

The Odyssey of TAVR

From Concept to Clinical Results

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

► Consulting Fees/Honoraria

Company

► Edwards Lifesciences

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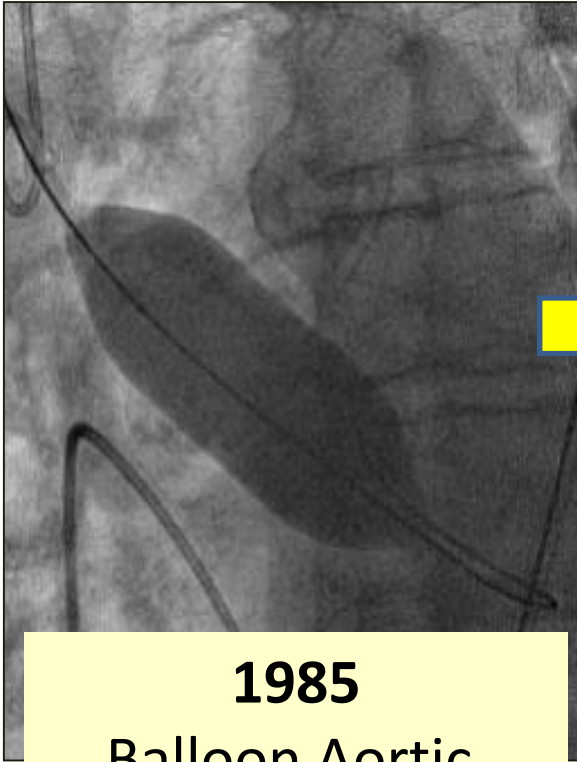
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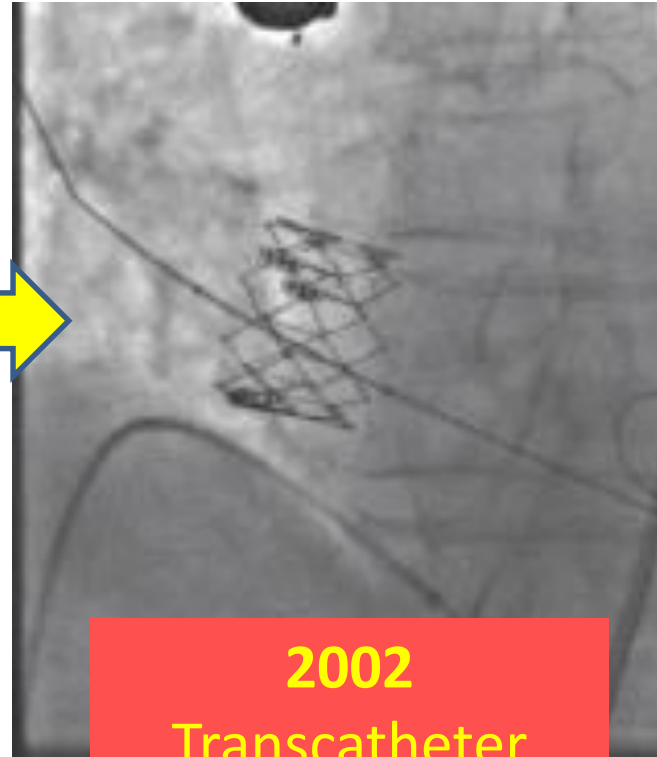
Company

► Edwards Lifesciences

Rouen: Since 1985, development of new catheter therapies in the field of Aortic Stenosis



1985
Balloon Aortic
Valvuloplasty (BAV)



2002
Transcatheter
Aortic Valve (TAVI)

« Don't undertake a project unless it is manifestly important and nearly impossible » Edwin Land

Rouen team: The key of success for developing TAVR

A “Dream Team” of nurses, technicians, TAVR coordinator, cardiologists and surgeons

Since 2013



Pr Eric Durand



2002

Pr J.P. Bessou
*Head of
Cardiac Surgery*

Pr H. Eltchaninoff
*Head of
Cardiology*

An incredible high and rare relationship, support and interaction between cardiac surgeons and interventional cardiologists

Rational for Transcatheter Techniques in AS

Recognition of an important / unacceptable unmet clinical need

AS: most frequent acquired valvular disease in adults: 5-7% of people > 65-y
Very high short-term mortality after the onset of symptoms

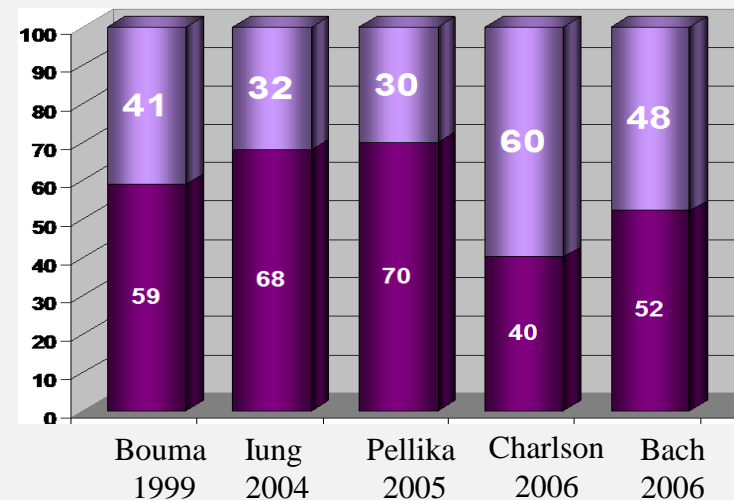
SYMPTOMATIC AS = SAVR

The only life-saving treatment,
and the standard of care for decades



No operation in 1/3 of patients

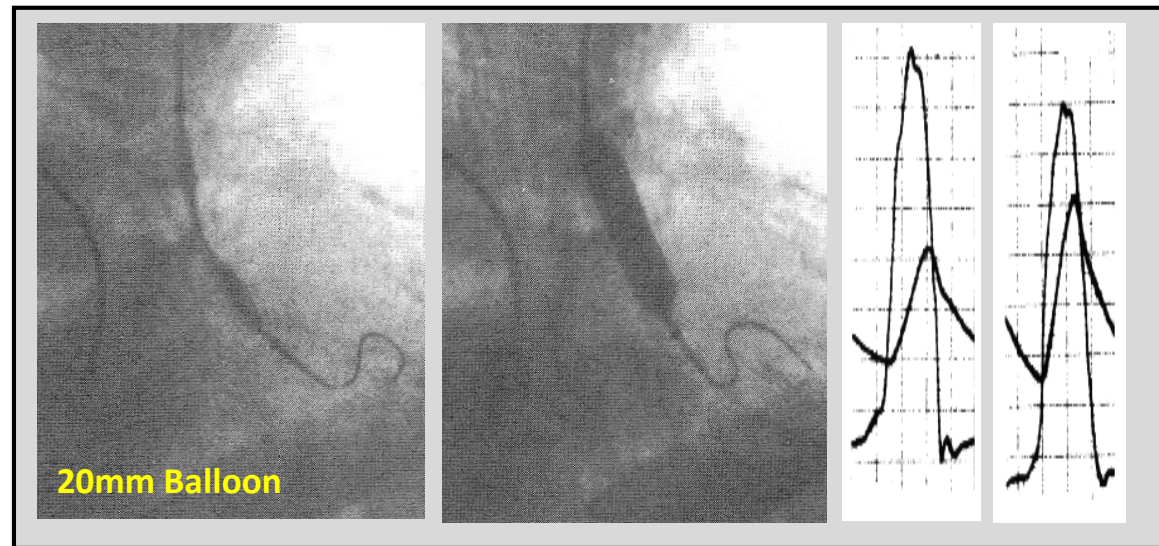
■ No AVR ■ AVR



- *In the late 1980s, age per-se was a contra-indication to SAVR*
 - *95% of SAVR patients in Rouen were < 70-y*
- *Early death of all others patients after multiple re-hospitalizations*
UNACCEPTABLE !

Daring to think out of the box: Enlarging the aortic valve with a balloon

Sept 1985: F-I-M Balloon Aortic Valvuloplasty



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

ALAIN CRIBIER
NADIR SAOUDI
JACQUES BERLAND

THIERRY SAVIN
PAULO ROCHA
BRICE LETAC

THE LANCET, JANUARY 11, 1986

- Two years without symptom !
- Return to normal life



**A memorable reaction
of the medical community !**

Facing the success, then the failure, without giving-up !

1985-1991: Explosive growth of BAV worldwide

1991: Evidence of a lack of long term benefit

- Thousands of patients enrolled in national and international registries

- > 1000 index articles on BAV

➤ Symptomatic improvement, less rehospitalization

➤ Single BAV: No effect on survival

➤ **Early valvular restenosis**

BAV progressively abandoned

Solving the issue of early restenosis became my obsession



A TRANSCATHETER VALVE ?

Which optimal solution?

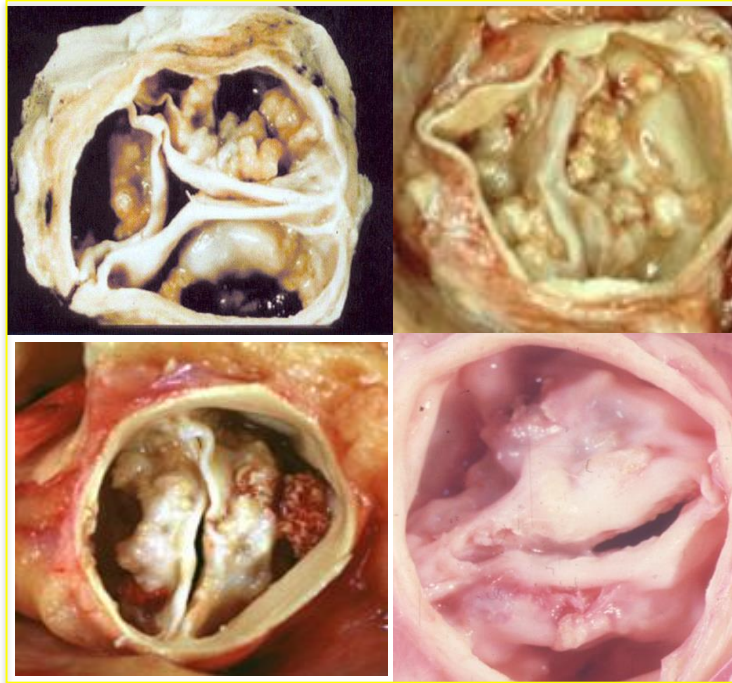
1994: Claiming the most challenging goal

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

At first sight, the most « crazy » idea

IMPOSSIBLE !

Heavily calcified valves !



DANGEROUS !

Surrounding Structures !

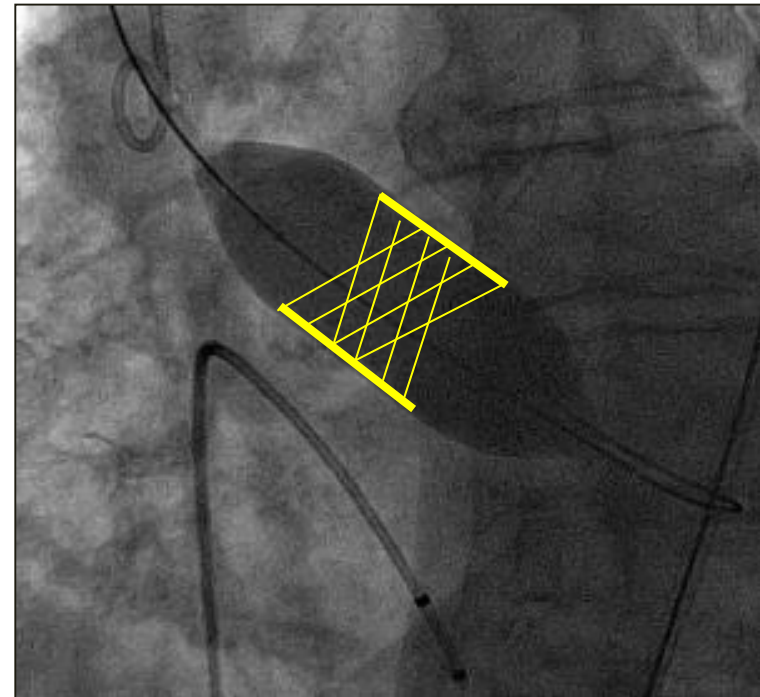
Which arguments for a stented-valve in AS ?

In BAV, high pressure balloon inflation (4-5 Atm) is able to open any calcified aortic valve!

A stent with a **high radial force** could be used during BAV to prevent post-BAV restenosis

A **valvular structure** should be attached within the stent

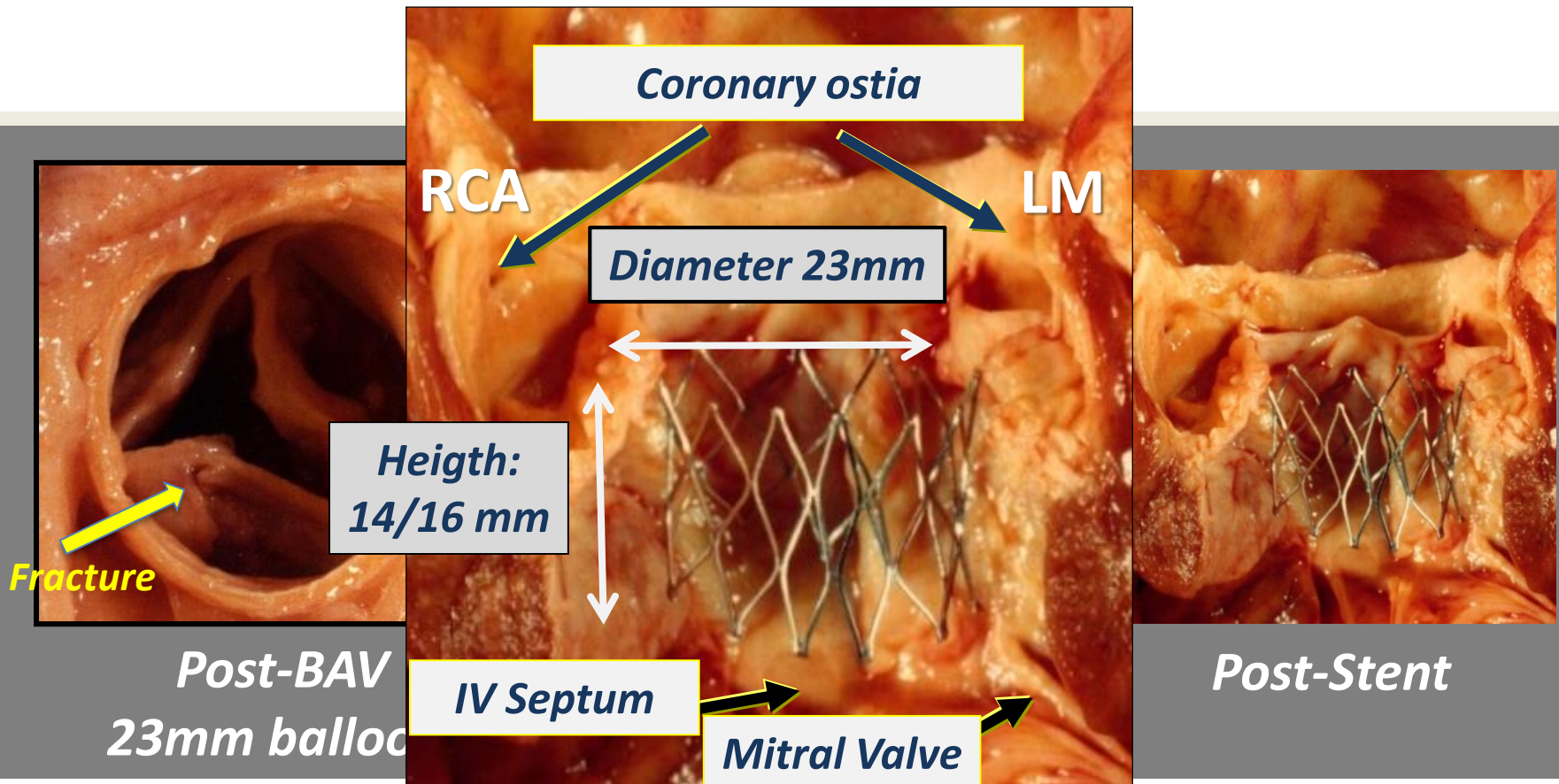
The diseased native valve *should not be retrieved* but used as **a support to anchor the stent**



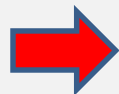
The « stented-Valve »: A challenging combination of balloon expandable frame and valvular structure

Validating the concept of intra-valvular stenting in calcific AS

1994: Autopsy study: The landmark step to move forward



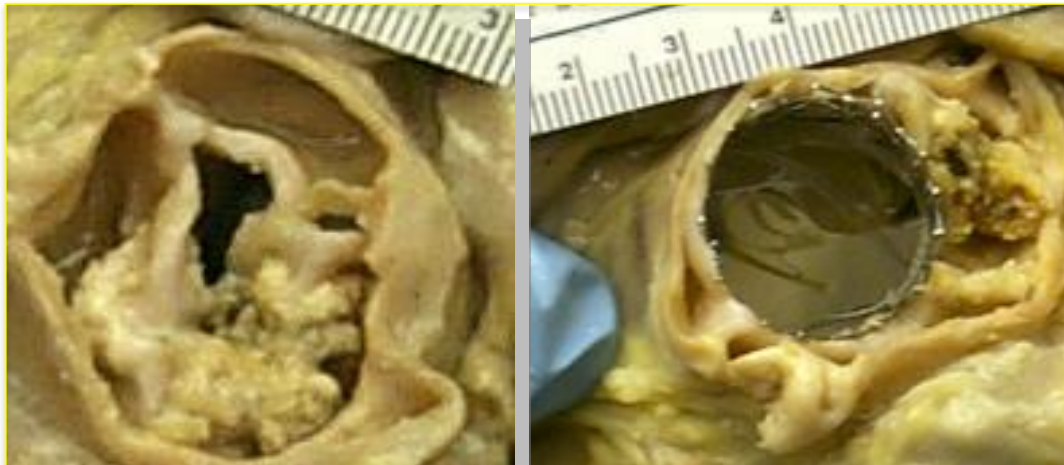
Forceps needed to retrieve the stent



Low risk of device embolization

Confirmative cadaver study (April 2002)

Renu Virmani, MD, Washington DC, and US PVT members



Circular Palmaz stent opening



***Traction force >2kg
to dislodge the stent***

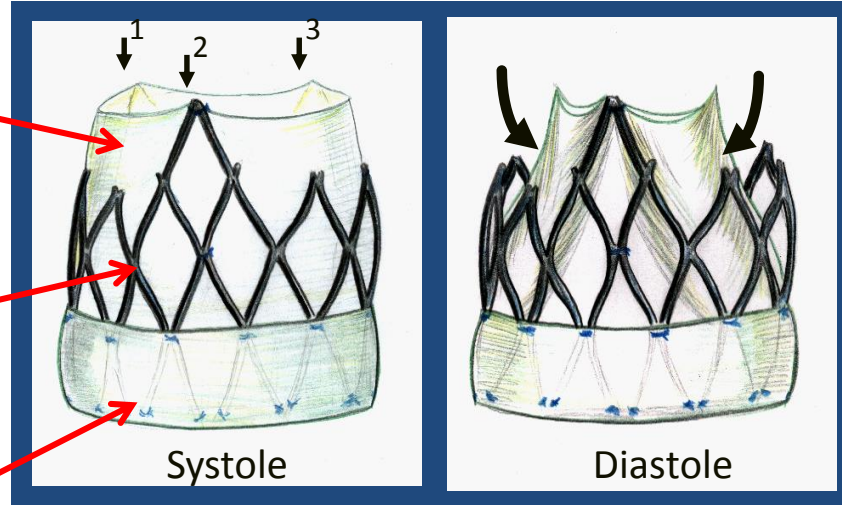
1994: Conceiving a patentable model of transcatheter valve

A. Cribier, 1994

Tri-leaflet
Valve ?

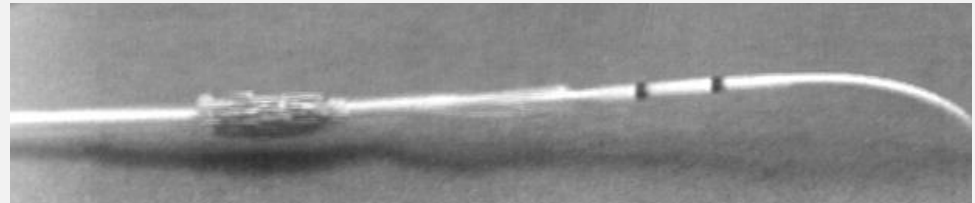
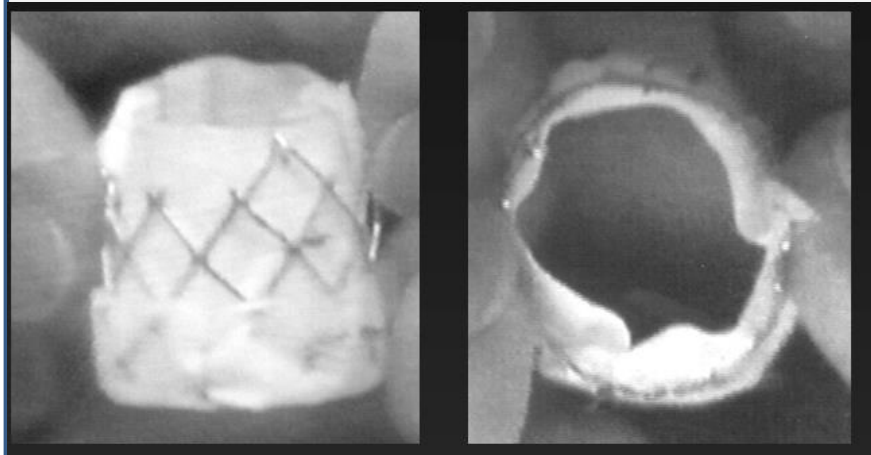
Stainless steel stent
highly resistant
to compression

External coverage



Polymer or
Biologic Valve?

JP Bessou, Cardiac Surgeon, Rouen, 1994 : Hand-made model of stented valve



Crimped diameter: 8mm

Compatible with transfemoral access

**How to deal with the negative opinion of experts ?
Listen..., take a deep breath, and keep going !**

1994-1999: *Project turned down by all biomedical companies*

All experts (cardiac surgeons) steadfastly against the idea:

- *Technically impossible and clinically irrelevant*
- *Major life-threatening issues*
- *Stroke, coronary occlusion, valve embolization, mitral and aortic regurgitation, endocarditis...*
- *Would never be approved by FDA*

The most stupid idea ! Just forget it!

Keeping intact the power of conviction after 5 years of failure when meeting bright open-minded people

July 1999: Creation of Percutaneous Valve Technologies



December 1999

**Signed agreement with
ARAN R&D, Caesarea, Israel**

➡ Investment, Development



Aran R&D, Caesarea, Israel

Starting a great translational research program

1999: PVT first Valve Design Concepts



The PVT Heart Valve

Finalized device: the PVT Valve

Tri-leaflet valve (polymer, then equine pericardium)
Stainless steel stent, single diameter of 23mm

Multiple laboratory testing: new tools for a new technology

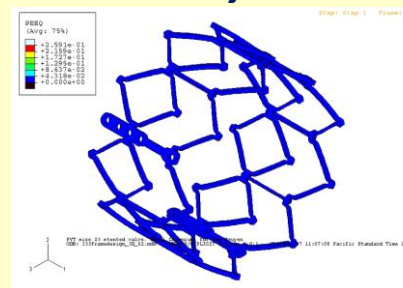
Hemodynamics



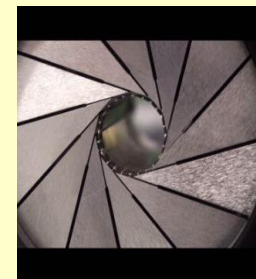
Durability (5 years)



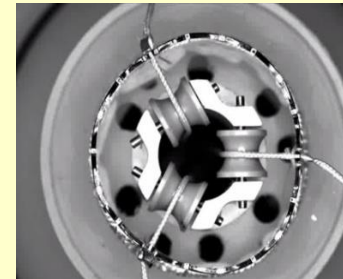
Finite Element Analysis



Radial Force



Fatigue



Moving to pre-clinical in-vivo testing

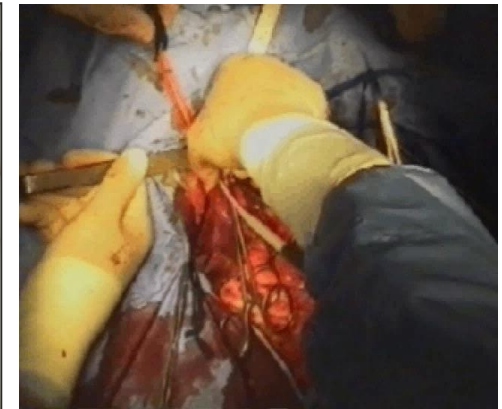
CERA, Montsouris Hospital, Paris



Crimped THV



Carotid approach

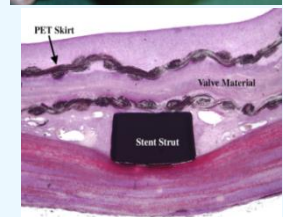


1999-2002: Animal program (sheep model): acute & chronic studies

In-Ao and pulmonic THV implantation



5-Mth echo and anatomic / histologic findings



Being aware of significant deficiencies of the animal model for evaluating THV implantation in human

Minor differences in physiology and anatomy can lead to profound differences in treatment safety & efficacy in human

- 
- No aortic valve calcification / degeneration
 - Different arch anatomy, size of vessels, and other structures

BUT multiple

Start thinking about a first human application
The most difficult decision !

sheaths

aspects

coagulant regimen

Have nerves of steel to deal with the first human case especially in a critically ill patient

April 16th, 2002, Rouen, F.I.M. – TAVR: *From Dream to Reality*

57-y/o man, cardiac... LVEF 12%
Multiple comorbidities... aortic thrombus
Aorto Bi-furcated... femoral access
→ ... 4V

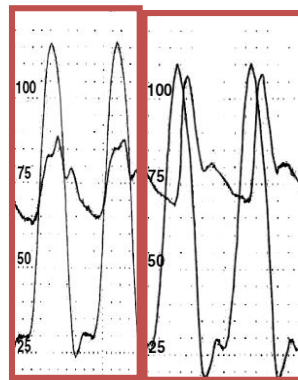
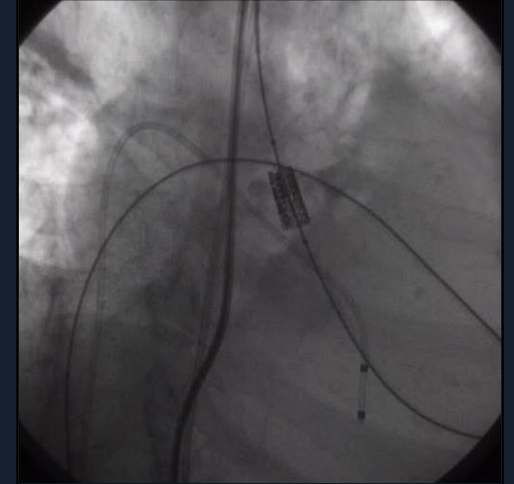
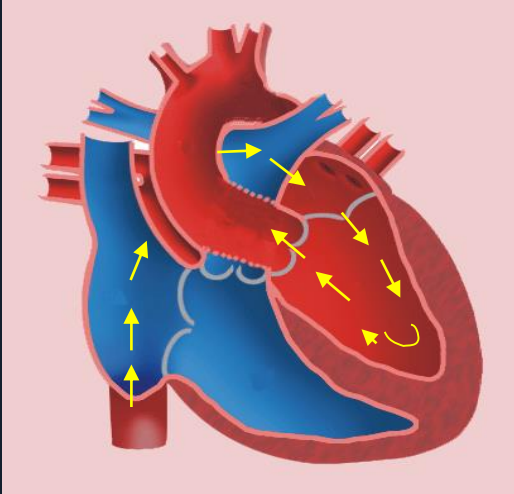
M. Leon:
High likelihood of failure
but... it just might work
and save his life!

Go Ahead !....

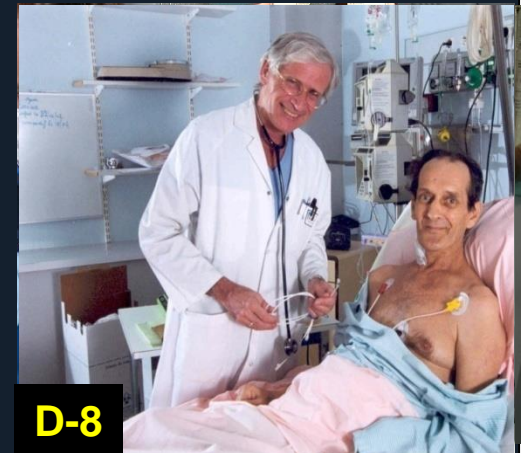
**→ Most challenging of unplanned
transseptal... a live saving procedure
in a young dying patient**

All current contra-indications of TAVR!...

April 16, 2002- First-In-Man TAVI



It works!

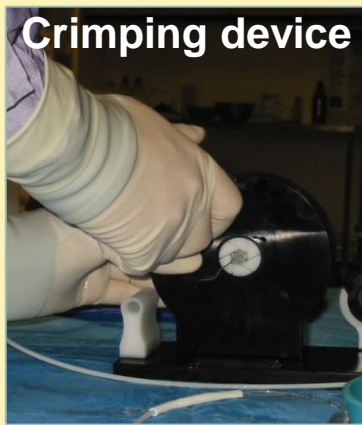


D-8

Remaining stoic when dealing with your country's Heath Regulation to start a first series of TAVR

Conditions: Imminent death (life expectancy 2 weeks), TS approach

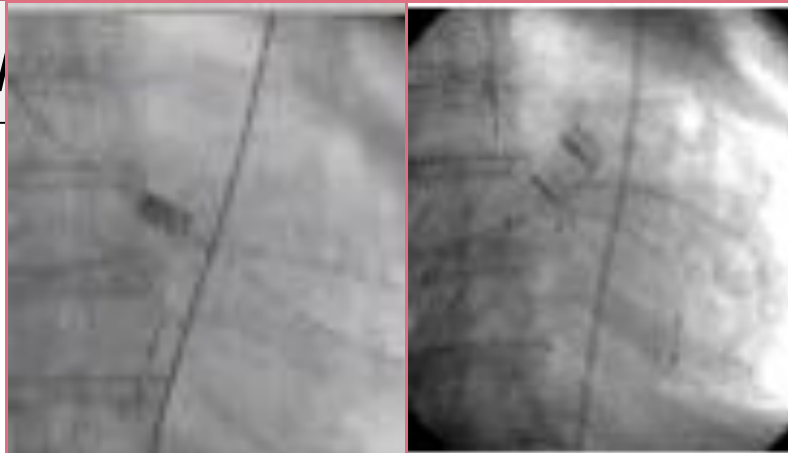
2002-2005: 40 Patients (I-REVIVE & RECAST Trials)



Equine Pericardium



Single size 23mm



4 Pts survived > 5-y

1 Pt survived 6.5-y

with no symptom
and optimal valve
function

Cribier et al: JACC 2004 & 2006

TAVR (Transseptal) takes its flight in the world

J. Webb



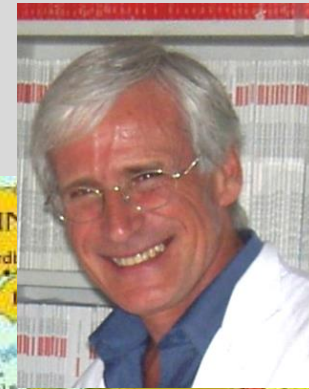
B. O'Neill



M. Leon



A. Cribier



Vancouver

New-York

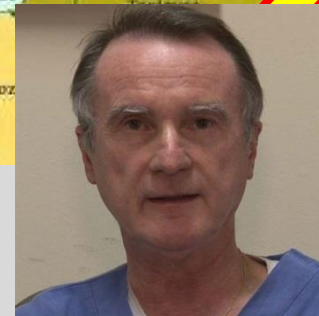
Rouen

Detroit

Milano

2004: a total # of 100 TAVR performed in the world...

A. Colombo



**Agreeing to see the baby grow in other hands
It's for his good !**



TAVI enters a

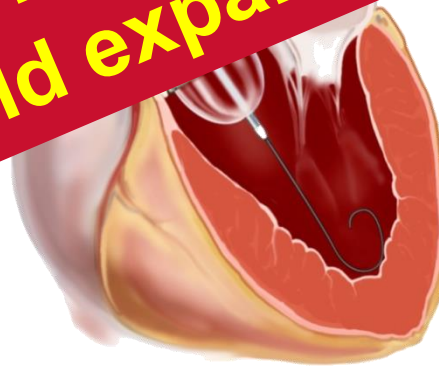
New valves

**The beginning of a fairy tale:
From concept to clinical reality:
15 years of continuous success
PARTNER 1, PARTNER 2, PARTNER 3...
Explosive world expansion of TAVR**

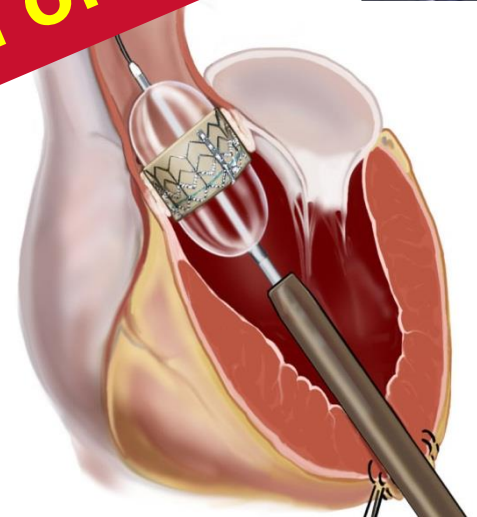
Cribier



- 50% external coverage



Vancouver, Canada
J. Webb



Leipzig, Germany
M. Mack, F. Mohr



TAVR: a 18 years long journey


From concept

2002 TAVI is conceived for patients who are not optimal candidates for SAVR



To clinical application

2020 SAVR is indicated in patients who are not optimal candidates to TAVR !

The background of the slide is a photograph of a sunset or sunrise. The sun is a bright, glowing orb in the center-right, casting a warm orange and yellow light across the sky. Silhouettes of trees are visible against the bright sky, particularly on the left and right sides.

Transcatheter Aortic Valve Implantation

*Thank You
very much !*

17 YEARS!

Happy to share with the media some particular cases

**A LITTLE PIECE OF NORMANDY
IN THE HEART OF MICK JAGGER !....**

Un peu de Normandie dans le cœur de Mick Jagger

Santé. Le chanteur des Rolling Stones a été opéré du cœur, hier, à New York, à l'âge de 75 ans. Il pourrait avoir bénéficié d'une technique, le Tavi, inventée à Rouen, il y a dix-sept ans.

Mick Jagger. Les Rolling Stones devaient commencer une nouvelle tournée de dix-sept dates à Miami le 20 avril, mais la série de concerts a en conséquence été reportée.

L'opération a été un succès

Vendredi, la nouvelle est tombée en fin d'après-midi : l'opération de Mick Jagger est un succès. A gauche, le professeur Cribier, inventeur de la valve aortique Tavi (photo Stéphanie Péron).

ancien chef du service de cardiologie du CHU Charles-Nicolas, un certain nombre d'éléments - parmi lesquels l'âge du chanteur - jouent en faveur du remplacement de sa valve aortique, c'est-à-dire la valve située au niveau du cœur et séparant le ventricule gauche de l'aorte. « J'ai lu dans la presse que Mick Jagger allait être opéré du cœur. A son âge, et s'il s'agit d'un rétrécissement aortique, il est possible qu'on lui implanter un Tavi (une valve aortique

ner 3) a été publiée aux États-Unis il y a une quinzaine de jours « qui indique que le Tavi obtient d'excellents résultats, sur tous les patients, même ceux à haut risque chirurgical. C'est l'apothéose de cette technique et la récompense du travail réalisé il y a dix-sept ans. Dans un avenir proche, le Tavi pourrait être proposé d'une façon généralisée. »

Avantage non négligeable : le délai de rétablissement est nettement moindre que pour une chirurgie lourde. Ce qui peut, par exemple, permettre à un rockeur de remonter rapidement sur scène.

En fin d'après-midi, la nouvelle est tombée : l'opération a été un su