

Developing TAVR:

Long journey from concept to human

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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

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

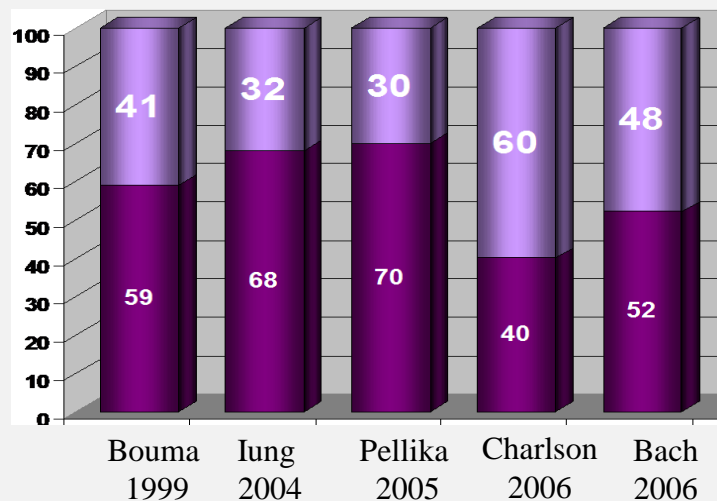


Low mortality

Return to normal life expectancy

No operation in 1/3 of patients

■ No AVR ■ AVR

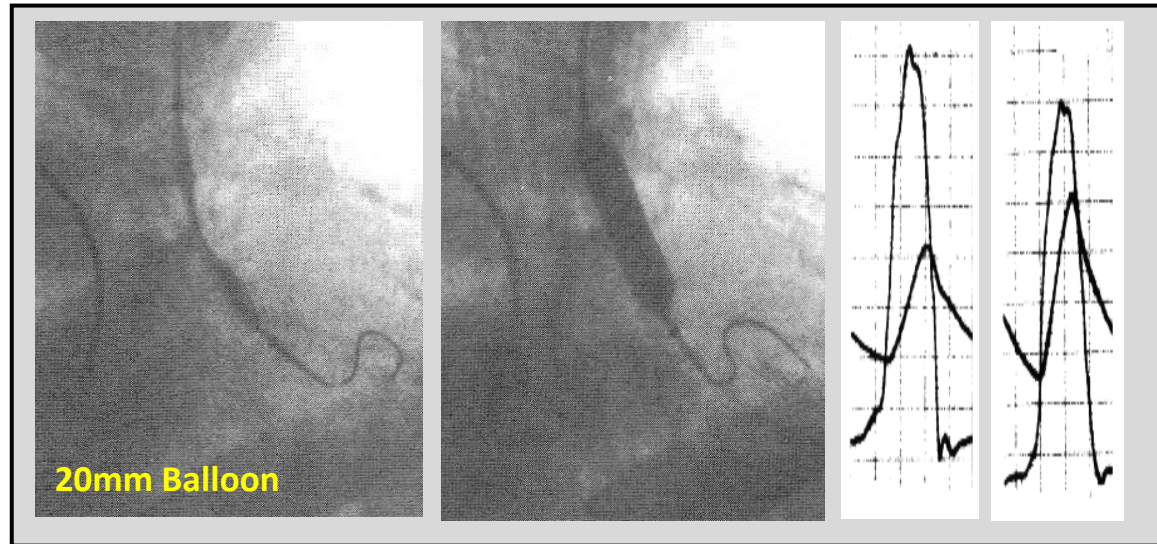


Mortality > 80% at 3 years

- 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 SAUDI
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: Incredible 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 an obsession



A TRANSCATHETER VALVE ?

Which optimal solution?

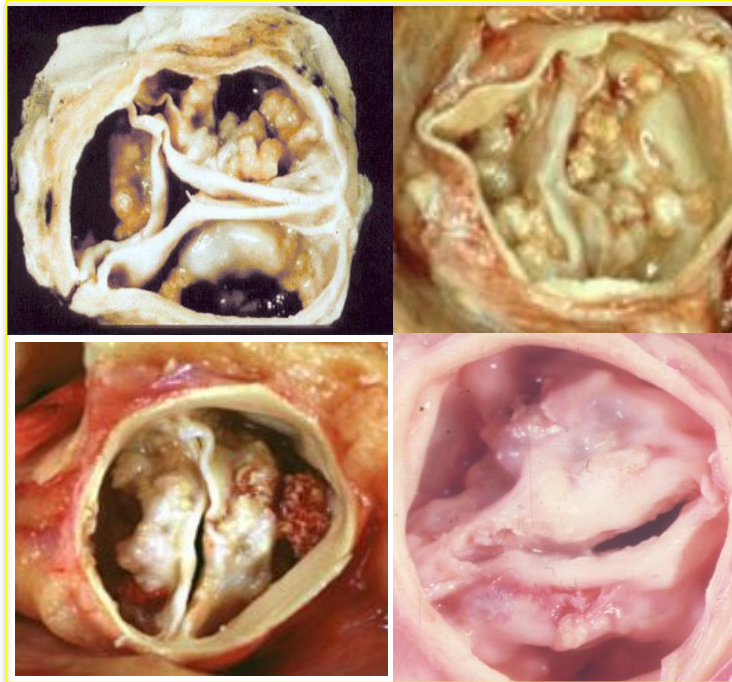
1994: Claiming the most challenging goal

“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 !

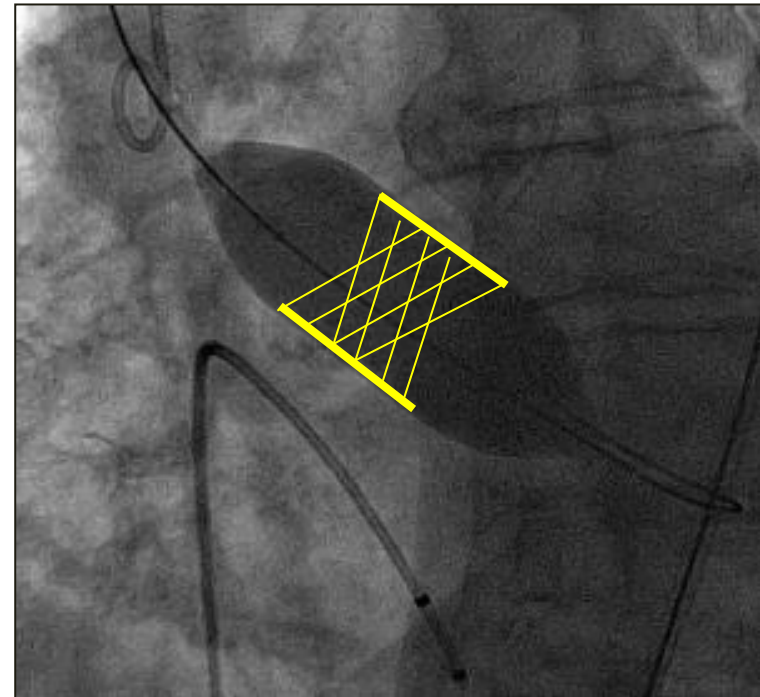
Which arguments for a stented-valve in AS ?

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

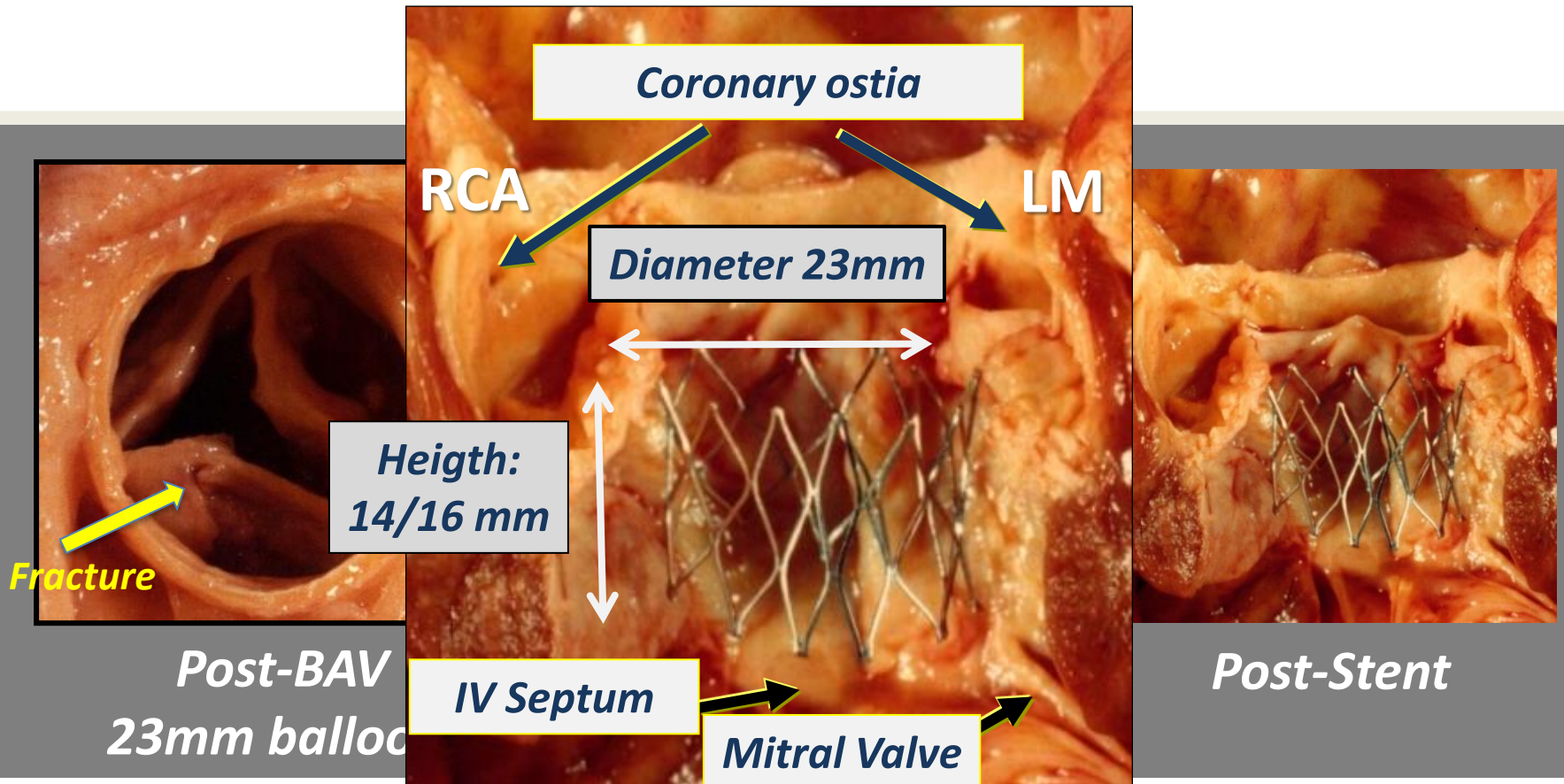
The diseased native valve *should not be retrieved* but used as **a support to anchor the stent**



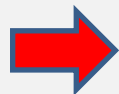
The « stented-Valve »: A challenging combination of balloon expandable frame and valvular structure

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

**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 your 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

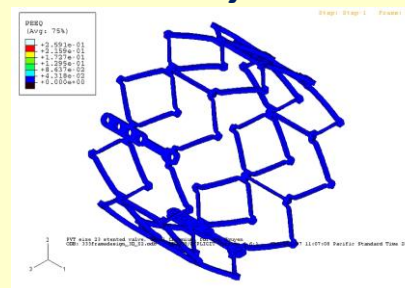
Hemodynamics



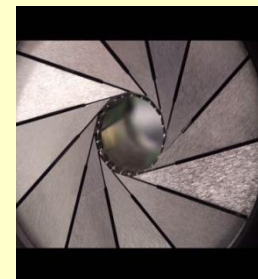
Durability (5 years)



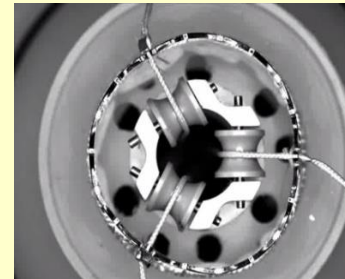
Finite Element Analysis



Radial Force



Fatigue



Moving to pre-clinical in-vivo testing

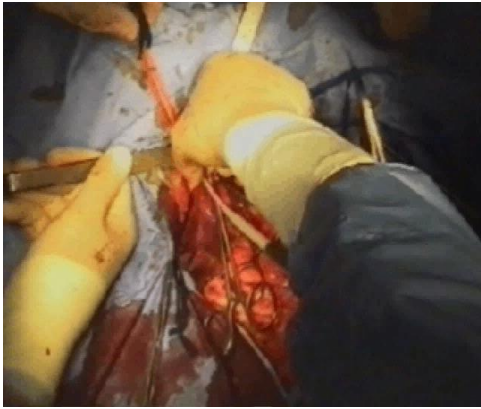
CERA, Montsouris Hospital, Paris



Crimped THV



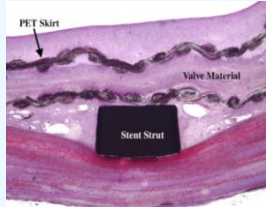
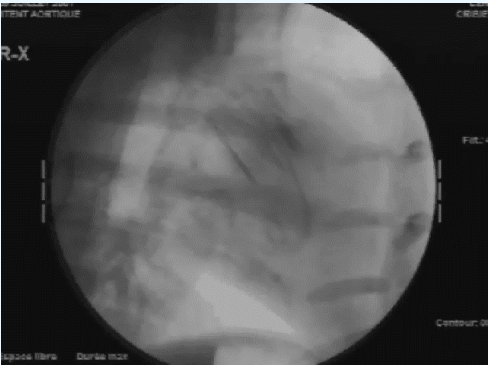
Carotid approach



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

In-Ao and pulmonic THV implantation

5-Mth echo and anatomic / histologic findings

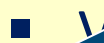


Being aware of significant deficiencies of the animal model for evaluating THV implantation in human

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 and site of branching structures

BUT multiple implants



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

regimen

Alain Cribier to Martin Leon

Cc: Rabinovich, Rowe

April 12, 2002

The F.I.M. TAVR

Martin Leon to Alain Cribier

Cc Rabinovich, Rowe

April 12, 2002

Dear Marty, I have a fascinating case that I would like to discuss with you!

57 y/o

EF 10%

Cardiogenic shock

Intra-LV thrombolysis

I am ready
What do you think?

Severe aortic stenosis with cardiac arrest

Blocked femoral arteries

We can make it transeptal

Externalization of guide wire

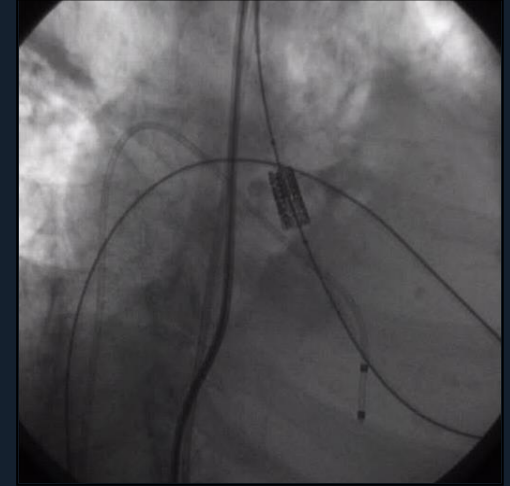
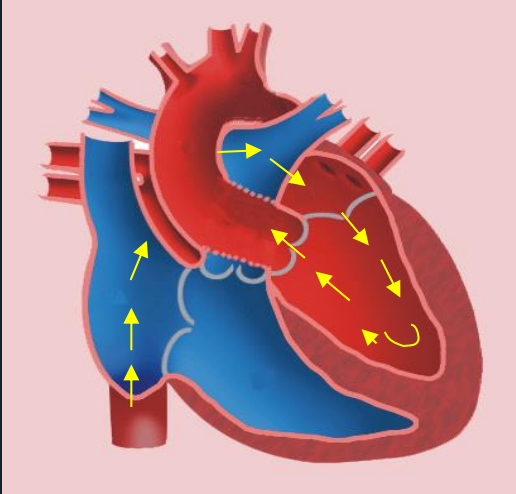
Highest risk !..

You have my complete support to move ahead with the first PVT clinical placement in... desperately

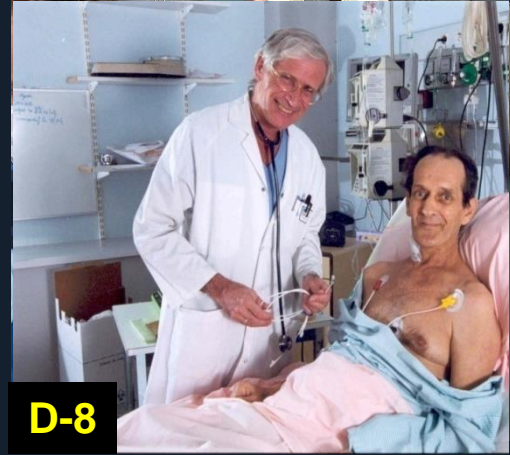
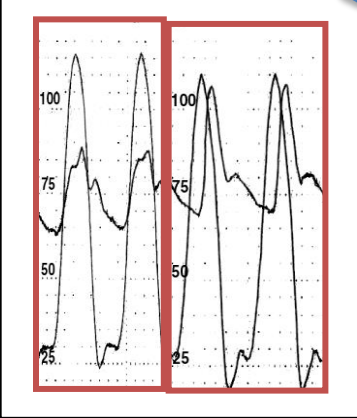
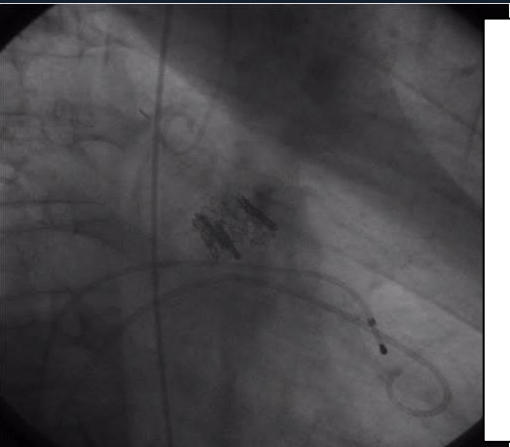
High likelihood of failure but... it just might work and save his life!

You are the best operator in the world!

April 16, 2002- First-In-Man TAVI



My god!
It works!

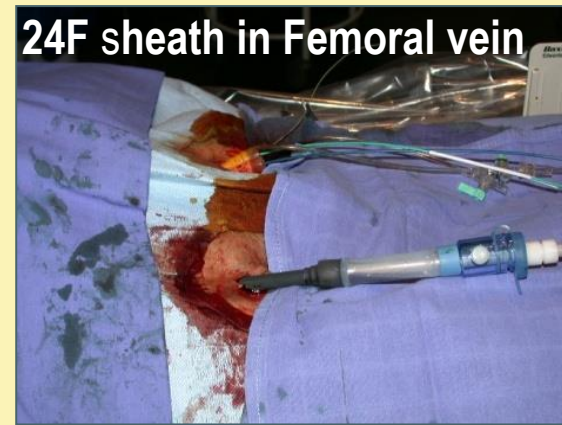
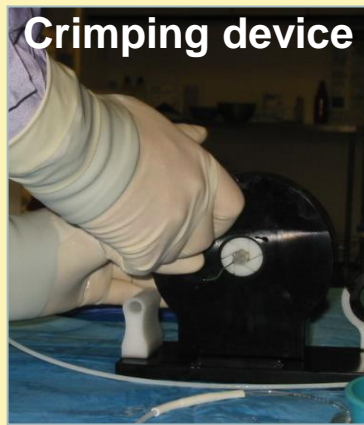


D-8

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

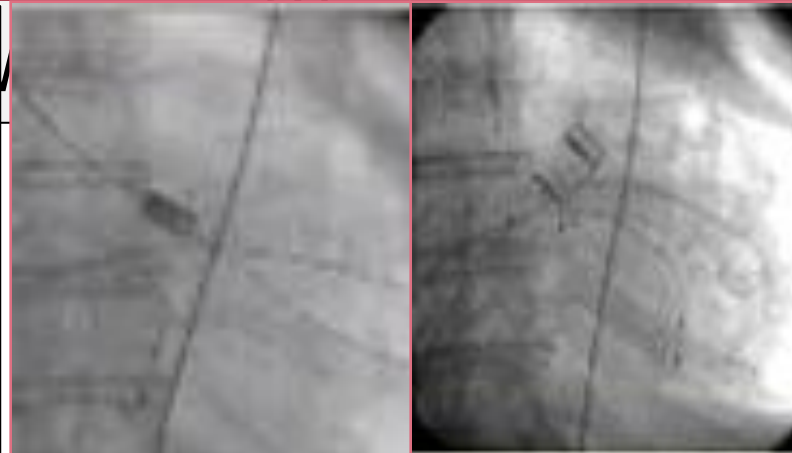
2002-2005: 40 Patients (I-REVIVE & RECAST Trials)



Equine Pericardium



Single size 23mm



4 Pts survived > 5-y

1 Pt survived 6.5-y

with no symptom
and optimal valve
function

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



TAVI enters a new era



Edwards

New valves, new delivery

Cribier-Edwards

23m



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



Vancouver, Canada
J. Webb

Leipzig, Germany
M. Mack, F. Mohr

TAVR: a 18-year long journey

From concept

2002 TAVR 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 !

Transcatheter

Aortic

Valve

Implantation

Thank You
very much !

17 YEARS!

Lesson 20

Be happy to share with the media some particular cases

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 ans.



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)

L'opération a été un succès

contacté vendredi après-midi au Medical Training Center qu'il préside à Rouen et où il continue à former des chirurgiens du monde entier, le professeur de médecine a répondu court : « C'est ridicule... » Selon un communiqué officiel de la star internationale, de ses proches ou de son chef de 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. À 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 succès.

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