New Technologies for Future Treatment of moderate AS

Emmanuel Messas, MD, PhD,FESC

Hôpital européen Georges-Pompidou, Paris, France

Hôpital européen Georges-Pompidou AP-HP

Physics for Medicine PARIS

Université Paris Cité

FACULTY DISCLOSURE

I disclose the following financial relationships:

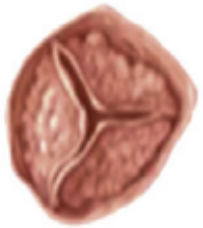
Consultant for the company Novartis,Bayer

Advisory Board for Cardiawave Company

Major shareholder of Cardiawave Company

Moderate Aortic Stenosis: Definition and Characteristics

Moderate aortic stenosis ?



Peak aortic velocity 3.0 to < 4.0m/s
or
Mean gradient 20 to < 40mmHg

and

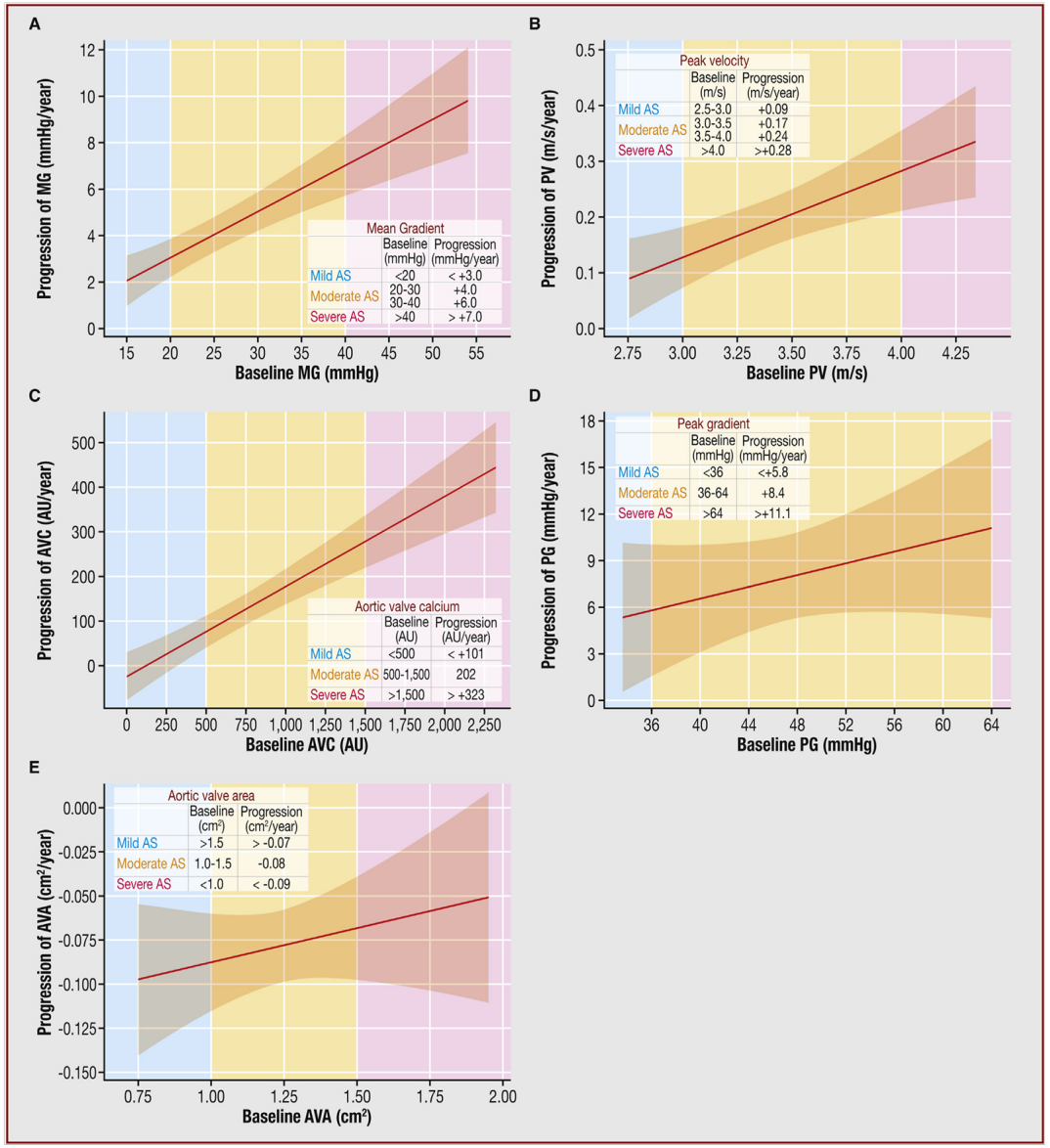
AVA 1.0 to 1.5cm²
or
AVA < 1cm² with AVA index > 0.6cm³/m² (BMI < 30) or
AVA < 1cm² with AVA index > 0.5cm³/m² (BMI ≥ 30) or
AVA > 1.5cm² with AVA index < 0.9cm³/m² (BMI < 30) or
AVA > 1.5cm² with AVA index < 0.8cm³/m² (BMI ≥ 30)

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

- **Epidemiology:** Prevalence of AS (mild to severe) above 75 yrs old is 12.4% **representing 5.4 million with AS and 3 million with 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



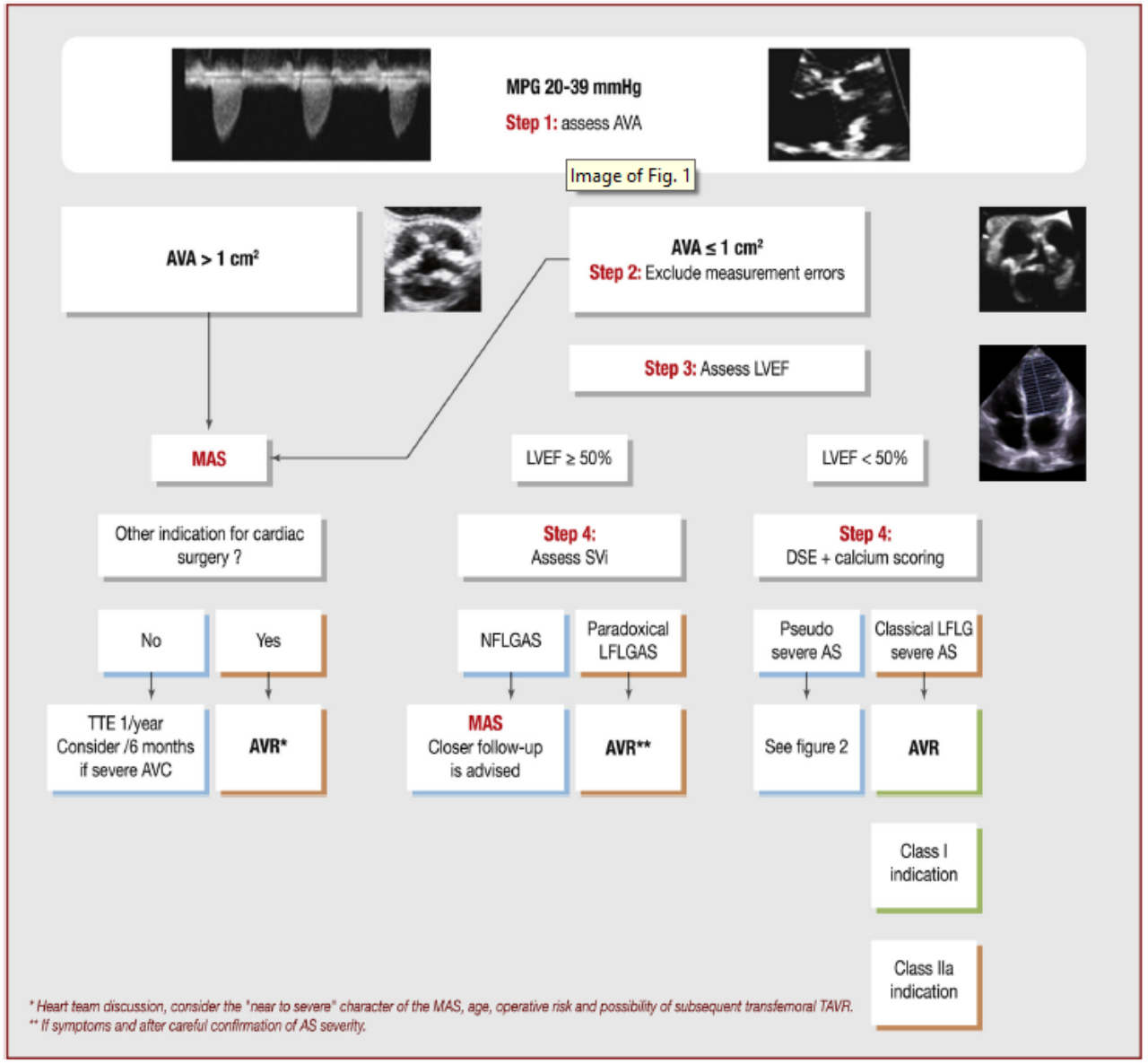
-AVA decreases by 0.08 cm^2/year

- Mean gradient increases by 6.0 mmHg/year

- Peak velocity increase by 0.2 m/sec/year

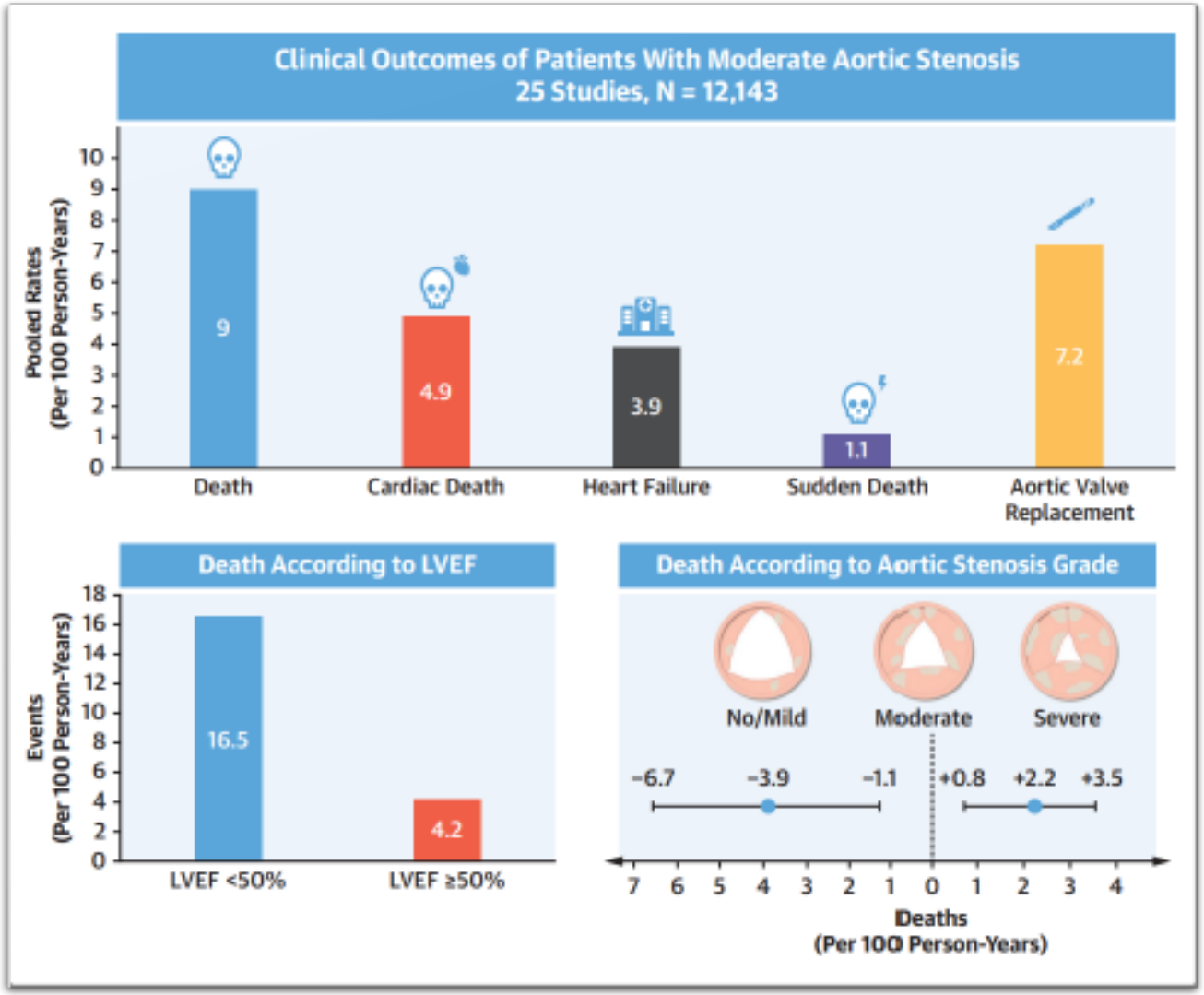
Willner N,Prosperi-Porta G, et al..Aortic Stenosis progression:a systematic review and meta-analysis. JACC Cardiovzasc Imaging 2023.
Total 24 studies and 5450 patients

Current ESC Guideline for MAS



Vahanian A et al. Eur Heart J 2022;43:561-632

Impact of Moderate Aortic Stenosis on Long-Term Clinical Outcomes: A Systematic Review and Meta-Analysis

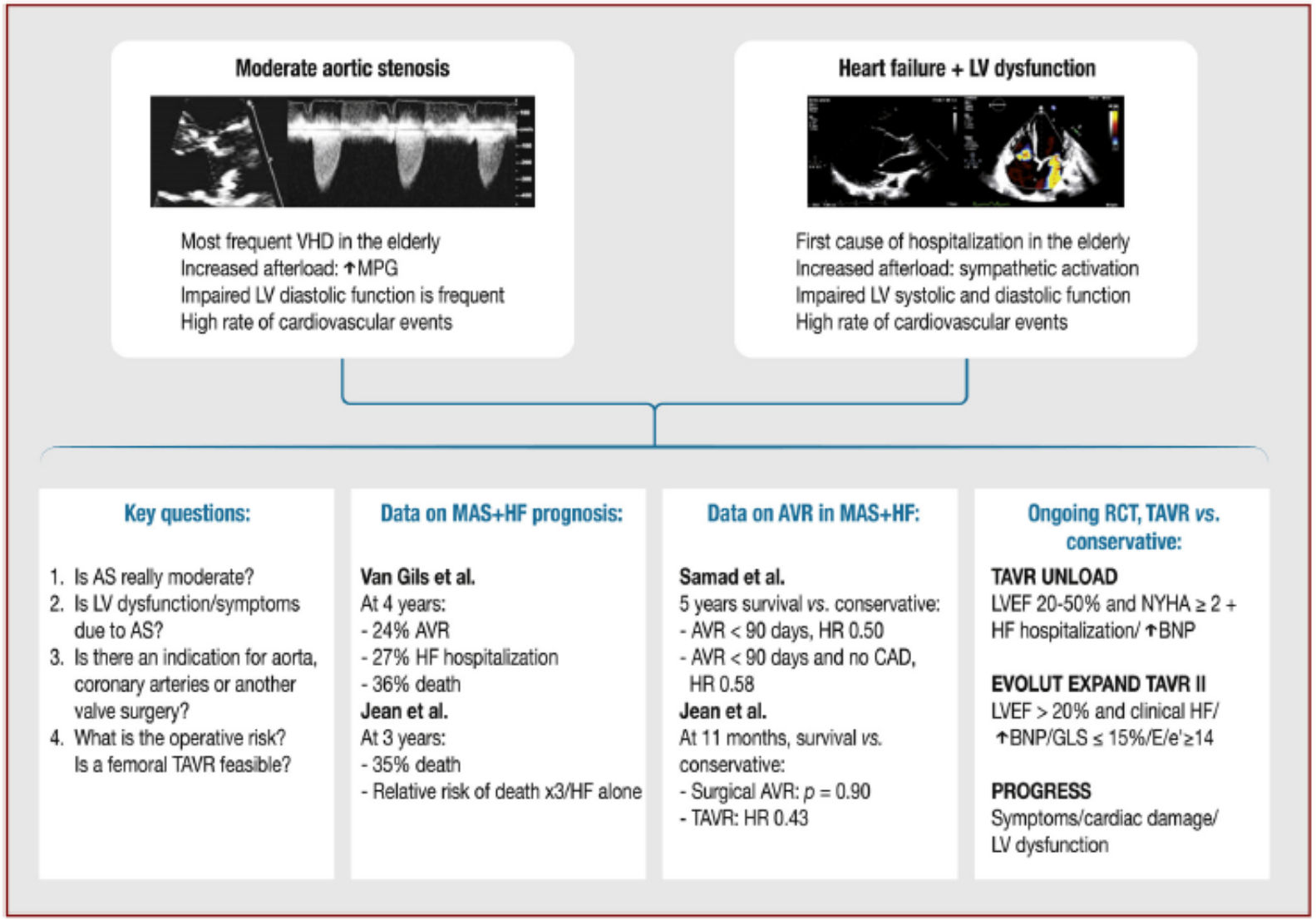


Meta-regression analyses detected that **diabetes** (P = 0.019), **coronary artery disease** (P = 0.017), presence of **symptoms** (P = 0.001), and **LV dysfunction** (P = 0.009) are associated with a significant impact on the overall estimate of all-cause death.

CONCLUSIONS Moderate AS appears to be associated with a mortality risk higher than no or mild AS but lower than severe AS, which increases in specific population subsets. The impact of early intervention in moderate AS patients having high-risk features deserves further investigation

Coisne A, et al. *JACC Cardiovasc Interv* 2022; **15**: 1664–74.

relationship

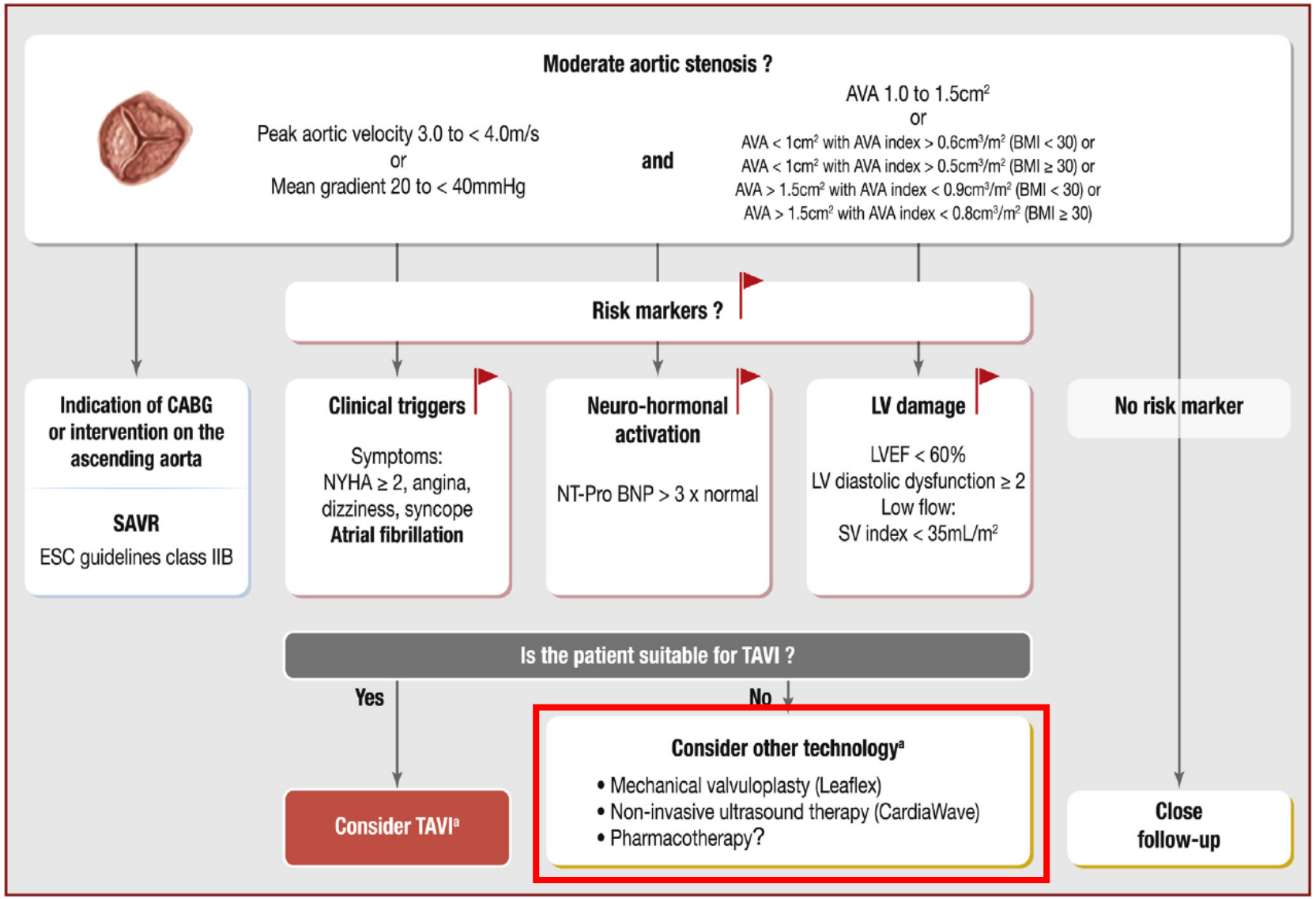


Y. Bohbot et al Archives of Cardiovasc Disease 116 (2023) 411-418

Moderate Calcified Aortic Stenosis: optimal therapeutic option

- Less invasive or Non-invasive
- “Prosthetic free”
- Minimal procedure risks
- Delay or avoid AVR
- Help to delay the time of patients becoming with severe CAS and lower the morbidity and mortality risks

MAS: recently proposed management

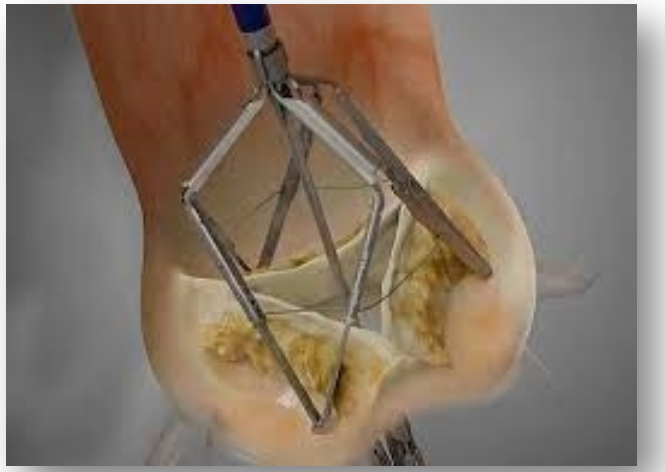


A. Théron, et al. Arc of Cardiovasc Dis. 2023;116:295-297

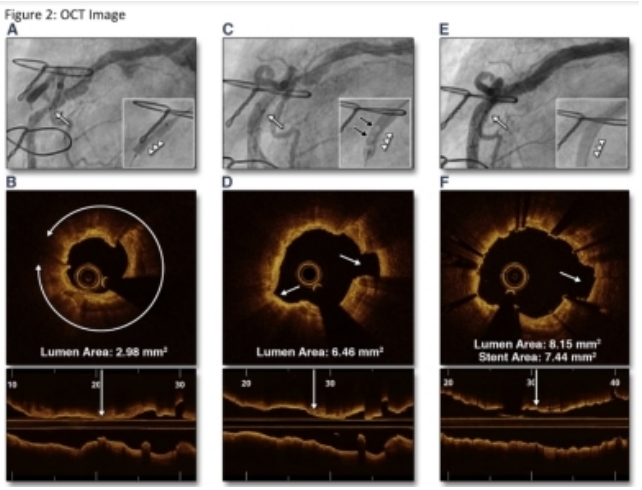
Pelacarsen: An antisense oligonucleotide targeting the apo(a) mRNA to lower Lp(a) levels

Parameter	Description
Study description	Phase II, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of pelacarsen to slow the progression of aortic valve stenosis Mechanistic endpoints chosen in this study are well-validated surrogates of disease status and have been used in previous studies[1-4]. In addition, they are commonly used as decision making for aortic valve replacement
Target population	Patients diagnosed with aortic valve stenosis (mild or moderate) and elevated Lp(a)
Treatment arms	Pelacarsen 80 mg QM, placebo
Study duration	**36 months**

“Prosthetic free” concepts of calcium fragmentation for improving leaflet mobility and increase valve opening



Leaflex™ catheter (Pi Cardia ©, Rehovot, Israel)



Intravascular lithotripsy (Shockwave Medical©, Santa Clara, USA)

INVASIVE

Non-implant valve repair for calcific aortic stenosis: the Leaflex study

Device used to score leaflets

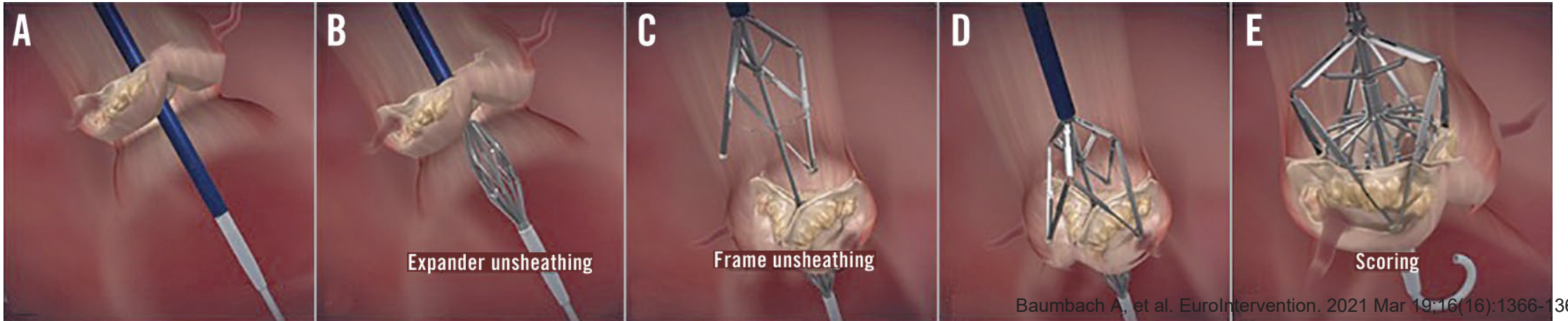
- **15 subjects treated followed by TAVR procedure**

First 4 subjects no full expansion of Leaflex

- one wire-related ventricular perforation
- Two disabling strokes

Echocardiography and haemodynamic measurements N=11 (fully expanded)	Pre (Mean±SD)	Post (Mean±SD)
Aortic valve area, cm^2	0.7±0.1	1.2±0.3*
Mean pressure gradient, mmHg	33±13	17±10*
Peak-to-peak pressure gradient, mmHg	51±29	21±23*
*Pre vs post: p<0.001.		

- **Pivotal Study ShortCut Study completion :It included 60 patients undergoing valve-in-valve procedures**, in whom ShortCut™ was used as a preceding step to TAVR implantation



Baumbach A, et al. EuroIntervention. 2021 Mar 19;16(16):1366-1369

“Prosthetic free” concepts of calcium fragmentation for improving leaflet mobility and increase valve opening

VALVOSOFT®: A NON-INVASIVE ULTRASOUND THERAPY DEVICE

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

NON INVASIVE

- **Non-invasive**
- Ambulatory outpatient setting, one hour treatment divided by 6 session of 10 min
- No need of a cathlab
- Ease of use, fast learning curve for operators
- Safe for operators, no radiation

Institute of Physics for Medicine at the ESPCI Paris

Mickael Tanter
Director

Mathieu Pernot
Deputy Director

ESPCI PARIS
EDUCATION SCIENCE INNOVATION

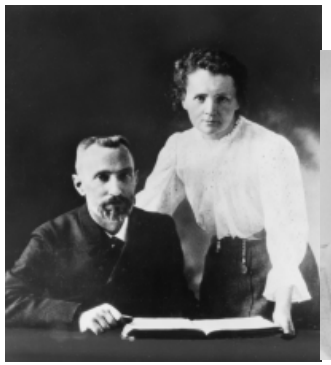
Ecole Supérieure de Physique et de Chimie Industrielle (E.S.P.C.I.), Paris, FRANCE

From Fundamental Physics to Medical applications

Cardio-Vascular department, HEGP, Paris

Hôpital européen Georges-Pompidou AP-HP

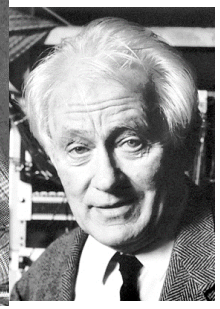
Université Paris Cité



Marie and Pierre Curie
1903
Marie Curie
1911

Frédéric Joliot-Curie

Pierre-Gilles de Gennes



Georges Charpak

5 Nobel Prizes

Experienced, Multidisciplinary & committed team since 2015

CARDIAWAVE

Management Team

Benjamin Bertrand

CEO, Cofounder & Chairman of the board

- French-American entrepreneur
- 20+ years experience in Life Sciences start-ups and M&A in France and abroad

Maurice Delplanque

Chief Operating Officer

- 10 years experience on the Cardiac and Vascular product lines at GE Healthcare
- Former EOS Imaging VP

Dirk Pauwels

Clinical Director

- 20 years in the MedTech and mainly cardiology space
- Participated to the first EU trials of TAVR

Luc Morisset

Quality and Regulatory Affairs Director

- Experience of medical device certification for the French Ministry of Health in the cardiology field
- 10 years in MedPass International, a CRO specialized in medtech & cardiology

Team

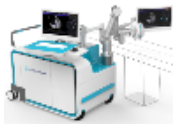
Unique skills and expertise in ultrasound therapy & imaging

- R&D and Manufacturing: 20 FTEs
- Clinical and precinical: 2 FTEs
- Quality and Regulatory: 2 FTEs
- Back office: 1 FTE

Team achievements: Key milestones reached, ready for CE-marking clinical trial

VALVOSOFT Generation 1

34 patients



VALVOSOFT Generation 2

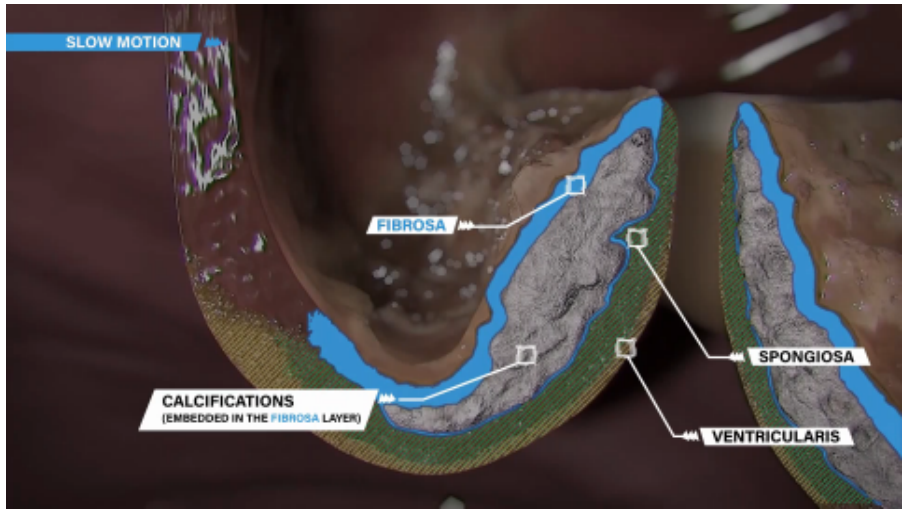
ISO 13485

PRIX GALIEN

MEDTECH INNOVATOR

HealthTech AWARD

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	NIUT
Ability to penetrate deep in tissue	-	-	+
Preservation of tissue through which ultrasounds pass	-	+	+
Energy	**Heat**	**Mechanical**	**Mechanical**
Therapeutic effect	**Tissue ablation by coagulation necrosis**	**Break-up of stone**	**Tissue softening**

** HIFU: High Intensity Focused Ultrasound*

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).***

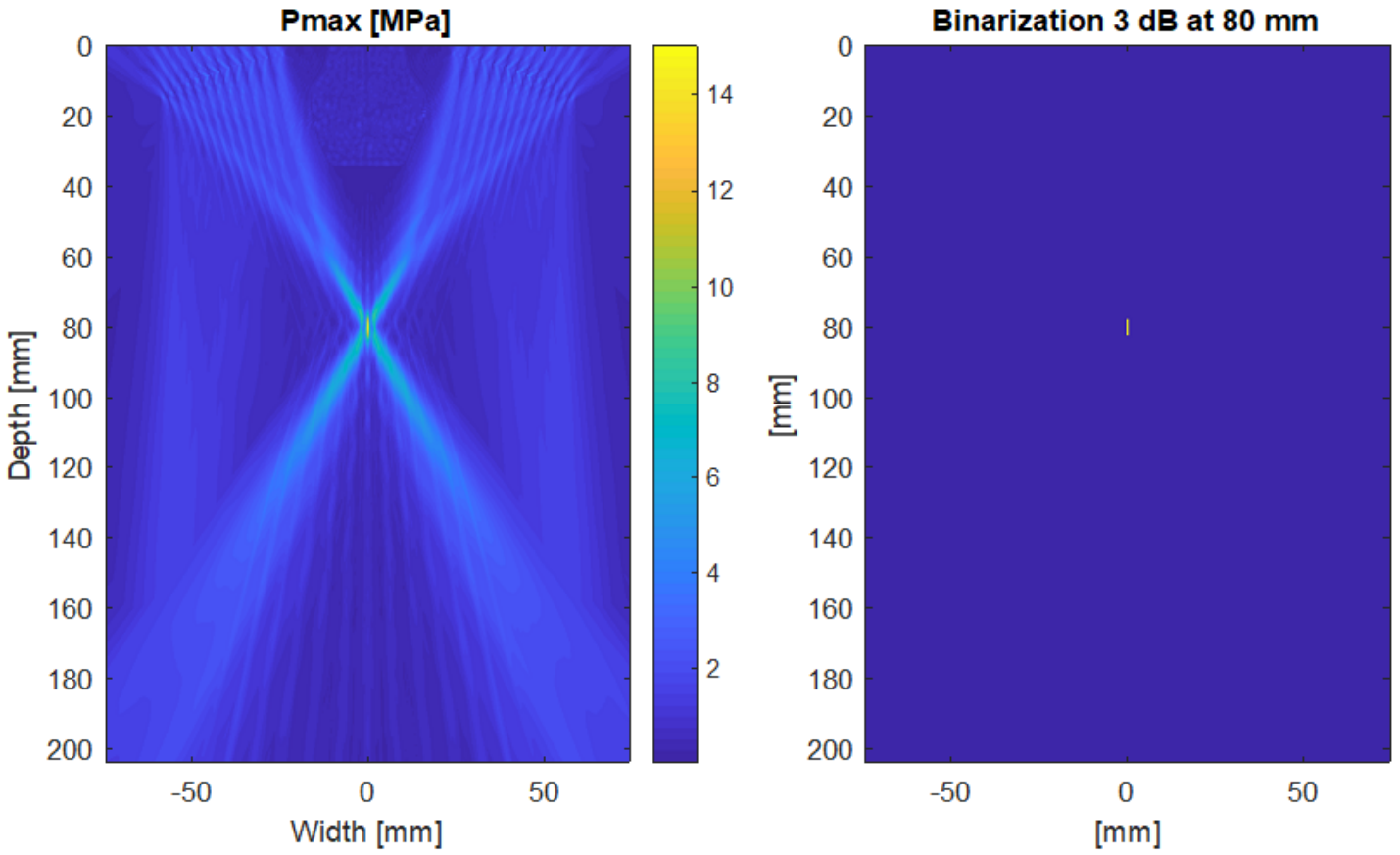
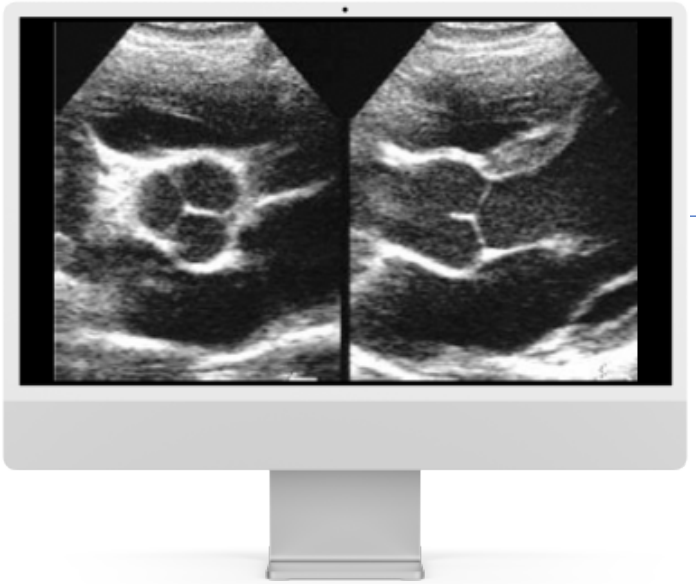
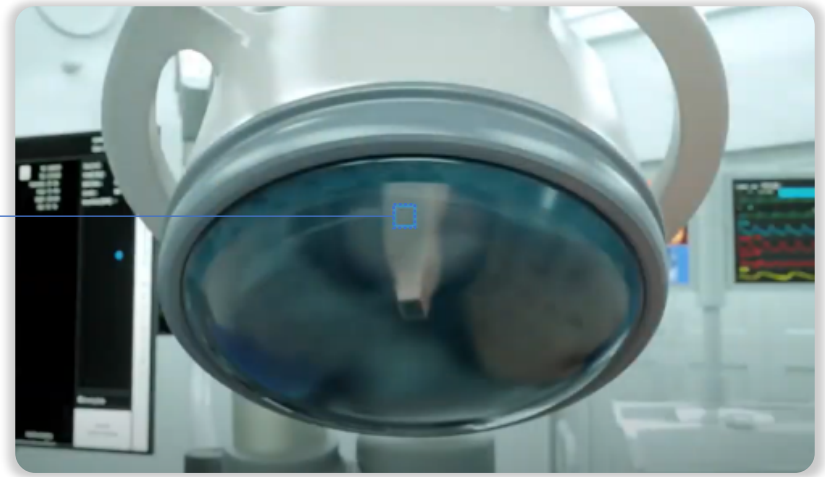


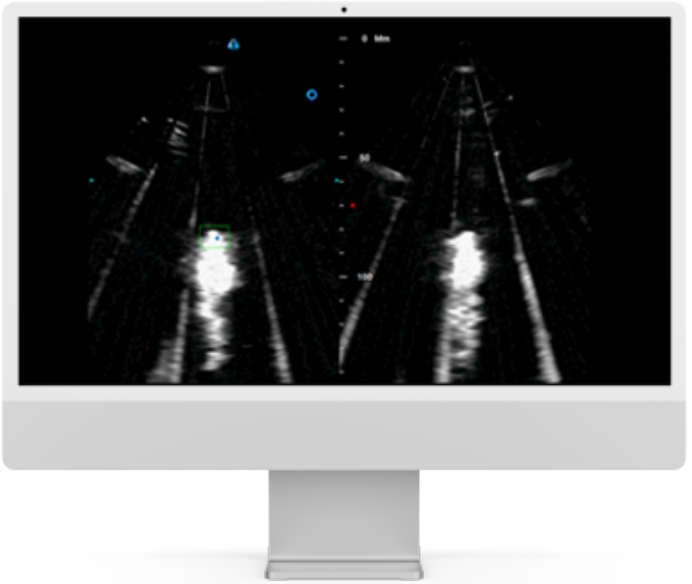
Figure: example of Pressure field simulation in water in a high-pressure regime at a Therapeutic target depth of 80mm (left) and corresponding thresholded Focal spot at -3dB (right).

Real-time echographic image guidance & monitoring

Therapy accuracy targeting & real-time monitoring of the therapy







Targeting Accuracy

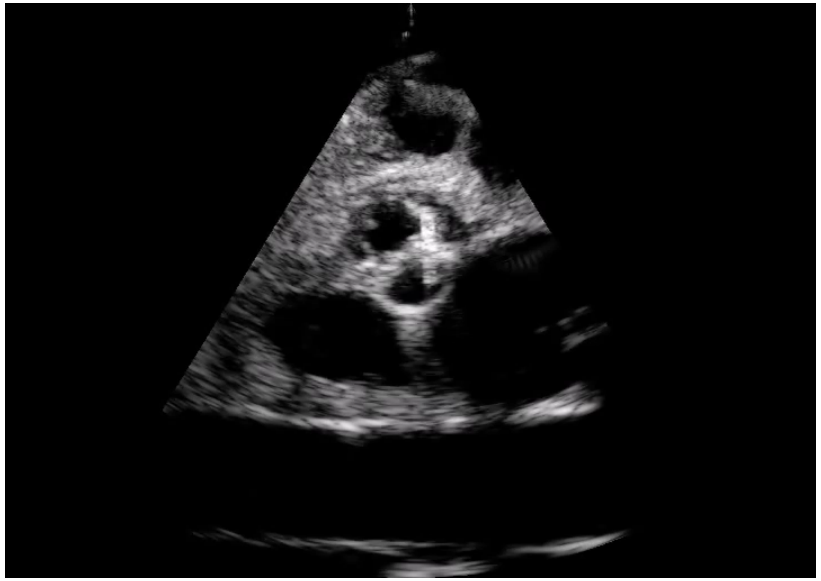
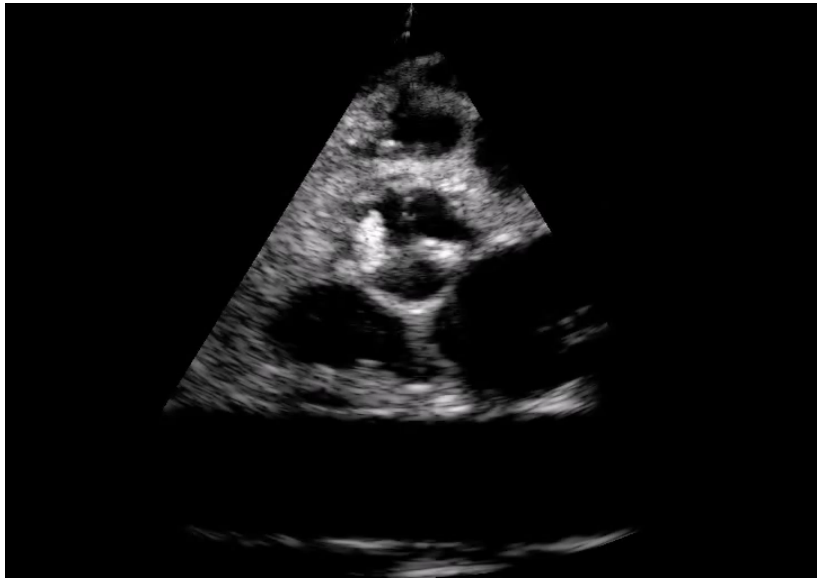
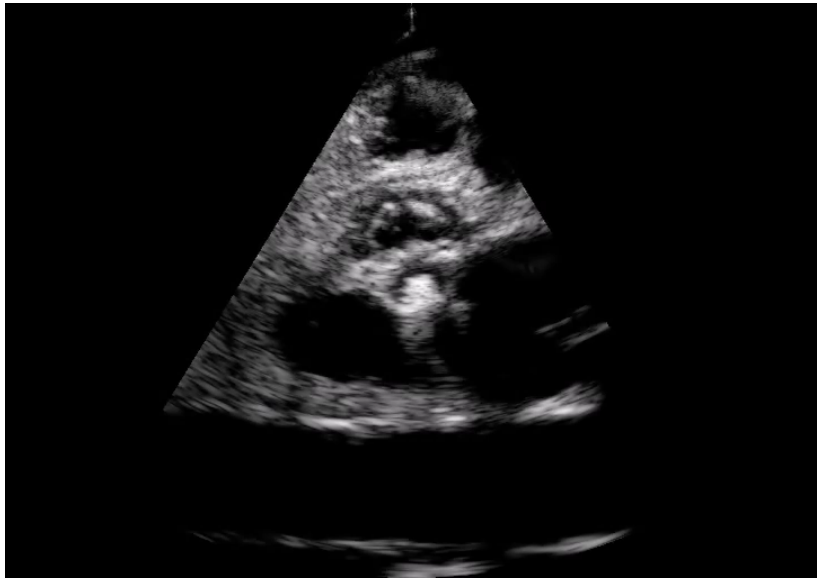
with biplane images &
robotic arm assistance

Monitoring

Real-time visualization
of the cavitation bubbles

Ultrasound imaging allows for lower cost of procedure
(no need for MRI)

BUBBLE CAVITATION DETECTION WITH ECHO IMAGING

PRE CLINICAL STUDY

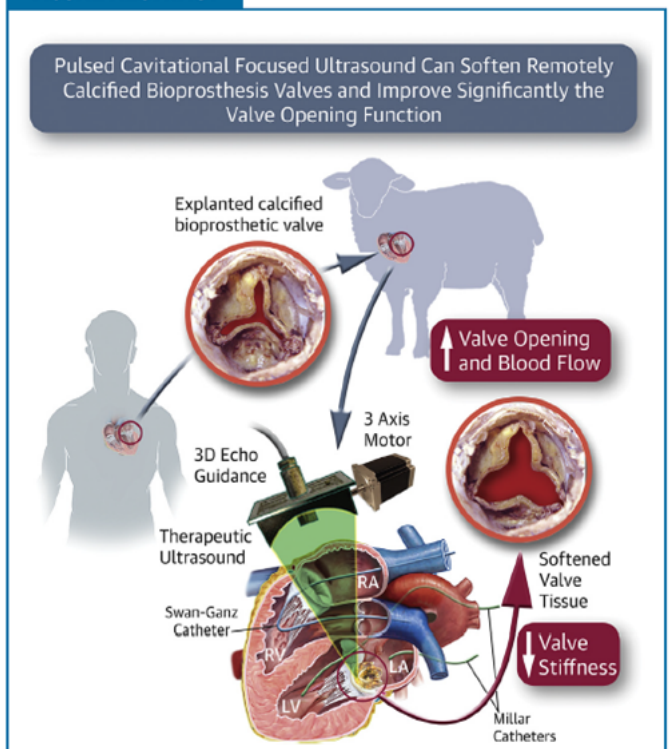
CARDIAWAVE

Pulsed Cavitational Ultrasound Softening

A New Noninvasive Therapeutic Approach for Calcified Bioprosthetic Valve Stenosis

Olivier Villemain, MD,[a,b] Justine Robin, MS,[a] Alain Bel, MD,[c] Wojciech Kwiecinski, PhD,[a] Patrick Bruneval, MD,[d] Bastien Arnal, PhD,[a] Mathieu Rémond, PhD,[e] Mickael Tanter, PhD,[a] Emmanuel Messas, MD, PhD,[b] Mathieu Pernot, PhD[a]

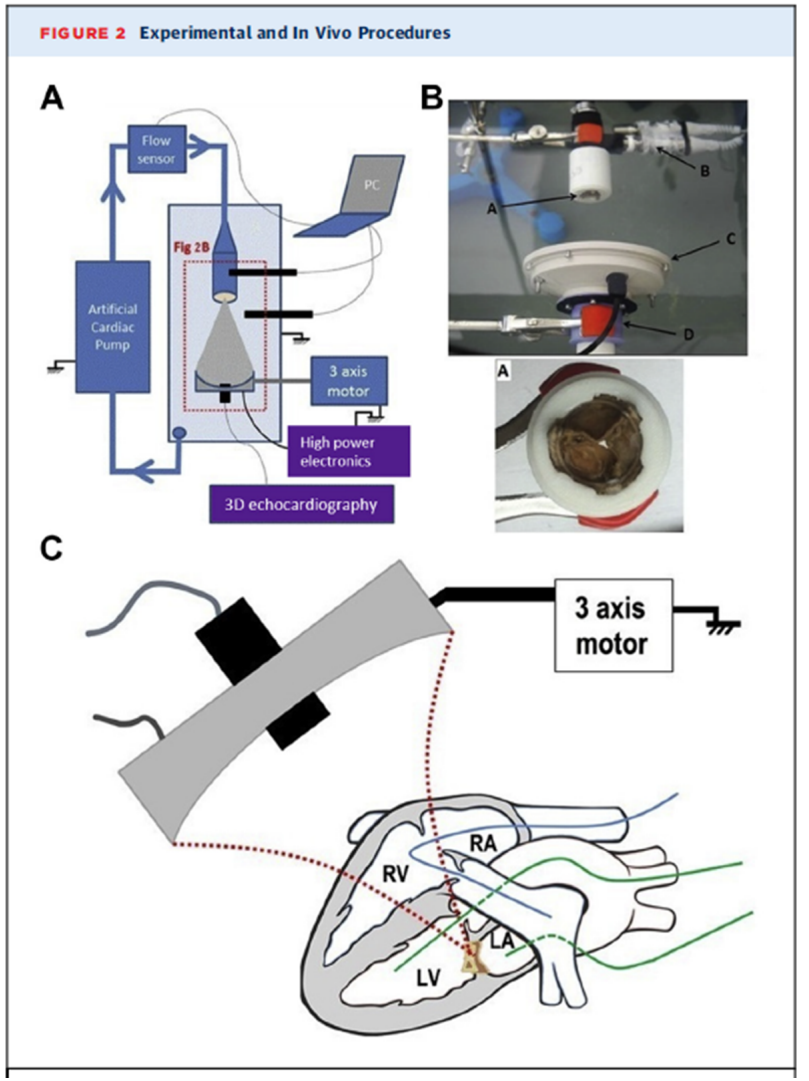
VISUAL ABSTRACT



Villemain, O. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(4):372-83.

HIGHLIGHTS

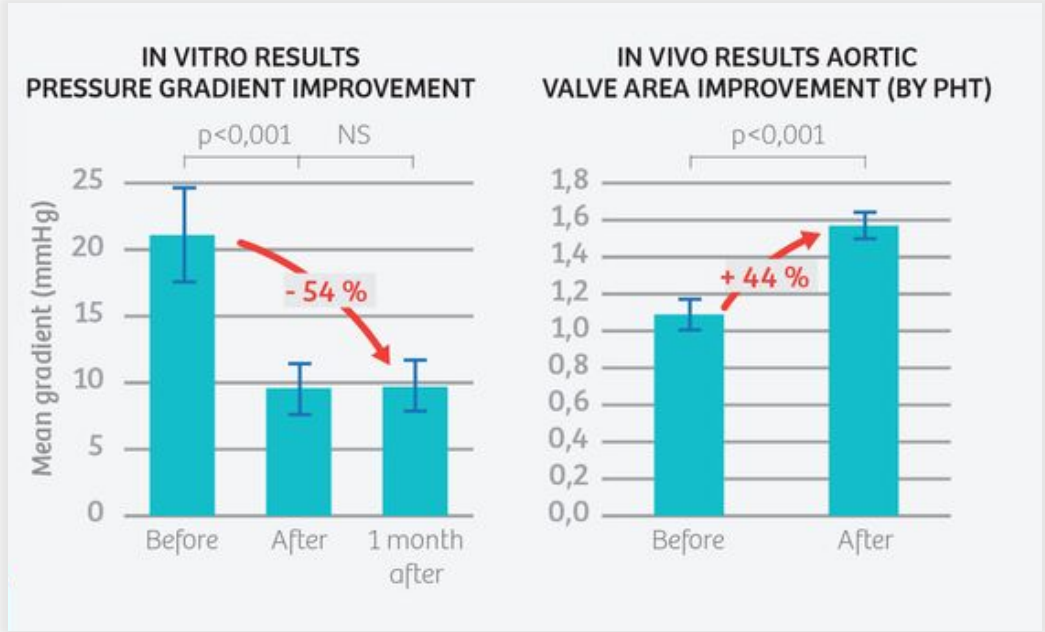
- Bioprosthetic heart valves have limited durability, with a progressive deterioration of the bioprosthesis after 12 to 15 years, mainly due to intravalvular calcifications.
- In this proof-of-concept study, we demonstrated in vivo using an ovine model and in vitro that pulsed cavitational focused ultrasound can be used to remotely soften human degenerative calcified bioprosthetic valves and significantly improve the valve opening function.
- This new noninvasive approach has the potential to improve the outcome of patients with severe bioprosthesis stenosis.

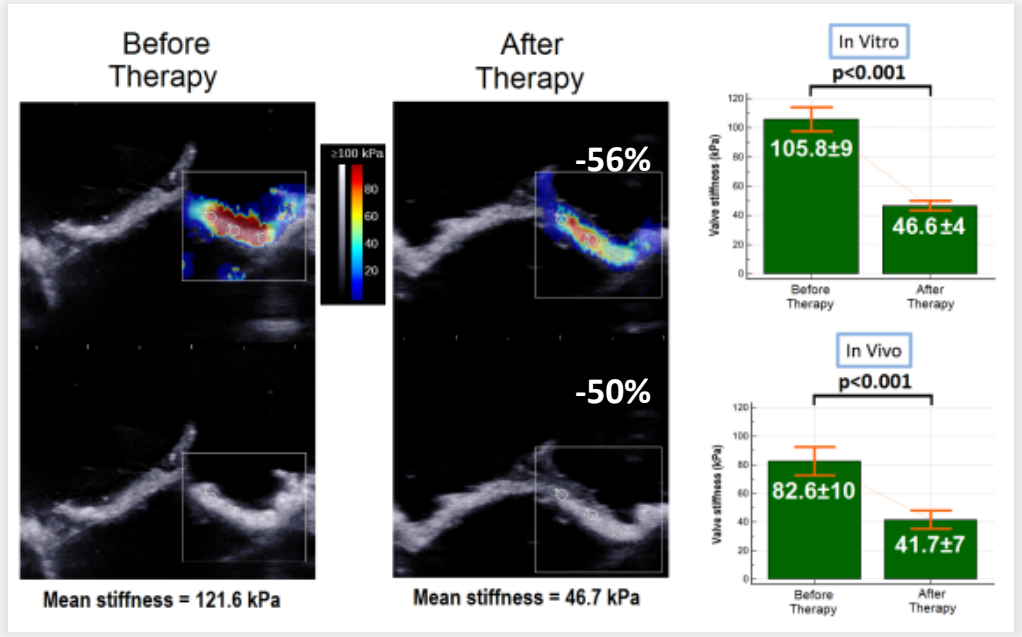


JACC Basic Transl Sci. 2017 Aug;2(4):372-383

- 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.

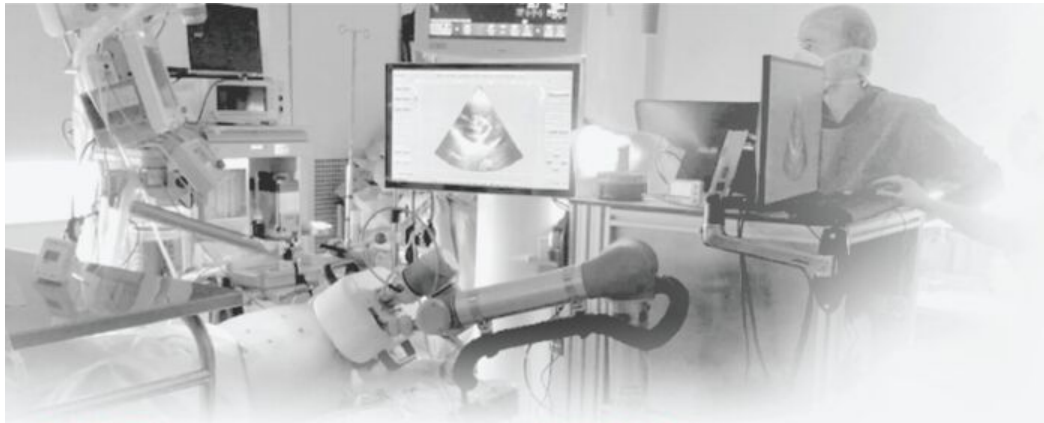
Messas E. et al, Safety study published in July 2020 in Physics in Medicine & Biology: Feasibility and Safety of Non-Invasive Ultrasound Therapy (NIUT) on Porcine Aortic Valve.

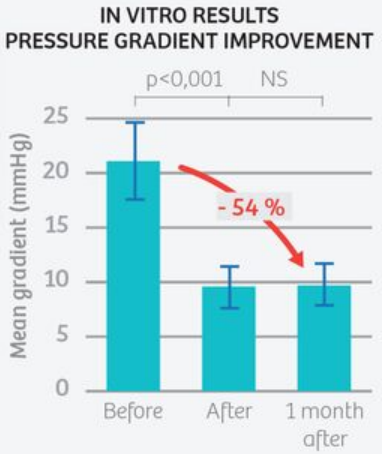
IN VIVO PRECLINICAL VALIDATION

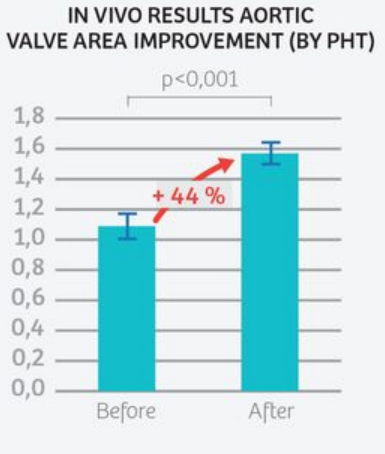
CARDIAWAVE

Large animals: **n > 55**:

- Healthy valves: therapy performed in > 35 pigs with average 30-days follow-up
- Calcified valves (degenerated biologic valves): intervention performed on bench test, 8 sheeps and 7 pigs + 7 rabbits







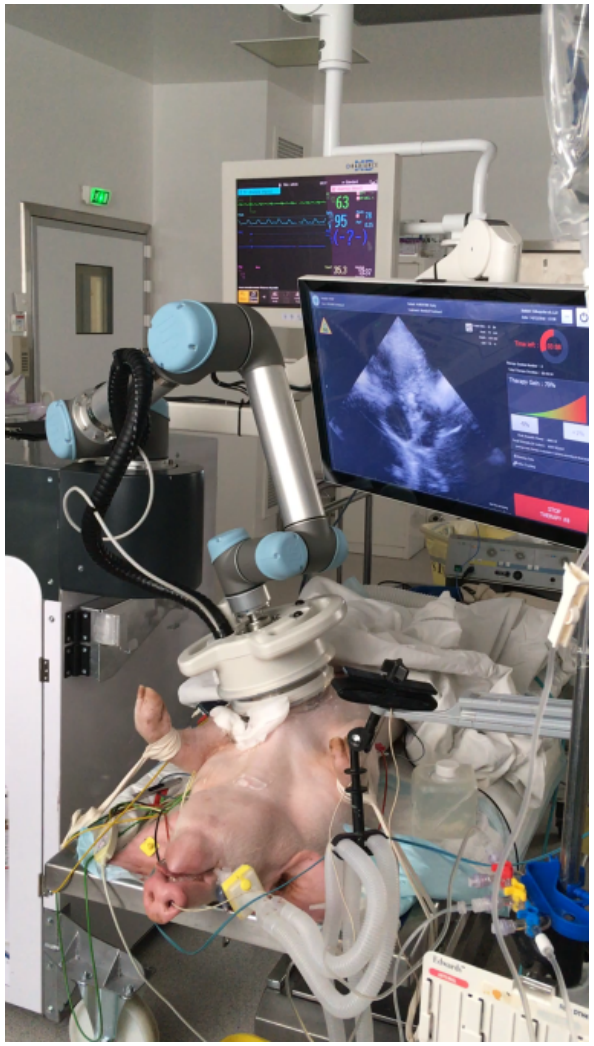
SAFETY

- No large debris, tiny particulates
- No tissue perforation (histology)
- No acute stroke
- No heart failure
- No aortic regurgitation

EFFICACY

Statistically significant modification of key parameters:

- Pressure gradient decreased by half
- Wider opening of the valve area >1.5cm²
- Reduction in stiffness by half



① 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. doi: 10.1016/j.jacbts.2017.03.012.) ② 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. DOI 10.1088/1361-6560/aba6d3.

First-In-Human Studies

- **Study Design**:
  - Prospective**, single-arm**, multi-center clinical evaluation of NIUT safety and feasibility
  - **Severe symptomatic CAS patients *not eligible to TAVR and SAVR.***

- **Endpoints**:
  - **Primary safety endpoint**: procedure related mortality at 1-month
  - **Primary performance endpoint**: ability to modify the structure of the calcified valve leaflets to improve their mobility immediately post-procedure compared to baseline
  - **Secondary endpoints**: safety and performance beyond 1-month

➢ First patient enrolled: March 2019
➢ Last patient 24 month follow-up completed: May 2024

40 patients included up to May 2022:
- Amphia: 19 patients
- HEGP: 11 pts
- Clinical Centre of Serbia: 10 pts

Hôpital européen Georges-Pompidou AP-HP

Amphia

Clinical Centre of Serbia

CARDIAWAVE

Non-invasive therapy to treat aortic stenosis

Valvosoft® Procedure

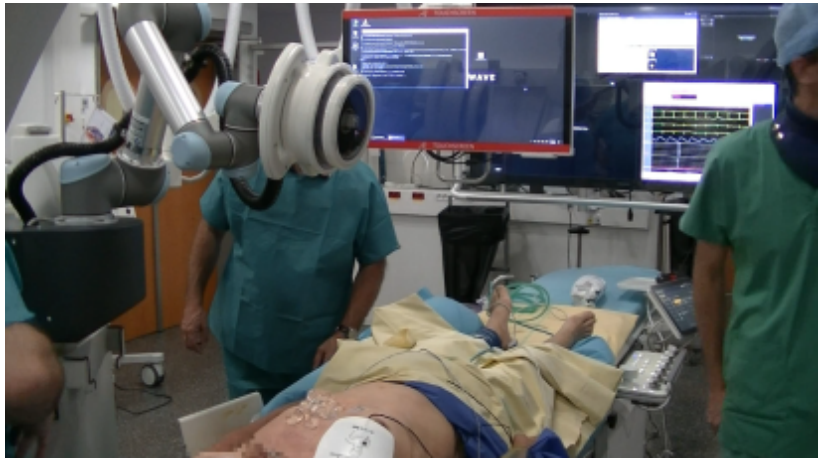
Treatment room

BREDA – Hybrid room

BREDA – Cathlab

BREDA – CCU Patient room

PARIS – Hybrid room



PARIS – Cathlab

BELGRADE – Operating room

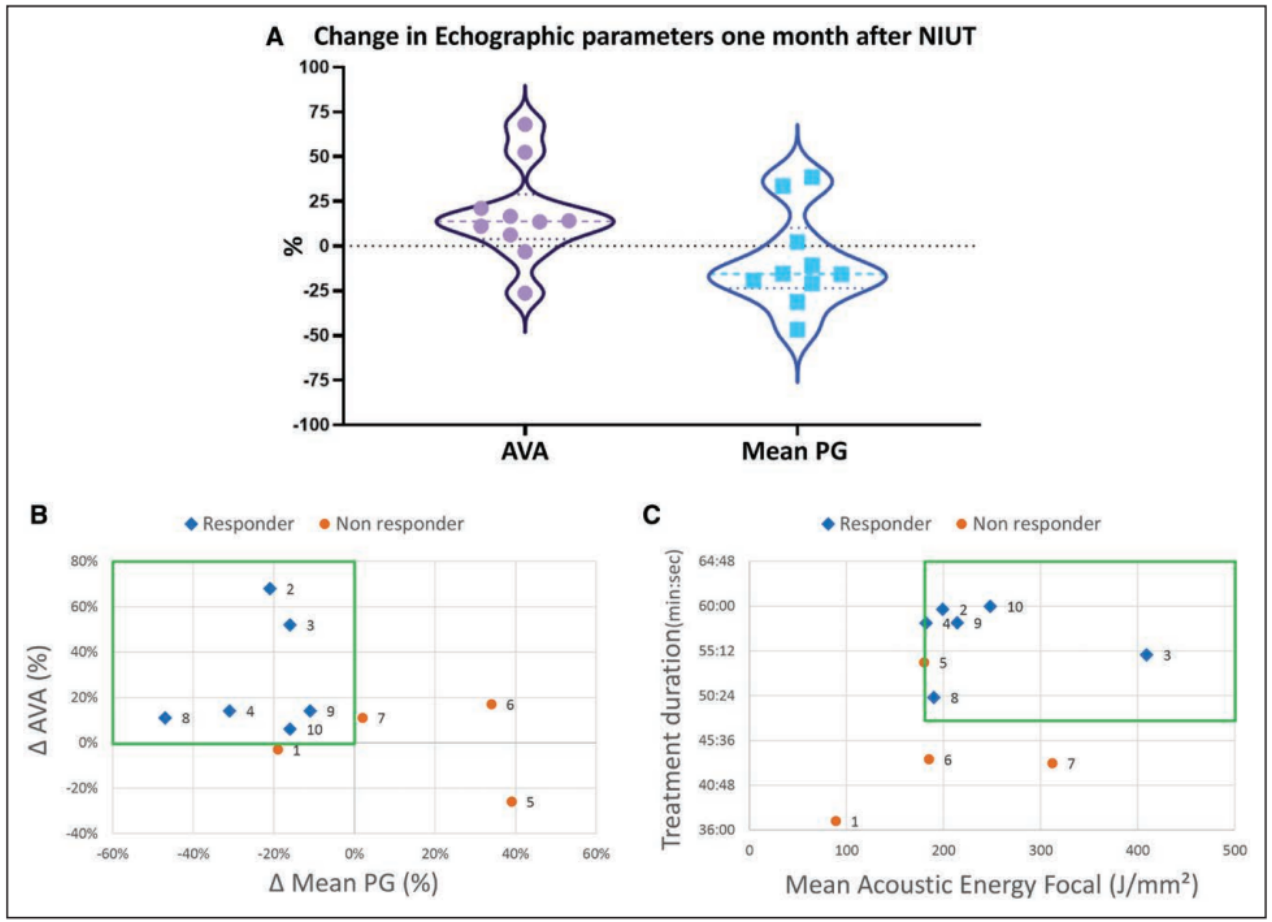
Valvosoft FIM: first 10 patients at 1 month (severe AS)

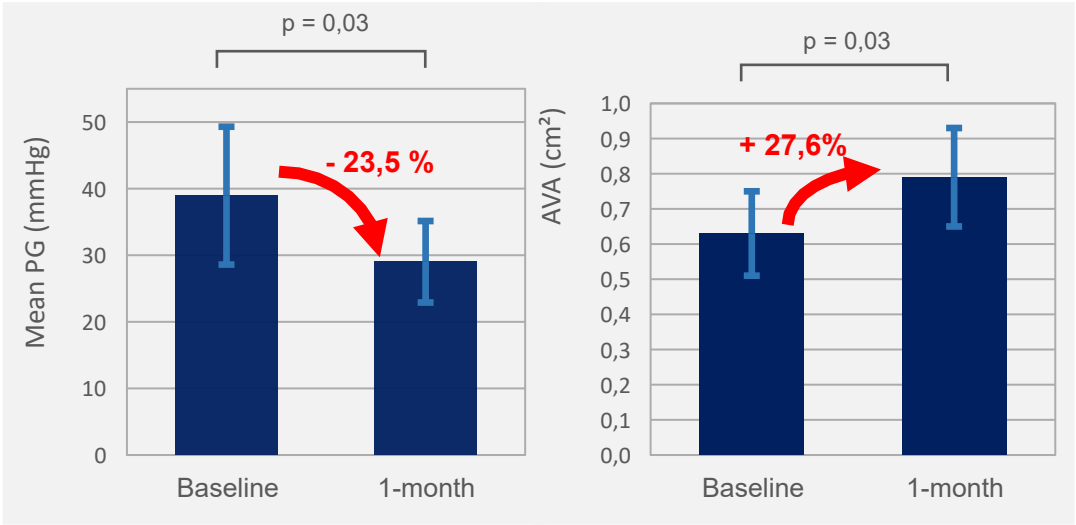
Circulation

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.

Valvosoft FIM: baseline data of treated patients

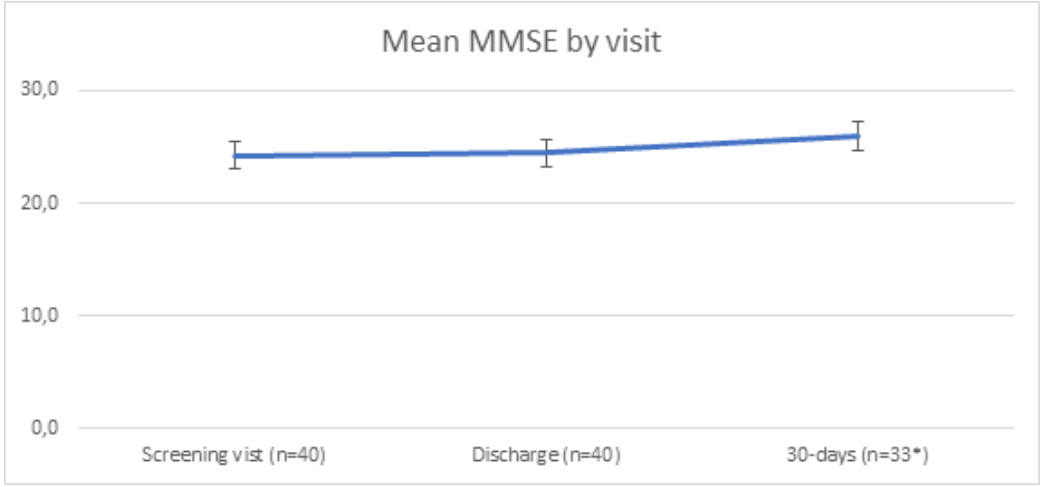
Very frail** patients with severe co-morbidities and **short life-expectancy**, **not eligible to SAVR/TAVR HEGP – Paris FR, Amphia – Breda NL, Clinical Center Serbia, Belgrade, RS

Characteristic	(n=40)	
Age (years)	83.00 ± 8.45	11 patients over 90
Male / Female	19 (48%) / 21 (52%)	
Left Ventricular Ejection Fraction (LVEF) (%)	49.54 ± 11.61	
Aortic Valve Area (AVA), cm^2	0.57 ± 0.18	<1 cm^2 severe & < 0.7cm^2 very severe
Aortic Valve Mean Pressure Gradient (PG), mmHg	41.41 ± 20.09	Majority of high gradient patients > 40 mmHg (57,5%)
New York Heart Association (NYHA)		
2	10 (25%)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results is undue breathlessness, fatigue or palpitations.
3	19 (48%)	Marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in undue breathlessness, fatigue or palpitations.
4	11 (28%)	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased

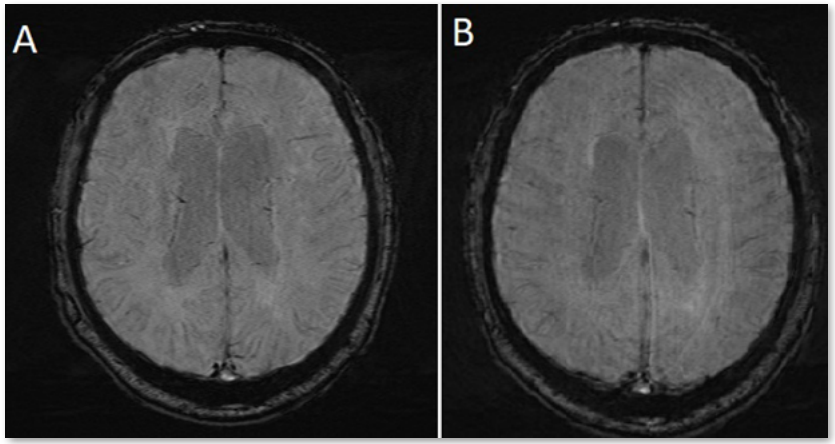
Data are mean ± SD for continuous variables and n (%) for ordinal/categorical data.

Valvosoft FIM: Safety

- **No death per procedure, at discharge and at 1-month adjudicated as procedure or device related**
- No life-threatening event, no stroke, no myocardial infarction at 1-month follow-up
- No Major Adverse Event (MAE) adjudicated related to device over 12-months
- **Stable Mini-Mental State Examination (MMSE)**
- No use of Embolic Protection Device in 40 patients
- **No brain MRI abnormalities** detected in Serbian study: 10 patients assessed[1]



MRI at A) baseline and B) discharge



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

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2023) **00**, 1–2
https://doi.org/10.1093/ehjci/jead089

RESEARCH LETTER

Systematic brain magnetic resonance imaging and safety evaluation of non-invasive ultrasound therapy for patients with severe symptomatic aortic valve stenosis

Danijela Trifunovic-Zamaklar[1,2†], Miloš Velinović[2,3†], Nataša Kovačević-Kostić[2,4†], and Emmanuel Messas [5,6,7*]

[1]Cardiology Department, University Clinical Center of Serbia, Pasterova 2, 11000 Belgrade, Serbia; [2]Medical Faculty, University of Belgrade, Dr Subotica Starijeg 8, 1100 Belgrade, Serbia; [3]Cardiosurgery Department, University Clinical Center of Serbia, Pasterova 2, 11000 Belgrade, Serbia; [4]Department for Anesthesia and Intensive Care at Clinic for Cardiac Surgery, Centre for Anesthesiology and Reanimatology, University Clinical Centre of Serbia, Pasterova 2, 11000 Belgrade, Serbia; [5]Cardiovascular Department, Hôpital Européen Georges-Pompidou, Université Paris-Cité, 20 Rue Leblanc, 75015 Paris, France; [6]RHU STOP-AS Research Consortium, 1 Rue de Germont, 76031 Rouen, France; and [7]PARCC, INSERM UMR U970, 56 Rue Leblanc, 75015 Paris, France

Keywords aortic stenosis • calcification • non-invasive ultrasound therapy • stroke • MRI

- No MRI abnormalities detected in Serbian study: 10 patients assessed

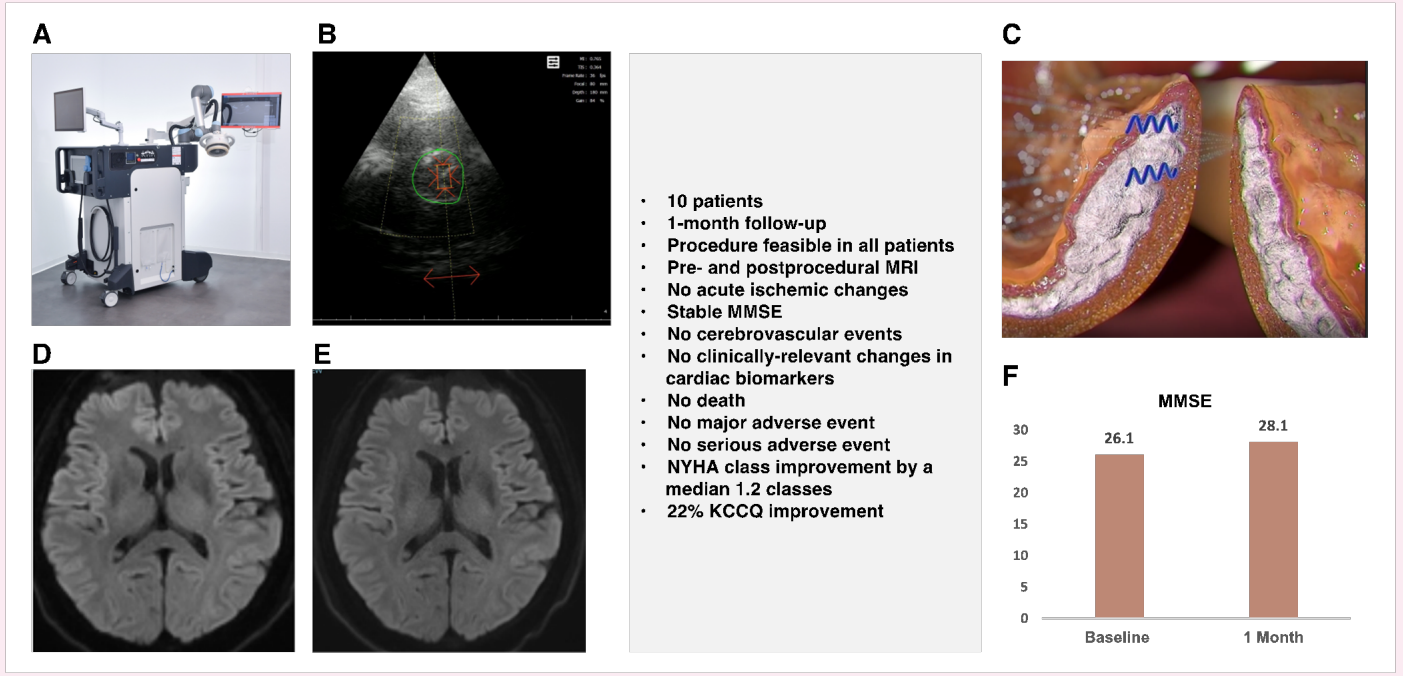


Figure 1 Summary of study outcomes and the mechanism of the Valvosoft device. Valvosoft device (*A*): during treatment, the applicator, which contains an imaging ultrasound and an independent therapeutic transducer, is positioned against the patient's chest, the aortic valve is targeted and imaged using 2-D echo live monitoring (*B*); the treatment aims to soften the valve tissue, improving leaflet mobility and enabling a wider opening of the valve through delivering precise, focused, high-intensity ultrasound (*C*), resulting in the formation of cavitation bubbles that implode, creating local shock waves that mechanically fracture the calcification embedded in the aortic valve without damaging the leaflets or surrounding tissue; the representative diffusion-weighted imaging MRI ($b = 1000$ s/mm^2) at baseline (*D*) and post-procedure (*E*) shows that the treatment did not result in any new ischaemic lesions; furthermore, the Minimental State Examination values did not decrease at one month (*F*).

Trifunovic et al EHJ CV Imaging 2023

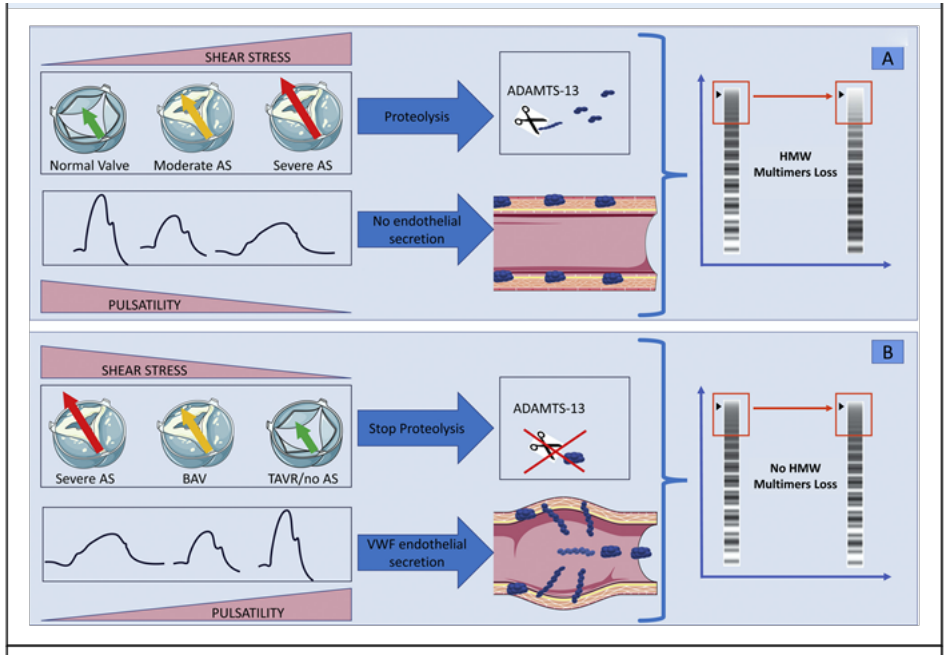
Angiogenesis
https://doi.org/10.1007/s10456-021-09803-8

LETTER

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

David M. Smadja[1,6] · Guillaume Goudot[2,3] · Nicolas Gendron[1,6] · Samuel Zarka[2,3] · Etienne Puymirat[3,4] · Aurélien Philippe[1,6] · Christian Spaulding[4] · Christophe Peronino[1] · Mickael Tanter[5] · Mathieu Pernot[5] · Emmanuel Messas[2,3]

Received: 22 April 2020 / Accepted: 20 May 2021



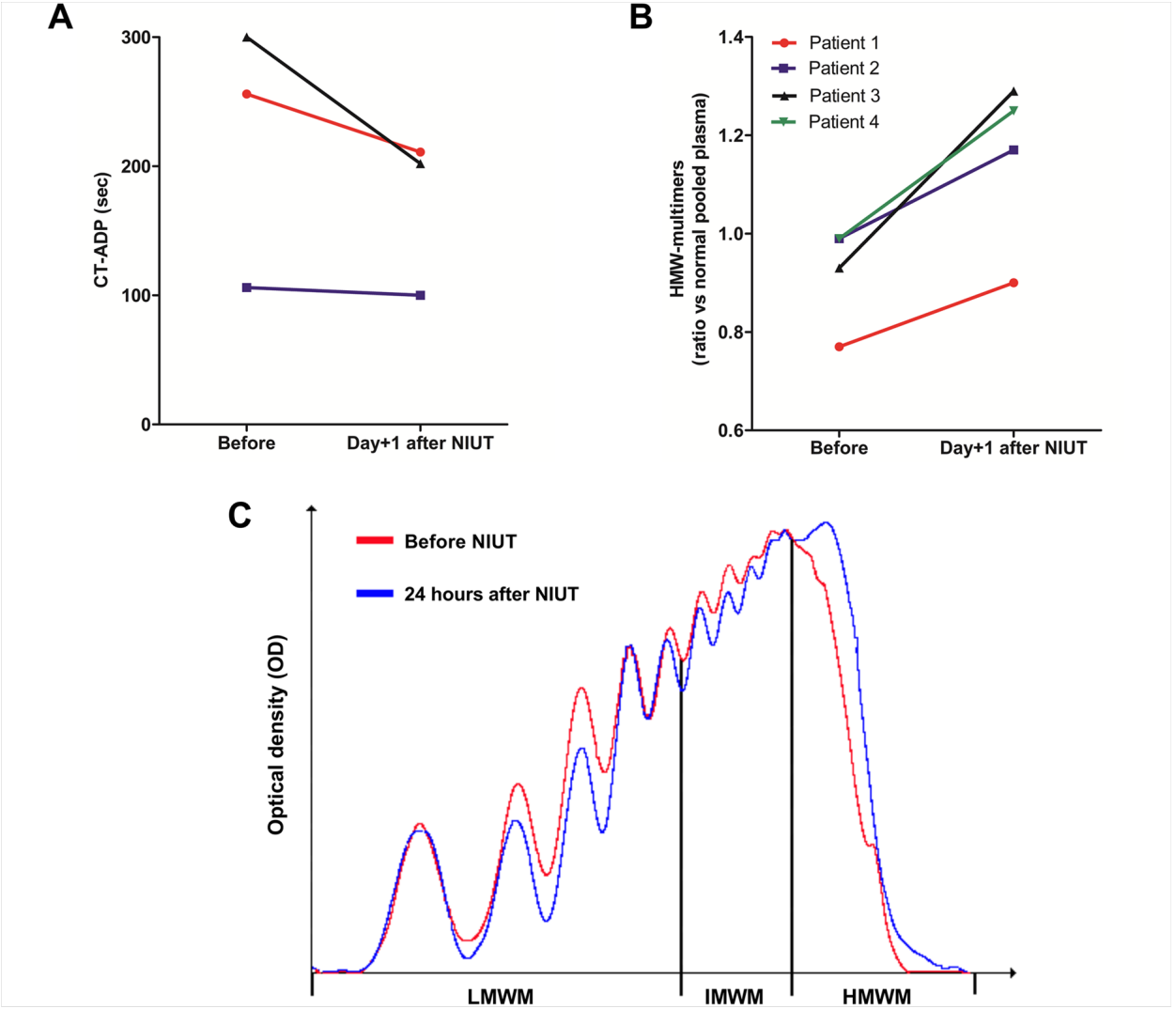


Fig. 1 Time course of high-molecular-weight multimers recovery in patients with CAVD undergoing valvosoft non-invasive ultrasound therapy (NIUT). **A** Platelet function analyzer-closure time adenine DI-phosphate (PFA-CADP) in patients before and 24 h after NIUT. We observed a decrease in PFA-CADP after NIUT in three patients explored. **B** Quantitative analysis of HMWM in patients undergoing correction of aortic stenosis by NIUT. HMWM increase in the four CAVD patients explored 24 h after NIUT. **C** Representative time course of von Willebrand factor (VWF) multimeric pattern (with densitometric analysis) in a patient before and after NIUT

Valvosoft® FIM 40 patients – 6 months follow-up

23TL2421

Articles

Matt I

This version saved: 16:08, 17-Aug-23

THELANCET-D-23-02421R3

S0140-6736(23)01518-0

Embargo: [add date when known]

Doctopic: Primary Research

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

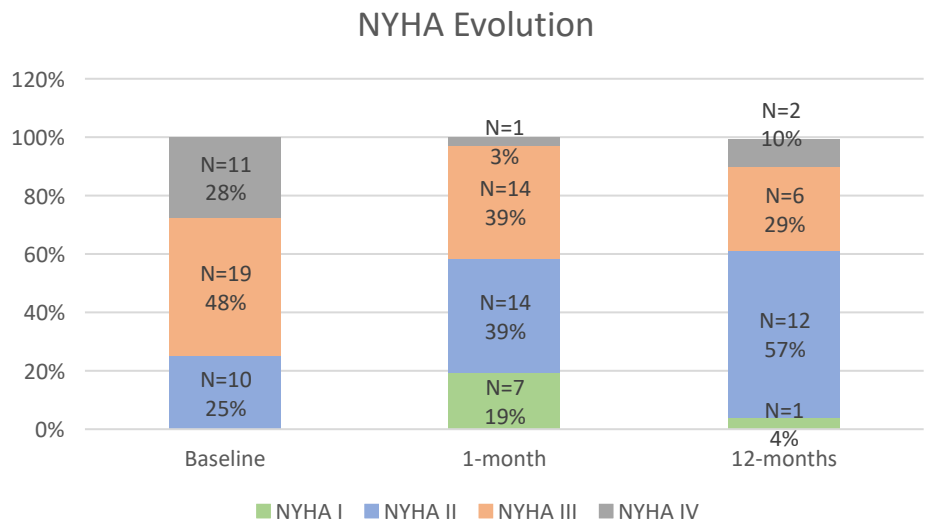
Summary

Background Calcific aortic stenosis is commonly treated using surgical or transcatheter aortic valve replacement; however, many patients are not considered suitable candidates for these interventions due to severe comorbidities and limited life expectancy. As such, non-invasive therapies might offer alternative therapeutic possibilities in these patients. This study aimed to assess the safety of non-invasive ultrasound therapy and its ability to improve valvular function by softening calcified valve tissue.

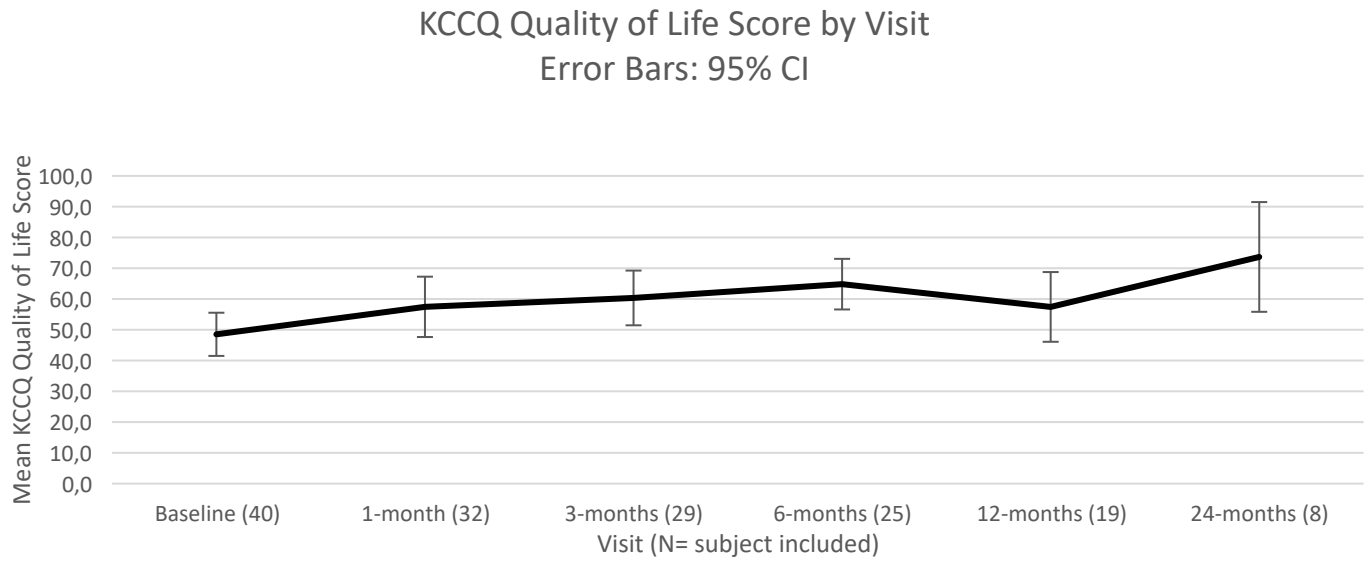
Cardiovascular Department, Hôpital Européen Georges-Pompidou (E Messas MD PhD, E Puymirat MD, G Goudot MD) **Paris Cardiovascular Research Center, Inserm UMR_U970** (E Messas, E Puymirat),

31

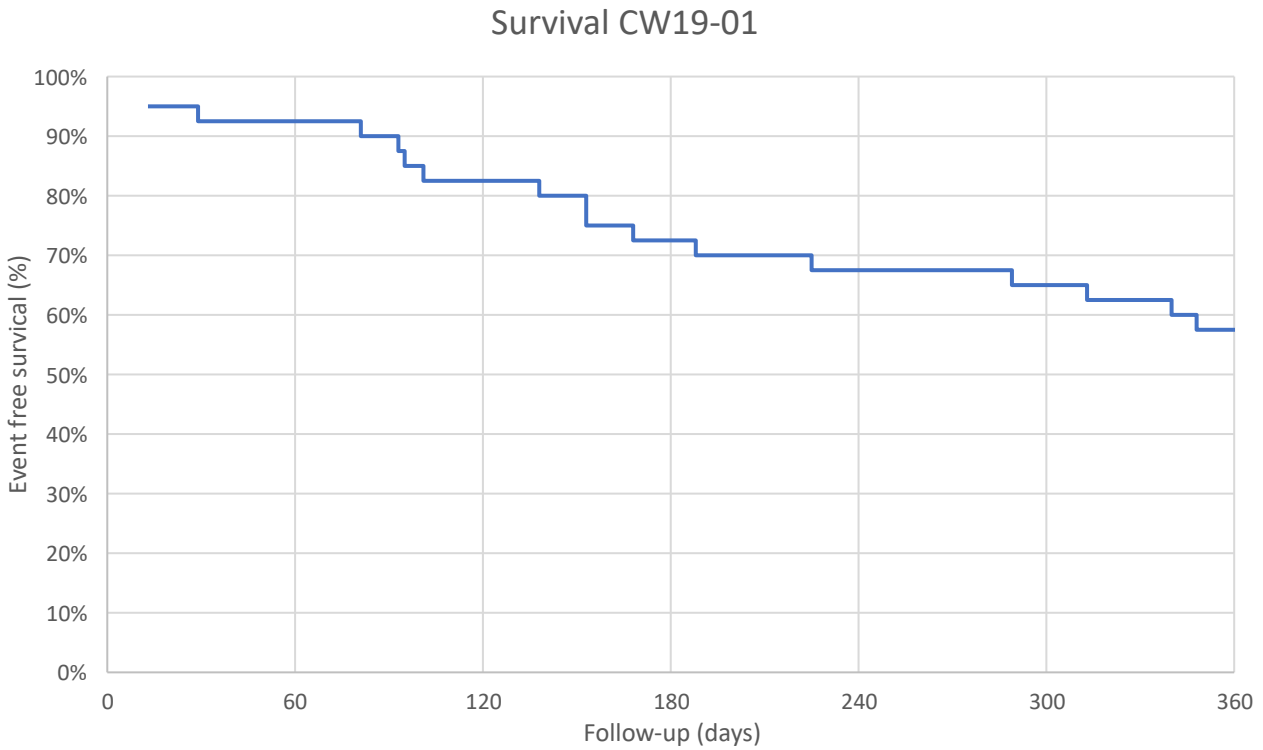
Valvosoft® FIM: clinical improvements 12 months



NYHA evolution	Baseline (N:40)	1-month (N = 36)	12-months (N = 21)
Improvement	NA	23 (64%)	9 (43%)
Stabilization	NA	12 (33%)	11 (52%)
Deterioration	NA	1 (3%)	1 (5%)
Number of subjects and n (%).			



Valvosoft® FIM: Survival



Reported survival at 1 year in Partner B was 54.8 %

S Kapadia, et al. JACC Cardiovasc Interv, 2015;8(2): 324-33

	Baseline	30 days	180 days	365 days
# subjects (40)	40	37	28	23
# subjects with events (cumulative)	0	3	12	17
Event free survival (%)	100.0	92.5	70	**57,5**

CE-marking Pivotal Study

France, the Netherlands, Germany – 60 patients

Main inclusion criteria:

Subject suffering from severe symptomatic calcific aortic valve stenosis; and

Subject is not recommended by the local Heart Team for immediate TAVR/SAVR; or

Subject who refuses TAVR/SAVR (not in France)

Main exclusion criteria:

Left Ventricular Ejection Fraction ≤ 30%

Subject with mean AVAI < 0,24 cm^2/m^2

Myocardial infarction, stroke or transient ischemic attack (TIA) ≤1 month prior to enrollment.

- First patient enrolled: June 2022
- Last patient 12 month follow-up completed: July 2024

Primary endpoints at 1 month:

- **Safety: Rate of MACE at 30 days post procedure**
- Performance: **improvement in clinical status assessed by means of a decrease in NHYA functional class at 30 days post procedure**

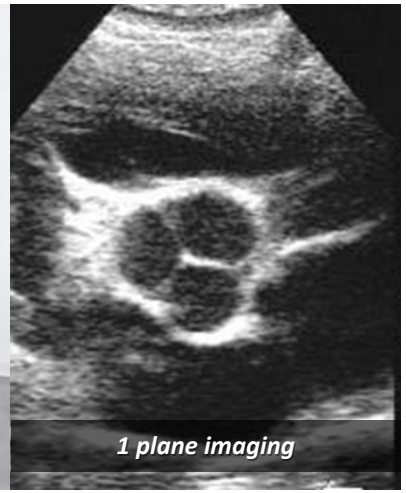
Secondary endpoints up to 12 months:

- Safety
- Performance: hemodynamic parameters
- Clinical
- Exploratory

NEW Valvosoft® GEN2 device FOR AN improved performance

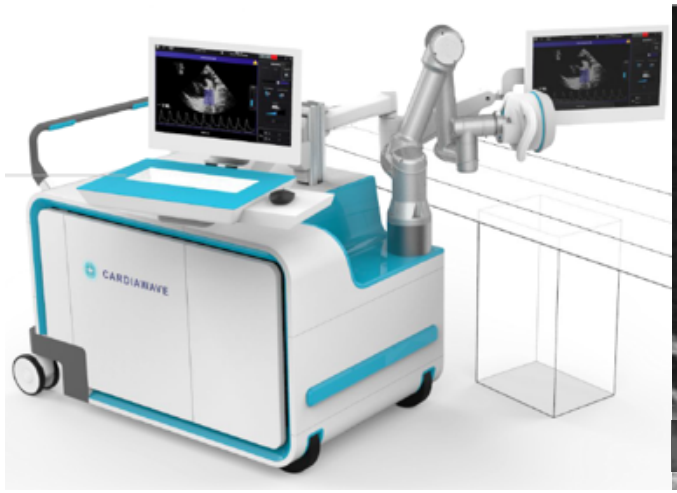
Gen-2 is used in CE-marking and EFS/IDE clinical trials

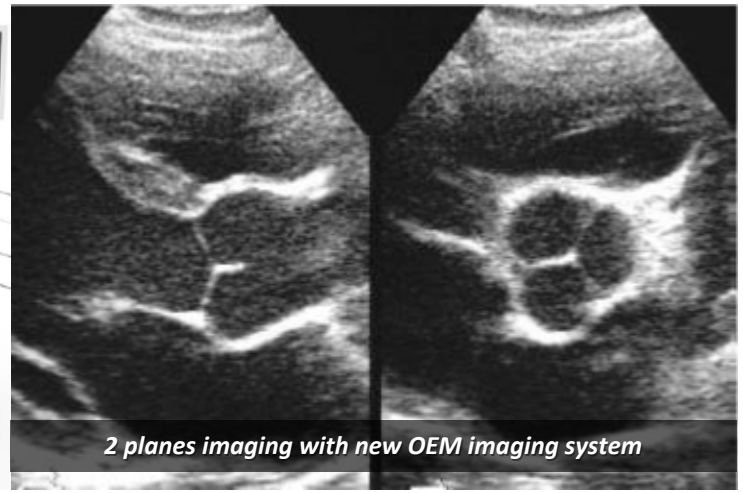
VALVOSOFT® GEN-1



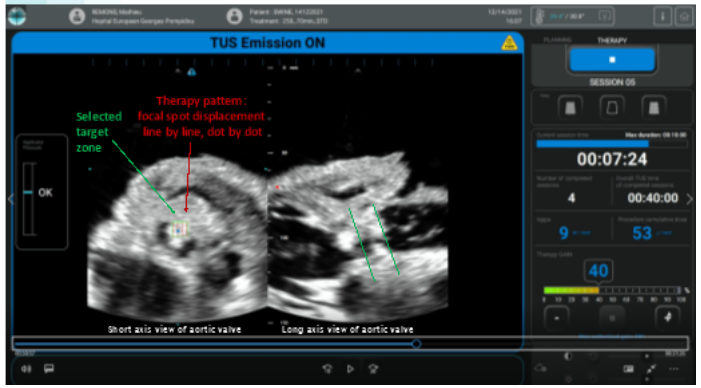
- Gen-1 used for first clinical trials in France, the Netherlands and Serbia.

VALVOSOFT® GEN-2

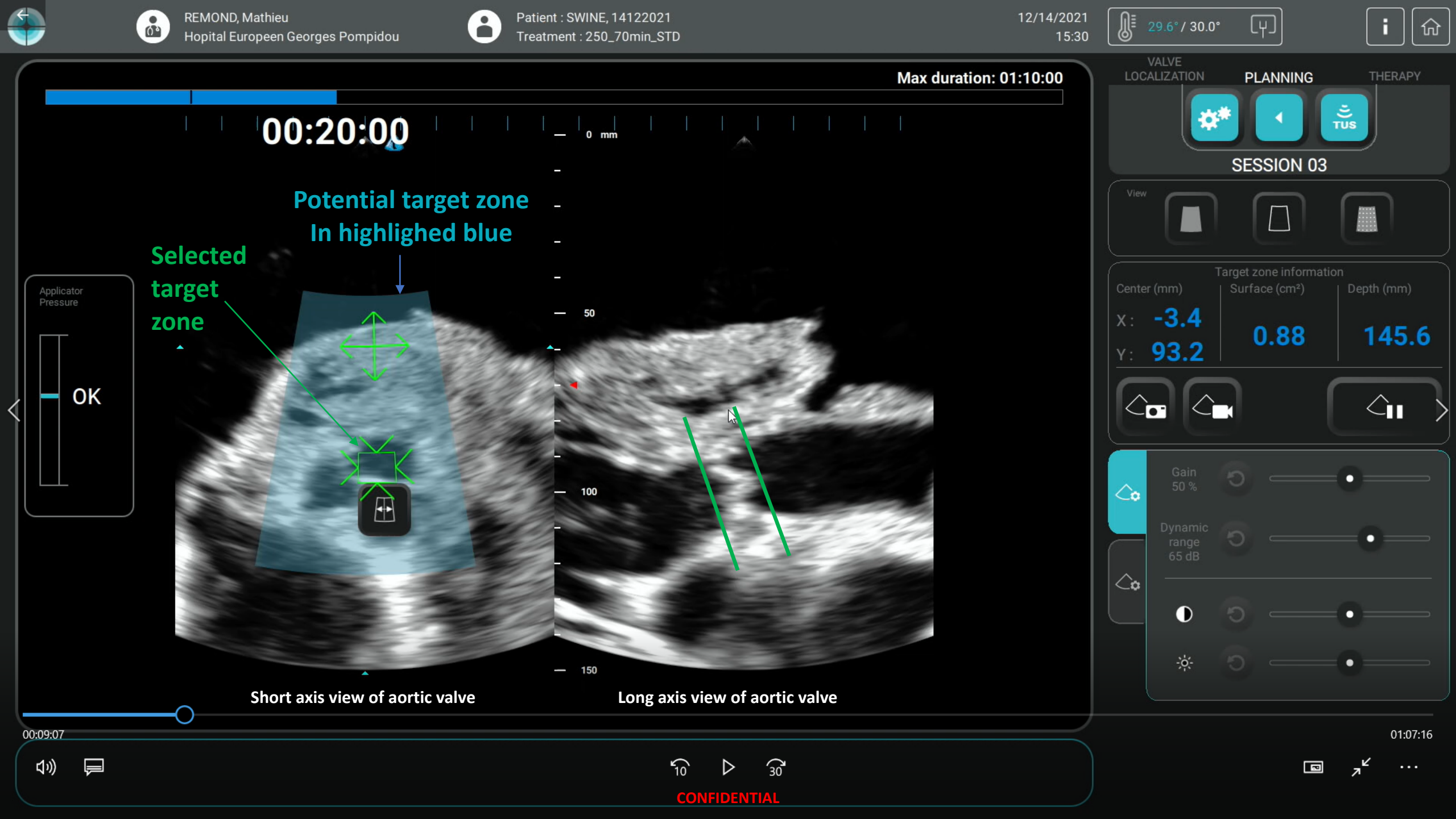




Improved Performance with Gen-2



- New OEM imaging system improves image quality, guidance, target accuracy and therapy monitoring
- Improved usability with new robotic arm easier to handle and position
- New Graphical User Interface (GUI)
- Learning curve from first clinical studies
- New patient population and new Clinical Protocol for European pivotal study


REMOND, Mathieu
Hopital Europeen Georges Pompidou
Patient : SWINE, 14122021
Treatment : 250_70min_STD
12/14/2021
15:30
29.6° / 30.0°
Max duration: 01:10:00
00:20:00
VALVE LOCALIZATION
PLANNING
THERAPY
TUS
SESSION 03
View
Target zone information
Center (mm)
Surface (cm²)
Depth (mm)
X : -3.4
Y : 93.2
0.88
145.6
Potential target zone
In highlighed blue
Selected target zone
Applicator Pressure
OK
0 mm
50
100
150
Gain 50 %
Dynamic range 65 dB
Short axis view of aortic valve
Long axis view of aortic valve
00:09:07
01:07:16
10
30
CONFIDENTIAL

Valvosoft Procedure

CE MARK STUDY PROCEDURE

PATIENT IN AMBULATORY OPERATING ROOM

Hopital Europeen Georges Pompidou

Cardiovascular Department

Site of Enrollement :

Country	Hospital Name	PI name
FR Pi. H. Eltchaninoff	HEGP	E Puymirat
	CHU Rouen*	H Eltchaninoff
	Hopital Bichat	B lung
	CHRU Lille	E van Belle
	Cl Pasteur	L Lepage
NL **Pi.** A Ijselmuiden	Amphia Hospital	A Ijselmuiden
	OLVG Amsterdam	R Riezebos
	RadboudUMC	M van Wely
DE	Kerckhoff-klinik	C Hamm

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

Pooled data : N=100
Valvosoft® FIM +Pivotal baseline data of treated patients

Characteristic	Pooled data (100)	Pivotal (N=60)
Age (years)	84.3 ± 8.9	
Female/Male	60 (60.0%)	
Left Ventricular Ejection Fraction (LVEF) (%)	53.6 ± 11.1	
Aortic Valve Area (AVA), cm^2	0.62 ± 0,18	
Aortic Valve Mean Pressure Gradient (PG), mmHg	43,39 ± 16.96	
Aortic Valve Peak Velocity, m/sec	4.18 ± 0.74	
LFLG	35 (45%)	
Calciumscore (agatston)	-	3198.6 ± 1859.2
New York Heart Association (NYHA)		
1	2 (2%)	
2	37 (37%)	
3	45 (45%)	
4	16 (16%)	
EuroSCORE II (%)	6.7 (6.2)	
STS Score (%)	6.7 (5.5)	
Frailty Score	-	5.07 ± 1.33
EQ-5D	-	57.95 ± 16.29
KCCQ	56.4 ± 23.0	
6MWT (m) (20 ND)	-	198.45 ± 114.43

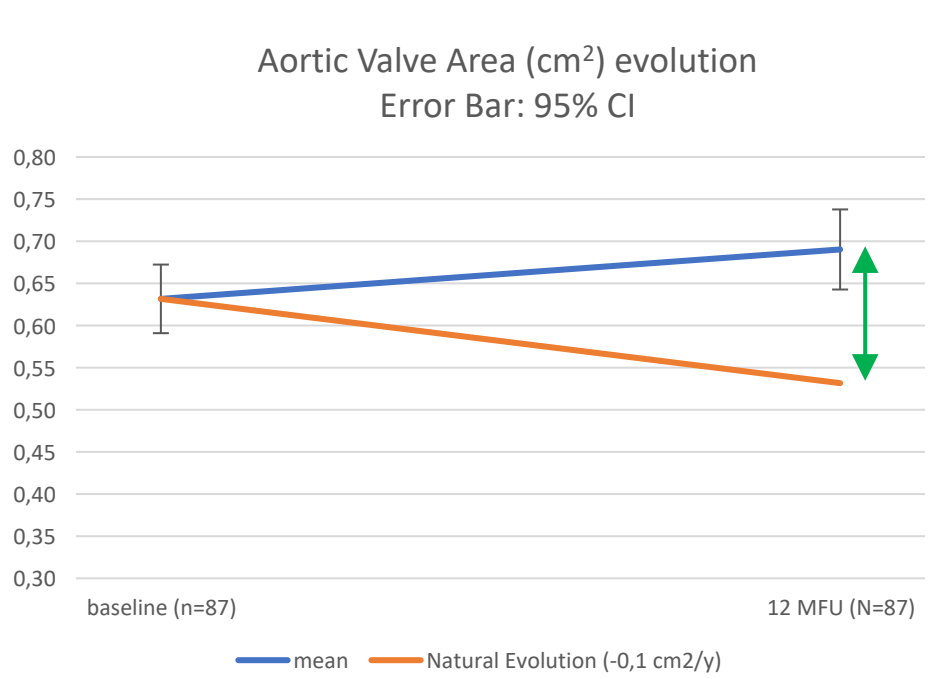
Valvosoft® treatment : improvement up to 12 months (pooled data, review in progress)

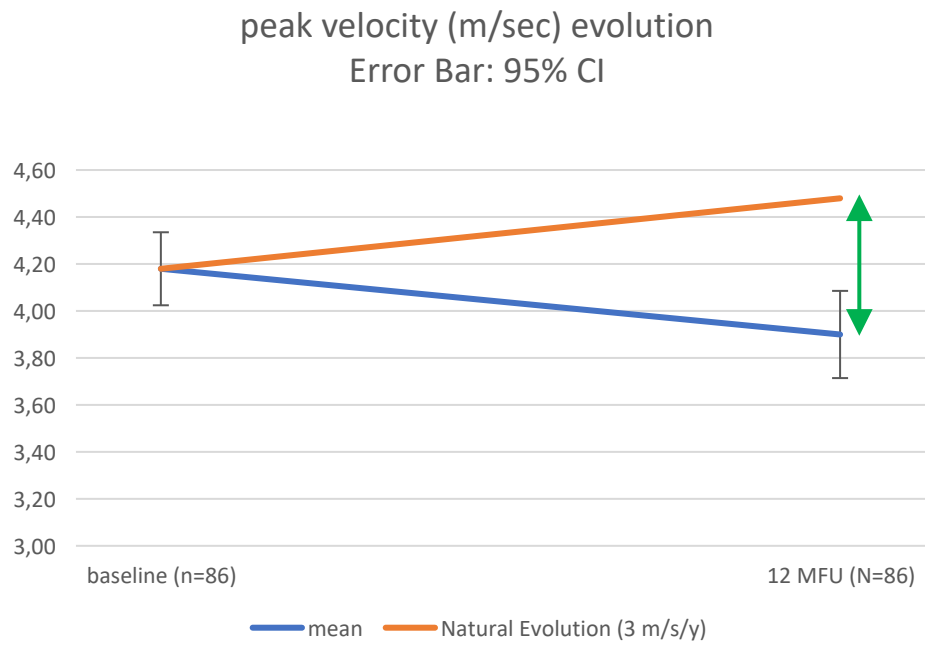
NIUT slows down disease progression compared to natural history of AS

Time point		Baseline	12 Months
AVA results (N=86)	Mean (cm²)	0.63	0.69
	Standard deviation	0.19	0.23
	Change vs. Baseline (%)		**10%**
	Natural History	0.63	0.53
p=0.003			

Time point		Baseline	12 Months
Peak velocity results (N=87)	Mean (m/Sec)	4.18	3.90
	Standard deviation	0.74	0.88
	Change vs. Baseline (%)		**-7 %**
	Natural History	4.18	4.48
p=0.001			

<u>Interim</u> clinical results (pooling of all available data of FIM and Pivotal study)





Valvosoft is an investigational device exclusively for clinical investigation

Valvosoft® Potential Efficacy improvement

- **Longer** session
- **Increase** Intensity
- Retreated: 14 (FIM 5, Pivotal 9)
- Improved image quality
- **Less severe patient** : **Moderate AS** with less calcification because Valvosoft proved to be efficace to soften fibrosis tissue
- Improve mechanism comprehension: Effect on VIC and VEC

New & unique therapeutic ultrasound energy

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

Valvosoft® Short Story

- Valvosoft : **6 prototypes** in fonction (2 Gen 1 (FIM) and 4 Gen 2 (Pivotal))
- **100 patients** (FIM 40 + CE 60) treated
- **4 countries** (DE, FR, NL, RS)
- **12 centers (**FIM 3 , Pivotal 11**)**
- Follow up **until 24 months** for some patients

New & unique therapeutic ultrasound energy

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

NIUT indications for Use Complementary to TAVI

First indication for use (CE-marking):

Patients not recommended for AVR

Bridge to AVR

Patients refusing AVR*

Future potential indications:

Delay disease progression in symptomatic moderate patients (POC study)

Pre-TAVR or pre BAV to optimize procedural outcomes

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

Bioprosthesis treatment to prolong implanted bioprosthesis durability

In countries where TAVR remains unavailable

* within CE study not allowed in France

Conclusion MAS

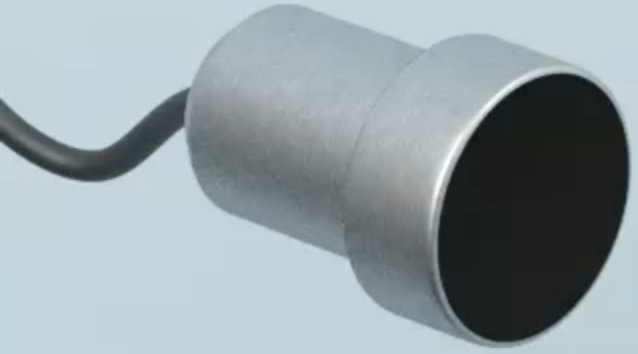
- MAS patient is an **important population with global poor outcome**
- MAS **progression is heterogenous we need tool to predict its progression**
- **Therapeutic strategy are ongoing** with TAVI and medication
- **Prosthetic free calcium fragmentation** could be an option for MAS patient
- **Non invasive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

Back-up

All mortality 100 pat

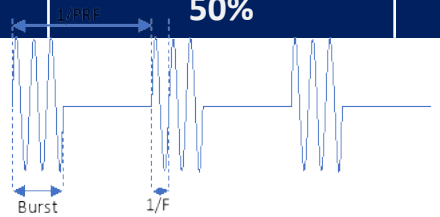
Pivotal mortality up to 3 months

Ultrasound wave



Unique Non-invasive Ultrasound Therapy solution

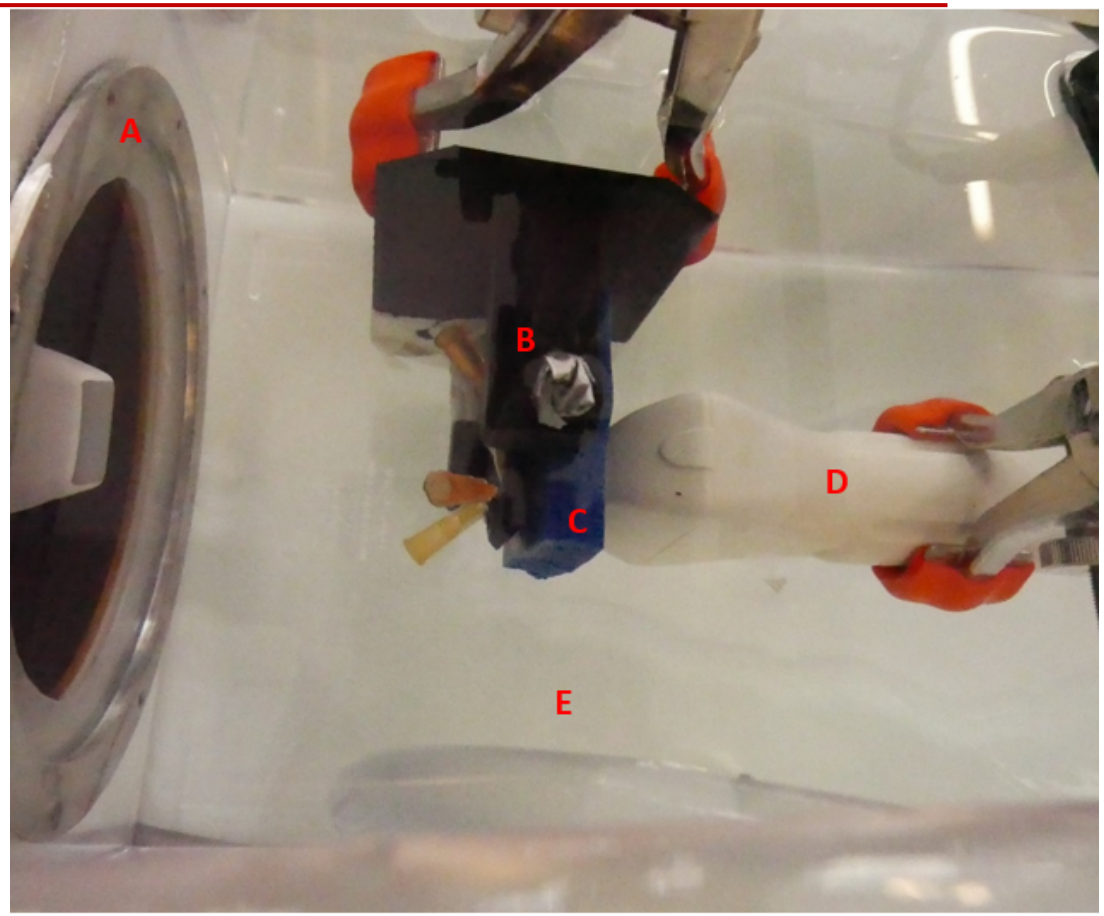
Therapeutic ultrasounds	HIFU*	Lithotripsy	Histotripsy	NIUT
Mechanism	Continuous waves	Shock wave (minimized / non desired cavitation bubbles)	Pulse cavitational ultrasound With electronic steering (Sustained inertial cavitation bubbles implosion generates localized streaming, shockwaves)	
Pulse Repetition 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%	



- 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).*

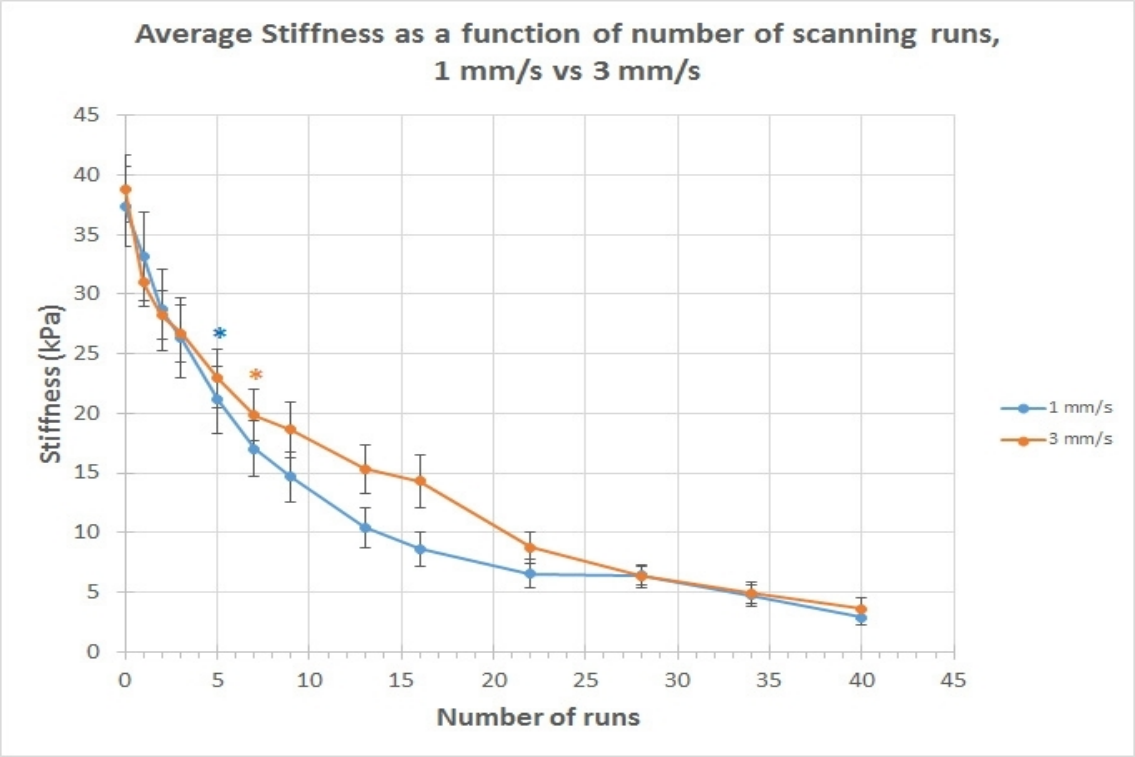
Ex vivo trial of PCUT treatment performance on bovine pericardium. Tissue softening

- 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.



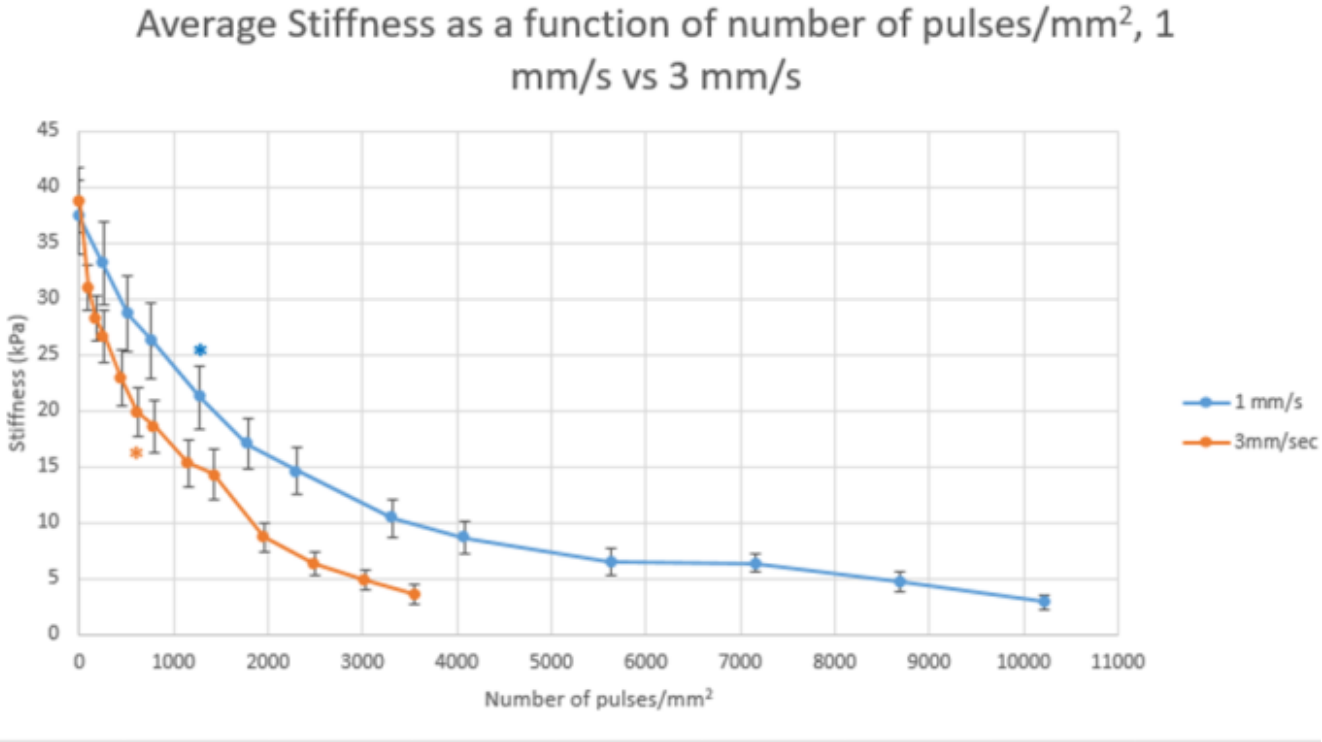
A) PCUT device. B) Sample holder connected to computer-controlled motors. C) Absorber, to protect elastography probe during therapy D) 20 MHz elastography probe. E) Aquarium filled with degassed saline.

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



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).