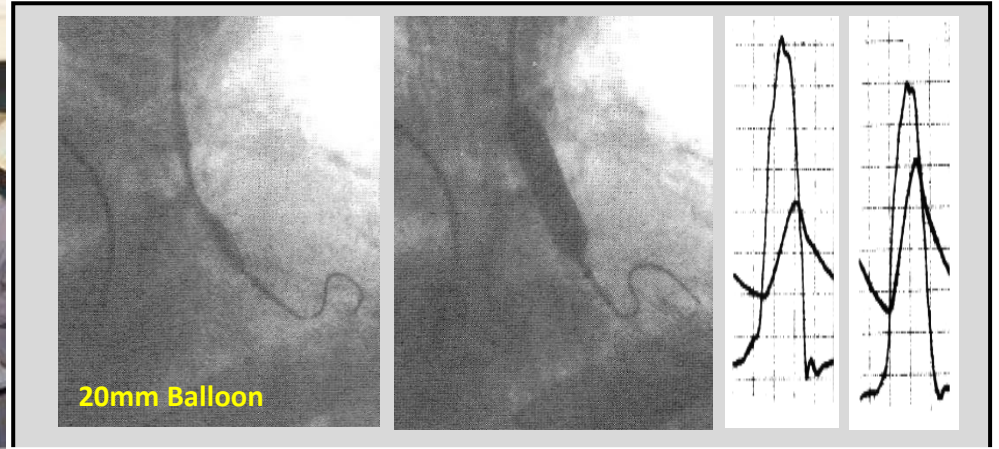
F.I.M. Circulation, 2002

Attempt to solve a major unmet clinical need

1985: F-I-M Balloon Aortic Valvuloplasty

Trying to enlarge the aortic valve orifice by balloon dilatation

**Rouen, Sept 1985
F-I-M BAV in a
72-yo woman**



PERCUTANEOUS TRANSLUMINAL VALVULOPLASTY OF ACQUIRED AORTIC STENOSIS IN ELDERLY PATIENTS: AN ALTERNATIVE TO VALVE REPLACEMENT?

A. Cribier et al,

THE LANCET, JANUARY 11, 1986

Two years without symptom – return to normal life

➔ A bomb effect in the medical community!

1986-1992: Tens of thousands of BAV worldwide

- > 1250 index-articles on BAV, NHLBI and Mansfield registries
- **FDA approval in selected cases**
- Improvement of symptoms but one major *unacceptable limitation:*

EARLY RESTENOSIS

➔ WHAT TO DO NEXT ?

1990: Birth of the idea of TAVI

As a solution against early restenosis post-BAV

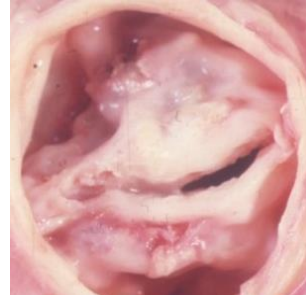
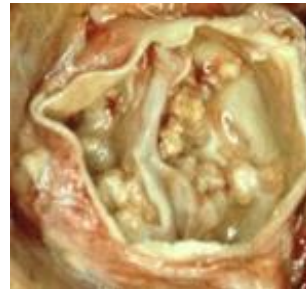
The most challenging “crazy” concept

“Implanting a valve prosthesis within the diseased calcific native valve, on the beating heart, using regular percutaneous catheter-based techniques and local anesthesia !...” A. Cribier, 1990

IMPOSSIBLE !

Heavily calcified valves !

No chance of crossing the diseased valve with a prosthesis and deploy it



DANGEROUS !

Surrounding structures !

- **Above:**
 - Coronary ostia
- **Below:**
 - Mitral valve
 - His bundle

1994 -TAVI: From the idea to validation of concept

A Landmark autopsy study

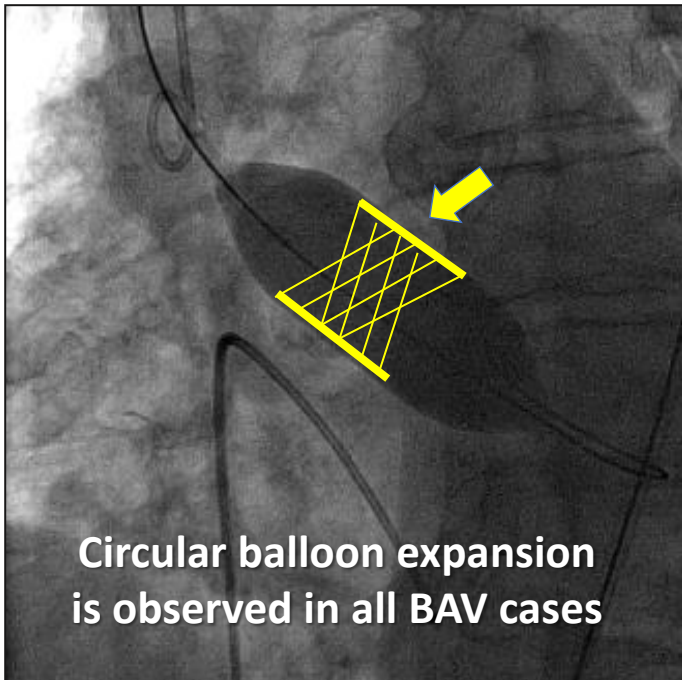


Rouen 1994

(16 fresh specimen of calcific AS)

With H. Eltchaninoff and R. Koning

Regular observation during BAV

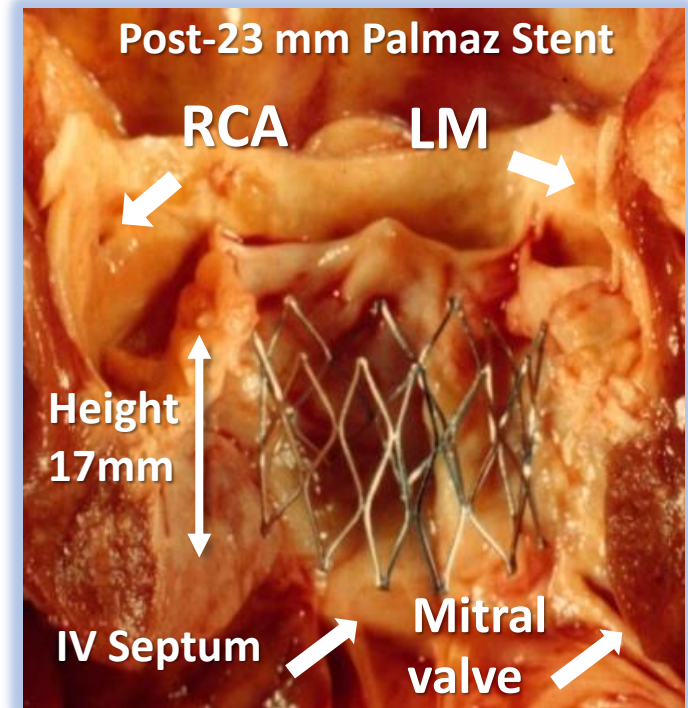


Question:
Could a balloon expandable stent be used to maintain the valve open?



Renu Virmani, MD
Washington DC, 2002

Confirmative findings

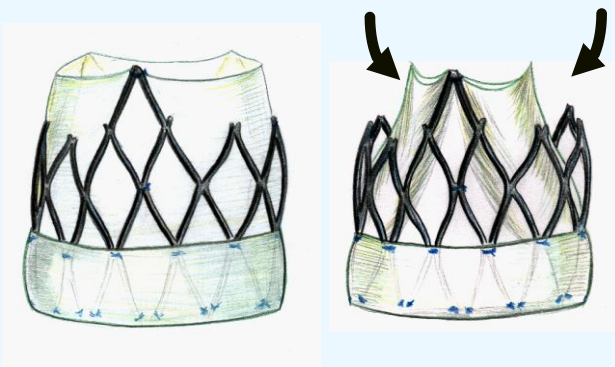


- Respect of adjoining structures

- Forceps needed to remove the stent (traction force 2kg)

1994 - Figuring the stented valve and the procedure of TAVI

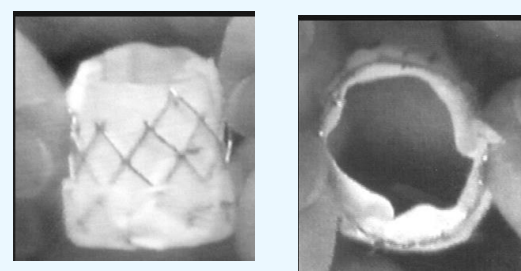
EU Patent application



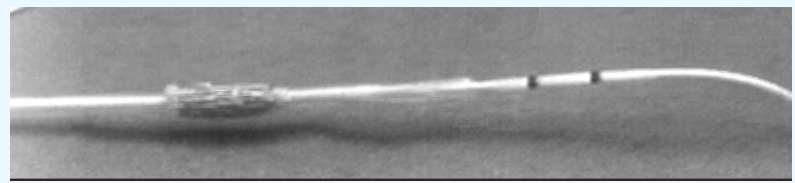
Systole

Diastole

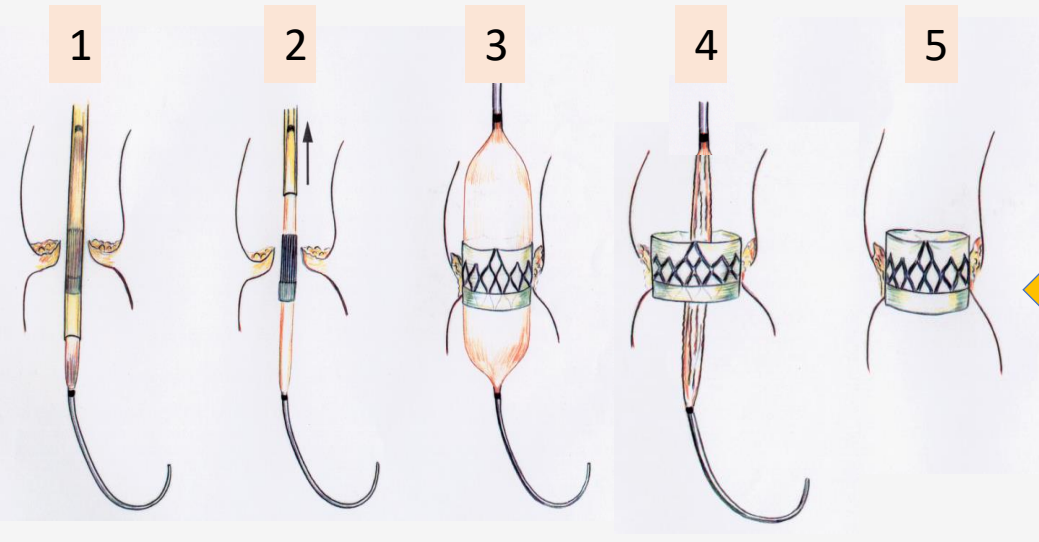
- Valve structure: biologic or polymer?
- High radial force balloon expandable stent
- External cuff



Rouen, Hand-made Model of THV
(with Pr JP Bessou)



Crimped diameter = 8mm



1 2 3 4 5

**Transfemoral approach
conceivable**

1994- 1999 – Looking for a sponsor

*Comments from experts of all biomedical companies
(Including Edwards and Medtronic)*

“ Totally unrealistic, major technical issues ”

“ Definitely impossible to stent a calcific aortic valve ”

“Unavoidable life-threatening complications:

Stroke, myocardial infarction, annulus rupture, ventricular arrhythmias and conduction disturbances, endocarditis, THV embolization

“Would never be approved by FDA”

“Surgery covers 100% of the need. No indication”

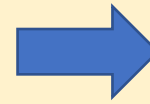
“Most stupid project ever heard...” Just forget it !!!

**End of
the story?**

1999 – Project of TAVI still alive

Creation of a start-up:

Percutaneous Valve Technologies Inc, NJ, USA



Challenging requests to the engineers

- A prosthesis made of a highly resistant frame
- Containing a uni-, bi-, or tri-leaflet valvular structure
- Able to be homogeneously compressed over a high pressure balloon, for its introduction into a sheath (femoral artery) of 7 to 9 mm in diameter
- Enlarged by balloon inflation to an external \varnothing of 23mm without damaging the frame and valvular structure

December 1999: Signed agreement
with ARAN R&D, Caesarea, Israel
Investment, Development

**And they
made it!**

2000-2002 – The PVT Valve

Preclinical evaluation

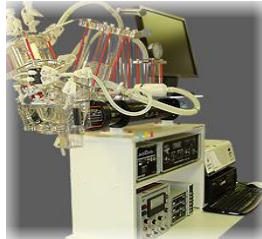


*Tri-leaflet valve
(polymer, then bovine pericardium)
Stainless steel stent
Single diameter 23mm
24F crimped size*

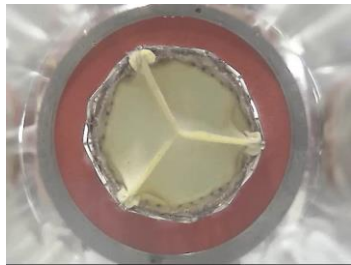
2000-2002 – The PVT Valve

In-Lab VALVE TESTS

Hemodynamics

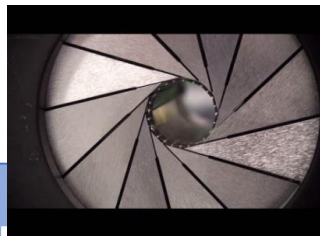


Durability (5 years)



FRAME TESTS

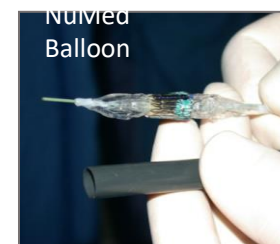
Radial force



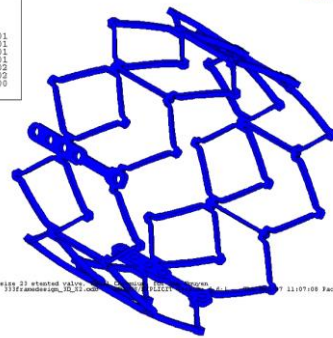
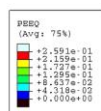
IN-VIVO TESTING, Sheep model, at CERA, Paris

(A. Cribier, H. Eltchaninoff, N. Borenstein)

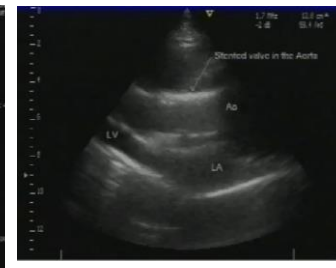
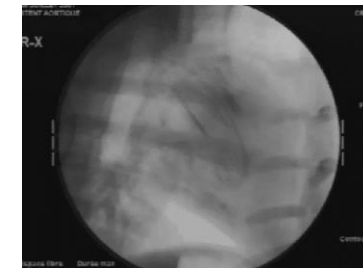
Preclinical evaluation



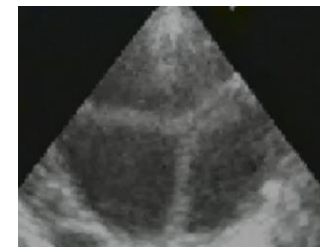
Stent geometry



5 Months in aorta



Orthotopic Ao implantation



1999-2002: THV implantation in Animal Model

Important lessons on:

- Vascular access
- Use of large sheath introducers
- Delivery system
- Guidewires
- Most procedures

**Moving to human
the hardest decision to make !**

Deficiencies in animal model:

- *No aortic valve calcification*
- *No aortic valve degeneration*
- *Different arch anatomy*

April 16th, 2002, Rouen, F.I.M. - TAVI

From Dream to Reality

57-y/o man, cardiogenic shock, LVEF 12%

Multiple comorbidities, intraventricular thrombus

Aorto Bi-femoral graft occluded: no femoral access

Turned down by 3 surgical teams

 *FAILED EMERGENT TRANSSEPTAL BAV
(back in shock in 24h)*

 ***Challenging decision of Transseptal TAVI
as a live saving procedure***

All current contra-indications of TAVI!...

Rouen, April, 16th, 2002

From dream to reality: F-I-M TAVI

A. Cribier, H. Eltchaninoff, C. Tron



April 16th, 2002
First-In-Man TAVI

Cribier.A et al, Circulation 2002

One year to, get French approval for starting a prospective series on compassionate cases



First series
(Rouen, 2002-2004)

38 Compassionate cases

(life expectancy 2 weeks...)

I-REVIVE / <RECAST trials

Trans-septal approach

Lessons

- 1- Feasibility of TAVI
- 2- Accuracy of valve placement
- 2- No THV embolization
- 3- No coronary occlusion
- 4- No MR
- 5- No AV - Block
- 6- Optimal valvular function
- 7- Excellent hemodynamics
- 8- Paravalvular AR ≥ 2 in 25%
(single size 23mm too small)

A. Cribier et al,
JACC, 2004 & 2006



Rouen, 2002-04: 1st series of 40 critically ill patients (TS approach)

The spectacular patients improvement: a key element for the acceptance and future expansion of TAVI

Patient # 3



- 83 y/o woman
- Multi comorbidities
- 2 BAV procedures
- Cardiogenic shock

Transseptal TAVI as a last resort option



1 year post-TAVI

Invited guest at TCT, Washington, DC



6.5-Y post-TAVI (2010)

Hemodynamic results unchanged since 2004

Patient # 10

- 85 y/o Woman with severe AS
- Massive pulmonary edema,
- Cardiogenic shock *Declined for SAVR*
- Transferred from Paris in pre-mortem state
- *Associated MS: no possible TS approach*

First planned retrograde approach

Local anesthesia

Procedure duration: 60 min



First vision of a TAVI valve implanted retrogradely

Hemodynamic results unchanged since 2004



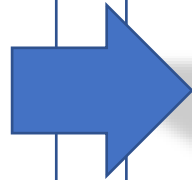
5 years post-TAVI

2004: Edwards LifeSciences acquires PVT



Cribier-Edwards

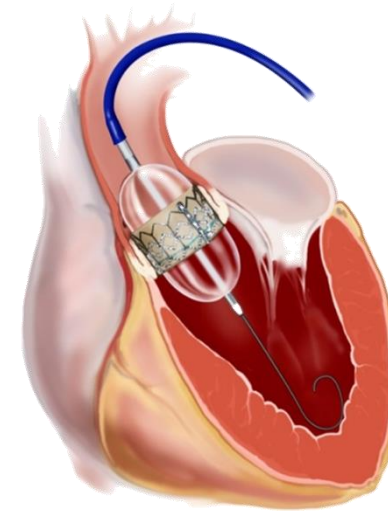
- 23mm size
- Equine pericardium
- 1/3 external coverage
- Sheath size 24F
- Mainly implanted via the transseptal approach



Edwards- SAPIEN

- 23mm and 26mm sizes
- Treated bovine pericardium
- 50% external coverage
- Sheath size 22F and 24F
- Conceived for implantation via the retrograde TF approach

Transfemoral approach



John Webb
Vancouver
Canada



2004: RetroFlex
Steerable Delivery system

2006-2009: European Registries including SOURCE

2009: Pivotal randomized PARTNER US Trial

2006: RetroFlex 3

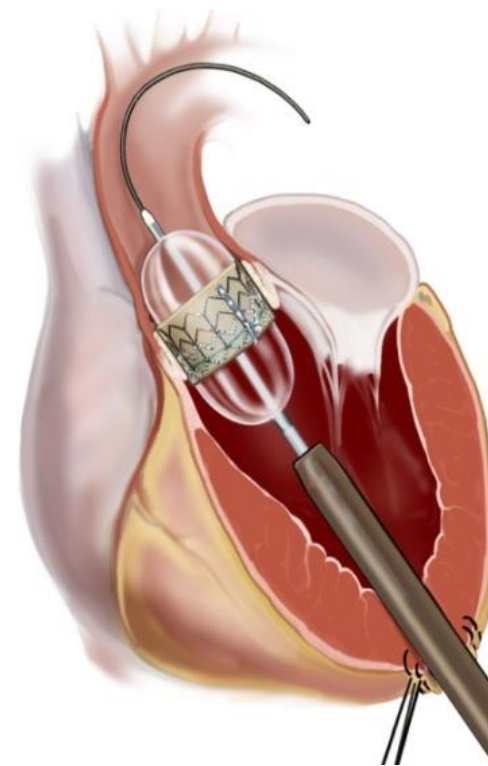


2005: An alternative approach

Transapical access

Surgeons start being involved with in TAVI

The devil enter the OR !



F. Mohr
M. Mack
T. Walther
Leipzig, Germany

SV Lichtenstein
Vancouver, Can

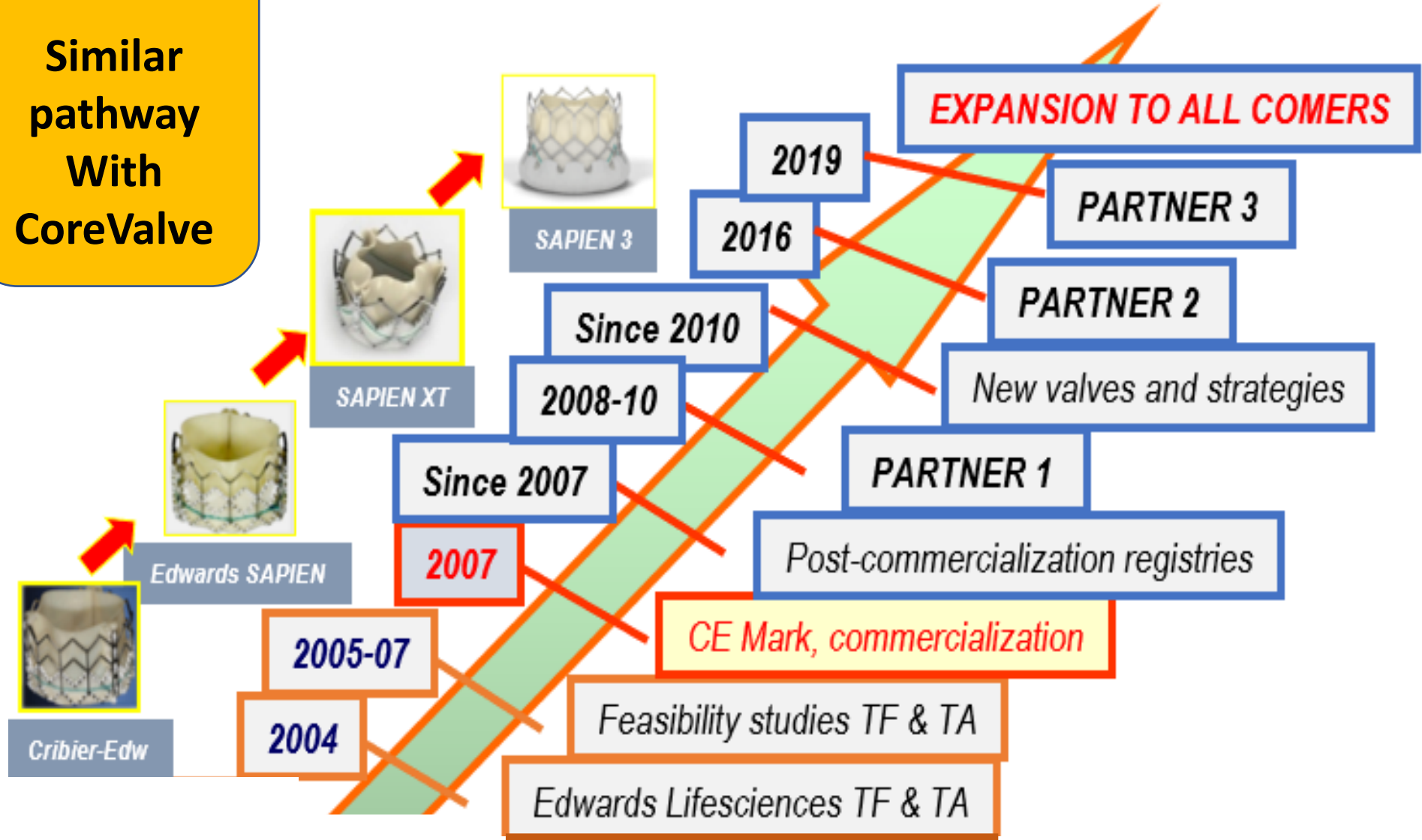


With TF and TA, almost 100% of TAVI candidates can be treated

TAVR Pathway with Edwards

From 2004

Similar pathway
With
CoreValve



Since 2004- Launch of the self-expanding CoreValve

This concurrent device has highly contributed to the incredible expansion of TAVR



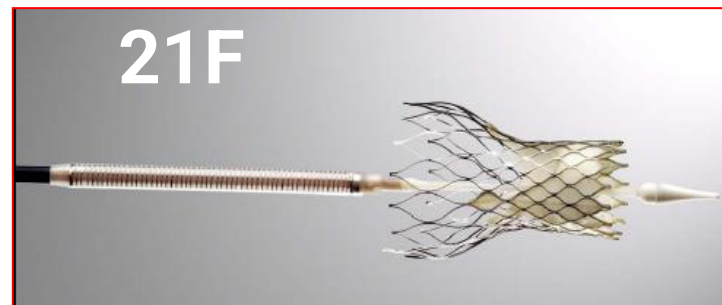
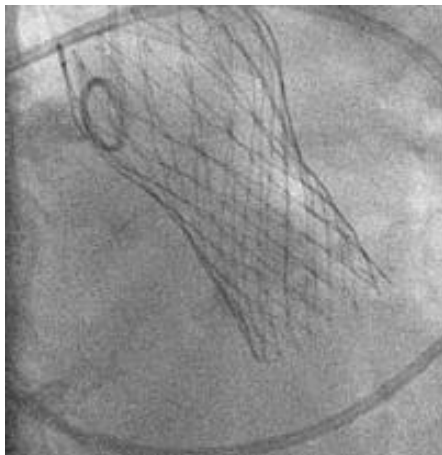
Jacques Seguin



Eberhard Grube



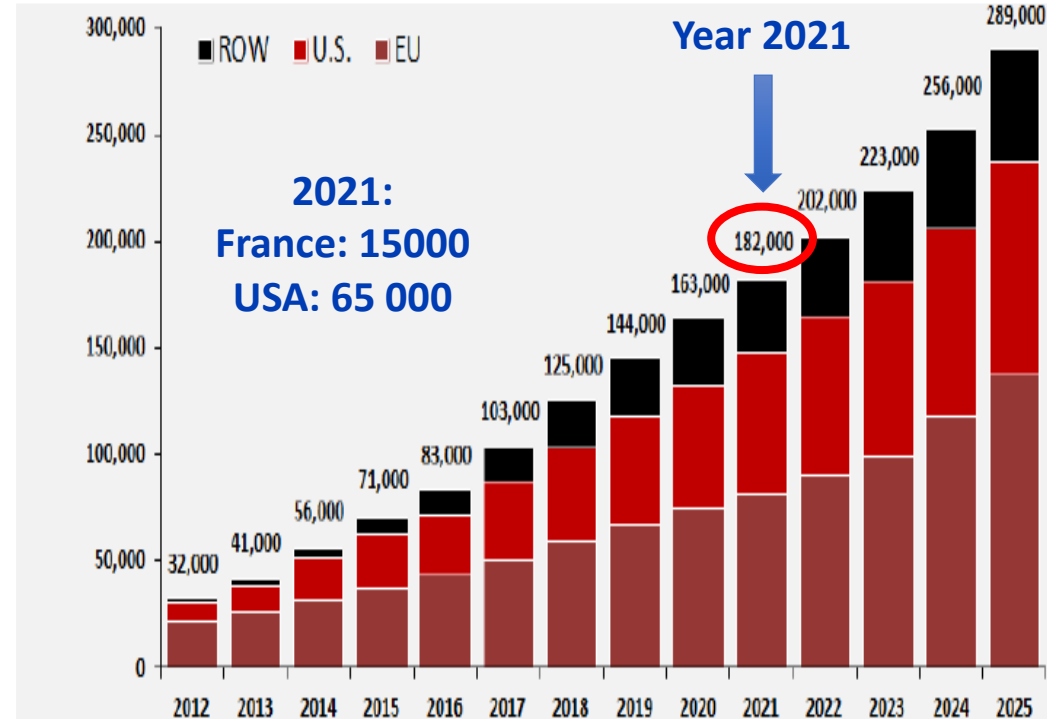
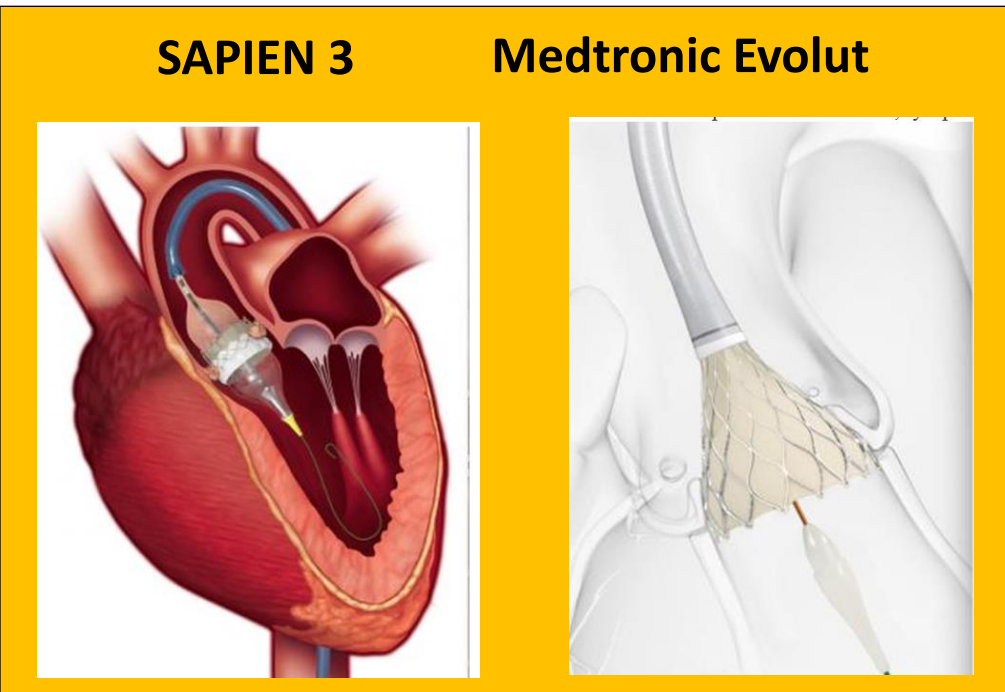
J.C. Laborde



A similar successful pathway

Since August, 2019: the apotheosis of TAVI

FDA Approval for LOW-RISK Patients > 65 years



A spectacular worldwide expansion

> 1.5 000 000 patients treated with TAVR in the world in # 80 countries



A predicted X 4 TAVI growth within 10 years

Transcatheter
Aortic
Valve
Iplantation

Developing TAVR, a
long road but the fight
was worth it!

20 YEARS!