Game-changers in valvular heart disease

Non-Invasive Ultrasound Therapy: A New Frontier in Moderate Aortic Stenosis Treatment?

Emmanuel Messas, MD, PhD,FESC

Hôpital européen Georges-Pompidou, Paris, France

Hôpital européen Georges-Pompidou AP-HP

Physics for Medicine PARIS

Université Paris Cité

CARDIAWAVE

FACULTY DISCLOSURE

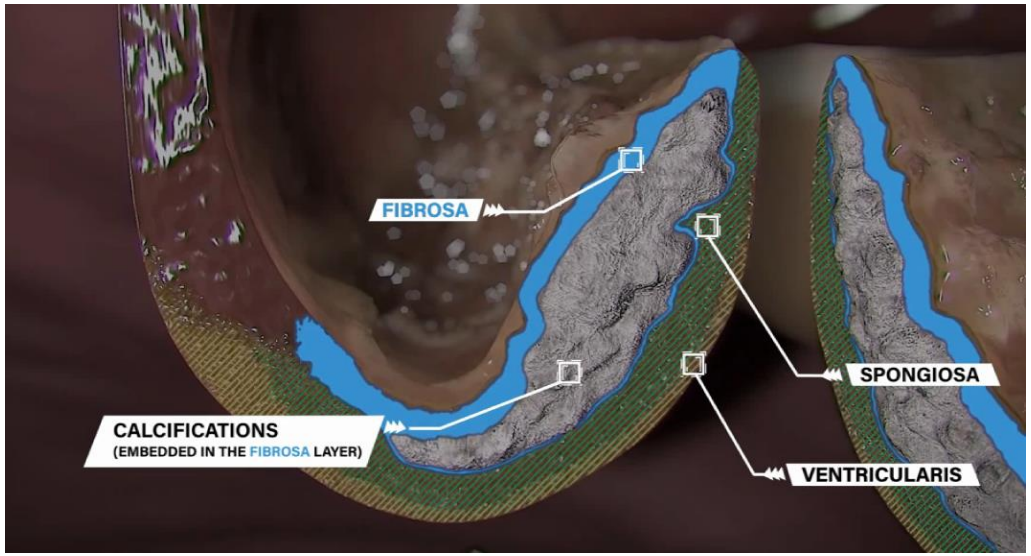
I disclose the following financial relationships:

Consultant for the company Novartis,Bayer

Advisory Board for Cardiawave Company

Minor shareholder of Cardiawave Company

Moderate Aortic Stenosis (MAS): Definition and Characteristics (1)



MODERATE AORTIC STENOSIS

Peak aortic velocity 3.0 to <4.0 m/s or Mean gradient 20 to <40 mmHg	**AND**	AVA 1.0 to 1.5 cm^2 or AVA < 1cm^2 with AVA index >0.6cm^3/cm^2 (BMI < 30) or AVA < 1cm^2 with AVA index >0.5cm^3/cm^2 (BMI ≥ 30) or AVA > 1.5cm^2 with AVA index <0.9cm^3/cm^2 (BMI < 30) or AVA > 1.5cm^2 with AVA index <0.8cm^3/cm^2 (BMI ≥ 30) or

A. Théron, et al. Arc of Cardiovasc Dis. 2023;116:295-297

MAS: Definition and Characteristics (2)

- **Epidemiology:** Prevalence of AS (mild to severe) above 75 years old - 12.4% representing 5.4 million people with AS and **3 million mild to moderate AS in Europe**[1,2]

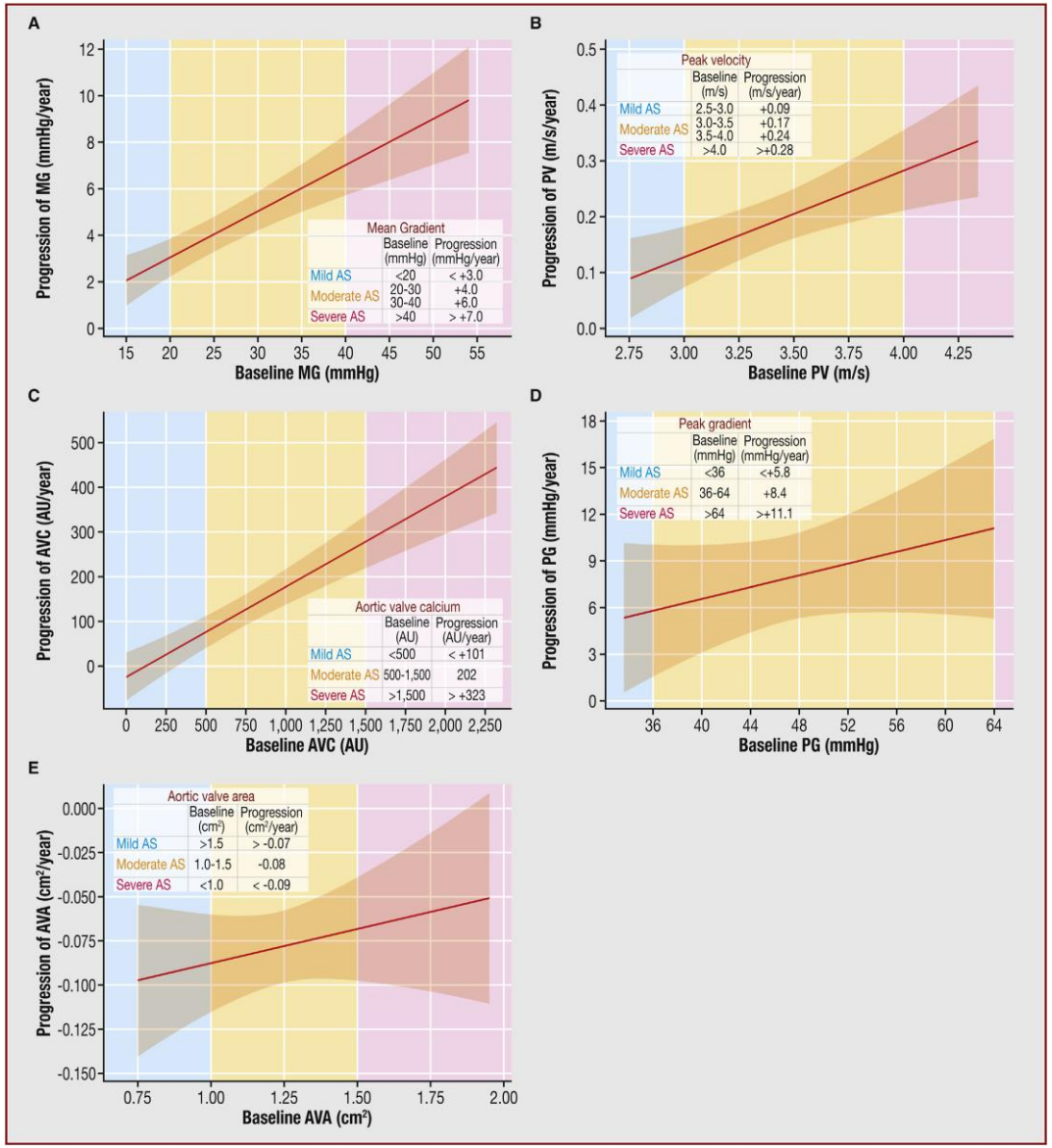
- **Risks and symptoms:** Sudden death, chest pain, fatigue, shortness of breath, hospitalization for congestive heart failure

- **Outcome: 5-year mortality rate of 56%** (*67% for patients with severe AS*)[3]

- **Moderate → Severe CAS**[4]
  - On average, **in the 5 years** after diagnosis
  - **Rapid-progression patients as fast as 2 years**

[1]EUROSTAT.2020ec.Europa.eu/Eurostat/data/database.(accessed November 27,2022
[2]Kebed K, et al.Eur Heart J Cardiovasc Imaging 2020;21:737–43
[3]Strange G, et al. J Am Coll Cardiol 2019;74:1851–63
[4] Everett RJ, et al. Heart. 2018;104:2067–2076

Natural History of the Disease: MAS



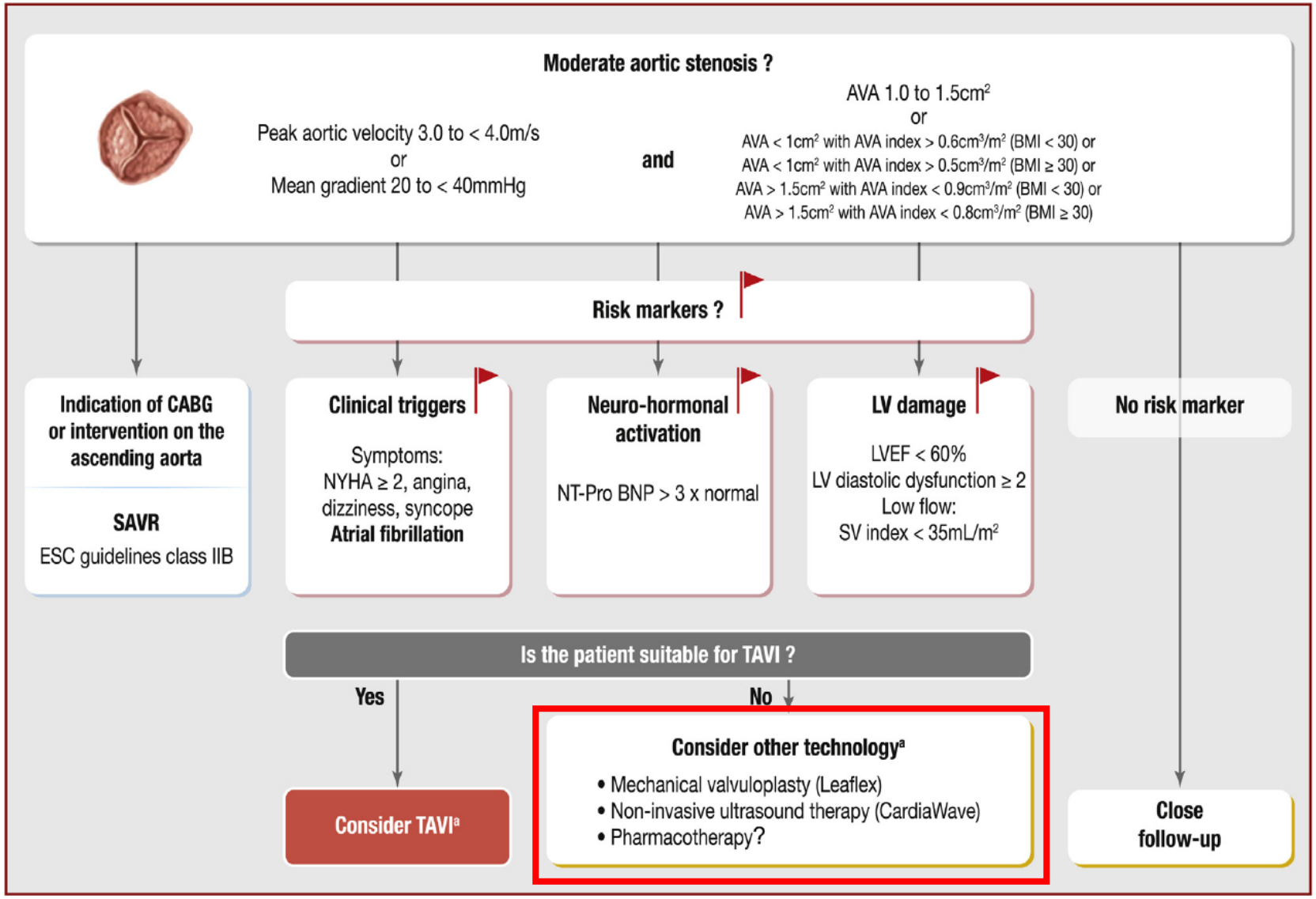
-AVA decreases by 0.08 cm^2/year

- Mean gradient increases by 6.0 mmHg/year

- Peak velocity increase by 0.2 m/sec/year

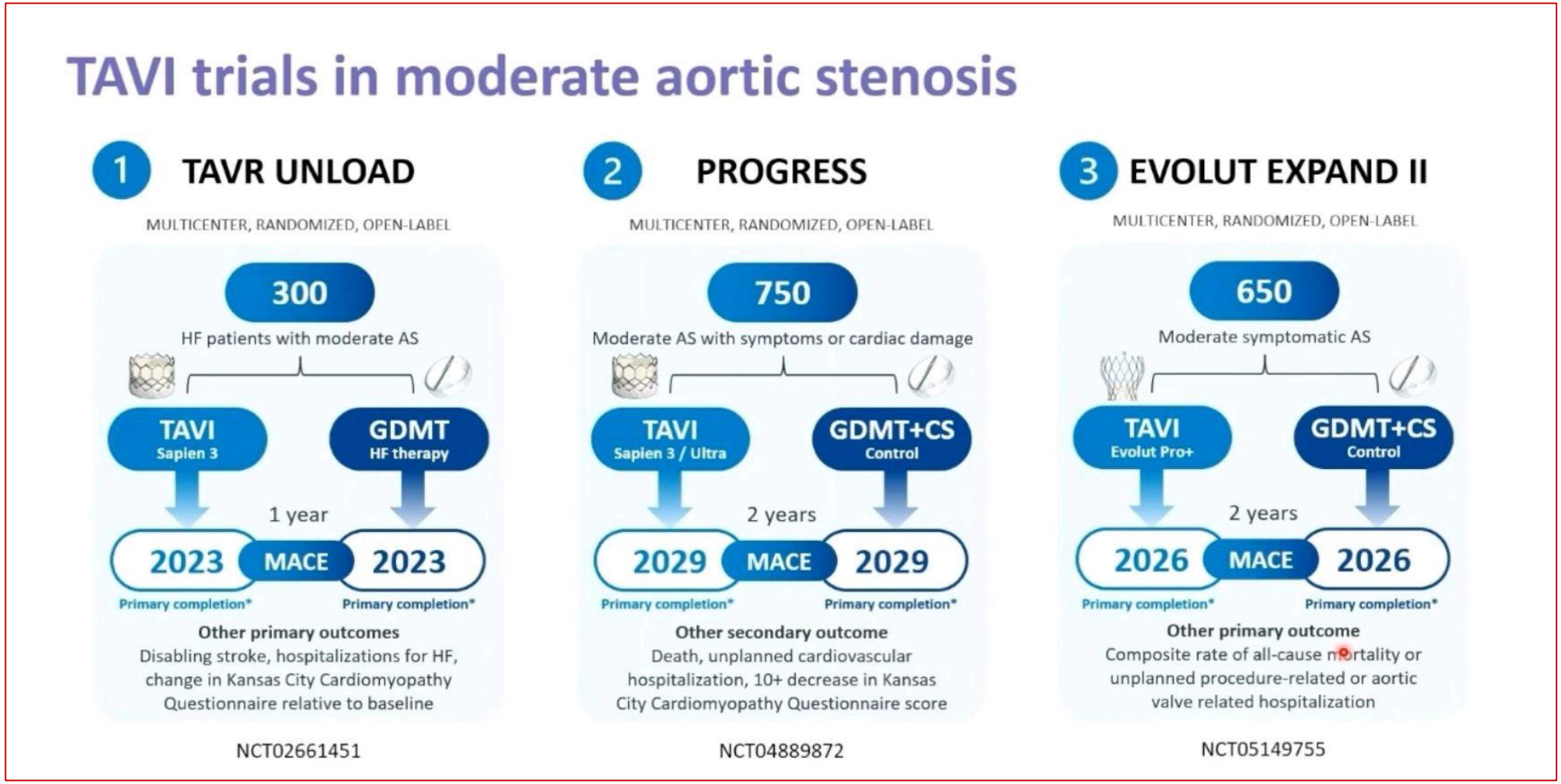
Willner N,Prosperi-Porta G, et al..Aortic Stenosis progression:a systematic review and meta-analysis. JACC Cardiovzasc Imaging 2023.
Total 24 studies and 5450 patients

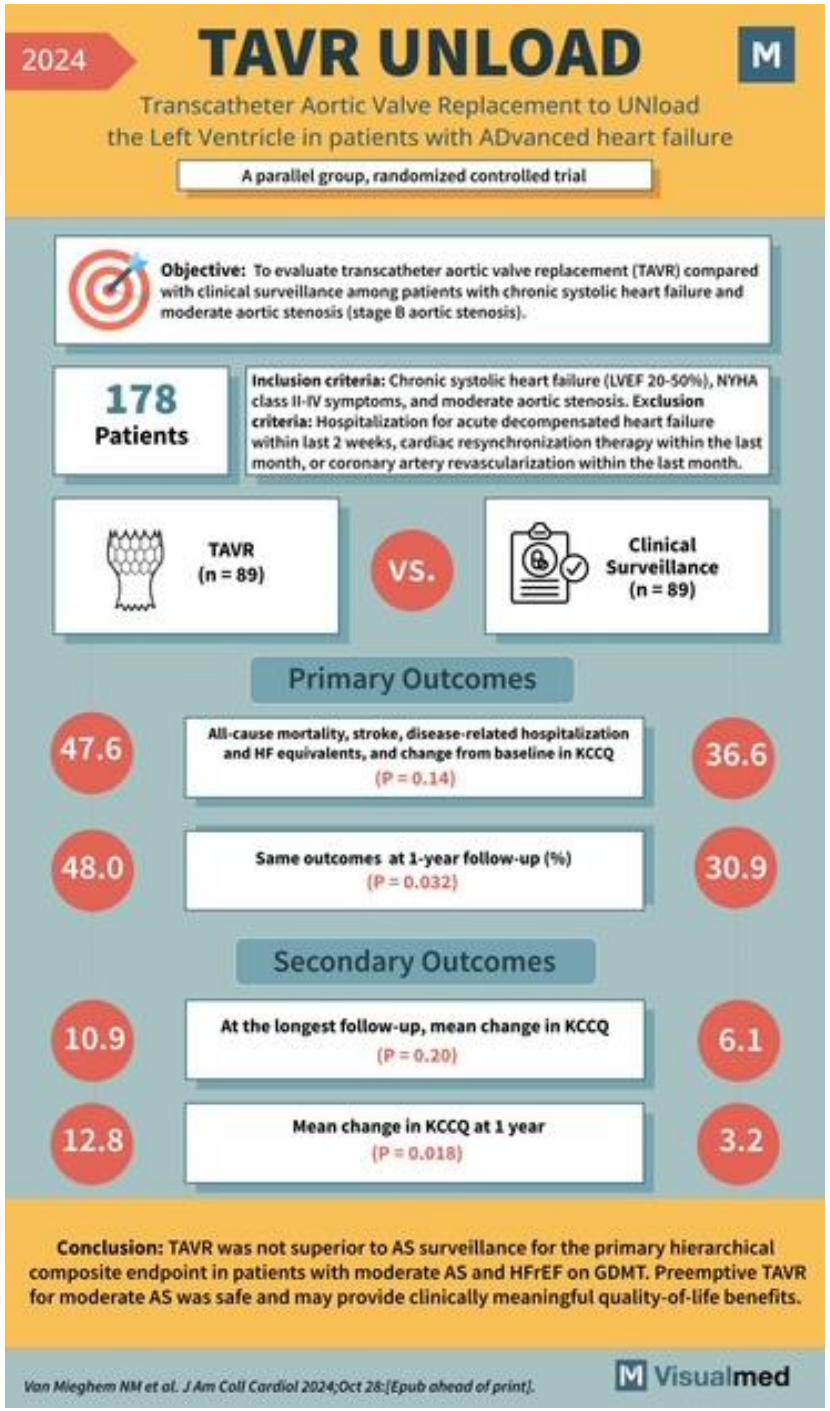
MAS: recently proposed management

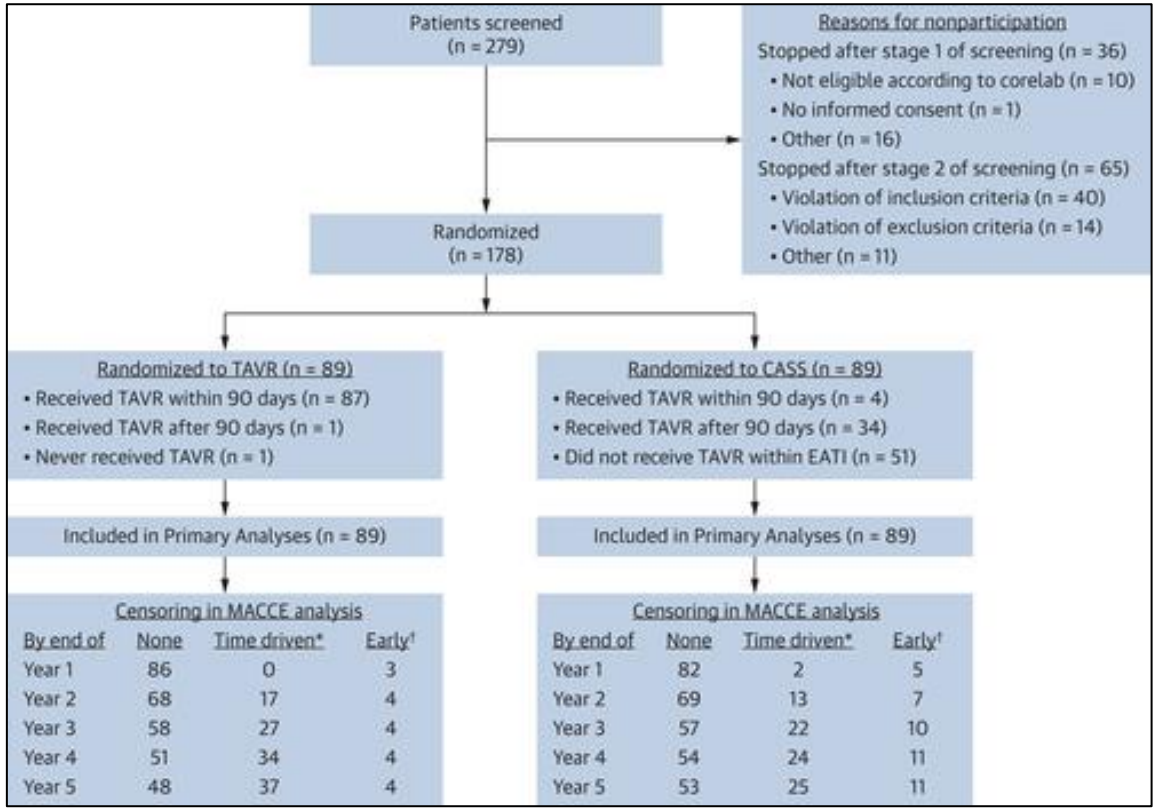


A. Théron, et al. Arc of Cardiovasc Dis. 2023;116:295-297

Now treating patients at an earlier stage to prevent cardiac damages and to slow down disease progression







The primary endpoint was the hierarchical occurrence of:
1) all-cause death; 2) disabling stroke; 3) disease-related hospitalizations and heart failure equivalents; and 4) change from baseline in the Kansas City Cardiomyopathy Questionnaire

Nicolas M. Van Mieghem et al. *JACC* 2024; 85:878-890.

MODERATE AORTIC STERNOSIS : Active Studies

	Device studies		Pharmaceutical studies			
	PROGRESS	**EXPAND TAVR II**	**Lp(a) FRONTIERS CAVES**	**EPISODE**	**EVOID-AS**	**KATALYST-AV**
Sponsor	Edwards Lifescienses	Medtronic	Novartis	Beijing Anzhen Hospital	Redniva Co	Kardigan Inc
Device/Drug	Sapien 3/Sapien 3 Ultra/Sapien 3 ultra RESILA	Evolute PRO/Evolute FX	Pelacarsen SiRNA targeting Lp(a)	PCSK9 Inhibitors + Statins with or without ezetimibe	DA-1229 (Evogliptin) DPP4 inhibitor	Ataciguat (stimulator of soluble guanylate cyclase (sGC)
Comparator	Clinical surveillance	GDMT*	Placebo	Statins with or without ezetimibe	Placebo	Placebo
Design	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized
Primary endpoints	Safety	Safety	Safety	Performance	Performance	Performance
N	Initial: 750 Extended: 2250 (2024-12)	650	502	160	580	1410
Start date	2021-10-12	2022-04-07	2024-03-07	2024-03-22	2022-06-27	2025-06-17
Primary completion	2029-06	2026-02	2030-03	2027-12	206-05-15	2028-08-31
ClinicalTrials.Gov	NCT04889872	NCT05149755	NCT05646381	NCT04968509	NCT05143177	NCT07001800

*Guideline directed medical therapy

Moderate Calcified Aortic Stenosis: optimal therapeutic option

- Non-invasive
- “Prosthetic free” (MAS are younger than those with severe AS, and their life expectancy is generally >15 years)
- Minimal procedure risks
- Help to delay the time of patients becoming with severe CAS and lower the morbidity and mortality risks
- Targeting the whole MAS population with preserved LV EF and no need for indirect biomarker

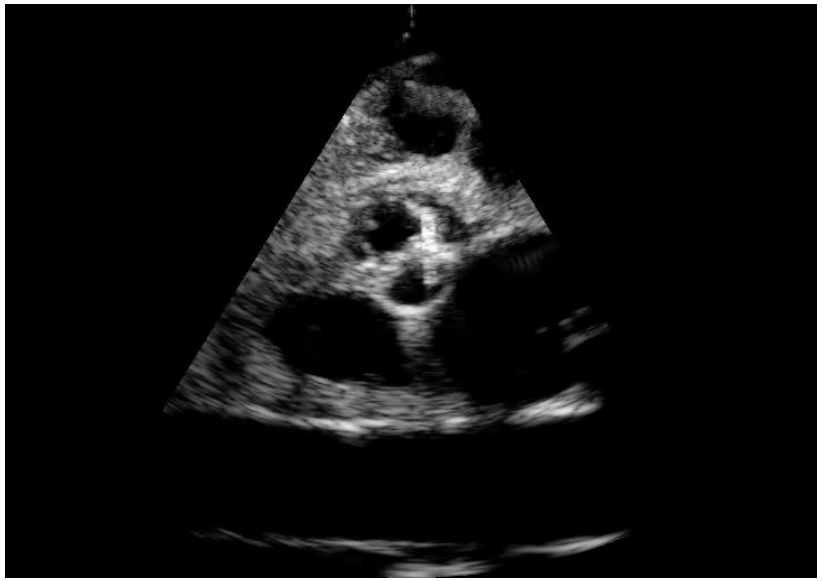
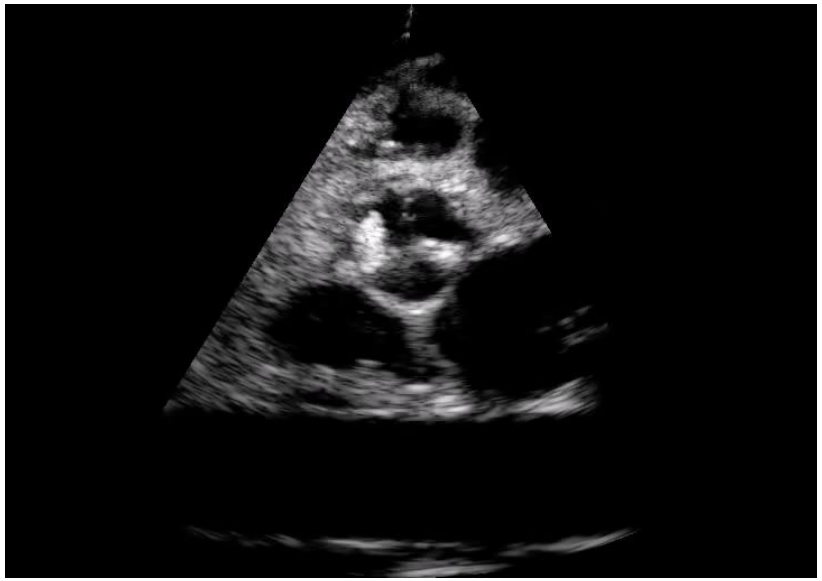
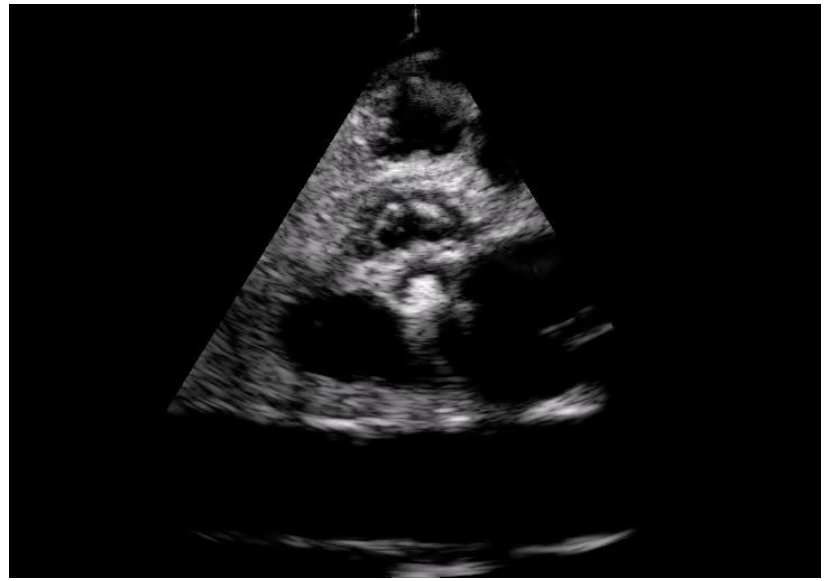
Valvosoft®: a non-invasive ultrasound therapy device

An innovative ***repair*** device with advanced robotic and visualization technologies

CARDIAWAVE

- Non-invasive, transthoracic delivery of focused ultrasound pulses
- Ambulatory outpatient setting
- Treatment divided in 10 min sessions (max. 70 minutes)
- No need of a cathlab
- Ease of use, fast learning curve for operators (2-4 cases)
- No radiation (also safe for operators)

Bubble cavitation detection with Echo Imaging

Institute of Physics for Medicine at the ESPCI Paris

Mickael Tanter
Director

Mathieu Pernot
Deputy Director

Pr Mathias Fink
Cofounder, Physicist

CARDIAWAVE

ESPCI PARIS
EDUCATION SCIENCE INNOVATION

Ecole Supérieure de Physique et de Chimie Industrielle (E.S.P.C.I.), Paris, FRANCE

Cardio-Vascular department, HEGP, Paris

Hôpital européen Georges-Pompidou AP-HP

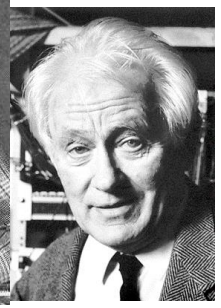
Université Paris Cité

From Fundamental Physics to Medical applications

Marie and Pierre Curie
1903
Marie Curie
1911

Frédéric Joliot-Curie

Pierre-Gilles de Gennes



Georges Charpak

5 Nobel Prizes

TEAM Supported by EXPERIENCED board and SCIENTIFIC ADVISORS

Medical advisory board

Pr Alain Cribier

Cardiologist, CHU Rouen France

- TAVR inventor
- Training center in Rouen

Pr Ehud Schwammenthal

Cardiologist, Sheba Medical Center Israel

- Founder and consulting CTO of Ventor Technologies, founder and CMO of Magenta Medical

Pr Roxana Mehran

Cardiologist, Mount Sinai Hospital New York

- Clinical trial specialist in the field of interventional cardiology

Dr Robert A. Levine

Cardiologist, MGH USA

- Expert in cardiac imaging and valve disease

1945-2024

RHU STOP AS

Co-founders

Pr Emmanuel Messas

MD, Cofounder, Cardiologist (HEGP)

- Professor at Paris Descartes University
- Massachusetts General Hospital & Harvard Medical School

Mathieu Pernot

Cofounder, Physicist

- Deputy director of Physics for Medicine Paris, Research director at INSERM

Pr Mathias Fink

Cofounder, Physicist

- Founder of Institut Langevin
- Professor at ESPCI Paris and member of the French Academy of Sciences
- Co-founder of Supersonic Imagine

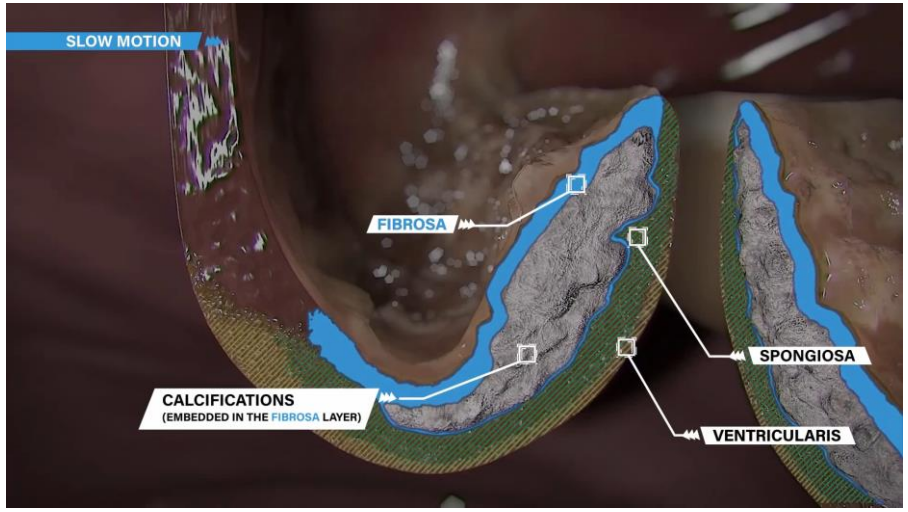
Michael Tanter

Cofounder, Physicist

- Director of Physics for Medicine Paris, Research director at Inserm
- Director of the Accelerator of Technology Research in Biomedical Ultrasound
- Co-founder of Supersonic Imagine

5 Nobel Prizes Physics

NIUT: Non-Invasive Ultrasound Therapy



- Focused, very high frequency and short ultrasound pulses create microscopic cavitation bubbles.
- When cavitation bubbles burst, they produce shockwaves.
- Shockwaves cause micro cracks in valve calcifications without tissue damage.
- NIUT softens the valve, restores leaflet mobility and enables a wider opening of the valve

Therapeutic ultrasounds	HIFU	Lithotripsy	Histotripsy	NIUT
Ability to penetrate deep in tissue	-	-	+	+
Preservation of tissue through which ultrasounds pass	-	+	+	+
Energy	Heat	Mechanical	Mechanical	Mechanical
Therapeutic effect	Tissue ablation by coagulation necrosis	Break-up of stone	Cell membrane destruction and cells annihilation	Tissue softening

NIUT Pulsed Cavitation for Calcified Aortic Valve

FocalPoint

*We used "In Silico" simulation techniques to estimate the size of the focal points depending of their depths and of the therapy parameters (**Focal point size: 0.75*5mm² to 1.5*19.5mm²).***

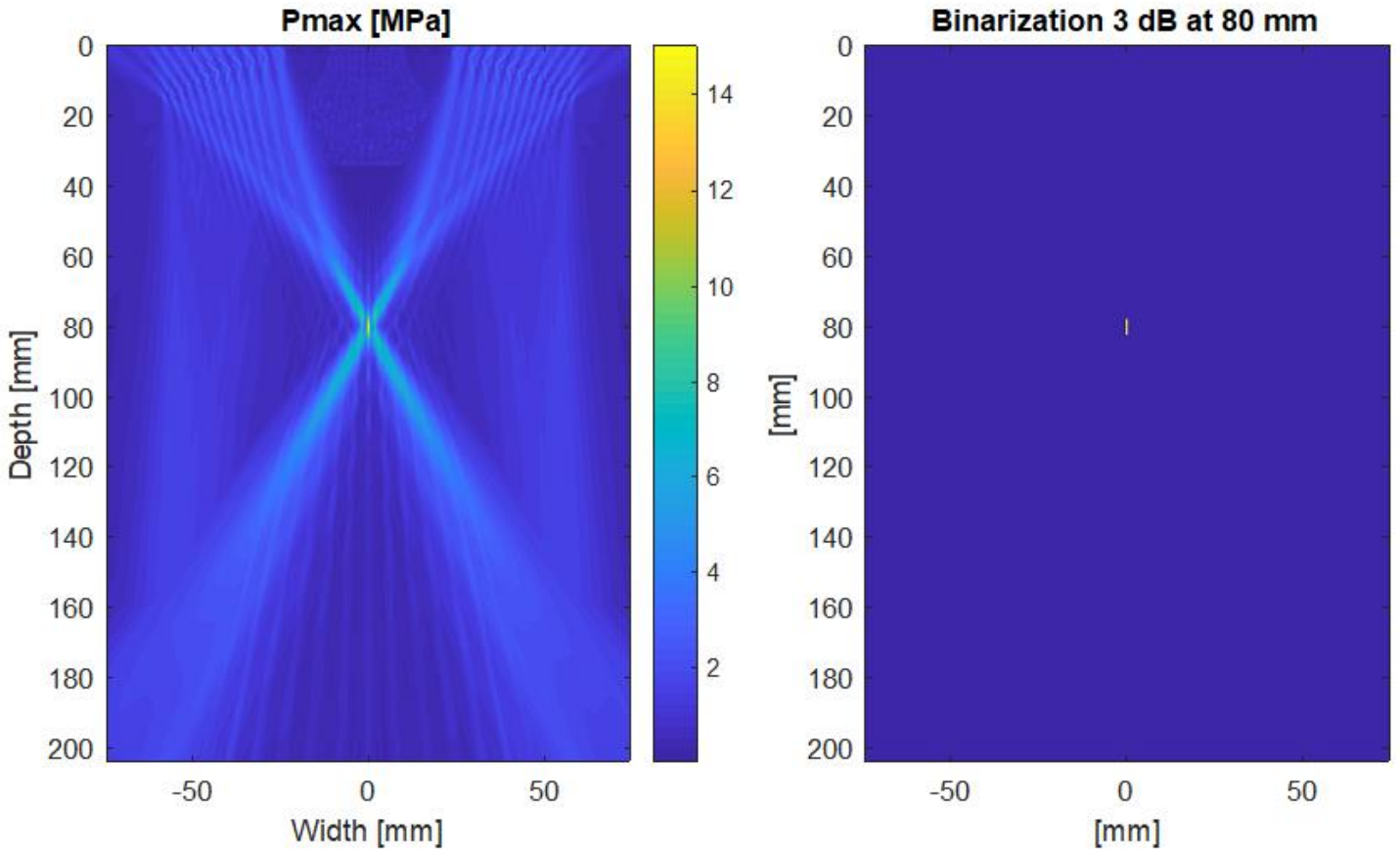
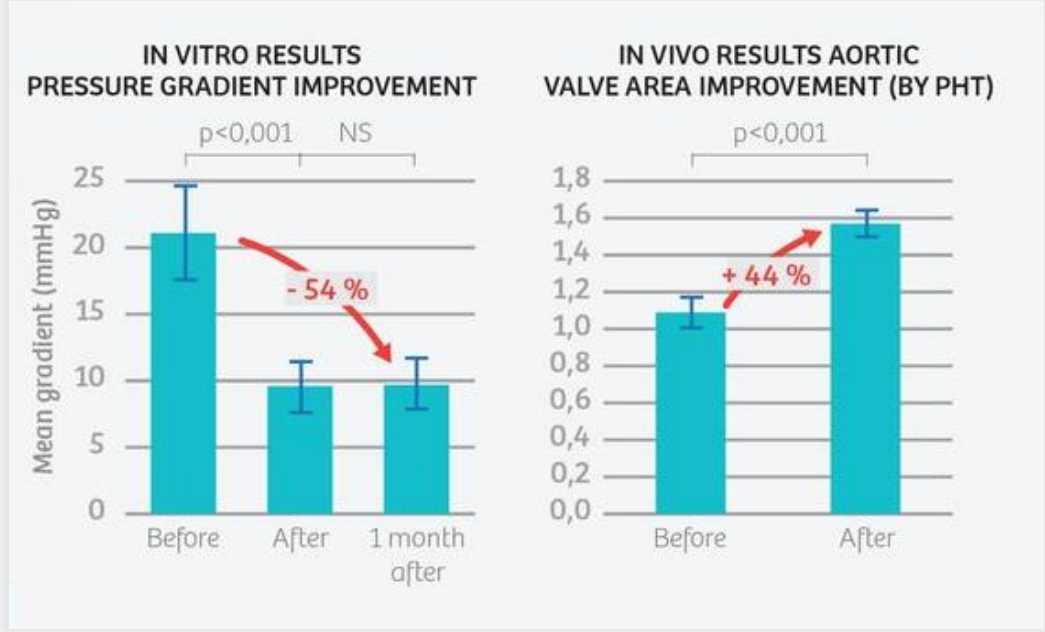


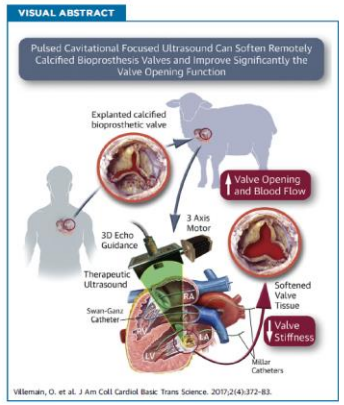
Figure: example of Pressure field simulation in water in a high-pressure regime at a Therapeutic target depth of 80mm (left) and corresponding thresholded Focal spot at -3dB (right).

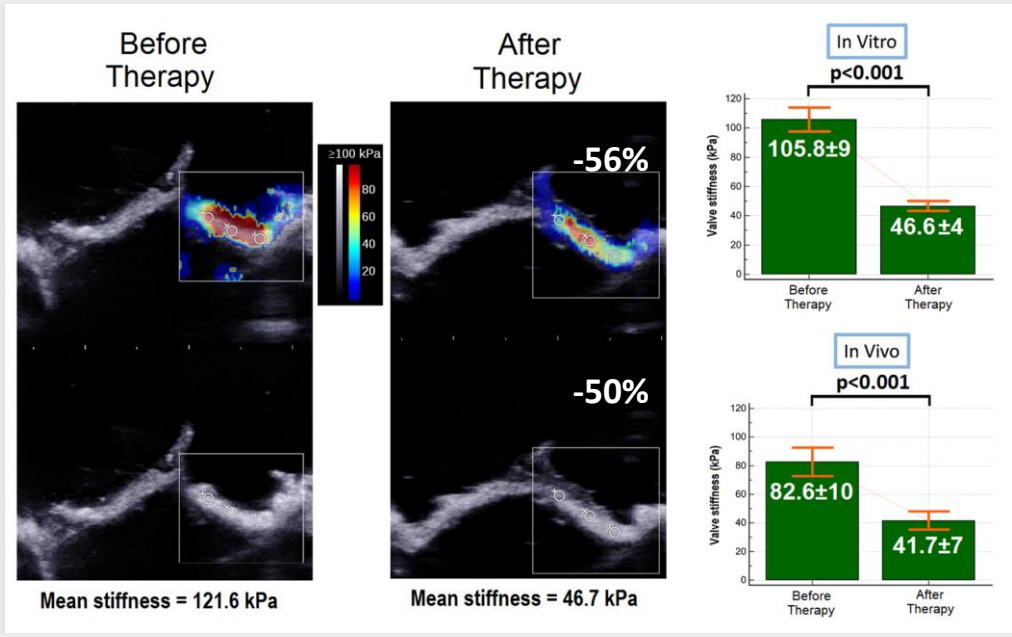
NIUT showed good efficacy in preclinical studies

Statistically significant improvements of key parameters

Pressure gradient is decreased by half + ***Tissue stiffness is decreased by half*** + ***Wider opening of the valve area***







Villemain O, Robin J, Bel A, Kwiecinski W, Bruneval P, Arnal B, Rémond M, Tanter M, Messas E, Pernot M. Pulsed Cavitational Ultrasound Softening: a new non-invasive therapeutic approach of calcified bioprosthetic valve stenosis. Journal of the American College of Cardiology Basic Transl Sci. 2017 Aug;2(4):372-383.

Messas E. et al, Safety study published in July 2020 in Physics in Medicine & Biology: Feasibility and Safety of Non-Invasive Ultrasound Therapy (NIUT) on Porcine Aortic Valve.

First-In-Human and Pivotal Studies: 100 patients (1)

- Three prospective, multi-centre, single-arm studies to treat severe AS patients with Valvosoft :
  - **Two first-in human studies**, to demonstrate safety and feasibility (FIH I extended to FIH II)
  - **One pivotal study**, to demonstrate safety and performance
  - **1M, 3M, 6M and 12M follow-up**
  - DSMB and CEC installed to monitor safety and performance and **external corelab for echo evaluation**
- **Symptomatic Severe AS patients declined by Heart Team for TAVR/SAVR or refusing AVR**
- **Patients with LVEF ≤ 30% or iAVA < 0.24cm²/m² were excluded**
- **Expected benefits of the treatment: Slow down the natural progression of AS, clinical cardiac improvement, quality of life (QoL) improvement**

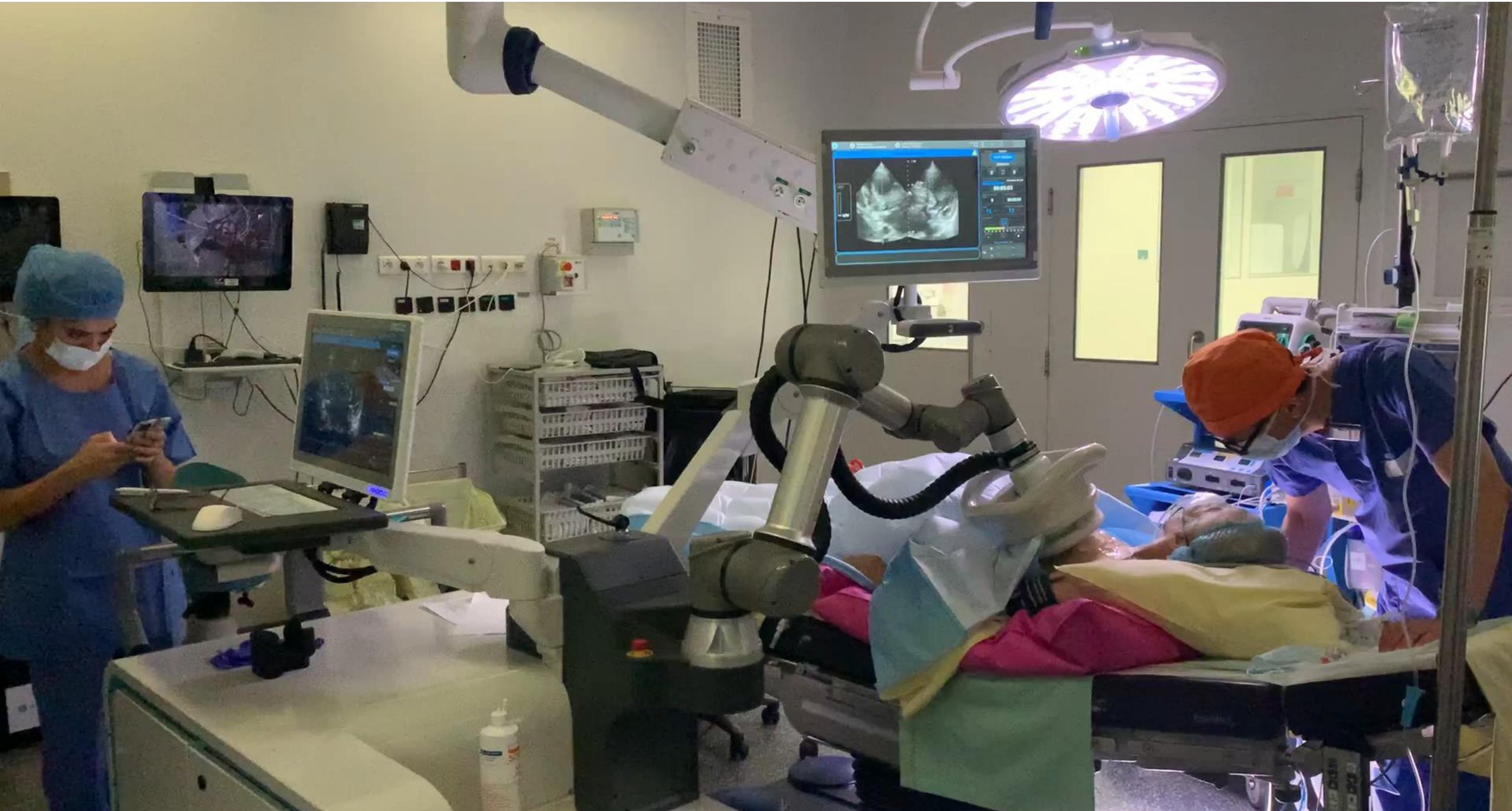
First-In-Human and Pivotal Studies: 100 patients (2)

	FIH studies (NCT03779620 and NCT04665596)	PIVOTAL study (NCT05235568)
Patients included	40: 30+10 (FIH I and FIH II)	60
Number of centers	3 centers, in 3 countries (France, The Netherlands for FIH I, Serbia for FIH II)	11 centers, in 3 countries (France, Germany, The Netherlands)
Primary safety endpoint	Procedure related mortality at 1-month	Rate of Major Adverse Cardiac Events <25% at 1MFU
Primary performance endpoint	Ability to modify the structure of the calcified valve leaflets to improve their mobility immediately post-procedure compared to baseline	Decrease in NYHA functional class at 1 MFU
Secondary endpoints	Safety and performance beyond 1-month	Safety and performance beyond 1 month
Corelab	Cardialysis	CORRIB

- *First patient enrolled: March 2019*
- *Last patient 24-month follow-up completed: May 2024*
- *Retreatments: 25*

Valvosoft® studies baseline data of treated patients

Characteristic	FIH (N=40)	Pivotal (N=60)	Pooled data (N=100)
Age (years)	83.00 ± 8.45	85.15 ± 9.14	84.3 ± 8.9
Female/Male	21/19	39/21	60/40
Left Ventricular Ejection Fraction (LVEF) (%)	52.79 ± 9.92	55.00 ± 11.02	53.6 ± 11.1
Aortic Valve Area (AVA), cm^2	0.58 ± 0.19	0.65 ± 0.19	0.62 ± 0,18
Aortic Valve Mean Pressure Gradient (PG), mmHg	40.94 ± 20.06	46.08 ± 14.52	43,39 ± 16.96
Aortic Valve Peak Velocity, m/sec	4.07 ± 0.94	4.27 ± 0.59	4.18 ± 0.74
LFLG	18 (45)	17 (28,3)	35 (45%)
Calcification Volume, mm^3	976.8 ± 1451.46	3211.89 ± 1873.97	84.3 ± 8.9
New York Heart Association (NYHA)			
1	-	2 (3.3%)	2 (2%)
2	10 (25%)	27 (45.0%)	37 (37%)
3	19 (48%)	26 (43.3%)	45 (45%)
4	11 (28%)	5 (8.3%)	16 (16%)
EuroSCORE II (%)	5.56 ± 4.38	7.35 ± 7.03	6.7 ± 6.2
STS Score (%)	5.82 ± 4.70	7.35 ± 6.00	6.7 ± 5.5
Frailty Score	-	5.07 ± 1.33	-
EQ-5D	-	57.95 ± 16.29	-
KCCQ	45.5 ± 22.64	61.48 ± 21.65	56.4 ± 23.0
6MWT (m) (20 ND)	-	198.45 ± 114.43	-



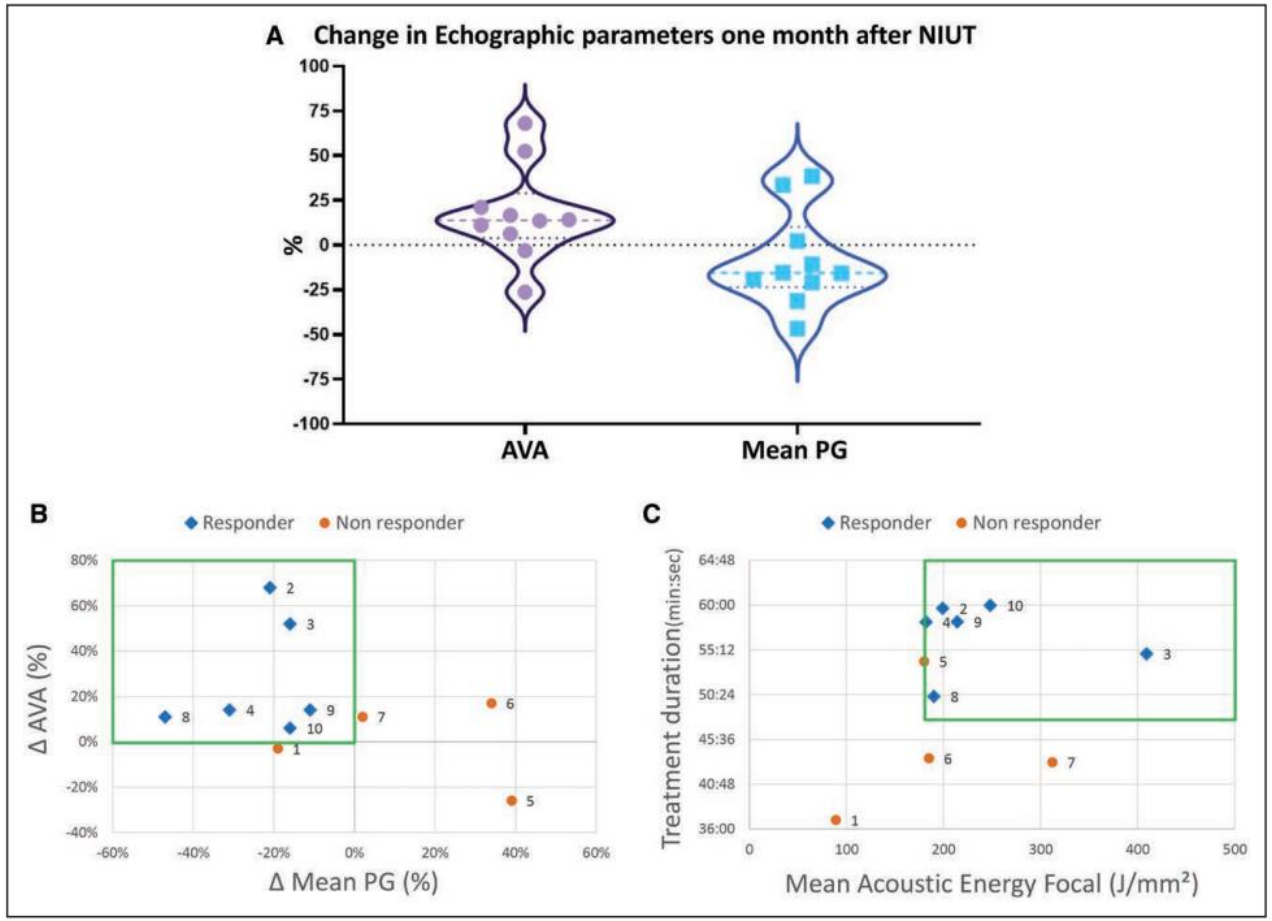
Valvosoft FIM: first 10 patients at 1 month (severe symptomatic AS contra indicated to TAVR and SAVR)

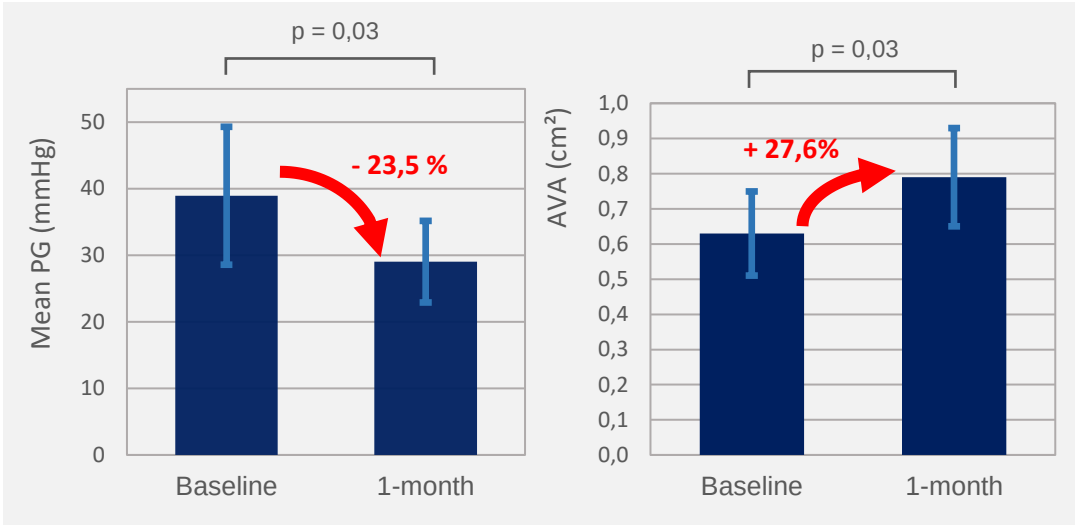
Circulation

RESEARCH LETTER

Feasibility and Performance of Noninvasive Ultrasound Therapy in Patients With Severe Symptomatic Aortic Valve Stenosis

A First-in-Human Study





During the procedure and at one-month FUP:

- No death
- No CVA
- No MI

HEGP – Paris FR, Amphia – Breda NL

Messas E et al, . Circulation. 2021; : 968–70.

First In Human Study (n=40)
6 month follow up
(HEGP, Amphia, Clinical centre Belgrade)

Lancet Dec 2023

Articles

Treatment of severe symptomatic aortic valve stenosis using non-invasive ultrasound therapy: a cohort study

Emmanuel Messas, Alexander Ijsselmuiden, Danijela Trifunović-Zamaklar, Bernard Cholley, Etienne Puymirat, Jonathan Halim, Radmila Karan, Menno van Gameren, Duško Terzić, Vladimir Milićević, Mickael Tanter, Mathieu Pernot, Guillaume Goudot

E. Messas *et al.*, *The Lancet*. 2023 Dec 16;402(10419):2317-2325..

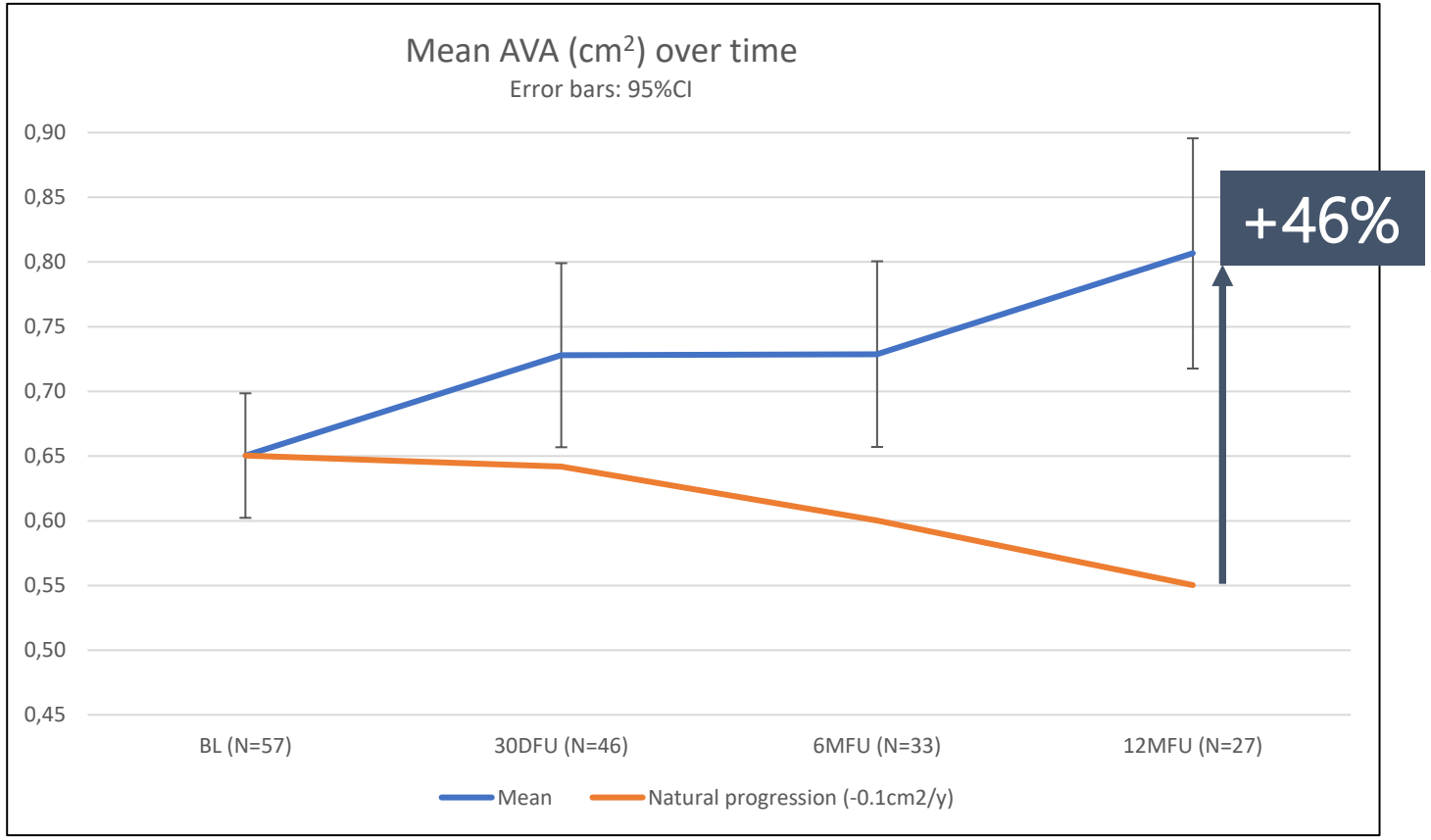
CE-marking Pivotal Study

France, the Netherlands, Germany – 60 patients SEVERE AS not recommanded for AVR

FOLLOW UP 12 MONTH

Aortic Valve Area (AVA)

Increase by 23%vs baseline and by 46% vs natural progression of the disease



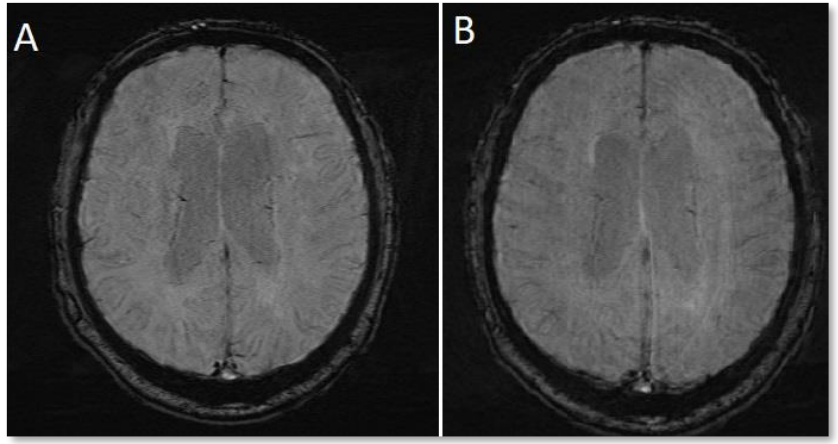
Results: Valvosoft® Safety 12 months – 100 patients

- 100 patients treated in 11 centers in 3 countries
  - Very old: 84.3y ± 8.9
  - Multiple comorbidities
  - **All alive after the procedure no CVA or MI per procedure**

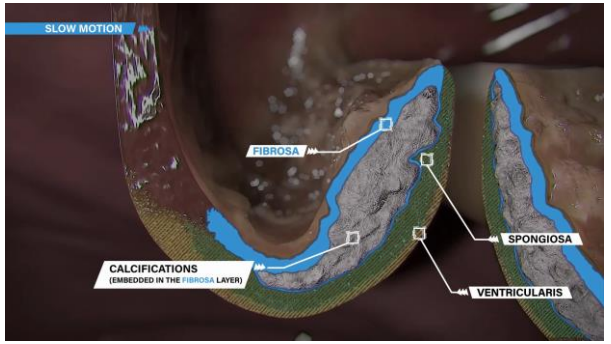
- Strong safety profile at 30 days
  - **no stroke, no coronary revascularisation**
  - 9% MACE rate (*<25% as defined in Pivotal study: All cause mortality, major or life-threatening bleeding, MI, coronary revascularisation, stroke and hospitalisation due to heart failure)*

  - MACE included (CEC adjudicated):
    - 3 deaths unrelated to device and procedure
    - 2 deaths possibly related to procedure
    - 1 periprocedural MI - related
    - 1 hospitalization for heart failure –unrelated
    - 1 major bleeding (fall at home – subdural hematoma) unrelated

- Sub study MRI (FIH II) : no micro-emboly detected[1]



MRI at A) baseline and B) discharge

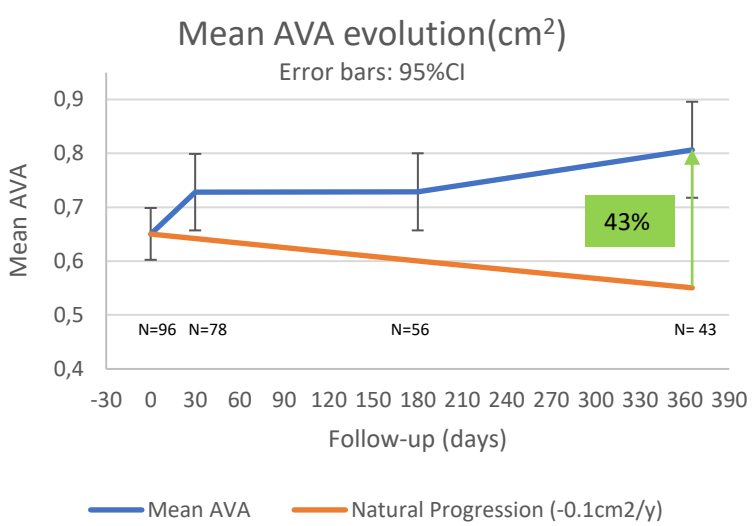


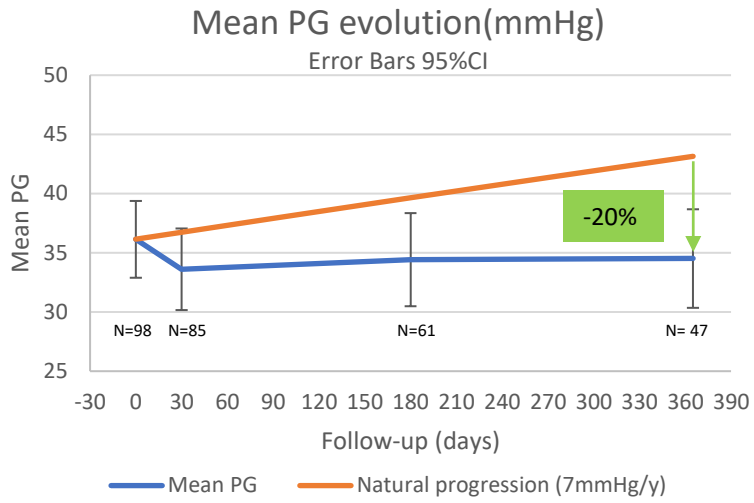
Cavitation bubbles over the aortic valve
Calcifications embedded in the tissue

[1]*D Trifunovic-Zamaklar, et al. Eur Heart J Cardiovasc Imaging. 2023 Jul; 24(7): e108–e109*

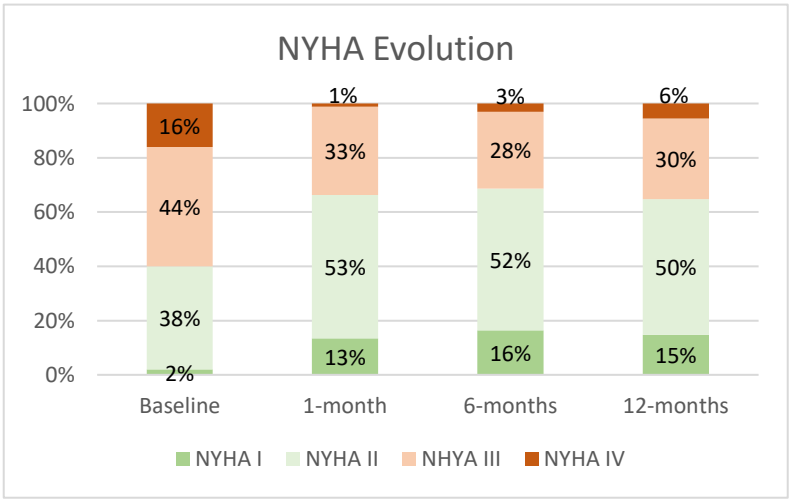
Results: Valvosoft® clinical improvements 12 months – 100 patients

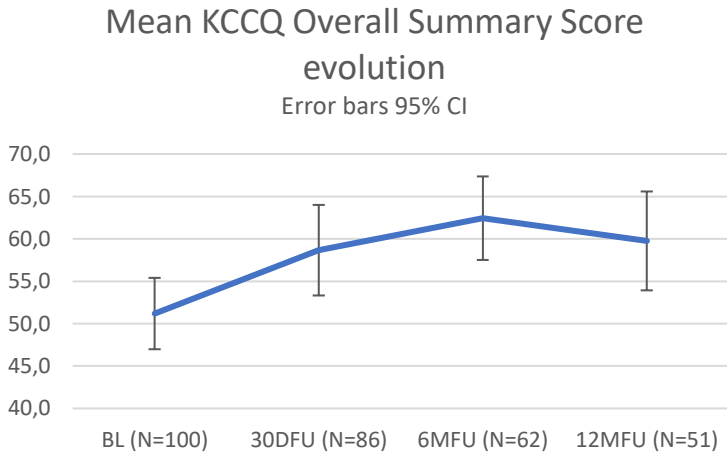
- Echographic improvements were noticed with:
  - AVA increase of 20% at 12 MFU or 43% compared with Natural Progression[1] (*NP AVA in AS: -0.1 cm²/y*)
  - Mean pressure gradient decrease of 5% at 12 MFU or 20% compared with NP (*NP of mPG in AS +7 mmHg/y*)





- Overall QoL improved with:
  - 85% of the population improved or stabilised NYHA class
  - Average KCCQ score improvement of 9 points





[1] Prosperi-Porta G., Archives of Cardiovascular Diseases 2023

FUTUR PERSPECTIVE

Disease progression

Valvosoft® device is complementary to TAVR

Patient profile

Bicuspid valve young females and males

Moderate AS often with other cardiovascular co-morbidities

Asymptomatic Severe AS

Symptomatic Severe AS - personal choice not to receive AVR

Symptomatic Severe AS- ineligible for TAVR/SAVR

Symptomatic Severe AS - younger, healthier patients

Symptomatic Severe AS - degenerated bioprosthesis

Current therapy

Not optimal medical therapy

TAVR

TAVR ViV

Cardiawave's values to pts

Offers a choice for Non-invasive treatment for AS

Preserves the "native valve" while allowing the valve to open properly

Improve QOL at the end of life

1. Pre-treatment before TAVR can minimize PVL and optimize valve function
2. Delay TAVR to reduce re-do's later
3. Bridge to TAVR

1. Treat degenerated implanted valve to prolong its durability
2. Delay Valve-in-Valve (ViV) either SAVR to TAVR or TAVR to TAVR

Cardiawave's indication

Delay disease progression/ Delay surgery or TAVR

Destination Therapy

FUTUR PERSPECTIVE

Disease progression

Valvosoft® device is complementary to TAVR

Patient profile

Bicuspid valve young females and males

Moderate AS often with other cardiovascular co-morbidities

Asymptomatic Severe AS

Symptomatic Severe AS - personal choice not to receive AVR

Symptomatic Severe AS- ineligible for TAVR/SAVR

Symptomatic Severe AS - younger, healthier patients

Symptomatic Severe AS - degenerated bioprosthesis

Current therapy

Not optimal medical therapy

TAVR

TAVR ViV

Cardiawave's values to pts

Offers a choice for Non-invasive treatment for AS

Preserves the "native valve" while allowing the valve to open properly

Improve QOL at the end of life

1. Pre-treatment before TAVR can minimize PVL and optimize valve function
2. Delay TAVR to reduce re-do's later
3. Bridge to TAVR

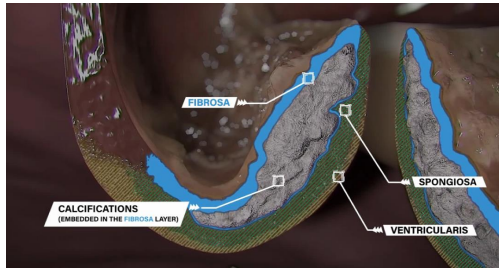
1. Treat degenerated implanted valve to prolong its durability
2. Delay Valve-in-Valve (ViV) either SAVR to TAVR or TAVR to TAVR

Cardiawave's indication

Delay disease progression/ Delay surgery or TAVR

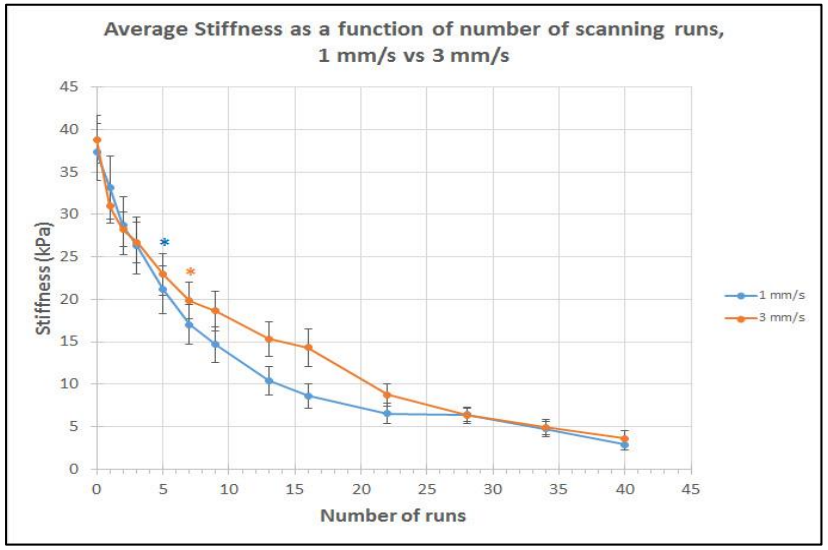
Destination Therapy

Moderate Aortic Stenosis and Valvosoft



- Less Calcified and more fibrous tissue?
- Risk to accelerate the calcification process ?

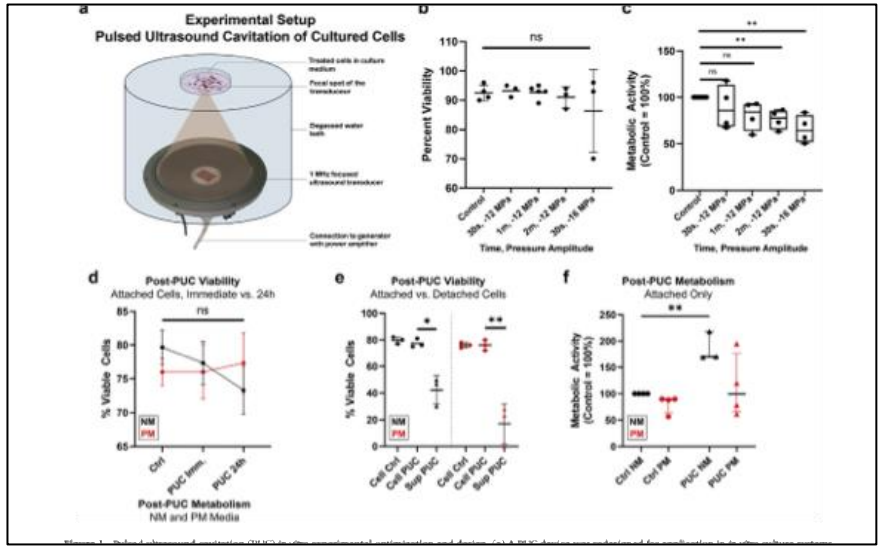
Ex vivo trial of VALVOSOFT performance on bovine pericardium. Tissue softening



Original Contribution

Short- and Long-Term Effects of Pulsed Ultrasound Cavitation Therapy of Calcified Valvular Interstitial Cells in Culture

Clift et al . Ultrasound Med Biol 2025 Nov;51(11):1936-1944.



Results: hVICs viability and metabolism were not significantly altered as a function of PUC treatment at short- (48 hour) or long-term (21 day) time points. Furthermore, PUC treatment did not increase hVICs calcification in vitro.

VALVOSOFT MAS TRIAL

- **VALVOSOFT MAS is a prospective, double-blind RCT that will be conducted in France and Canada, in which 386 patients with MAS and preserved LV ejection fraction** will be 1:1 randomly assigned to receive NIUT
- with: i) therapeutic ultrasound energy delivery at full-dose thus generating cavitation (Active Arm)
- OR ii) same procedure but with no ultrasound energy delivery (Sham-Control Arm).
- **The primary objective of the VALVOSOFT-MAS RCT is to demonstrate that Valvosoft® NIUT at full-dose reduces the progression rate of AS compared to Sham NIUT in patients with MAS.**
- **The primary endpoint is the annualized change in aortic valve area (AVA) from baseline to 2 years.**

- **<u>Trial Design</u>**
- **VALVOSOFT-MAS trial is a prospective, double-blind, parallel-arm, multicenter RCT (10 centers in France and 8 in Canada).**
- **A total of 386 patients with MAS, defined as AVA >1.0 cm^2, peak aortic jet velocity between 2.5 and 3.5 m/s** on echocardiography and **at least moderate aortic valve calcification on CT with preserved LVEF**
- will be 1:1 randomly assigned to receive NIUT with: i) therapeutic high-dose ultrasound energy delivery with cavitation (Active Arm) or ii) non-therapeutic zero-dose ultrasound energy delivery (Sham Control Arm). **The intervention will be performed at baseline and repeated at 1 year**

VALVOSOFT MAS TRIAL

Eligibility Criteria

Inclusion criteria:

i) Age ≥50 years and ≤ 85 years;

ii) LVEF >50%;

iii) MAS defined as echo-derived AVA >1.0 cm^2 AND peak aortic jet velocity between 2.5 and 3.5 m/s AND at least moderate aortic valve calcification (AVC) defined as CT AVC score > 400 arbitrary units (AU) in women; >1000 AU in men.

Exclusion criteria:

i) ≥ moderate-to-severe (≥ Grade 3) aortic or mitral regurgitation;

ii) Severe mitral stenosis or tricuspid regurgitation;

iii) Unstable arrhythmia not controlled by medical treatment;

i**v)** Prosthetic valve in any position;

v) Cardiogenic shock or other hemodynamic instability;

vi) significant kidney disease (eGFR ≤ 30 mL/min/1.73m^2 or on dialysis);

vii) Uncontrolled hypertension (blood pressure of ≥160/100 mmHg);

viii) Cardiac amyloidosis;

i**x)** Participation to another interventional study.

VALVOSOFT MAS TRIAL
French Governmental Granting Agency Program

Screening & Randomization

NIUT Procedure

Follow-up and Outcomes

VALVOSOFT MAS Trial
10 Centers in France (240 patients)
8 Centers in Canada (146 Patients)

Patients with moderate AS, moderate AVC, and preserved LVEF

Screening/Baseline demographic, clinical characteristics, TTE

TTE, CT, QoL, and blood biomarkers at baseline pre-procedure

386 Patients 1:1 Randomized

Active Arm (n=193)	VS.	Control Sham Arm (n=193)
NIUT – Full Dose at Baseline and 1 year		NIUT – Non-therapeutic Zero Dose at Baseline and 1 year years

Brain CMR in a subset of 60 patients at 30 days (Canada)

Non-Contrast CT at 2 years
Contrast-Enhanced CT in a subgroup of 128 patients at 2 years

TTE, QoL, and blood biomarkers at 30 days, and 1, 2, 3 years

Primary Endpoint: Annualized Change in AVA Baseline to 2 yrs.

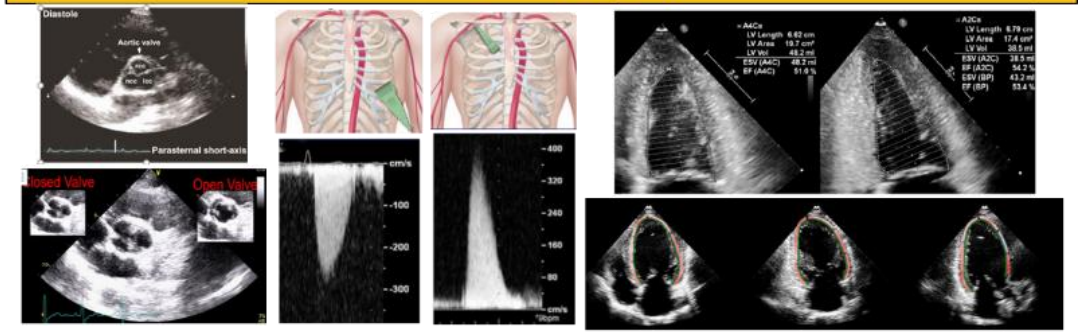
Key Secondary endpoints:

i) MACEs: cardiac mortality, all stroke, myocardial infarction, hospitalization for heart failure, aortic valve replacement;
ii) Changes in aortic valve hemodynamics, valve leaflet mobility and LV function, and cardiac damage by TTE; **iii)** Changes in aortic valve leaflet calcium score, density, and stiffness measured by CT; **iv)** Changes in aortic valve leaflet mobility and fibro-calcific burden measured by contrast-enhanced CT;
v)Changes in Quality of Life measured by KCCQ and EQ-5D-5L.

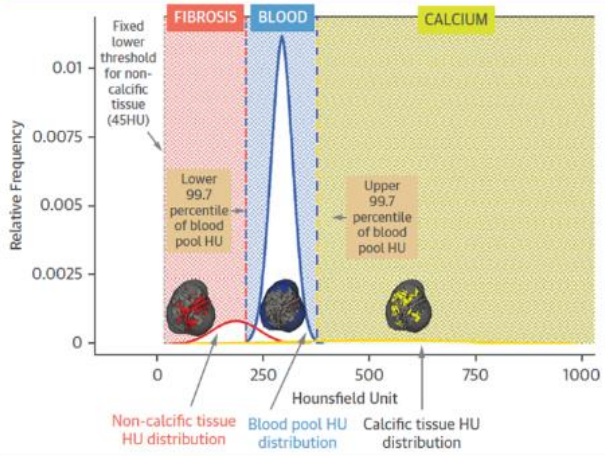
Imaging CoreLabs in QHLI, Canada

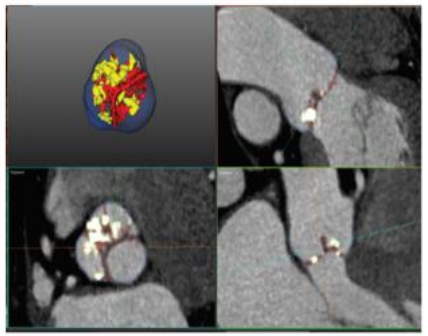
Analyses of brain CMR for detection of silent cerebral emboli at 30 days

Analyses of valve hemodynamics (AVA, gradients, DVI), valve leaflet mobility, and LV dysfunction (LVEF, SV, GLS, Zva), and cardiac damage stage by QHLI echo CoreLab at baseline, 30 days, 1, 2, 3 years



Analyses of: i) aortic valve calcification score, density, stiffness in all patients (non-contrast CT) and ii) of valve leaflet mobility , fibro-calcific burden, fibro / calcific ratio in a subset of 128 patients (contrast-enhanced CT) by QHLI CT CoreLab at baseline and 2 years.





Average image analysis duration: 5.8±1.0 minutes

New Cardiac stiffness Biomarker
Real Time Myocardial 3D Shear Wave Elastography
Benchmark Study on HpEF
Boston MA,USA
www.emyosound.com

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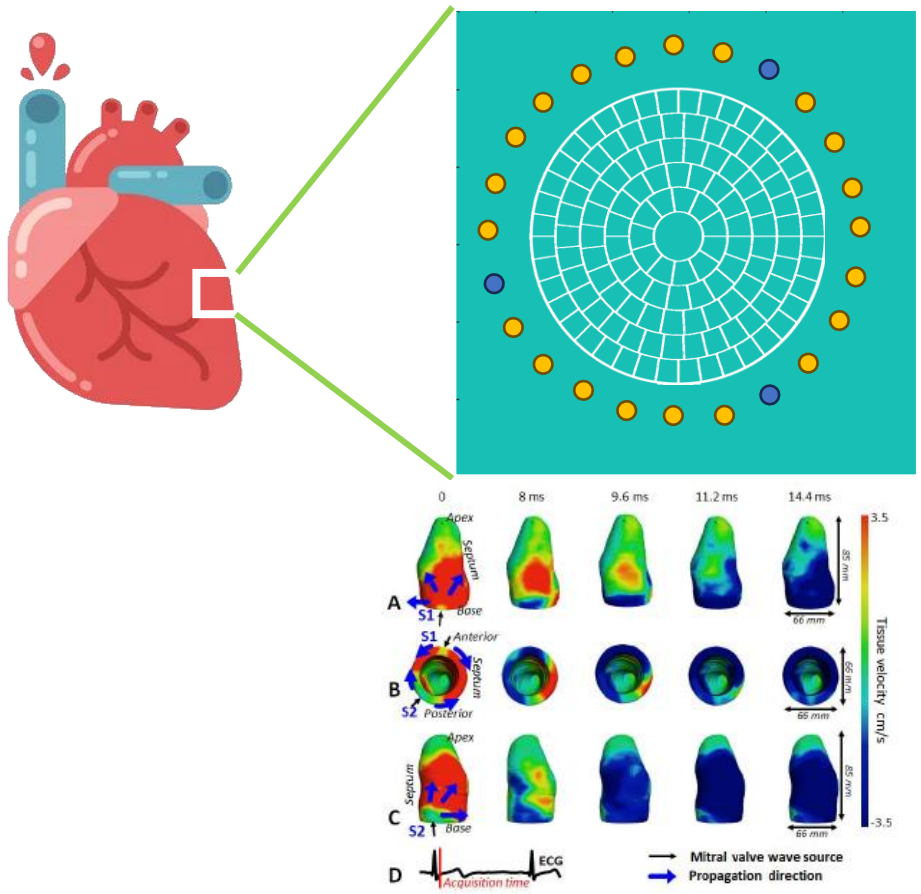
Physics for Medicine PARIS

Hôpital européen Georges-Pompidou AP-HP



C. Papadacci and al, « 4D ultrafast ultrasound imaging of naturally occurring shear waves in the human heart », 2019

Conclusion

- We demonstrated for the first time a prosthetic free non-invasive ultrasound therapy (NIUT) to soften aortic valve leaflets in 100 patients - 12 centres, 4 countries as:
  - Feasible
  - Safe
  - Performance up to 12 months
  - Improvement in quality of life

- VALVOSOFT MAS RANDOMIZED TRIAL will provide critical information for Valvosoft indication in mild to moderate CAS
- Other indication : BAV, Preparation to TAVR, MAC

FUTUR PERSPECTIVE

- CE Mark end of this year
- FDA application to go to US
- Other indication : Thrombotripsy
    - HALT prevention after TAVR
    - SPT prevention after Deep veinous thrombosis

Goudot et al J Thromb Haemost. 2020 Nov;18(11):2889-2898.

Science Review Sept 2024

RESEARCH

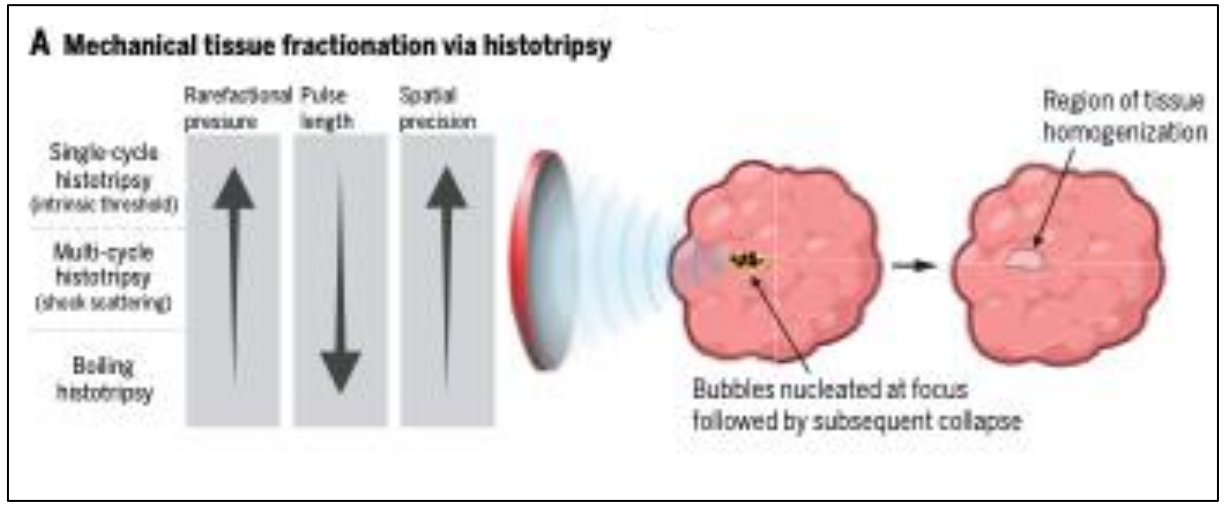
REVIEW

ULTRASOUND

Exploiting the mechanical effects of ultrasound for noninvasive therapy

Meaghan A. O'Reilly

O'Reilly, Science 385, eadp7206 (2024)



3MPa 8MPa 40MPa 100MPa

Echography

HIFU (High Intensity Focused Ultrasounds)

THERAPY

THERAPY

Histotripsy

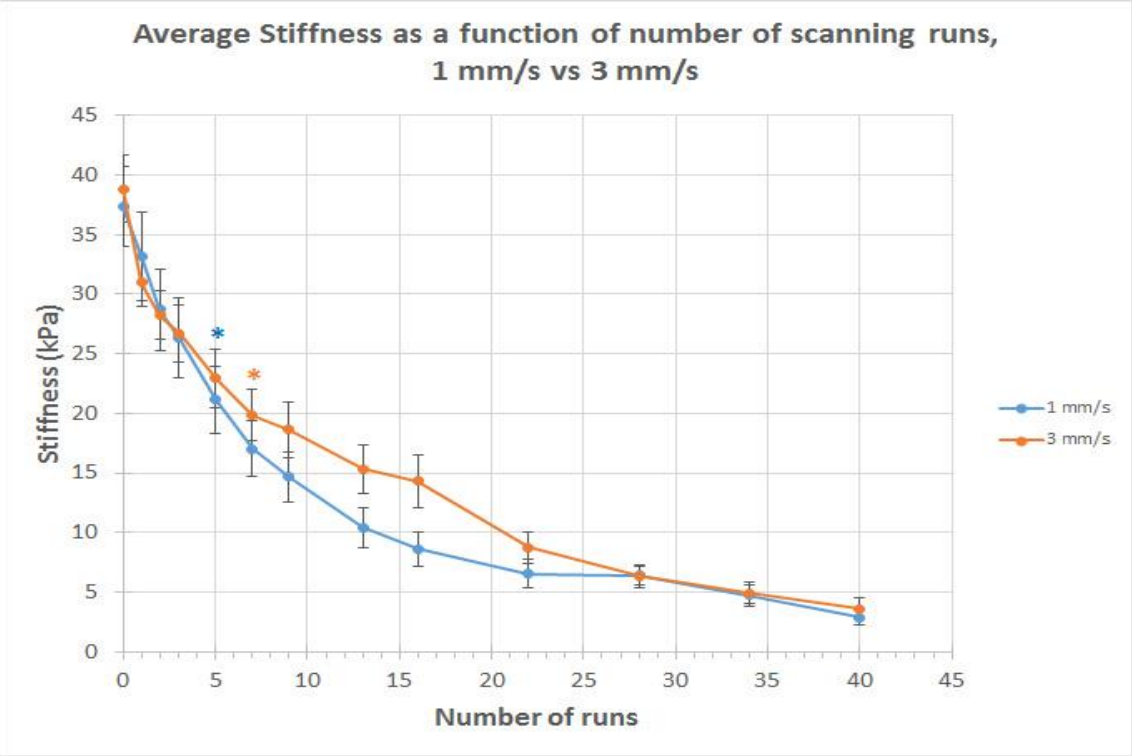
Table 1. Nonthermal applications of therapeutic ultrasound. For the four application areas summarized in this review, the peak rarefactional pressure (a measure of exposure level), use of exogenous cavitation agents, primary bioeffect, major target organ, and clinical trials to date, with select references, are listed. All of these applications use pulsed ultrasound. Although some may have high pulse average intensity, the time average intensity is low compared with that of thermal HIFU, which uses continuous wave exposures.

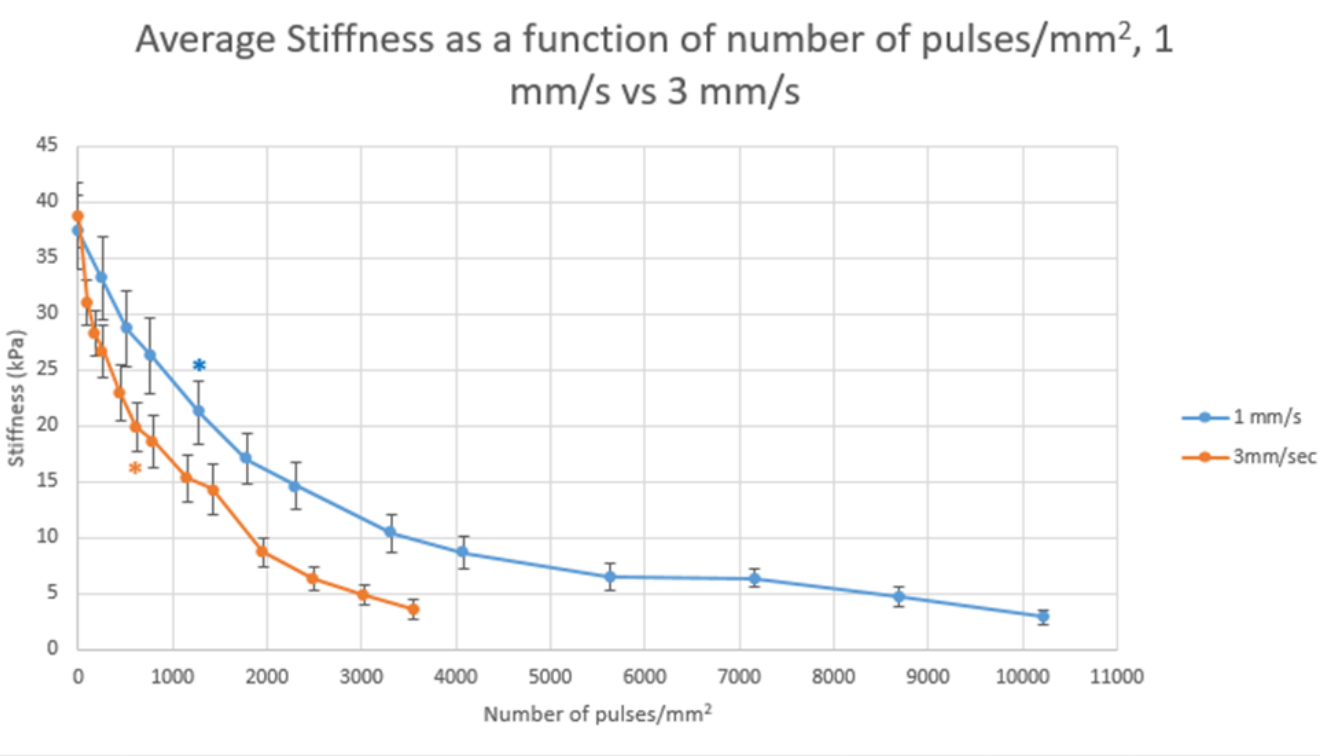
Application	Pulse average intensity	Pulse length	Peak negative pressure	Exogenous cavitation nuclei	Primary bioeffect	Target	Clinical trials
Brain drug delivery	Low	Milliseconds	<~1 MPa* (*24*)	Intravenous microbubbles	Transient enhancement of vascular permeability	Brain	Primary and metastatic brain tumors (*19–26*), Alzheimer's disease (*27–32*), Parkinson's disease (*33*, *34*), amyotrophic lateral sclerosis (*35*)
Neuromodulation	Low	Microseconds to milliseconds	<~1.5 MPa† (*95*)	None	Stimulation of neural circuits	Brain	Depression (*87–89*), essential tremor (*90*, *91*), Parkinson's disease (*92*), epilepsy (*93*), disorders of consciousness (*94*), addiction (*95*)
Nonthermal tissue destruction	High	Microseconds (intrinsic threshold, shock scattering), milliseconds (boiling histotripsy)	>10 MPa (boiling histotripsy), >15 MPa (shock scattering), >25 MPa (intrinsic threshold) (*118*)	None	Tissue homogenization	Varied	Benign prostate hyperplasia (*132*), liver tumors (*133*), aortic valve stenosis (*139*)
	Low	Milliseconds	~0.2 to 9 MPa‡ (*165*)	Intravenous microbubbles	Targeted vascular damage alone or adjuvant to chemotherapy or radiation therapy	Varied	Hepatocellular carcinoma (with transarterial radioembolization) (*142*), breast cancer (with external beam radiotherapy) (*143*)
Immune modulation	Either (secondary to above exposures)	Varied	Varied	Either	Stimulation of innate and adaptive immune response	Varied	Glioblastoma multiforme (with ultrasound enhanced drug and checkpoint inhibitor delivery) (*164*)

*Peak negative pressure in investigations of brain drug delivery varies with frequency. The pressure range listed here is limited to clinical trials, where the highest reported pressures are seen in studies using an implanted device (*24*). †Listed peak negative pressure for neuromodulation studies is based on the parameters reported in clinical trials, with the listed upper bound based on an intensity of 80 W/cm^2 reported in (*95*) (assumed to be pulse average intensity), with the remainder of cited studies ≤1 MPa. This excludes the transcranial pulse stimulation method described in (*52*, *88*), which uses a fundamentally different exposure scheme based on ultrashort low-intensity shockwaves. Preclinically, neuromodulation has been explored over a much larger parameter space. ‡Antivascular effects have been explored over a wide range of pressure levels. For further details, see the appendix of (*165*).


CARDIAWAVE
emyosound
Physics for Medicine PARIS
Thank you for your attention
ASSISTANCE PUBLIQUE
HÔPITAUX DE PARIS
Hôpital Européen Georges Pompidou
Photo J-L. Ginolin (AP-HP) 2008

Ex vivo trial of PCUT treatment performance on bovine pericardium. Tissue softening





Average Stiffness as a function of number of scanning runs, 1 mm/s vs. 3 mm/s

A significant decrease in stiffness of 50% was observed after 5 repetitions at 1mm/s (n= 6) and after 7 repetitions at 3mm/s (n= 7).

Average Stiffness as a function of number of pulses/mm², 1 mm/s vs. 3 mm/s

Scanning speed influenced the rate of decrease: at 3 mm/s a significant decrease in stiffness was observed with a smaller number of pulses (622) than at 1 mm/s (1277).

Conclusion MAS

- MAS patient is an **important population with global poor outcome**
- MAS **progression is heterogenous we need tool to predict its progression**
- **Therapeutic strategy are ongoing** with TAVI and medication
- **Prosthetic free calcium fragmentation** could be an option for MAS patient
- **Non invasive ultrasound therapy could be an option for slower the progression of the disease**

Back-up

All mortality 100 pat

Pivotal mortality up to 3 months

Decrease of AVA by 0.1 cm associated with siginifcant increase of 16% of all cause of death or Aortic Valve replacement Surgery

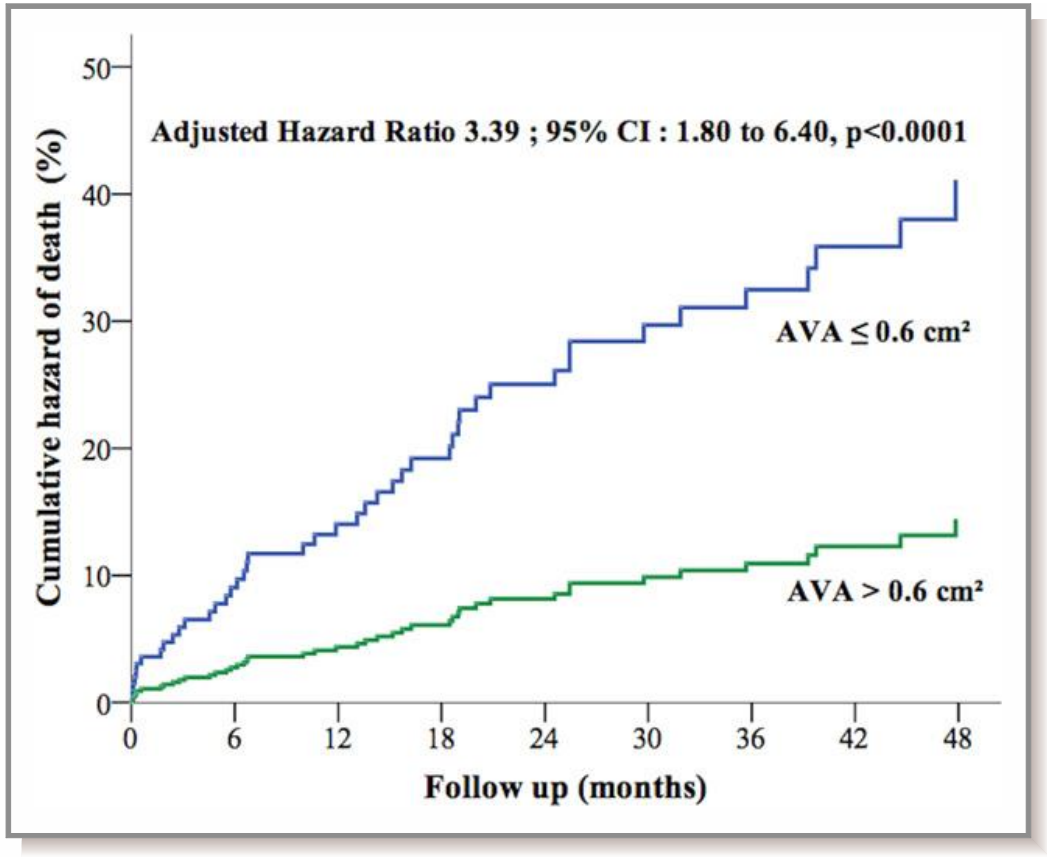


Figure 4. Cumulative hazard of death according to AVA ≤0.6 and >0.6 cm^2. Curves are adjusted for age, sex, comorbidity index, coronary artery disease, hypertension, atrial fibrillation, left ventricular ejection fraction and aortic valve replacement as a time-dependent variable. AVA indicates aortic valve area.

Table 3. Relative Risk of Events (All-Cause Death or Aortic Valve Replacement Surgery) During Follow-up Associated With Aortic Valve Area

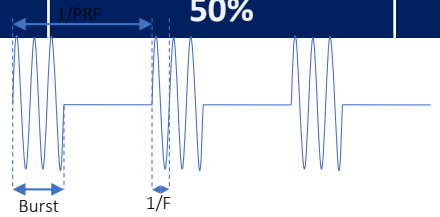
	Hazard Ratio	95% CI	*P* Value
AVA categories			
Unadjusted			
AVA ≤0.6 cm^2	2.19	1.40–3.40	0.001
AVA >0.6 to ≤0.8 cm^2	1.35	0.91–1.99	0.13
AVA >0.8 to ≤1.0 cm^2	Referent		
Adjusted*			
AVA ≤0.6 cm^2	2.22	1.41–3.52	0.001
AVA >0.6 to ≤0.8 cm^2	1.38	0.93–2.05	0.11
AVA >0.8 to ≤1.0 cm^2	Referent		
Per 0.1 cm^2 AVA decrement			
Unadjusted	1.16	1.06–1.28	0.002
Adjusted*	1.17	1.06–1.29	0.002

AVA indicates aortic valve area.
*Adjustment for age, sex, hypertension, coronary artery disease, history of atrial fibrillation, Charlson comorbidity index, and left ventricular ejection fraction.

Marechaux et al JAHA 2016

Unique Non-invasive Ultrasound Therapy solution

Therapeutic ultrasounds	HIFU*	Lithotripsy	Histotripsy	NIUT
Mechanism	Continuous waves	Shock wave (minimized / non desired cavitation bubbles)	Pulse cavitational ultrasound With electronic steering (Sustained inertial cavitation bubbles implosion generates localized streaming, shockwaves)	
Pulse Repetition Frequency of Bursts (PRF)	NA	0.5 to 2 Hz	1 to 1000 Hz	
Number of oscillations in a Burst / Duration	few seconds	1 osc. = 4µs per pulse	1 to 20 osc.=10µs per pulse	
Central Emission Frequency (F) / Pulse duration	0.25 to 3 Mhz	700 kHz	High frequency ermission.	
Duty cycle (<4% no thermal effects)	50%	0.0008%	<1%	

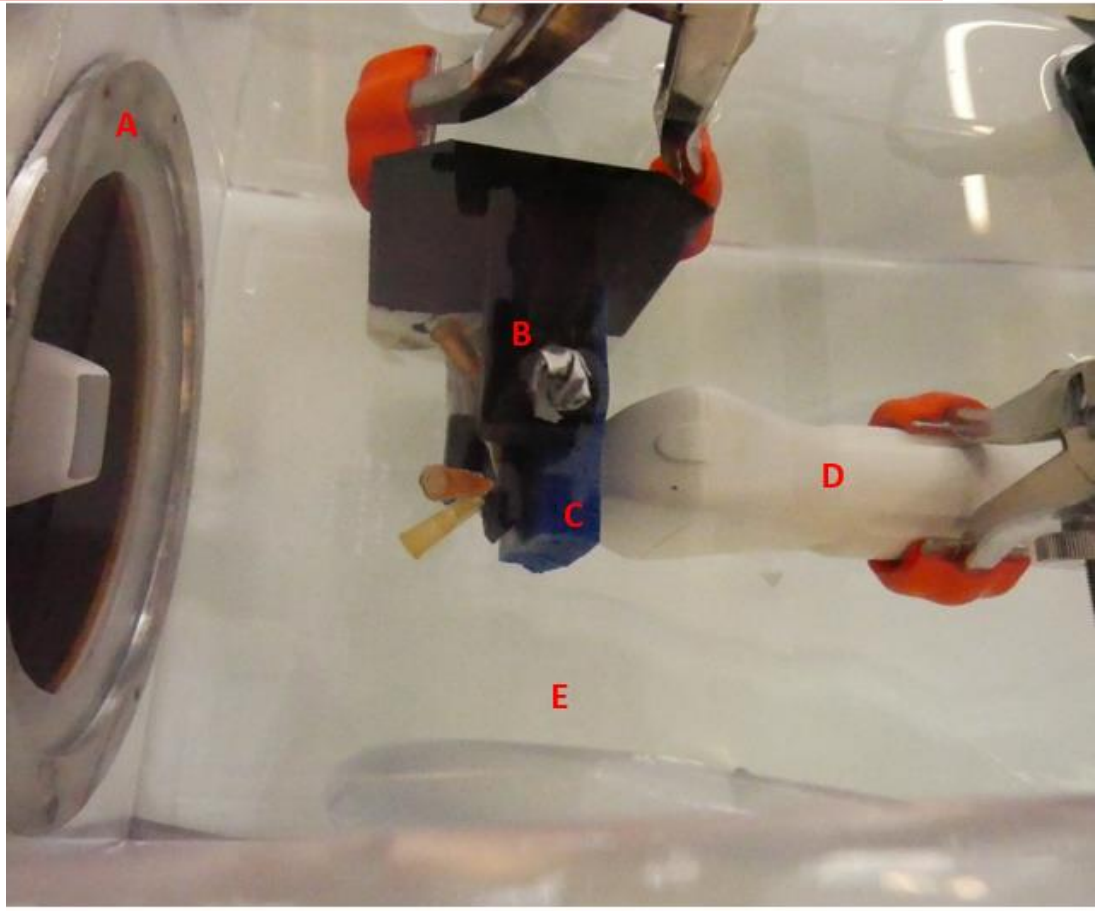


with:

- Burst: Sinusoidal signal portion used in a repetitive sequence.
- F: (Central) Frequency of the sinusoidal signal in a burst.
- PRF: Frequency of the burst repetition sequence.
- Nosc: Number of sinusoid periods or oscillations in a burst. *(e.g., Nosc=3).*

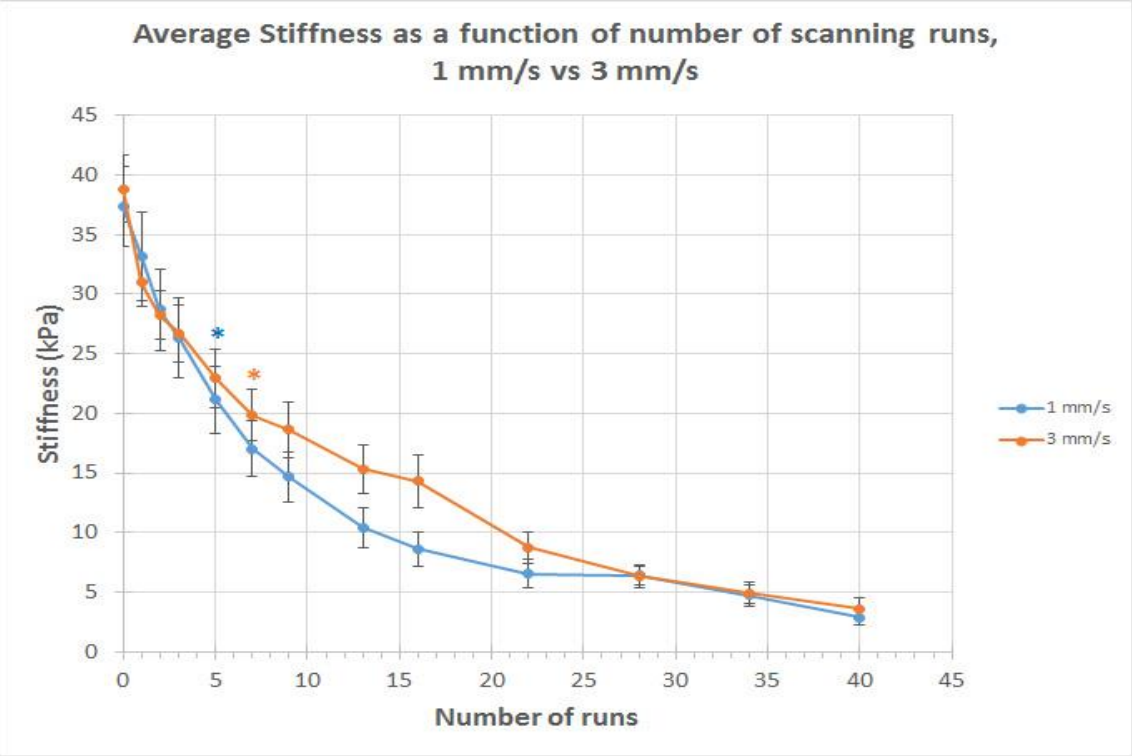
Ex vivo trial of PCUT treatment performance on bovine pericardium. Tissue softening

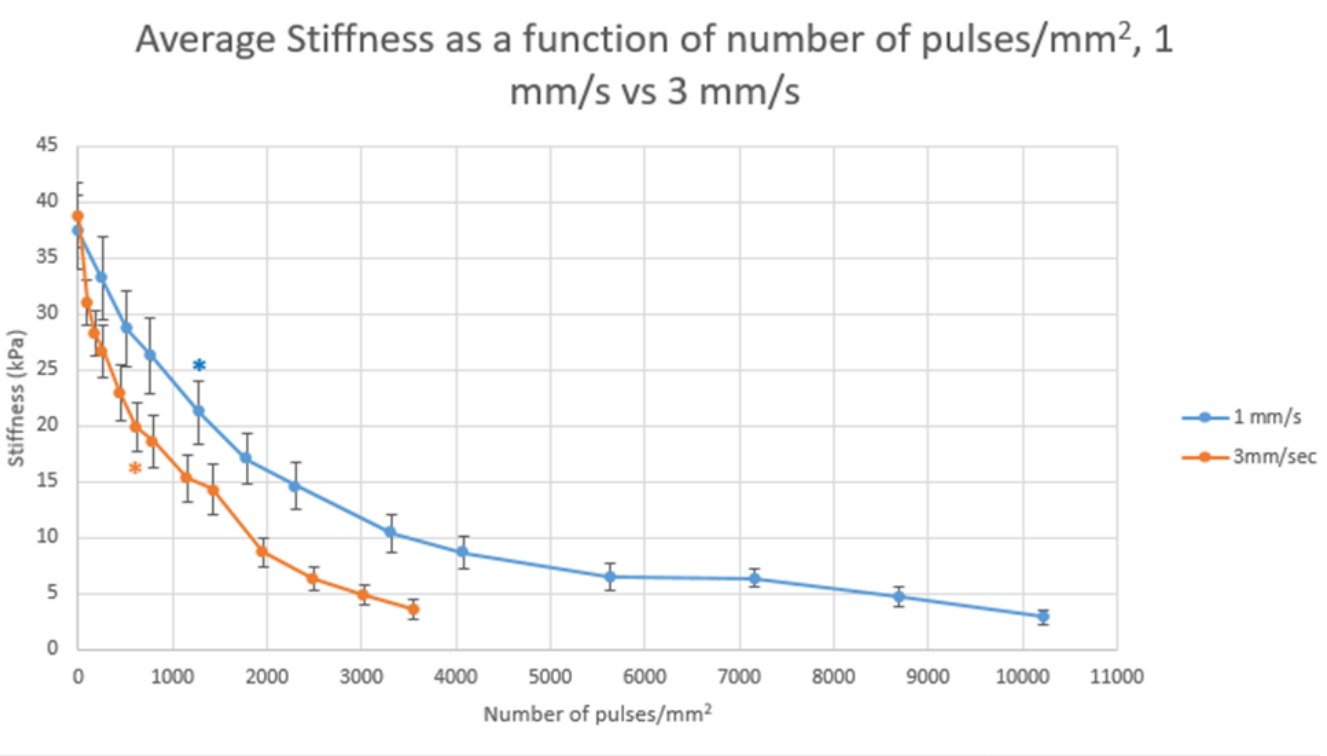
- Surgical bovine pericardium is the component used to make aortic valve bioprostheses and was therefore selected as an equivalent test material.
- Strips of pericardium were placed in a bench with their stiffness measured by elastography.
- Verification of the performance of focused cavitation therapy on pericardium strips: gradual decrease of stiffness with increasing PCUT repetition.



A) PCUT device. B) Sample holder connected to computer-controlled motors. C) Absorber, to protect elastography probe during therapy D) 20 MHz elastography probe. E) Aquarium filled with degassed saline.

Ex vivo trial of PCUT treatment performance on bovine pericardium. Tissue softening





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NIUT indications for Use

First indication for use (CE-marking):

Patients not recommended for AVR

Bridge to AVR

Patients refusing AVR*

Future potential indications:

Delay disease progression in moderate patients to delay 1st valve replacement

Asymptomatic severe patients

AVR deferral in young severe symptomatic patients to delay 1st valve replacement

Pre-TAVR to optimize procedural outcomes

Bioprosthesis treatment to prolong implanted bioprosthesis durability

In countries where TAVR remains unavailable

* within CE study not allowed in France

Valvosoft® FIM +Pivotal baseline data of treated patients

Characteristic	FIM (N=40)	Pivotal (N=60)
Age (years)	83.00 ± 8.45	85.15 ± 9.14
Female/Male	21 (52.0%)	39 (65.0%)
Left Ventricular Ejection Fraction (LVEF) (%)	52.79 ± 9.92	55.00 ± 11.02
Aortic Valve Area (AVA), cm^2	0.58 ± 0.19	0.65 ± 0.19
Aortic Valve Mean Pressure Gradient (PG), mmHg	40.94 ± 20.06	46.08 ± 14.52
Aortic Valve Peak Velocity, m/sec	4.07 ± 0.94	4.27 ± 0.59
LFLG	18 (45)	17 (28,3)
Calcification Volume, mm^3	976.8 ± 1451.46	3211.89 ± 1873.97
New York Heart Association (NYHA)		
1	-	2 (3.3%)
2	10 (25%)	27 (45.0%)
3	19 (48%)	26 (43.3%)
4	11 (28%)	5 (8.3%)
EuroSCORE II (%)	5.56 ± 4.38	7.35 ± 7.03
STS Score (%)	5.82 ± 4.70	7.35 ± 6.00
Frailty Score	-	5.07 ± 1.33
EQ-5D	-	57.95 ± 16.29
KCCQ	45.5 ± 22.64	61.48 ± 21.65
6MWT (m) (20 ND)	-	198.45 ± 114.43

Valvosoft : AVA improvement up to 12 months (pooled data, in progress)

NIUT slows down disease progression compared to natural history of AS

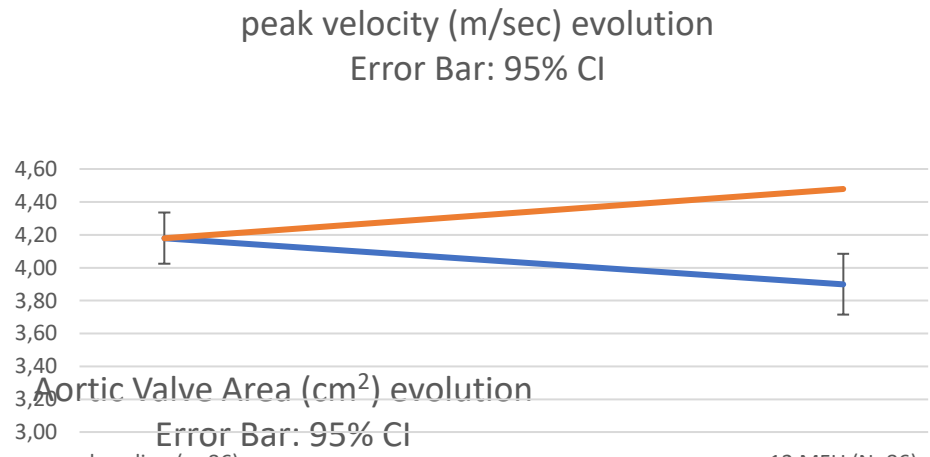
Time point		Baseline (N=87)	12 Months (N=87)
AVA results	Mean (cm^2)	0.63	0.69
	Standard deviation	0.19	0.23
	Change vs. Baseline (%)		**10%**

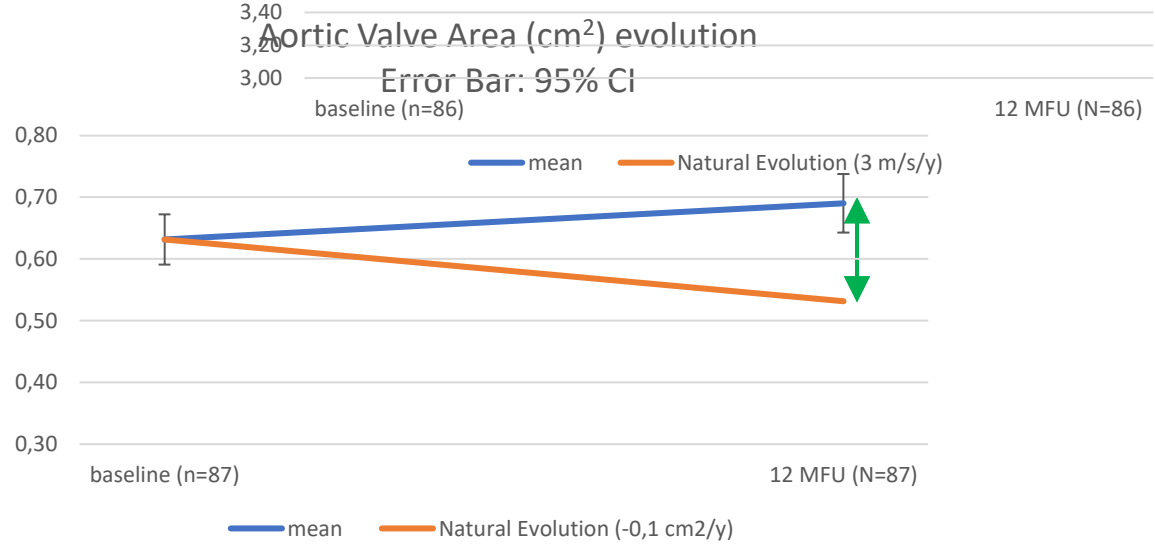
Interim clinical results (pooling of all available data in FIM and Pivotal study .

- AVA increase vs. Baseline up to 12-months
- AVA is after 12-months larger than the natural history decrease
- 3 patients received TAVR after Valvosoft treatment

  FIM = 21 @ 12 months
  Pivotal = 2 @ 12months

  Combine with Vmax 1 slide



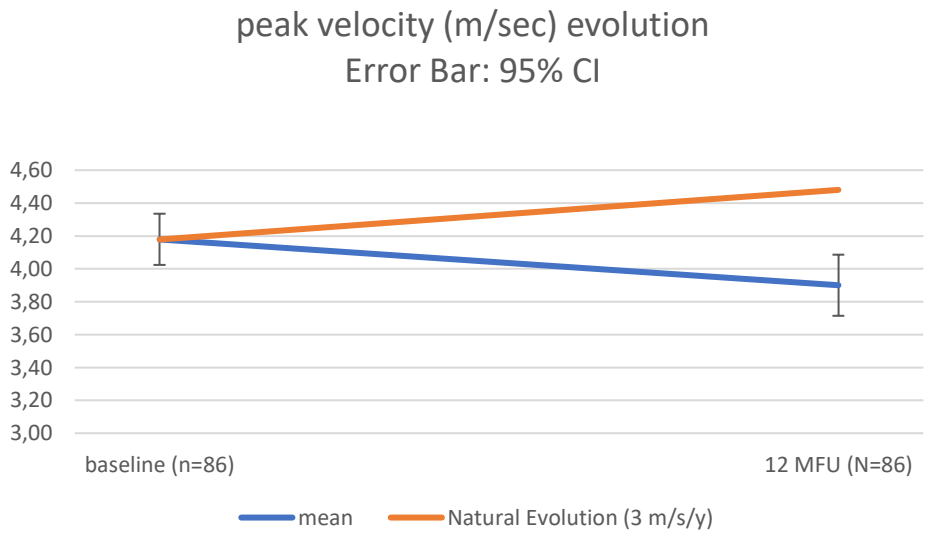


Valvosoft : Peak Velocity improvement up to 12 months

Time point		Baseline (N=86)	12 Months (N=86)
Peak velocity results	Mean (m/sec)	4.18	3.90
	Standard deviation	0.74	0.88
	Change vs. Baseline (%)		**-7 %**

Interim clinical results (pooling af all available data in FIM and Pivotal study .

- Peak Velocity decreases vs. Baseline up to 12-months
- Peak Velocity is after 12-months lower than the natural history increase



Valvosoft short story

- Valvosoft : **6 prototypes** in fonction
- **100 patients** (FIM+CE) treated (+ retreated: 14)
- **4 countries** (France, Netherlands, Germany, Serbia)
- **12 centers**
- Follow up **until 24 months** for some patients

- **Presentations** AHA, ESC, EuroPCR, EuroValve….

- **Publications - Clinical data:**
  - **Eur Heart J Cardiovasc Imaging. 2023 :**

    10 patients Serbia with brain MRI before and after treatment
  - **Circulation 2021** :

    10 first patient with one month follow up
  - **Angiogenesis. 2021**

    Von Willebrand factor multimers during non-invasive ultrasound therapy for aortic valve stenosis

New & unique therapeutic ultrasound energy

No cleared device on the market using our Non-Invasive Ultrasound Therapy (NIUT)

Potential indications

- Symptomatic moderate aortic stenosis (planned POC study)
- Subjects recommended for TAVR/SAVR suffering from severe symptomatic CAS patients as pre-BAV replacement

Conclusion

- Calcium-fragmentation therapy (invasive and non-invasive) can become an option (complementary to TAVR, SAVR or BAV) in patients where those therapies is not optimal.
- We demonstrate for the first time prosthetic free non-invasive ultrasound therapy for calcium-fragmentation can be:
  - Feasible
  - Safe
  - Some performance up to 12 months
  - Improvement in quality of life and NYHA

in 100 patients in 12 centres/4 countries

- Improvement of therapy by increasing power will further increase efficacy

Back-up

All mortality 100 pat

Pivotal mortality up to 3 months

Lancet in press

Non-invasive focused ultrasound (FUS) for therapeutic purposes

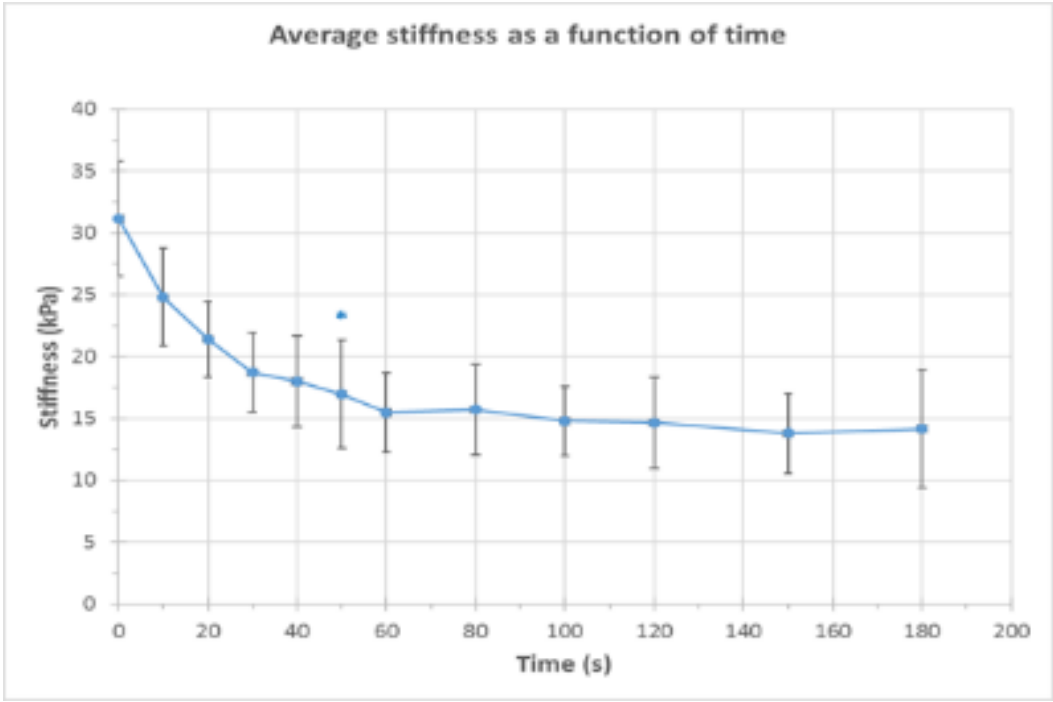
- Extracorporeal shockwave lithotripsy (SWL)
  - Based on the emission of shockwaves
  - Concentration of short high intensity ultrasound pulses in a focal point for non-thermal mechanical effects
  - Clinically available, intended to break kidney stones into smaller fragments

- SWL is associated to acute damage such as vascular trauma to the kidney and the surrounding organs that would be fatal for the heart

- The **Valvosoft NIUT treatment is an evolution** of SWL, **not shockwave-based**, more **controlled** and with **no damaging of the surrounding tissues**

Ex vivo trial of PCUT treatment performance on bovine pericardium. Tissue softening

- In steady shot PCUT, stiffness decreased as soon as 10 seconds of therapy, although not significantly. After 50 seconds of treatment a significant decrease of the pericardia stiffness was reached (denoted by "*" on graph). About 50% decrease was obtained after 60 seconds of steady shots (from about 31.13 to 15.45kPa) with no further decrease with the treatment duration although pericardia erosion was worsened. All pericardia were homogeneously perforated after 2 minutes (180 seconds) of steady shots.



Average stiffness of six independent experiments, as a function of steady shot duration.

Ultrasound wave