

# 20 years of TAVR

## *From concept to Human Application*

*Alain Cribier, Rouen University Hospital, France*

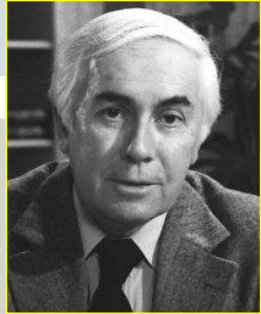
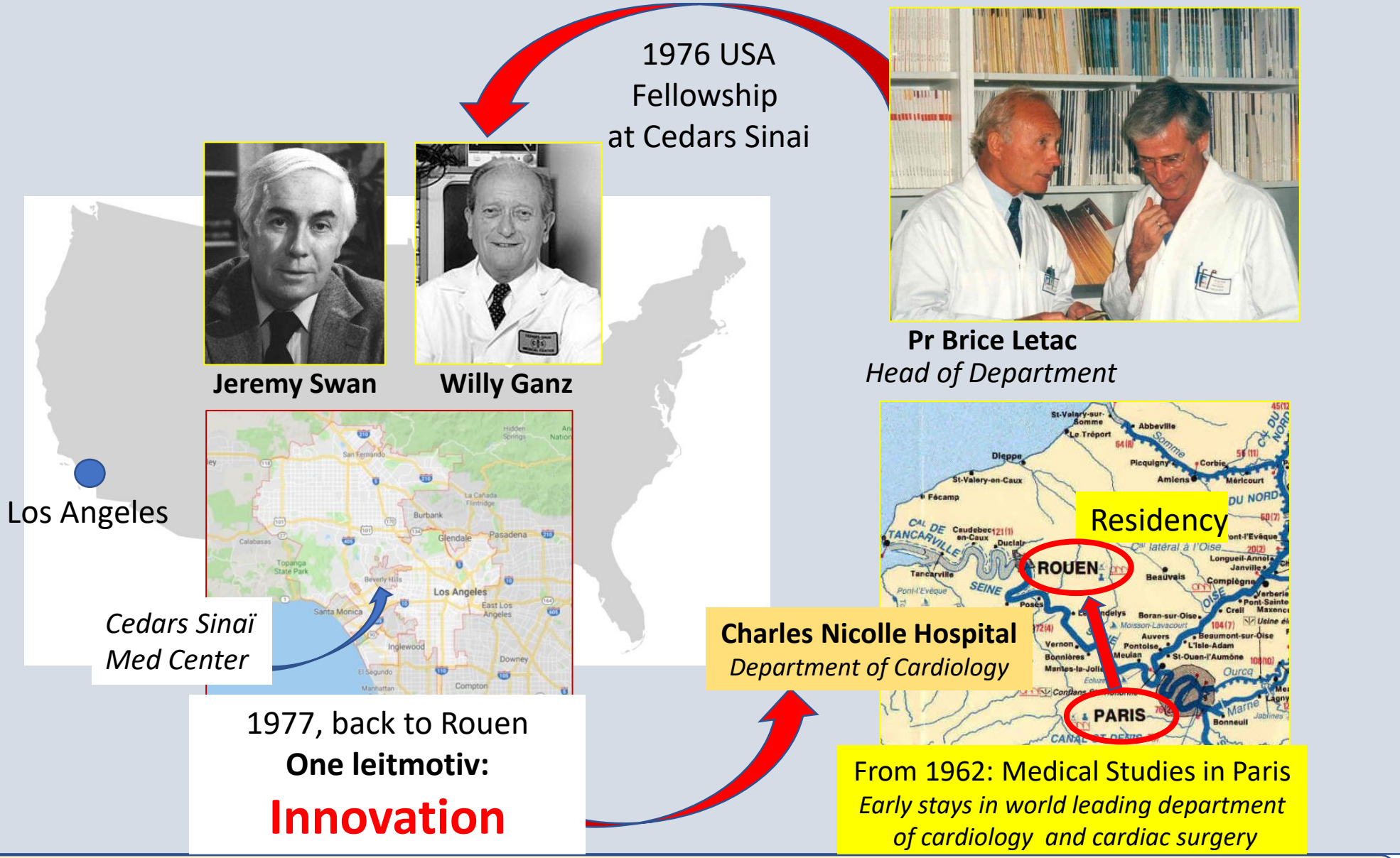


## Disclosure Statement of Financial Interest

<b>Affiliation/Financial Relationship</b>	<b>Company</b>
▶ Past Consulting Fees/Honoraria (from 2004 to 2020)	▶ Edwards Lifesciences (USA)
▶ Scientific Advisory Board Fees/honoraria	▶ Meril LifeSciences (India)
▶ Scientific Advisory Board Fees	▶ Cardiawave (France)

# Predisposing factors to the birth of TAVR in Rouen, France

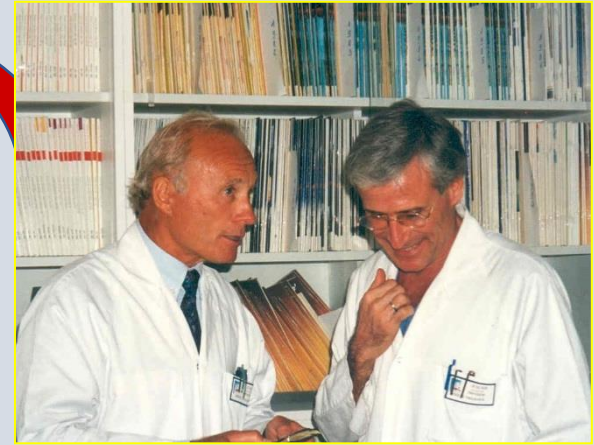
## 1 – Having outstanding mentors



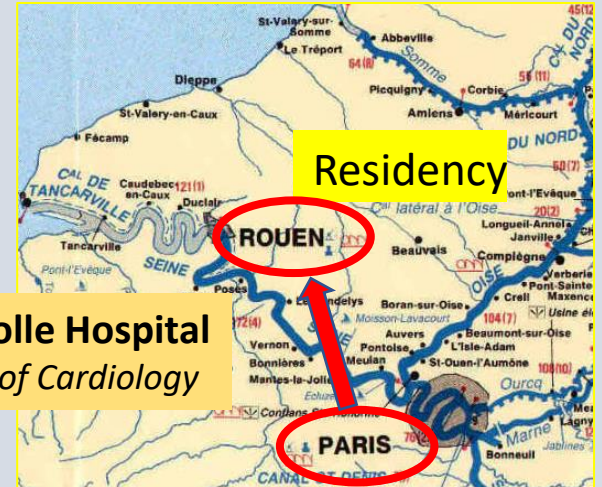
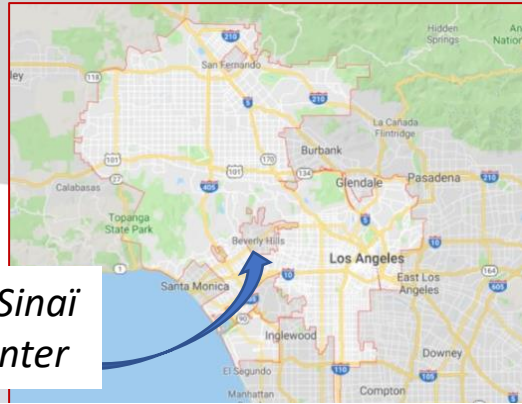
Jeremy Swan



Willy Ganz



Pr Brice Letac  
Head of Department



They taught me to never give up! “Perseverance” is the key word for innovation

# Predisposing factors to the birth of TAVR in Rouen, France

## 2 – Working with a wonderful supportive “dream team”

Since the 1990's

An outstanding and rare partnership between *interventional cardiologists* and *cardiac surgeons* and an outstanding team of nurses and technicians



# Since 1985 in Rouen

## Development of technological innovations in the field of *acquired Aortic Stenosis*

1985

**Balloon Aortic Valvuloplasty**



*F.I.M.*

*Lancet, 1986*

The same goal for these two linked innovations:

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

In the 2000s

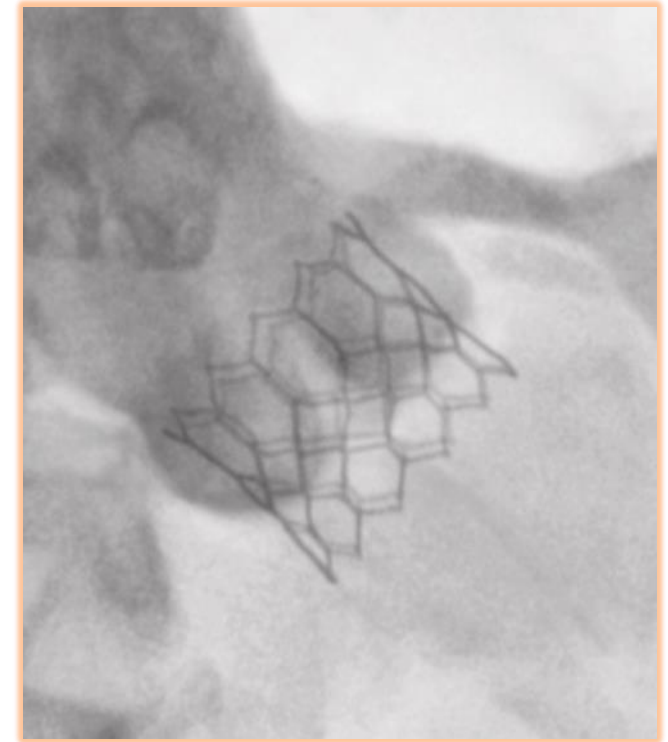
**Without SAVR (1/3 of pts):  
Mortality # 80% at 2 years**

In the 1980s,

**SAVR was declined in all patients older than 70-y  
(50% of symptomatic pts)**

2002

**Transcatheter Aortic Valve**



*F.I.M.*

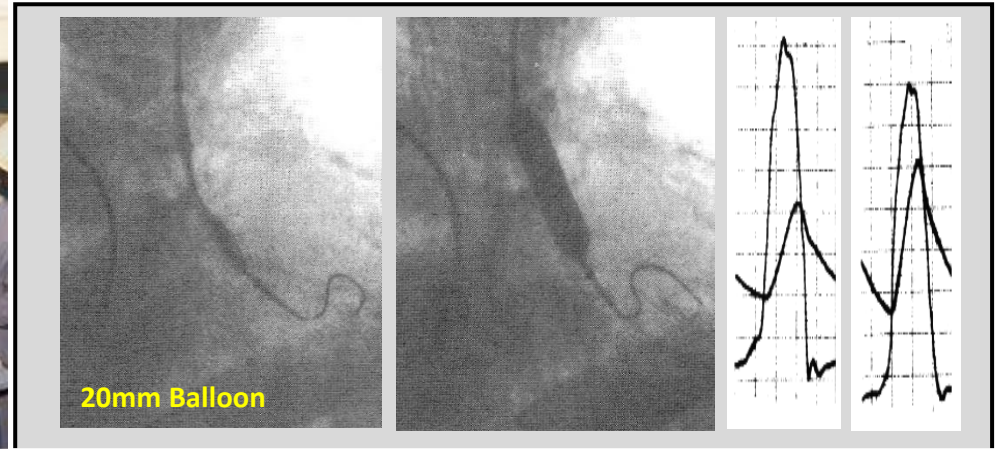
*Circulation, 2002*

**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 TAVR

As a solution to solve the issue of post-BAV restenosis

*The most challenging “crazy” concept*

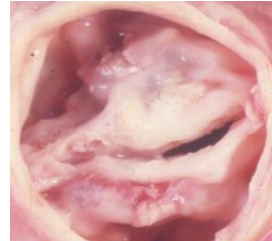
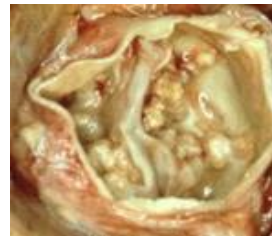
*“Implanting a valve prosthesis within the diseased calcific valve, on the beating heart, using regular percutaneous catheter-based techniques and local anesthesia !...” A. Cribier, 1990*

## First comments of cardiac surgeons

**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 Validation of valvular stenting in AS

**A Landmark autopsy study**

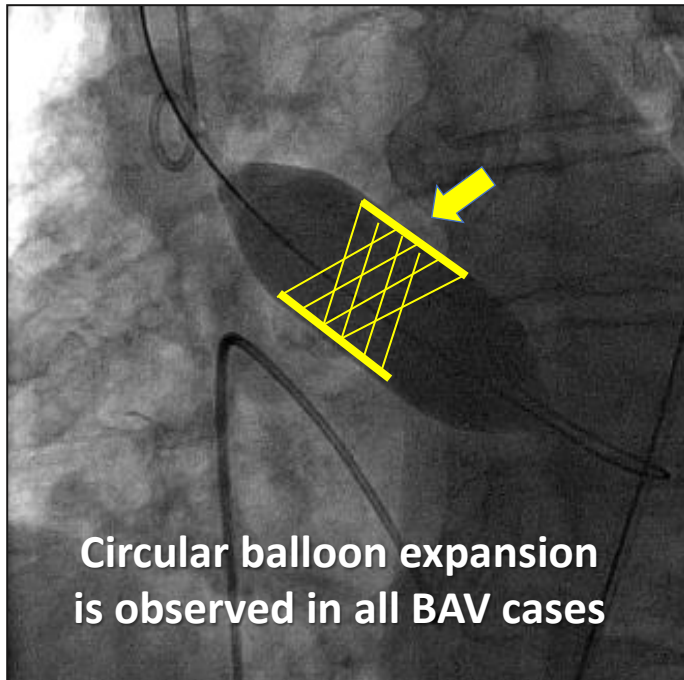


**Rouen 1994**

**(16 fresh specimen of calcific AS)**

*With H. Eltchaninoff and R. Koning*

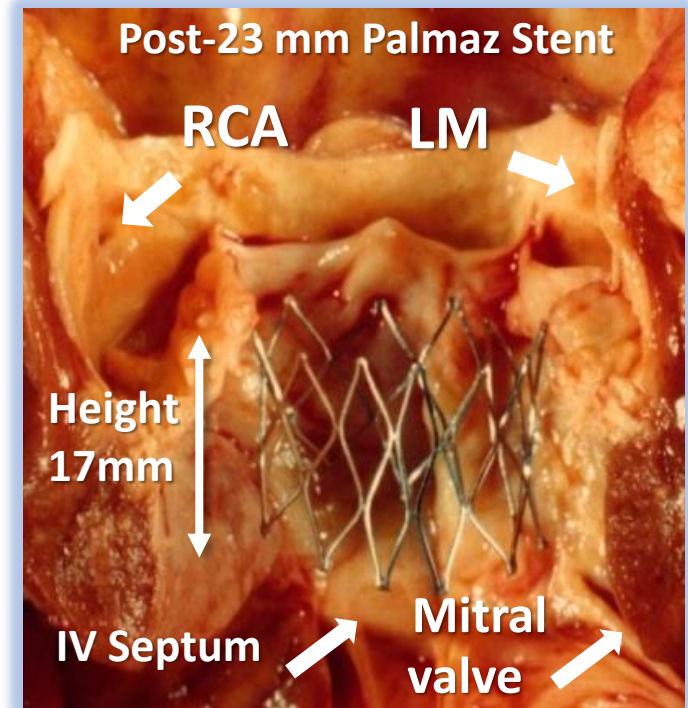
Regular observation during BAV



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



Renu Virmani, MD  
Washington DC, 2002  
**Confirmative findings**



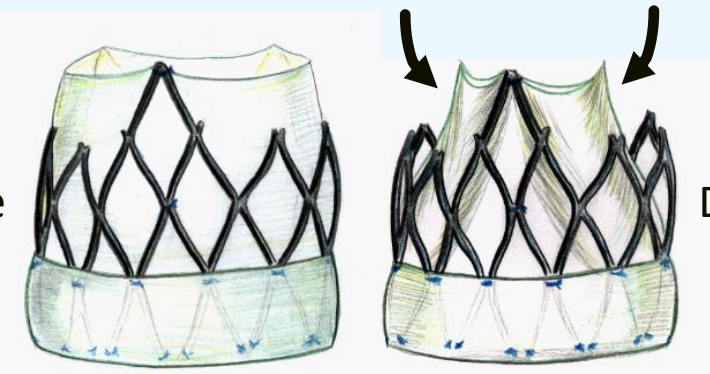
**- Respect of adjoining structures**  
- Forceps needed to remove the stent (traction force 2kg)



1994

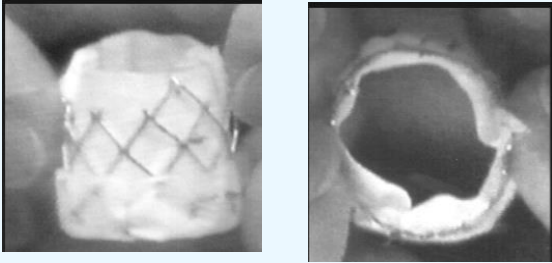
# Figuring the stented-valve and the procedure of TAVI

EU Patent application

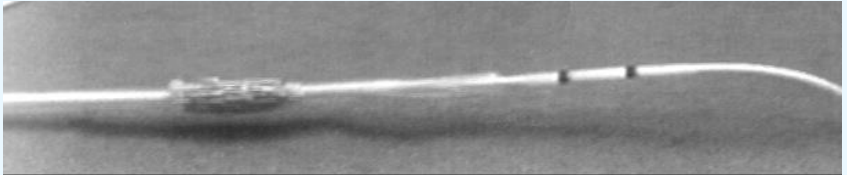


Systole                      Diastole

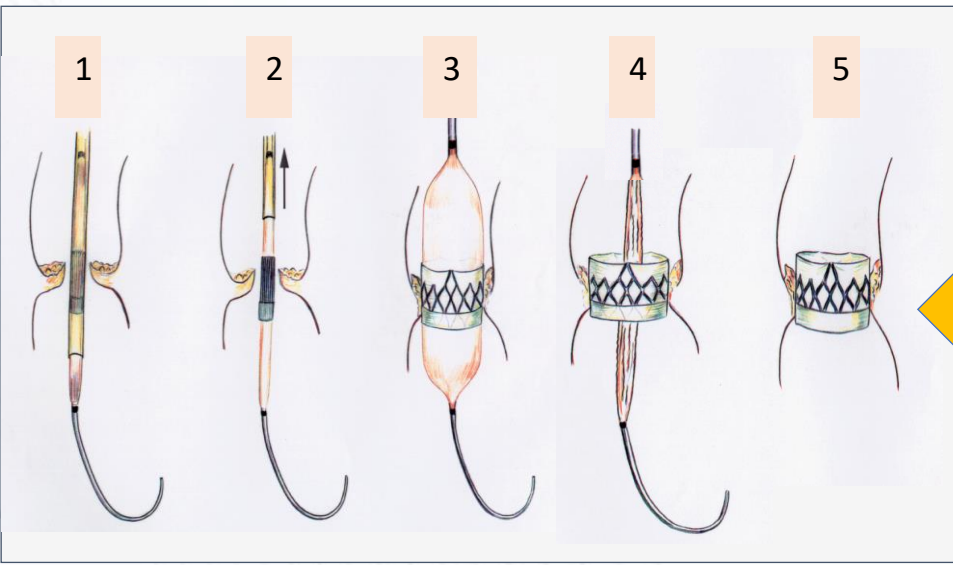
- Valve structure: biologic or polymer?
- High radial force balloon expandable stent
- External cuff



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



Crimped diameter = 8mm



1. Catheter with valve is inserted into the femoral artery.
2. The catheter is advanced towards the aortic valve.
3. The valve is deployed from the catheter.
4. The valve is positioned at the aortic valve.
5. The valve is fully deployed and seated.

Transfemoral approach  
conceivable

**Let's make it !**

# Looking for industrial support

*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



S. Rowe

A. Cribier

S. Rabinovich

M. Leon

## 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

Two engineers and two cardiologists

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

**And they  
made it !**

# 2000 The PVT Heart Valve



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

# 2000-2002 – The PVT Heart Valve

## Preclinical evaluation

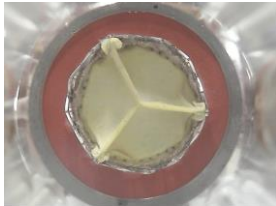
ARAN  
R&D

### VALVE TESTS

Hemodynamics

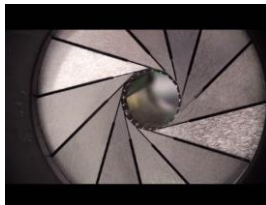


Durability (5 years)

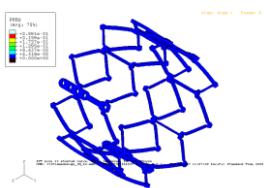


### FRAME TESTS

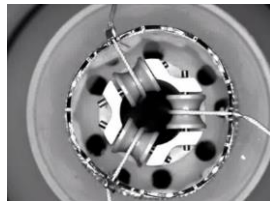
Radial force



Stent geometry



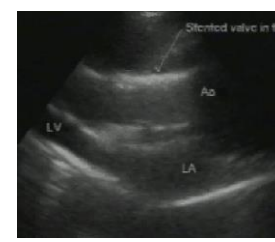
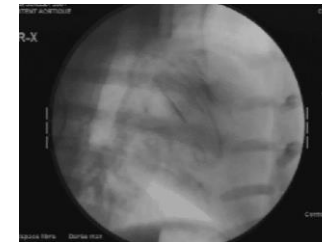
Fatigue testing



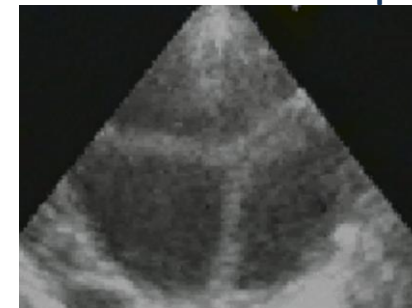
**Tri-leaflet valve**  
*(polymer, then bovine pericardium)*  
**Stainless steel stent**  
**Single diameter 23mm**  
**24F crimped size**

### IN-VIVO TESTING, Sheep model Montsouris Institute, Paris

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



Orthotopic Ao implantation



FDA  
request

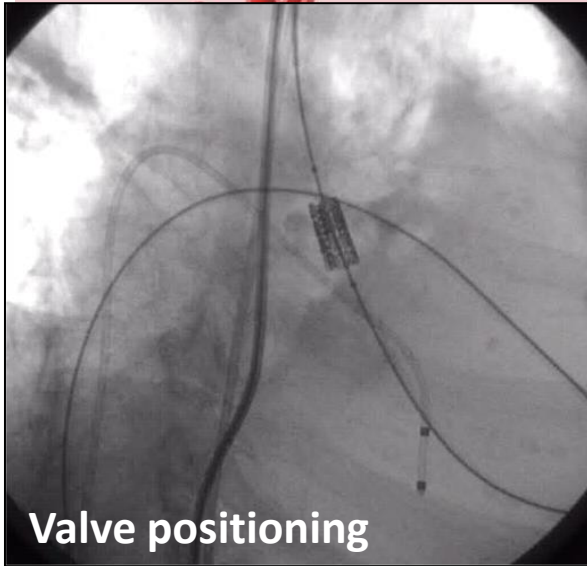


5 -Month in aorta

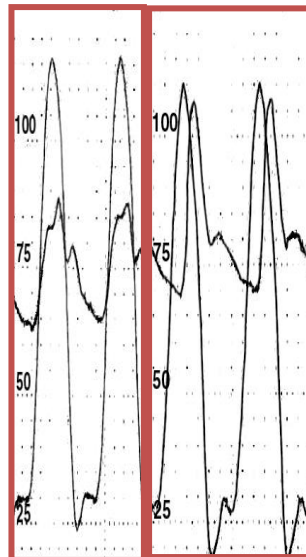
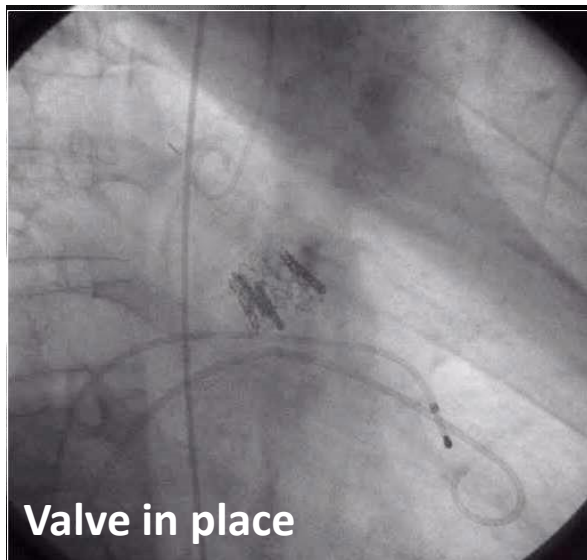
# April 16th, 2002 - The dream comes true

## F-I-M TAVR

No general anesthesia  
No TEE guidance



57 y/o dying patient  
**Cardiogenic shock, LVEF 12%**  
AVA: 0.68 cm<sup>2</sup>, bicuspid valve  
**Multiple comorbidities**  
**Subacute leg ischemia**  
(occluded Ao-bifemoral BP)  
**Floating thrombus in LV**  
No femoral access  
➤ **Failed transeptal BAV**  
➤ **TAVI as a last resort option**  
*Unplanned transeptal approach*



**A 2<sup>nd</sup> bomb blast within the medical community**

- Stupefaction
- Enthusiasm
- Incredibility and fury of cardiac surgeons

***"Him again !.."***

# 2002-2005 First Rouen series: 38 pts, compassionate basis

All inoperable - NYHA class 4 - imminent death - transeptal approach (TF retrograde in 7)

75% success (26% MACCEs) – 50% survival 1 to 6.5-year with return to normal life

*My intimate conviction that a revolution was underway*

## Patient # 3



- 83 y/o dying woman
- Multi comorbidities
- Recent anterior AMI
- Cardiogenic shock



6-month



TCT  
Washington DC  
1 year



2 years



6.5 years

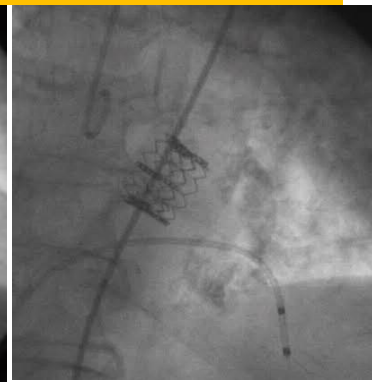
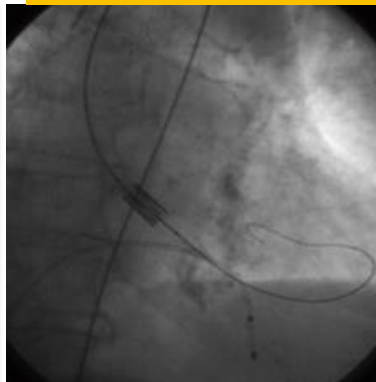
## Patient # 10

- 2004- 85 y/o woman with severe AS
- Massive pulmonary edema
- Cardiogenic shock
- **Associated MS: no possible TS route**

**First ever planned TF retrograde approach**

- Local anesthesia / sedation
- Uneventful procedure duration: 60 min

First vision of a THV implanted retrogradely



Unchanged hemodynamic results



- 2009 - 5-Years

**Better results could be anticipated in less severely diseased patients**

# The first steps of TAVR offshore

J. Webb



Vancouver

B. O'Neill



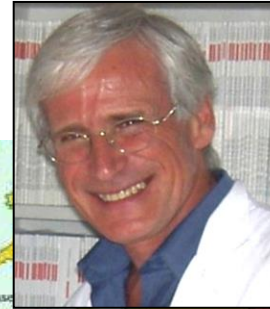
Detroit

M. Leon



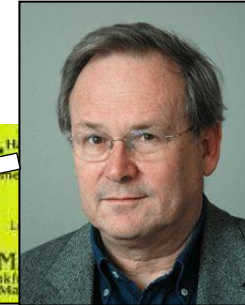
New-York

A. Cribier



Rouen

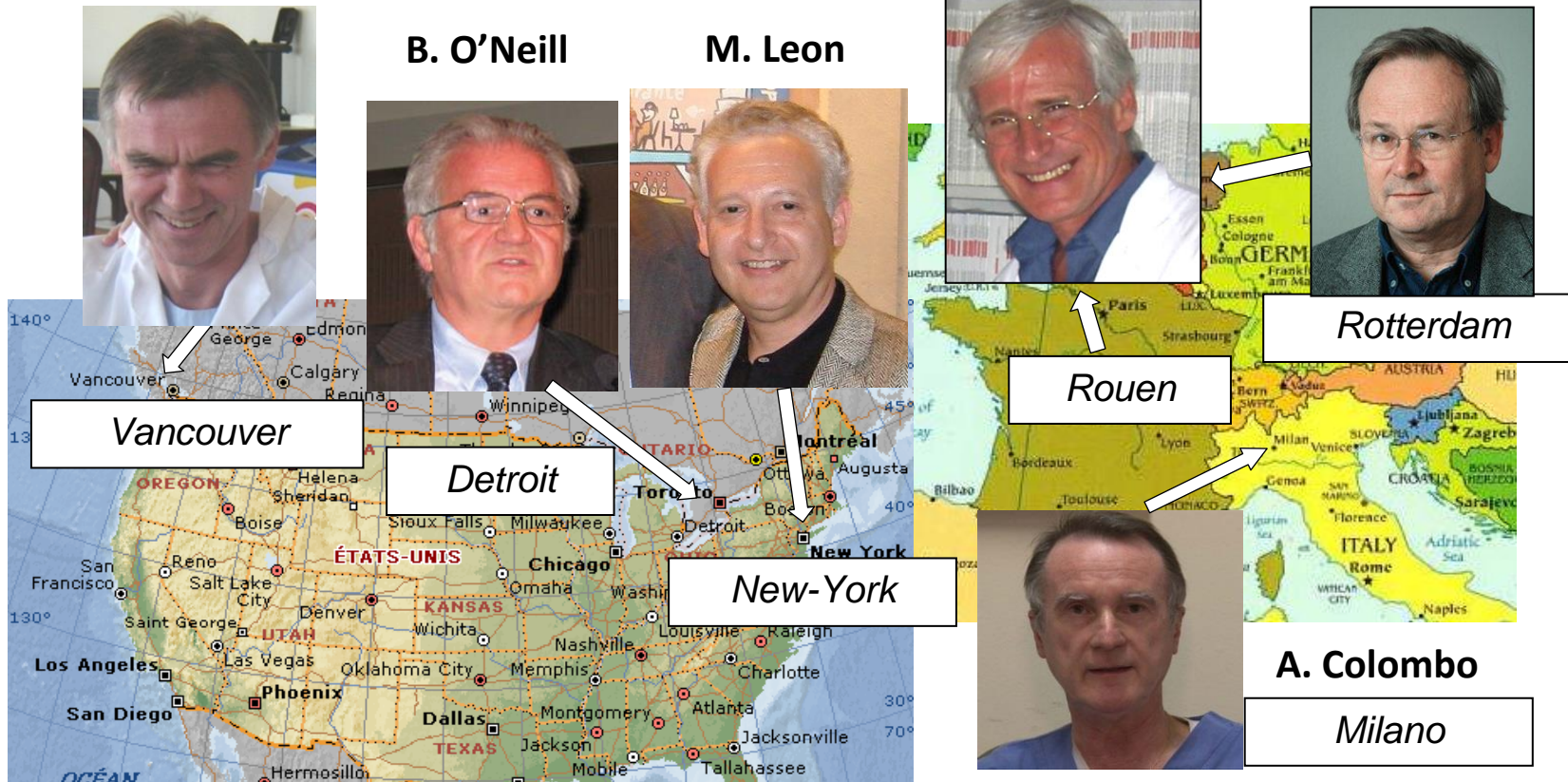
P Serruys.



Rotterdam

A. Colombo

Milano



Some breathtaking results,  
despite the technically difficult transeptal approach

2005: the 100-patient mark was passed



**2004**

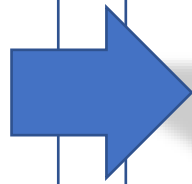
# A major milestone

## Edwards LifeSciences acquires PVT



**Cribier-Edwards**

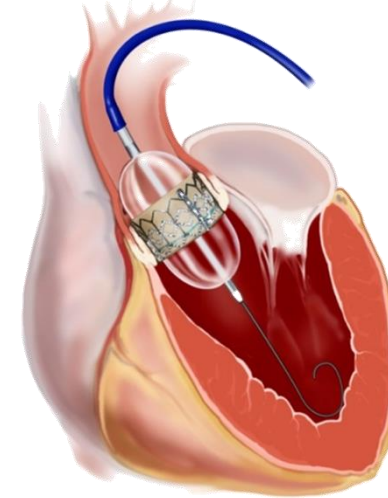
- 23mm size
- Equine pericardium
- 1/3 external coverage
- Sheath size 24F
- Mainly implanted via the transseptal approach



**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



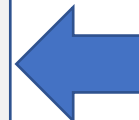
**2004: RetroFlex**  
*Steerable Delivery system*

### 2006: RetroFlex 3



**2006-2009: European Registries including SOURCE**

**2009: Pivotal randomized PARTNER US Trial**



**2005** Another revolution

*Transapical access*

*Surgeons start being involved with in TAVR*

*The devil enter the OR !*

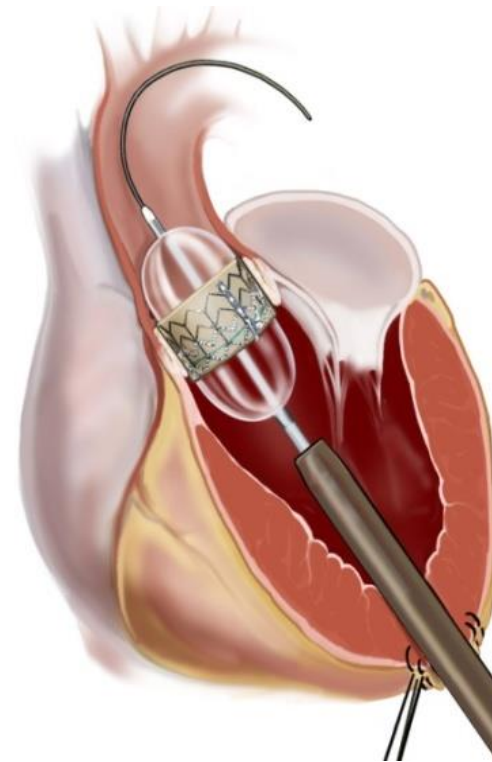


M. Mack

F. Mohr

A. Cribier

Leipzig 2005  
F-I-M Transapical TAVI



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

SV Lichtenstein  
*Vancouver, Can*



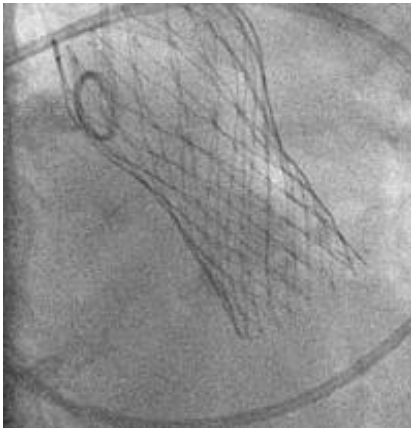
Double apical purse-string

**With TF and TA, almost all TAVR candidates can be treated**

# 2005 Launch of a concurrent device

*The self expanding CoreValve*

*later acquired by Medtronic*



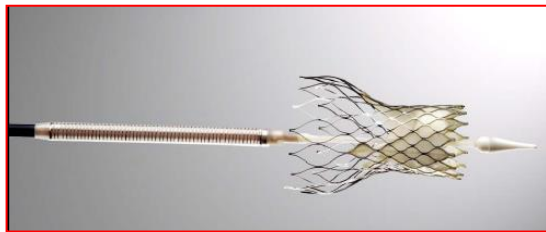
Jacques Seguin



Eberhard Grübe



J.C. Laborde



**Smaller 21F sheath size:**  
*A convincing feature for many operators*

*Start of a fair and ongoing competition between the two TAVR concepts*

**This device in addition to the balloon expandable system plaid an important role in the worldwide expansion of TAVR**

**From 2005** No one could have predicted  
the prodigious expansion of TAVR over 20 years

**The reasons of success**

**Continuous and rapid  
technological improvements  
making TAVR easier, faster, safer**  
*Major drop of severe complications*

**Rigorous scientific evaluation  
following a challenging and  
very unusual pathway in medicine**  
*from higher risk patients to all comers*

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## The reasons of success

**Continuous and rapid technological improvements making TAVR easier, faster, safer**  
*Major drop of severe complications*

- **Better patients screening (MSCT)**
- **Alternative approaches**
- **New TAVI systems,**  
*Medtronic CoreValve in first place*
- **Improved valves and delivery systems**  
(lower profile, multiple sizes, improved frame geometry, prevention of PVL)
- **New indications (V-in-V, bicuspid valves)**

- **Retrograde TF approach in # 95%**
  - **Minimalist strategy**  
➔ **«Democratization» of TAVR**

# From 2005 No one could have predicted the prodigious expansion of TAVR over 20 years

## The reasons of success

Continuous and rapid technological improvements making TAVR easier, faster, safer  
**Major drop of severe complications**

*Constant and rapid improvements of TAVI systems*

### « Historical » valves

**Edwards**

	<b>2005</b> Edwards SAPIEN	<b>2009</b> SAPIEN XT	<b>2012</b> <b>SAPIEN 3</b>
Sheath size	24F	18-20F	14-16F
Valve sizes	23, 26mm	23, 26, 29mm	20, 23, 26, 29mm

**Since 2020**

	<b>SAPIEN 3 Ultra</b>	<b>SAPIEN 3 Ultra Resilia</b>
Skirt 40% taller		Improved durability Advanced Ca-Technology
	14-16F	20, 23, 26, 29mm

**Medtronic CoreValve**

	<b>2006</b>	<b>2012</b> <b>EVOLUT</b>
Sheath size	21F → 18F	14F
Valve sizes	26, 29mm	23, 26, 29, 31mm

	<b>EVOLUT R</b>	<b>EVOLUT Pro</b>	<b>Pro +</b>
		External skirt	Advanced sealing Lower delivery profile
	23, 26, 29, 31mm	14 F	23, 26, 29, 31mm 16 F

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## The reasons of success


Continuous and rapid technological improvements making TAVR easier, faster, safer  
**Major drop of severe complications**

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## Newer TAVI systems


BOSTON SCIENTIFIC

**SYMETIS**



➔


**ACURATE NEO 2**



External skirt


ABBOTT

**PORTICO**



➔

**NAVITOR**

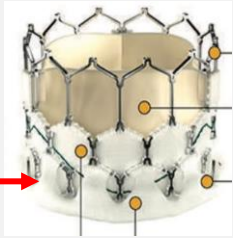


External skirt

*Self expansion  
 Intra-annular insertion  
 Easier coron access  
 Easier repositioning  
 Less PVL*

*Supra-annular insertion  
 Self alignment  
 Simple delivery  
 Easy coronary access*

MERIL (India)



External skirt

Large upper-cells

MYVAL

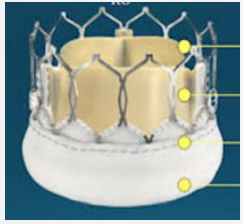
**Multiple sizes with *half sizes* from 20 to 32 mm for optimal annulus coverage – 14 F sheath for all sizes**

Frame:  
2 rows of interlaced octagonal cells

↓

OCTACOR

Reduced foreshortening by 50%



Precise and predictive deployment (new marker)

**A new balloon-expandable device**

# From 2005 No one could have predicted the prodigious expansion of TAVR over 20 years

## The reasons of success

Continuous and rapid technological improvements making TAVR easier, faster, safer  
*Major drop of severe complications*

Rigorous scientific evaluation following a challenging and very unusual pathway in medicine  
*from higher risk patients to all comers*

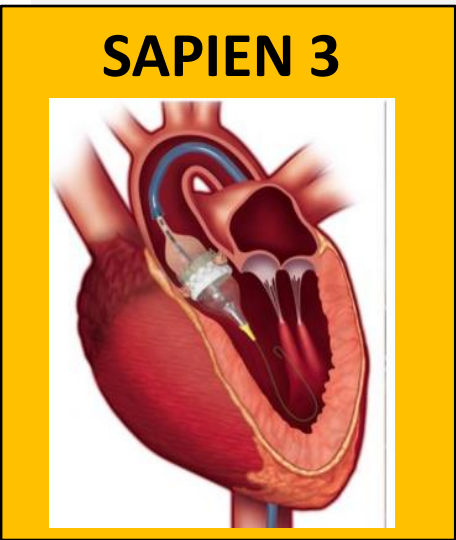
## A new paradigm

- *20 years ago, TAVR was conceived for inoperable or very high-risk patients*
- ↓
- *SAVR is now reserved for patients who are not optimal candidates for TAVR*

- Thousands of patients enrolled in
- Multiple national and international controlled registries
  - Matched registries versus SAVR
  - *Randomized trials vs SAVR*
- ➔ In patients at *decreasing risk*, with Edwards and Medtronic TAVI systems



# From 2005 No one could have predicted the prodigious expansion of TAVR over 20 years



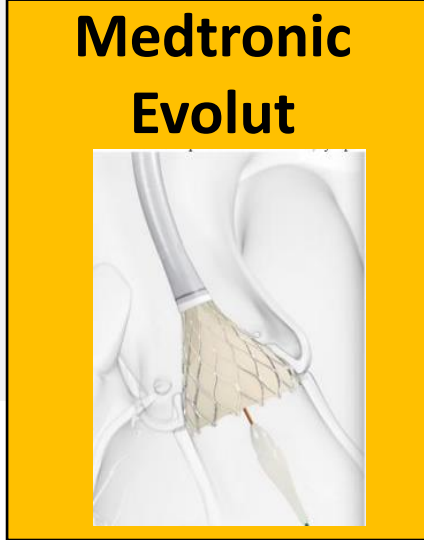
**PARTNER 3**

**2019**

## The apotheosis of TAVI

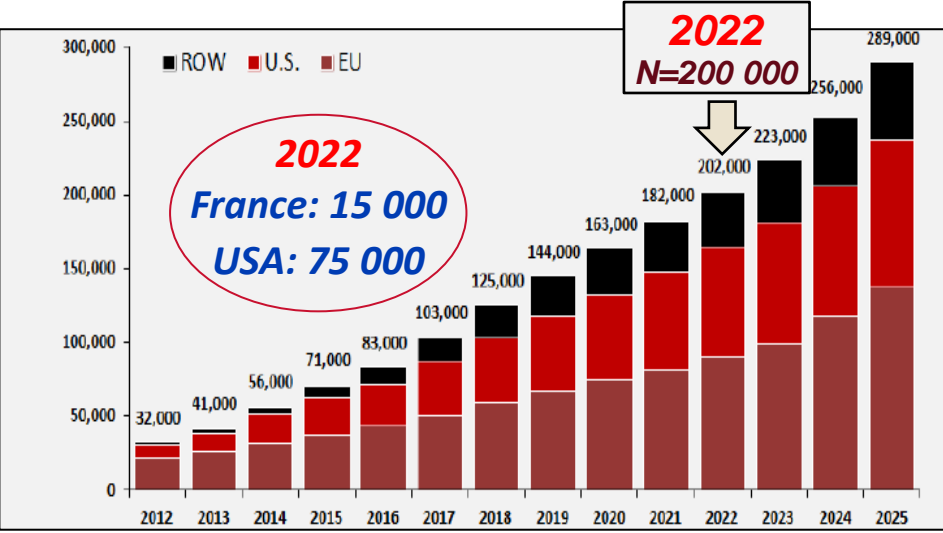
*FDA Approved TAVI for LOW-RISK Patients > 65 years*

2021 - European recommendations in Low-Risk patients: all patients > 75-year



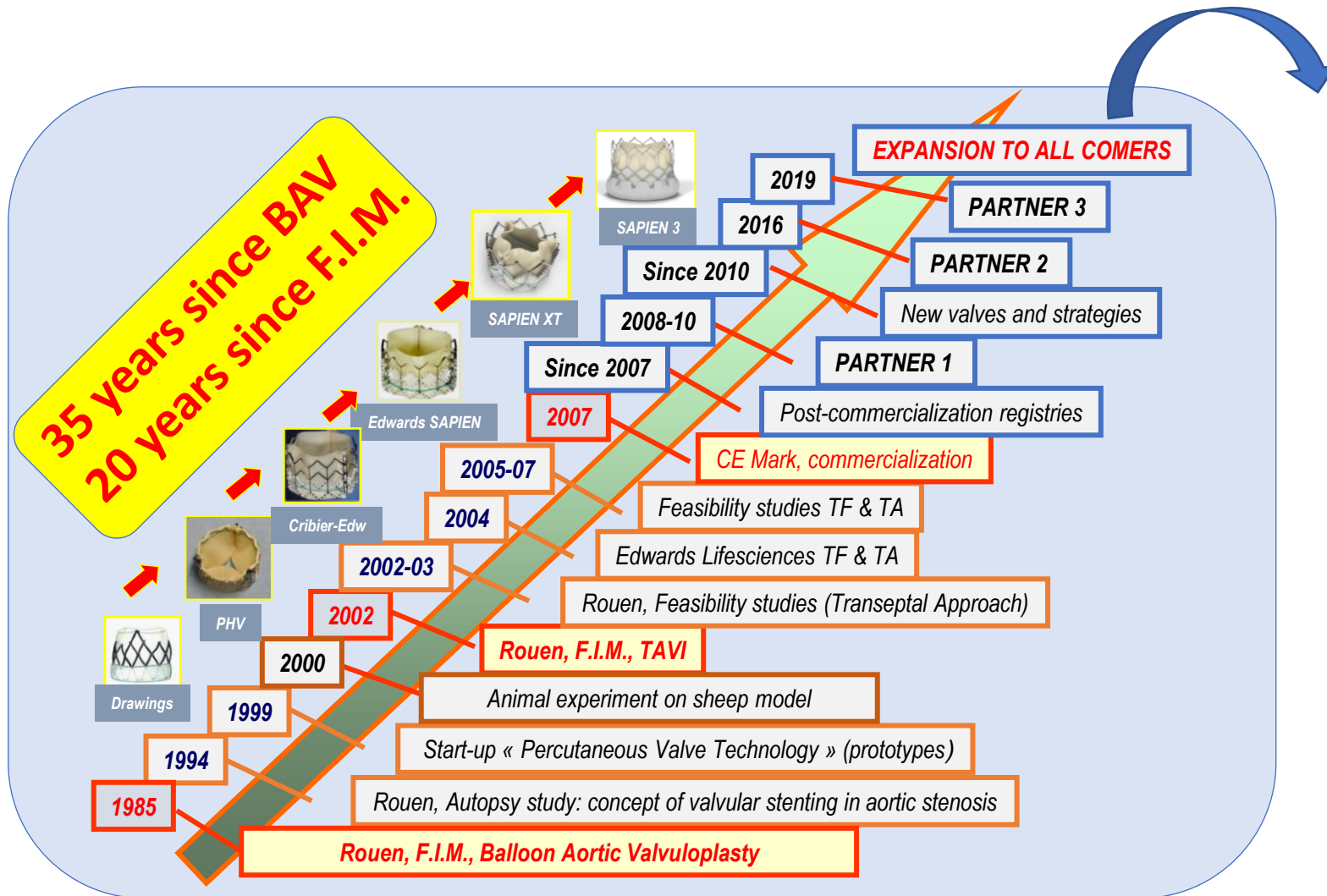
**EVOLUT LOW-RISK**

- **A total of # 2.000.000 TAVI performed worldwide (> 80 countries)**
- **TAVI market exceed SAVR market in many countries including USA**
- **Expected growth of >10% per year**



**And the future of TAVR looks even brighter !**

# Developing TAVR: A long bulky road



## Extension of TAVR indications

### Already achieved:

- Valve-in-Valve
- Bicuspid valves

### In progress:

- Asymptomatic AS
- Moderate AS + HF
  - High-risk AR
  - TAVR with concomittent diseases

➔ Besides paving the way for many interventional techniques for treating other valvular and structural heart diseases, TAVR has changed the entire medical culture by bringing the teamwork concept