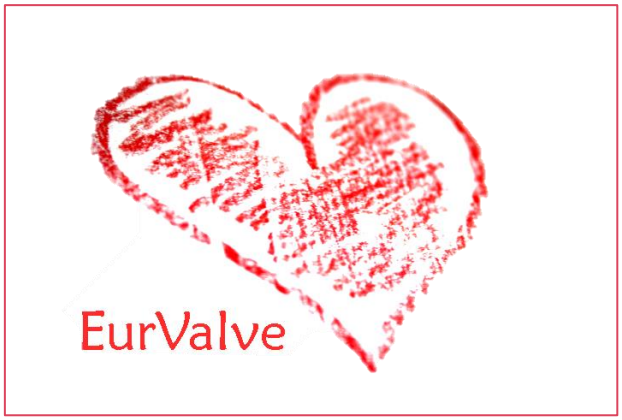
European Commission

Directorate General for Communications Networks, Content and Technology
Sustainable and Secure Society - Health and Well-being

H2020 PHC-30-2015 689617
Research and Innovation Action



Work Package: WP4

Digital Patient

Deliverable: D4.7

Comprehensive Data Summary and Review

Version: 1v7

Date: 2-Apr-19

DOCUMENT INFORMATION

IST Project Num	H2020 PHC-30-2015 689617	**Acronym**	EurValve
Full title	Personalised Decision Support for Heart Valve Disease		
Project URL	http://www.eurvalve.eu		
EU Project officer	Milan Popovic (Milan.Popovic@ec.europa.eu)		

Work package	**Number**	4	**Title**	Digital Patient
Deliverable	**Number**	4.7	**Title**	Comprehensive Data Summary and Review

Date of delivery	**Contractual**	28 Feb-19	**Actual**	02-Apr-19
Status	Version 1v7		Final ☑	
Nature	Prototype ☐ Report ☑ Dissemination ☐ Other ☐			
Dissemination Level	Public (PU) ☑ Consortium (CO) ☐		Restricted to other Programme Participants (PP) ☐ Restricted to specified group (RE) ☐	

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Abstract (for dissemination)	The development and testing of the EurValve Decision Support System included its application to patient data collected within a prospective clinical study. The data includes clinical information from each patient, and population and epidemiological data that are used both for data inference and for data and model interpretation. All data is appropriately annotated, organised and represented using the infrastructure developed in WP2. This document summarises the data available at PM30.
Keywords	Decision Support, Clinical Trial, Aortic, Mitral, Valvular

Version Log			
Issue Date	**Version**	**Author**	**Change**
19-Jul-18	1v1	M Kelm	Initial Draft
24-Jul-18	1v2	K El-Arifi	Minor changes, formatting
30-Jul-18	1v3	PMO	Release version
17-Jan 19	1v4	M Kelm	Draft for Resubmission with Updates
25 Feb 19	1v5	K El-Arifi	Updated
28 Feb 19	1v6	K El-Arifi	Additions
02 Apr 19	1v7	PMO	Post-Review update

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EXECUTIVE SUMMARY

The EurValve project's aim is to implement and test, in a relevant clinical target cohort, a Decision Support System (DSS) for aortic and mitral valve replacement and repair. The testing process will include the application of the DSS to patient data collected within a prospective clinical study, and WP4 is responsible for the collection of the data on which this element of the testing depends.

The data include clinical information from each patient, and population and epidemiological information that is used both for data inference and for data and model interpretation. All data is appropriately annotated, organised and represented using the infrastructure developed in WP2. This document gives a comprehensive summary of the data status at project end.

This version of the Deliverable has been significantly expanded, to include a description and discussion of the project's Augmented Data - that which is generated by the EurValve processes of simulation. In an extension of this, there is a major section addressing the issues of validation, a topic raised by many of the clinicians involved in the randomised controlled experiment. The thought processes that have driven the EurValve approach to validation of the computational measures are laid out, and the complex issues of association between measures of severity of disease and the acute and long-term effects of intervention are explored.

The document also includes two post-review updates (in coloured panels), discussing further aspects of model personalisation, and the work being done to investigate correlations between measured and computed results.

1 INTRODUCTION

In the EurValve project, we aim to implement and test a DSS for aortic and mitral valve replacement and repair in a relevant clinical target cohort. For this clinical component, testing is being conducted within a prospective clinical study, the data for which is discussed in this document, and the design of which is shown in figure 1. For completeness, a summary of all EurValve data is given in Appendix A.

WP4 collects the data on which this aspect of the project depends. These data include clinical information from each patient, and population and epidemiological data that are used both for data inference and for data and model interpretation. All data will be appropriately annotated, organised and represented using the infrastructure developed in WP2.

Not all of the assessments listed can be performed on every patient, but sufficient data available needs to be ensured to support the analysis processes. In brief: A total of 120 patients were intended to be enrolled, in two subgroups:

- Group 1: patients with aortic valve disease (N=60; per clinical centre N=20)
- Group 2: patients with mitral valve disease (N=60; per clinical centre N=20).

According to current hospital control data, we anticipated that approximately 30% of the patient to have combined aortic-mitral valve disease.

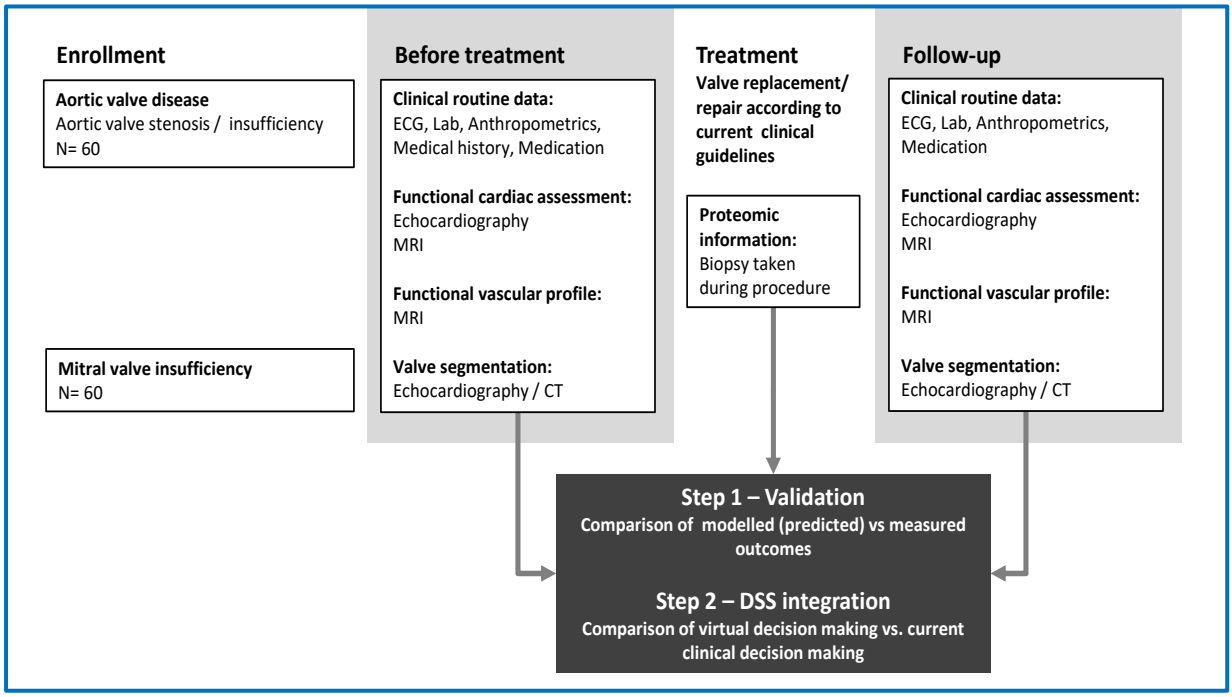


Figure 1: Prospective Clinical Study Design

At each of the three clinical sites (STHFT, CATH, DHZB) the following visits were planned:

- **Visit 1**: All patients will be investigated before valve intervention by imaging, ECG, laboratory tests, anthropometrics (blood pressure, body weight, clinical status etc.). These data will be used for modelling.
- **Operation** (valve replacement/repair). In EurValve all patients were treated according to current clinical guidelines. In the Berlin centre an additional myocardial biopsy was planned in patients undergoing surgery, with the biomaterial being used for proteomic analysis.
- **Visit 2**: After treatment patients were followed-up undergoing the study protocol again. This allows comparing the modelled (predicted) against measured outcome data needed for the validation of the model and the DSS. In this second step a comparison between virtual decision making using a DSS and current clinical decision making will be carried out.

Within EurValve two main model-based outcomes were validated: (I) model-based output before an intervention is performed and (II) model-based output after a virtual intervention is performed. Wherever available the diseased valve state was tuned according to the patient-specific 3D geometry (from CT or TEE) of the valve. In all remaining cases the 0D model was tuned using clinical imaging information obtained from routine diagnostics. We have sketched this out in the study diagram below.

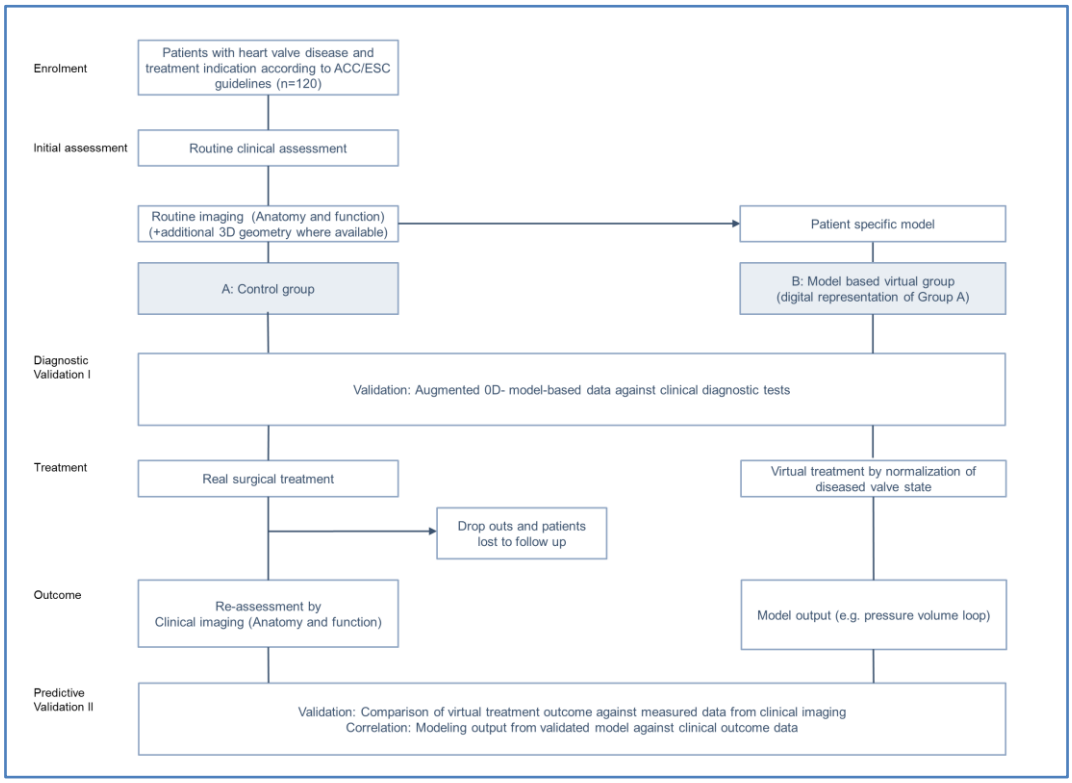


Figure 2: Study Diagram

This deliverable describes the patient data pool that was used as a reference for the model tuning and all subsequent clinical validation steps in the 0D model.

2 DELIVERED PROSPECTIVE CLINICAL RECRUITMENT

From an original target of 120 patients, a total of N=169 patients have been enrolled across all three clinical sites where follow-ups have been performed in N=164 patients, resulting in a total of N=333 individual disease states, and thus a slight over-performance in recruitment at all three clinical sites. This is a natural consequence of the slight over-recruitment employed to ensure adequate numbers in the face of probable later-stage dropouts.

Recruitment at all 3 clinical centres is shown in the figure below.

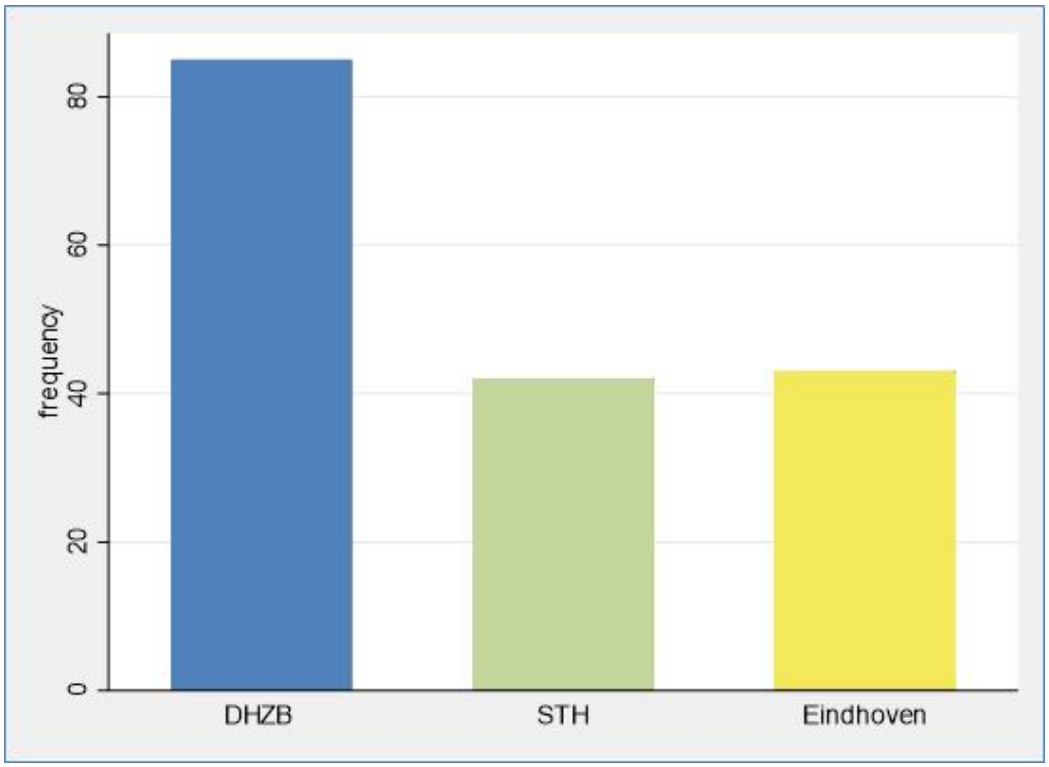


Figure 3 Recruitment at all 3 clinical sites

Completed preoperative and postoperative datasets are to date available in n=164 cases. Of those, n=98 had primary treatment indication for aortic valve disease cases and n=66 patients had primary treatment indication for mitral valve disease. All patients with treatment indication received surgical or interventional (TAVI) treatment procedures accordingly.

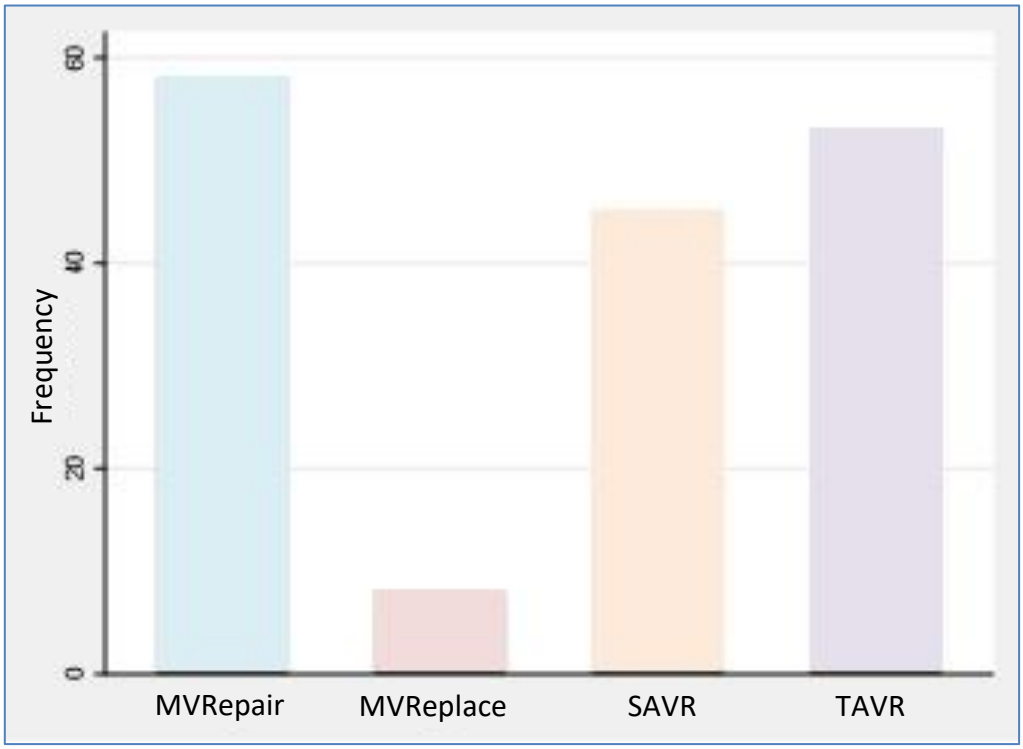


Figure 4 Treatment undertaken

Milder forms of valve disease and resulting overlap between both disease was found in N=24 patients (Table 1). In n=17 AVD patients there was also relevant mitral valve insufficiency, a common clinical combination.

3 BASELINE CHARACTERISTICS

The baseline characteristics are illustrated in Table 1:

Parameter	N	Value
Male Gender	98/169	57 %
Age	169	70.6±12.6 years
Body weight	169	78.3±15.5 kg
Body Mass Index (BMI)	169	27.1±4.4 kg/m^2
MITRAL VALVE DISEASE	91	54%
MI	89	98%
Mixed	1	2%
Aetiology	91/169	
degenerative/calcified		10%
Functional		10%
Infective		1%
Ischemic		3%
Prolapse		75%
Rheumatic		1%
AORTIC VALVE DISEASE	102/169	60%
AI	4/102	4%
AS	84/102	82%
Mixed	14/102	14%
Max pressure drop		68.1 ±30.46 mmHg
Mean pressure drop		42.7 ±19.88 mmHg
Aetiology	82	
Calcifications		94%
Bicuspid valve		3%
Other		3%
Thoracic aortic aneurysm	5	5%
Abdominal aortic aneurysm	2	2%
Symptoms		
Palpitations	46/167	28%
Edema	41/167	25%
Syncope	11/163	7%

Parameter	N	Value
Nycturia	37/163	23%
NYHA I	28/163	17%
NYHA II	69/163	42%
NYHA III	56/163	34%
NYHA IV	10/163	6%
CCS		
No CCS symptoms	106/168	63%
Class 1	40/168	24%
Class 2	14/168	8%
Class 3	5/168	3%
Class 4	4/168	2%
PHYSICAL ACTIVITY		
None	37/167	22%
Sporadically	48/167	29%
Regular	68/167	41%
Frequently	14/167	8%
OVERALL PHYSICAL WELLBEING		
very good	10/155	6%
Good	37/155	24%
Fair	56/155	36%
Poor	40/155	26%
very poor	12/155	8%
OPERATIVE RISK		
Arterial hypertension	118/168	72%
Previous pulmonary artery hypertension	8/163	5%
Frailty	4/168	2%
Urgency	13/168	8%
Smoking		
Smokers	18/167	11%
Previous smokers	80/167	48%
Non-Smokers	69/167	41%
Alcohol consumption		
History of alcohol abuse	3/164	2%
Regular	30/164	18%
Mild	40/164	24%
Rare	35/164	21%
None	53/164	32%

Parameter	N	Value
Previous coronary artery bypass surgery	10/168	6%
Previous aortic valve surgery	2/168	1%
Previous Stroke	17/166	10%
Previous episode of heart failure	21/159	13%
Existing permanent atrial fibrillation	33/168	20%
Existing intermittent atrial fibrillation	19/166	11%
Chronic rheumatic disease	12/162	7%
Chronic renal impairment	35/167	21%
Existing chronic liver disease	6/160	4%
Existing malignant disease	20/166	12%
Existing dementia	0/164	0%
Physiological parameters		
Heart rate		70.23±11.4 /min
Systolic blood pressure		138±21.6 mmHg
Diastolic blood pressure		74±12.1 mmHg
Mean blood pressure		95±13.4 mmHg

Table 1: Baseline Characteristics of the Study Cohort

Geometric and resulting parameters within the cohort are shown in Figure 5.

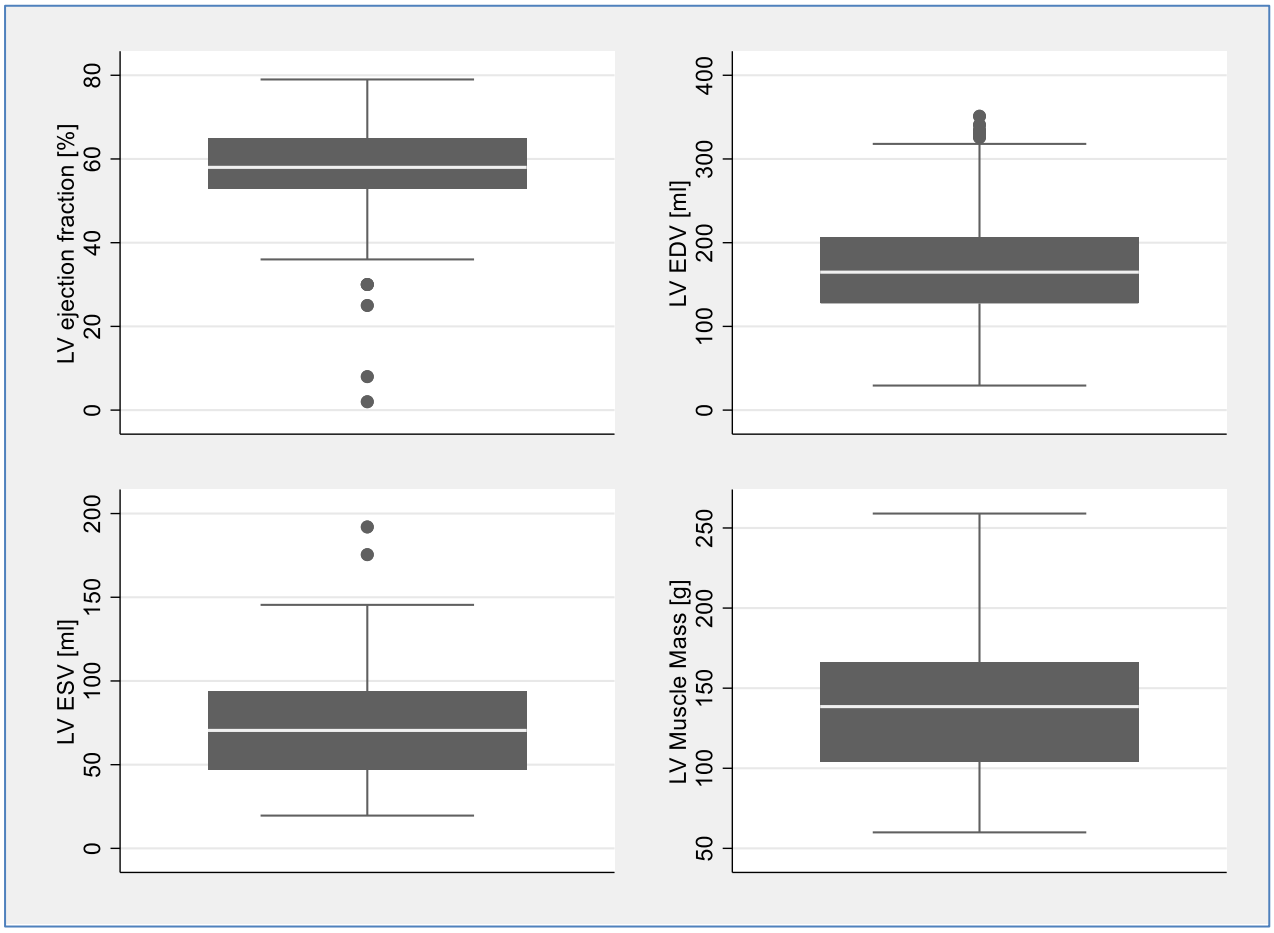


Figure 5 Geometric and Functional Myocardial Parameters of the Study Cohort

4 CLINICAL OUTCOME

The following figure shows a Kaplan-Meier survival curve of study participants during the course of the clinical study. N=7 of 164 died during the course of the study, accounting for an overall mortality of 4%. Considering included treatment groups with elderly patients with existing co-morbidities and TAVI patients the mortality was rather low. While the follow-up assessment was performed at 3-8 months after treatment, 2 out of 7 events were reported between 8 and 20 months. As patients were not included at the same time, the time frame between 8 and 20 months was not fully assessed within the entire study cohort. The mortality upon standardized follow between 3-8 months up was 5 out of 164 (3%), which is in line with existing literature date.

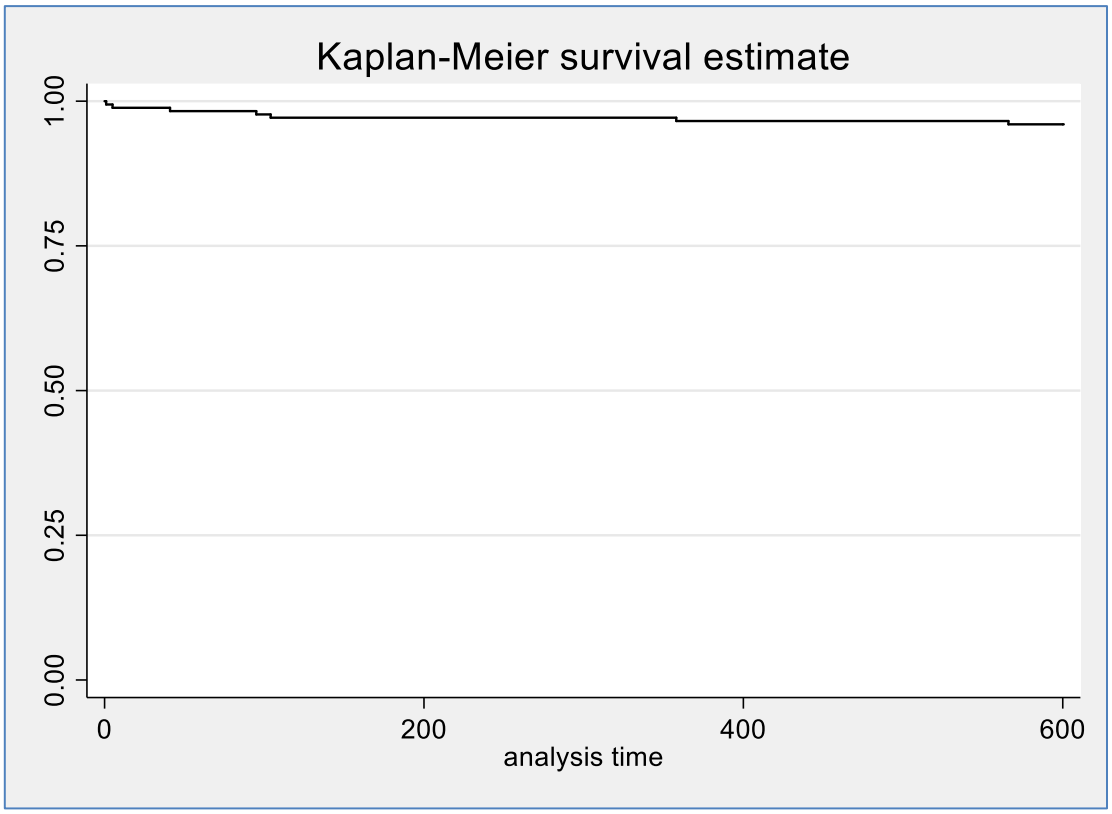


Figure 6 Kaplan-Meier survival curve
7 out of 164 (4%) died during the course of the study. Upon standardised follow up between 3-8 months was 5 out of 164 (3%)

The overall low mortality illustrates the already low rate of lethal complications during cardiothoracic surgery. Nevertheless, individual mortality varies and will depend on distinct risk factors that can be assessed using standardized scoring system (EUROSCORE I, EUROSCORE II, Society of Thoracic Surgery - STS).

5 QUALITY OF LIFE

Additionally to standardised cardiologic clinical data, quality of life has been assessed using the World Health Organisation (WHO) WHOQOL-BREF questionnaire. Responses can be grouped into four major life quality domains:

Physical Health

- Energy and fatigue
- Pain and discomfort
- Sleep and rest

Psychological

- Bodily image and appearance
- Negative feelings
- Positive feelings
- Self-esteem
- Thinking, learning, memory and concentration

Social Relations

- Personal relationships
- Social support
- Sexual activity

Environment

- Financial resources
- Freedom, physical safety and security
- Health and social care: accessibility and quality
- Home environment
- Opportunities for acquiring new information and skills
- Participation in and opportunities for recreation/leisure
- Physical environment (pollution/noise/traffic/climate)
- Transport

All four health domains are illustrated in Figure 7a and 7b for patients before and after surgery. No significant QoL differences were found before and after patients undergoing surgical treatment, which presents an opportunity for optimising treatment and post-treatment programs in the future.

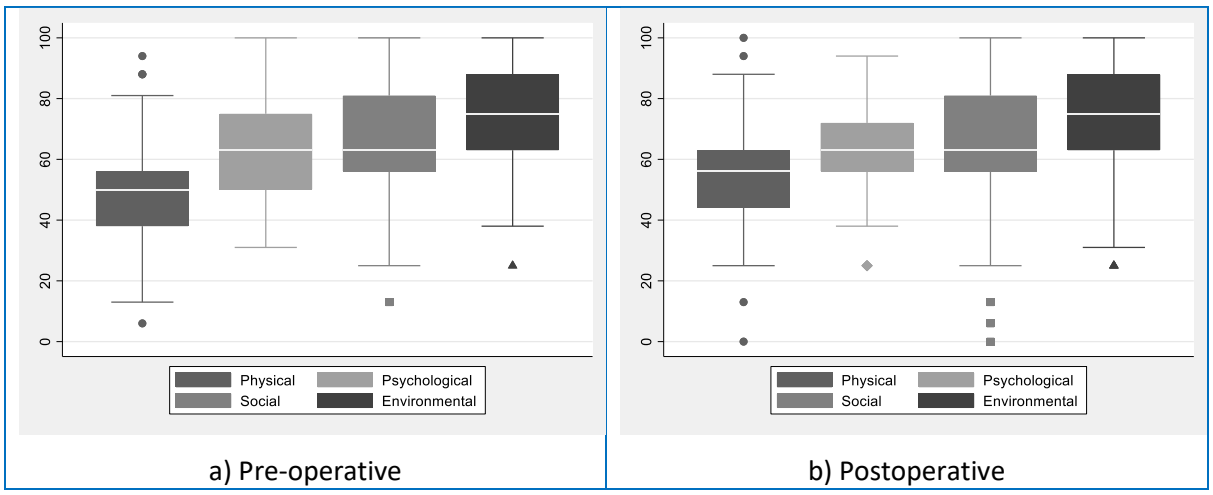


Figure 7: WHOQOL-BREF Quality of Life Domains in EurValve patients.
The scale ranges from 0 (lowest possible quality within the domain) to 100 (best possible quality within the domain)

The changes in quality of life scores are illustrated in the following figure. Despite slight, yet statistically insignificant, changes within the physical quality of life domain, overall scores remained almost unchanged within the entire cohort.

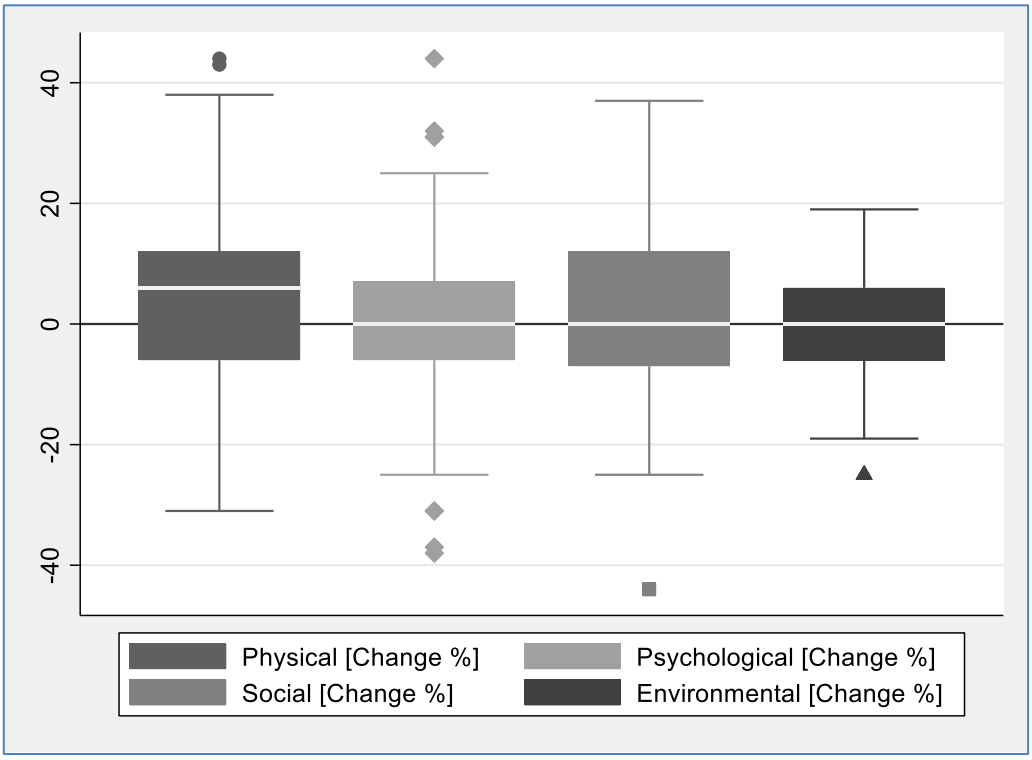


Figure 8: Quality of life changes after treatment.

Unchanged quality of life cores are based on the entire study cohort cannot exclude improvement or worsening for individual patients.

While QoL domains are correlated to each other, no direct association between guideline based standard imaging parameters (left ventricular ejection fraction, mean aortic valve pressure gradient, mitral valve regurgitation) were found, as illustrated in Figure 9.

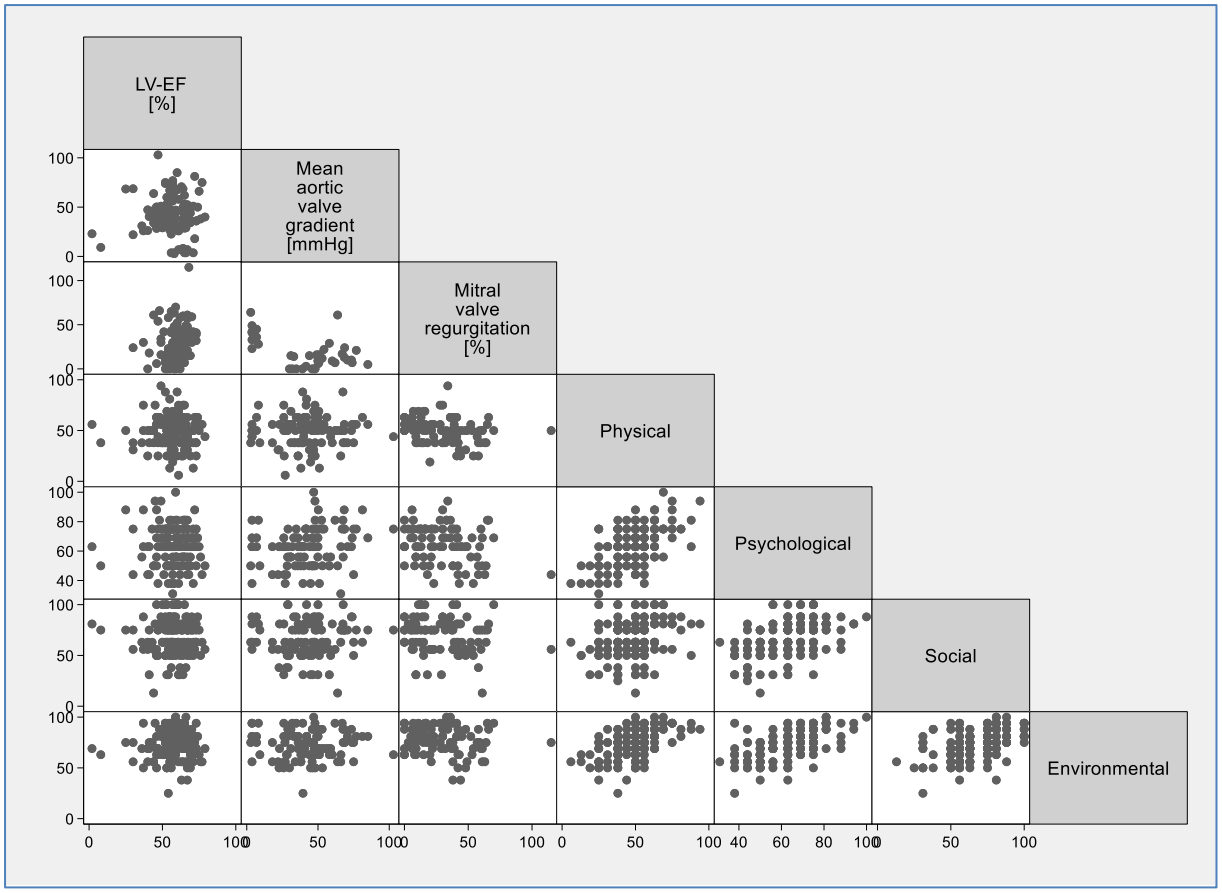


Figure 9: Guideline-based Standard Imaging Parameters and QoL Scores

The physical and environmental quality of life domain was associated to the absolute distance and patient-specific 6-Minute walk test – the longer the 6 Minute Walk test difference, the higher they rated environmental quality of life (Figure 10).

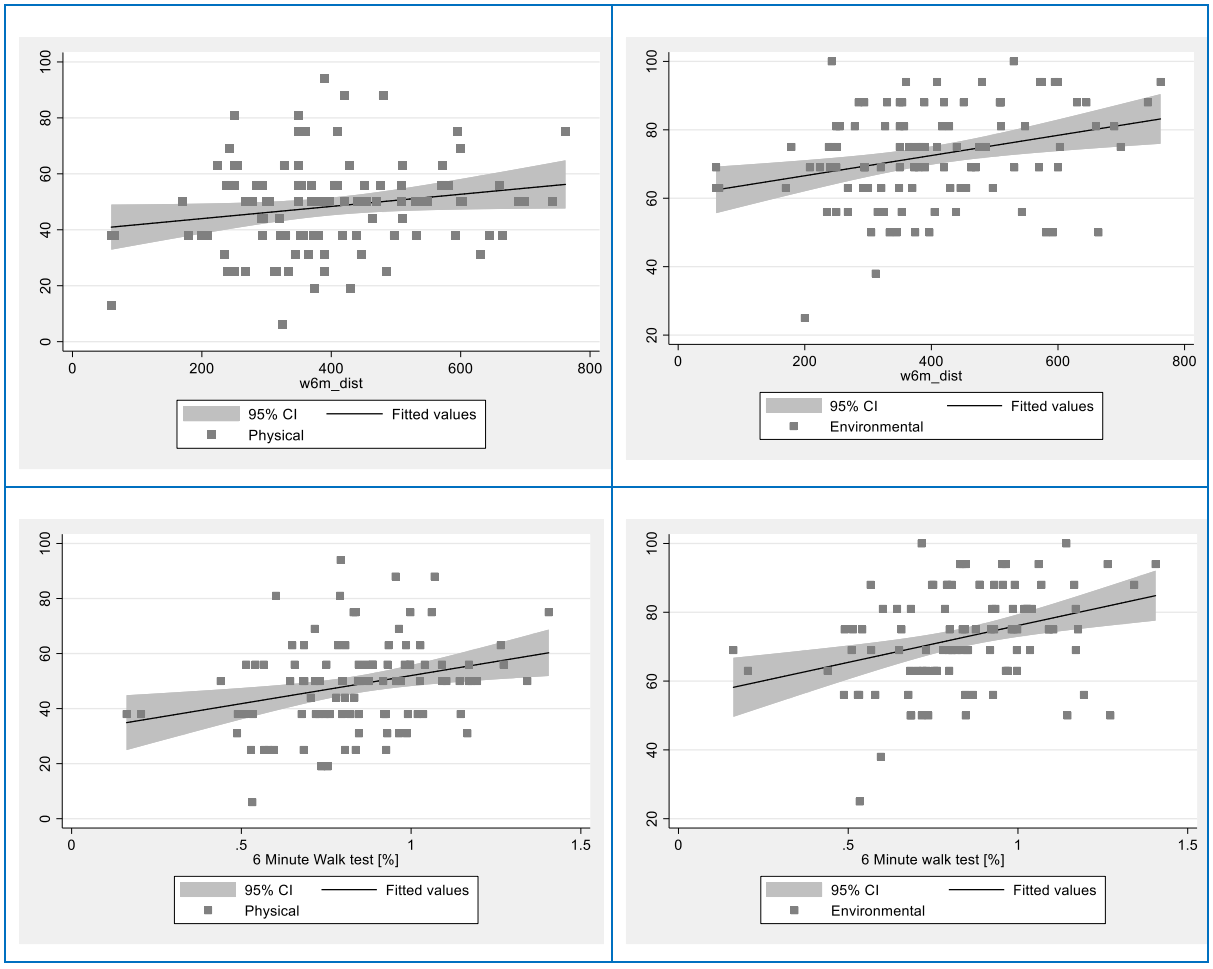


Figure 10: Patient Subjective/Objective Data Correlation
Correlation between environmental quality of life and 6-Minute Walk test distance in meters

6 6 MINUTE WALK DISTANCE

The results of the 6 minute walk distance test are shown in the figure below:

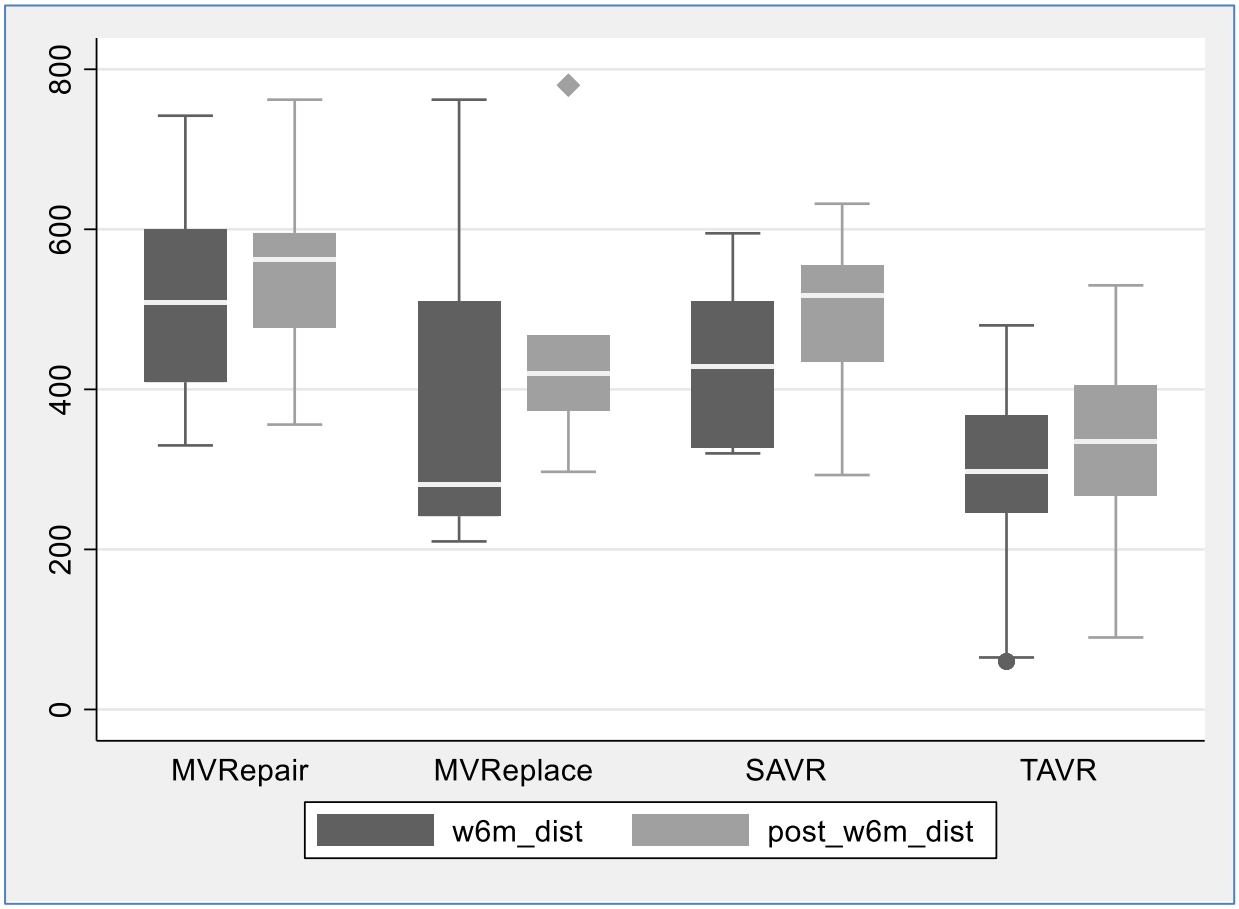


Figure 11 6 Minute walk test before and after treatment [distance in m]

7 AUGMENTED DATA

One of the primary aims of EurValve was to augment the measured clinical data with further parameters extracted from the operation of a computational model of the systems physiology. There are several aspects of these data that could provide valuable diagnostic or prognostic insight.

- Assuming that the model effectively represents the physiological processes, it embeds knowledge. For example, a variable elastance model has been shown to produce a simple but effective representation of ventricular contraction, and the concepts of maximal and minimal elastance are directly interpretable. EurValve has developed a process for personalisation of some of the model parameters, including elastance parameters, based on measured clinical data. These personalised parameters are returned as augmented data in the pseudonymised patient record.
- Subject to the underpinning assumptions, the models are able to compute parameters, such as valve pressure-flow characteristics from the image data or left ventricular peak power or energy expenditure in a specific exercise state, that are not easily measured in the clinic. These parameters contribute to the augmented data.
- Prospective interventions can be carried out in the model to predict the likely physiological benefit. For example the expected changes in the PV loop, or the expected reduction in left ventricular work associated with a valve replacement, can be computed. These also constitute augmented data.

Table 2 lists the augmented data associated with the system model, separated into two columns. The first column is the set of model input parameters, which includes several parameters that are personalised based on measured clinical data as well as the valve characterisation from the image data, and the second column is the set of output parameters.

Model inputs	Model outputs
Heart Rate [bpm]	Cardiac Output (lpm)
Elvmin [mmHg/ml]	LV End Diastolic Volume [ml]
Elvmax [mmHg/ml]	LV End Systolic Volume [ml]
Systemic Arterial Resistance [mmHg.s/ml]	Stroke Volume [ml]
Systemic Arterial Capacitance [ml/mmHg]	Ejection Fraction [-]
Mean circulatory filling pressure [mmHg]	Maximum LV Pressure [mmHg]
Start of left ventricular contraction [-]	Minimum LV Pressure [mmHg]
Peak of left ventricular contraction [-]	LV End Diastolic Pressure [mmHg]
End of left ventricular contraction [-]	Peak LVdp/dt
Volume offset in LV pressure equation [ml]	LV Stroke Work per Beat [mmHg.ml]
Elamin [mmHg/ml]	LV Stroke Power Expenditure [W]
Elamax[mmHg/ml]	LV Peak Power [W]
Start of left atrial contraction [-]	Whalley Wasted Power [W]

Model inputs	Model outputs
Peak of left atrial contraction [-]	Systolic Blood Pressure [mmHg]
End of left atrial contraction [-]	Diastolic Blood Pressure [mmHg]
Volume offset in LA pressure equation [ml]	Mean Arterial Pressure (True) [mmHg]
Aortic Valve quadratic coefficient [mmHg.s^2/ml^2]	Mean Arterial Pressure (nominal) [mmHg]
Aortic Valve linear coefficient [mmHg.s/ml]	LV End Diastolic Pressure [mmHg]
Aortic Valve regurgitant quadratic coefficient [mmHg.s^2/ml^2]	Forward Flow through Aortic Valve [ml/beat]
Aortic Valve regurgitant linear coefficient [mmHg.s/ml]	Forward Flow through Mitral Valve [ml/beat]
Aortic Valve smoothing threshold [mmHg]	Maximum Pressure Drop over Aortic Valve [mmHg]
Aortic Valve smoothing polynomial order	Mean Pressure Drop over Aortic Valve [mmHg]
Mitral Valve quadratic coefficient [mmHg.s^2/ml^2]	Stroke Power Lost to Aortic valve resistance
Mitral Valve linear coefficient [mmHg.s/ml]	Ratio of Stroke Power Lost to AV resistance: Stroke Power
Mitral Valve regurgitant quadratic coefficient [mmHg.s^2/ml^2]	Mitral Valve Regurgitation [ml/beat]
Mitral Valve regurgitant linear coefficient [mmHg.s/ml]	Mitral Valve Regurgitant Fraction [-]
Mitral Valve smoothing threshold [mmHg]	Stroke Power Lost to Regurgitant MV
Mitral Valve smoothing polynomial order	Ratio of Stroke Power Lost to Regurgitant MV: Stroke Power
Venous/Pulmonary Capacitance [ml/mmHg]	Aortic Valve Regurgitation [ml/beat]
Systemic Arterial Capacitance Unstressed Volume [ml]	Aortic Valve Regurgitant Fraction [-]
Venous/Pulmonary Capacitance Unstressed Volume [ml]	Stroke Power Lost to Regurgitant AV
Rest Heart Rate from Philips Watch Data [bpm]	Ratio of Stroke Power Lost to Regurgitant AV: Stroke Power
Exercise Heart Rate from Philips Watch Data [bpm]	

Table 2 List of model inputs and outputs

WP3 provided tools, operable through the MEE developed by WP2, to segment the valve images, to compute the pressure-flow characteristic of the valves, to personalise a 0D model of the systemic circulation and to quantify the uncertainty of the generated results. Further information on the model assumptions and operational details are provided in D3.4, and a summary of the final computational analysis protocol in D1.3. In summary, the Computational Fluid Dynamics model, or the Reduced Order Model, returns valve pressure-flow characteristics. The final systems model protocol is a seven stage analysis. Firstly model parameters are personalised using clinical observations at the time of examination, and then

the model extrapolates back to the rest state and forward to an exercise state. These three stages provide the augmented data to characterise the pre-intervention state, followed by four stages that predict the post-intervention data under a candidate intervention.

Two primary variations of the workflow were developed. The first uses the clinical image data to characterise the pressure/flow relationship of the valve. It was not possible to collect image data of adequate quality to perform accurate valve segmentation for approximately one half of the EurValve clinical cohort, and so in the second variation the measured pressure gradient (aortic valve) or measured regurgitant fraction (mitral valve) was used for diseased valve characterisation. For this second approach this means that these measures cannot be used for model validation, but the physiology characterisation and the prediction of the changes under intervention can still be performed. In fact the addition of this second workflow also increases the potential for post-project application to a wider spectrum of clinical cases.

The workflow, in one or both variations, was operated by WP6 on all cases.

Centre	Number of Unique cases		Cases processed with image-based workflow		Cases processed with measurement-based workflow	
	Mitral	Aortic	Mitral	Aortic	Mitral	Aortic
Berlin	46	36	23	4	46 (3)	36
Eindhoven	0	39	0	0	0	39
Sheffield	20	22	19 (4)	20 (1)	17 (1)	22 (1)
Total	**66**	**97**	**42 (4)**	**24 (1)**	**63 (4)**	**97 (1)**

Table 3 Case processing statistics
Figures in red indicate number of cases for which the analysis process failed

Table 3 shows the statistics of the case processing. The main entries in the table are the number of cases that were subjected to processing. The figures in red indicate the number of these cases for which the analysis protocol failed to produce the augmented data, usually because of a failure of the model personalisation step. Note that the process for the aortic valve is generally very robust, with only one case from 97 analysed failed to reach convergence. The process for mitral cases is slightly less stable, perhaps reflecting the complexity of the disease and/or the uncertainty of clinical measurements, but nevertheless only 1 mitral case failed to converge using one or other of the two work flows. **Model-augmented data has been generated for 96 aortic cases and for 65 mitral cases.**

Post-Review Update

Although detailed analysis for clinical publications is in progress, a summary of the statistics across the cohort was presented at the Final Review and is shown in figures A and B in this panel. This already provides interesting comparisons between the aortic and mitral cohorts. The mean and median elastance parameters for the aortic cohort are within the normal range, with relatively small standard deviations. In contrast, the mitral cohort have significantly increased elastance, in both filling and ejection phases, as well as increased

standard deviations. This might suggest that at least some of this cohort has already suffered negative cardiac changes as a result of their valve disease. It might be expected that there is a parabolic association between these parameters and outcome. If the changes from normality are small then it might be expected that there will be little positive remodelling (the heart is not yet compromised by the disease). There might come a time when the heart is so compromised that it can no longer remodel adequately and so will not have the full benefit of the unloading in terms of long term outcome. In the middle range, one might expect the most benefit. If we are able to demonstrate in the EurValve cohort, at least indicatively, that there might be an association between these parameters and outcome, measured by quality of life or activity measures then there is the potential already to influence the timing of the intervention.

This discussion also reinforces the need to follow-up at appropriate time intervals. There might always be a post-operative dip as the patient recovers from the trauma of the intervention, then an acute improvement as the benefits of the improved flow to the circulation become manifest, followed by a longer-term recovery phase as the heart remodels positively. Our hypothesis is that the EurValve analysis process implicitly represents and reports the parameters that will fundamentally influence the timing of the intervention. However, the data analysis, not only in the EurValve cohort but also in larger clinical trials, is required to determine the thresholds for effectiveness of intervention. We believe that even the preliminary and indicative analysis that will be provided by the EurValve cohort will prompt wider clinical interest in this interpretation of the personalised model data.

	Elvmin	Elvmax	Sys R	Sys C	MCFP
Median	0.10	1.55	0.94	1.08	21.9
Mean	0.11	1.71	1.01	1.10	22.0
STDEV	0.03	0.75	0.28	0.40	1.3

Figure A. Statistics for EurValve's Aortic Cohort

	Elvmin	Elvmax	Sys R	Sys C	MCFP
Median	0.15	2.90	0.95	0.78	20.7
Mean	0.17	3.32	1.13	0.86	20.9
STDEV	0.09	2.05	0.80	0.41	1.3

Figure B. Statistics for EurValve's Mitral Cohort

8 DATA CORRELATIONS

The primary output of EurValve is a Decision Support System (DSS) that seeks to improve diagnosis and interventional planning for heart valve disease. One of the aims is to present to the clinician augmented data, derived by the operation of a computational model, that provides additional information to aid the process of decision-making. Deliverable D6.3 focuses on the clinical evaluation of the usability and potential utility of the DSS. This evaluation is positive but, as should be expected, a consistent comment of the clinical review cohort was that extensive validation is required before clinical adoption. The purpose of this section is to explain the thought processes that have driven the EurValve approach, to validate the computational measures, and to explore the complex issues of association between measures of severity of disease and the acute and long-term effects of intervention.

EurValve is predicated on a series of assumptions and hypotheses, the key elements of which are summarised below.

- Important aspects of the systems physiology of an individual can be represented by a simple, zero dimensional, model that describes the distribution of pressure and flow, and from which key parameters such as left ventricular work and peak power expenditure can be determined.
- A relevant systems physiology model of an individual with valve disease must include a characterisation of the pressure-flow relationship of the diseased valve.
    - Hypothesis 1: *The pressure-flow relationship for the diseased valve can be estimated by computational fluid dynamics (CFD) analysis based on the valve anatomy in the appropriate configuration (open for a stenotic aortic valve, closed for a regurgitant mitral valve). A sub-hypothesis is that this relationship can be approximated by a Reduced-Order Model (ROM) constructed from the operation of many CFD models.*

  These are essentially physics/engineering focused issues, but the first validation of the primary hypothesis is performed against the clinical measures in the EurValve cohort and is presented in this section. The sub-hypothesis is simply a direct comparison of analytical approaches, and so this is covered separately in WP3.4.
- Often clinical decisions are made based on sparse data collected in the course of a series of clinical examinations performed whilst the patient is at rest, which might be in no way representative of the conditions under which the effects of the disease are most manifest. If a model could represent the physiological excursions of an individual as they go about their daily lives it might provide important diagnostic information.
- The model is able to represent a proposed intervention and to compute the estimated effects of the intervention on the systems physiology.
    - Hypothesis 2: *A primary effect of the valve disease is to increase the work that the heart does to generate the flow required to meet the metabolic demand. One of the clinical outcomes of valve disease is progression towards heart failure as the*

ventricle works harder, and if this work and associated peak power could be quantified reliably this might have immediate diagnostic value. Changes of these quantities after intervention might provide direct and quantitative measures of the physiological benefit of the intervention and be associated with the capacity for positive remodelling of the ventricle and recovery of the patient.

This hypothesis is explored in the following pages. It is important to recognise that there are two phases of response to the intervention. Theoretically the immediate and acute response to a valve intervention will (almost) always be positive because the work that the heart is wasting, either to drive flow through a diseased and restricted aortic valve or to push flow back into the atrium through a leaky mitral valve, will be reduced. EurValve recognises the other system characteristics, including the status of the systemic circulation and the elastance and contractility of the ventricle, but essentially it would be expected that the more severe the disease the greater the benefit of intervention. In fact both acute and longer-term benefits are complex. Acutely, intervention on either valve tends to increase systemic arterial pressures, and these are immediately regulated either by the patient's own homeostatic mechanisms or by pharmacological intervention. This response is recognised in the EurValve analysis protocol (see the WP3 section in D1.3). The positive acute response is also masked, over a recovery period, by the inevitable insult of, or complications associated with, the intervention.

The longer term benefit has two aspects, the direct benefit because the heart does less work to meet any particular metabolic demand even if the cardiac properties are unchanged and the potential for positive ventricular remodelling and improvement of cardiac performance. The latter is particularly complex. For this it would not be expected that there would be a proportional relationship between severity of disease, improved *valve* performance associated with intervention and remodelling outcome. Rather it might be expected that the benefit in terms of remodelling will be relatively low if the valve disease is a minor contributor to cardiac work or power, but also low if the failing heart (perhaps due to the valve disease) has progressed to the point at which it no longer has the biological capacity to recover. It might be expected that there is a 'sweet spot' in which there is significant immediate benefit and also long-term remodelling benefit. These issues are expanded below.

The primary focus of EurValve is the development of the DSS and the exploitation of the system model to provide the augmented data and the predictions of physiological outcomes of prospective interventions. EurValve has a cohort of 120 patients, 60 with aortic disease and 60 with mitral disease, on which the process has been operated and on which the hypotheses can be tested.

Hypothesis 1 centres around the representation of the haemodynamics of the valve. The computational fluid dynamics is performed using the Fluent software from ANSYS. This is arguably the leading CFD package in the world: it has been extensively validated and it is used in almost every branch of industrial fluid mechanics. There is no doubt that, if the problem is correctly formulated including appropriate definition of the anatomy and appropriate

boundary conditions, the resulting relationship will be accurate. EurValve assumes that the transient pressure/flow relationship can be approximated based on a series of steady-state simulations. Simulations performed in the first period of the project, and reported by WP3, support this assumption. The most important input to the CFD model is the anatomy, or the geometry of the diseased valve. The image segmentation to determine the geometry has been performed using state-of-the-art tools developed in WP3.2. We have learned that it is very difficult to capture valve images, at the appropriate point in the cardiac cycle, to provide images of sufficient quality to support the segmentation of the valve leaflets. This is especially true for the case of mitral regurgitation, for which we are seeking to identify a small orifice of complex geometry. Nevertheless, more than half of the cohort has been analysed to provide the data to test hypothesis 1. The valve pressure-flow relationship has been characterised using the CFD analysis protocol and the systems model operated to convergence over the cardiac cycle. The model provides the transient distributions of pressure, flow and volume that characterise the systems physiology, and from which the left ventricular pressure volume loop, amongst other features, can be computed. The most direct clinical measures of valve performance are the peak or mean pressure gradient across the diseased aortic valve and the regurgitant fraction of flow across the diseased mitral valve. These can be computed from the model and compared with the clinical measurements. The results are illustrated in Figure 12. These are the results for all cases.

For the aortic valve there is a clear trend and, in terms of a specific intervention threshold of 70 mmHg, six cases give an incorrect result (four false negatives and two false positives). At the project's final review some of the outliers were discussed (and see the panel immediately below): there are complications for several of these cases. For the mitral cases there is more scatter: this might reflect the difficulty of segmentation of the small orifice causing an inaccuracy of the computational result or difficulty in accurate clinical estimation of the regurgitant fraction, or both. Although the comparison is poorer for the mitral cases, there is perhaps a more urgent need for the model-based support because the current physiological parameters used for the decision are more difficult to determine and more subject to error. Figure 13 shows the measured versus computed end systolic and end diastolic volumes at rest post-intervention. These are regarded as more reliable clinical measures than the regurgitant fraction, and the correlation is stronger.

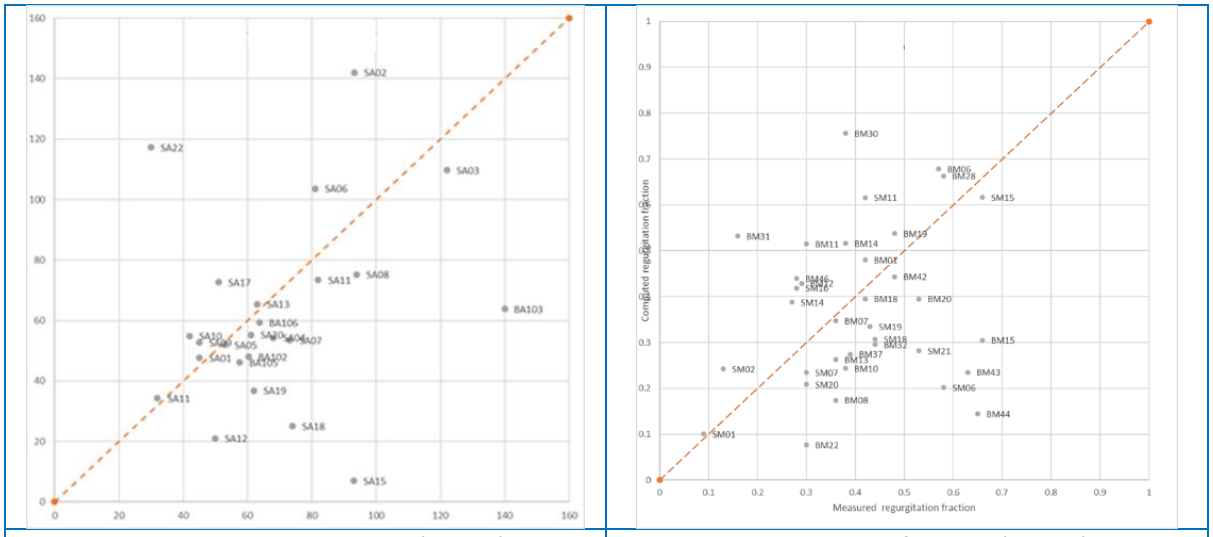
Post-Review Update:

Although there is a clear trend in the comparisons of the measured and computed aortic valve pressure gradients shown in Figure 12, several outliers are present and these compromise the expected correlation. In terms of a single decision threshold most of the cases fall into the appropriate quadrant, but this is biased in the clinical cohort because they were recruited from patients who had been determined to require intervention. In the final period of the project, the analysis partners performed extensive checking of the computational results, whilst the clinical centres performed further checks on the clinical data entered in the database.

A significant observation that arose during this process was that, in many cases, the heart rate at the time of measurement of the peak gradient was different to that at the time of

measurement of the left ventricular volumes, and the latter, together with the accuracy of segmentation of the valve leaflets in the open state, are critical elements in the computation of the gradients. Although this was highlighted by the examination of the outliers, the underlying issue will be resolved for the clinical publications that are in preparation, by introducing a consistent compensation mechanism for discrepancies in the physiological state for all patients. This is currently in process.

At a technical level, the ROM-based computation is compared with the CFD-based computation in deliverable 3.4. The ROM provides a very effective method of computation of valve characteristics for the aortic valve, and operates in near real-time. This is a major achievement in terms of potential clinical utility of the image-based DSS for aortic valve. It also suggests that there is significant potential for alternative pathways based on simpler image-based parameterisation of the aortic valve without necessarily full segmentation of the leaflets, which would make the product applicable more widely in routine clinical application.



a. Peak Pressure Gradient (Aortic) | b. Regurgitant fraction (Mitral)

Figure 12: Image-based analysis results
Patient at rest: a) Computed v Measured Peak Pressure Gradient for aortic cases, b) Computed v Measured Regurgitant Fraction for mitral cases

As summarised in Section 7 Augmented Data, two primary workflows have been operated in EurValve. The first is the valve-image based workflow, operated on more than half of the cohort, and the second is the measurement-based workflow, operated on the whole cohort. Note that hypothesis 1 and Figure 12 are entirely associated with the accuracy of the valve-image based processing workflow. It is not relevant to the second workflow, which uses the measured clinical values of the diagnostic parameters.

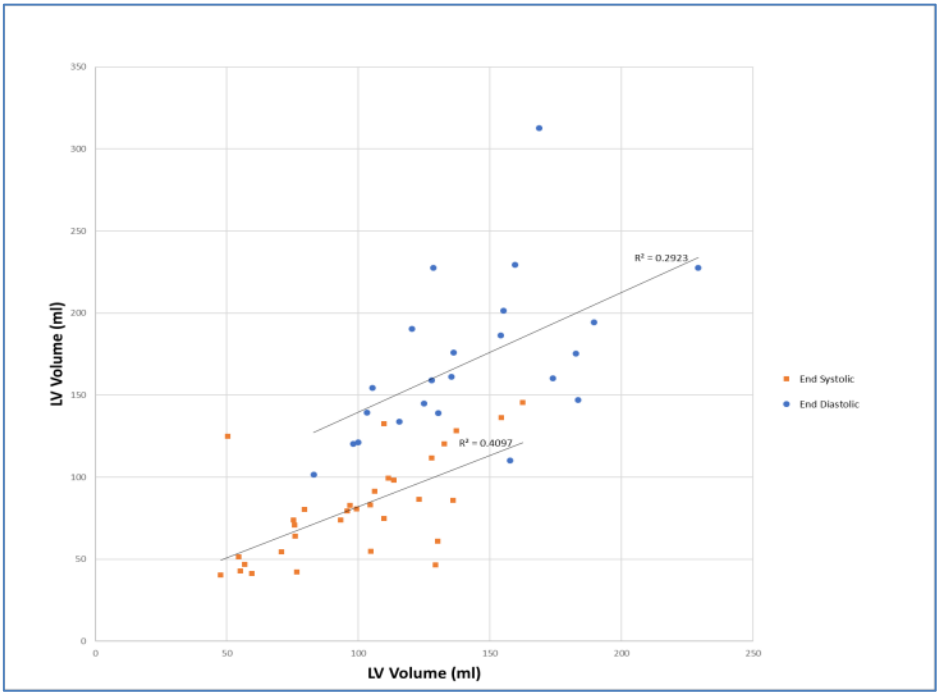


Figure 13: End diastolic volumes and end systolic volumes
Measured by cardiac magnetic resonance imaging plotted against volumes predicted by the model in the post-operative rest state

At a technical level, the ROM-based computation is compared with the CFD-based computation in deliverable 3.4. The ROM provides a very effective method of computation of valve characteristics for the aortic valve, and operates in near real-time. This is a major achievement in terms of potential clinical utility of the image-based DSS for aortic valve. It also suggests that there is significant potential for alternative pathways based on simpler image-based parameterisation of the aortic valve without necessarily full segmentation of the leaflets, which would make the product applicable more widely in routine clinical application.

Hypothesis 2 is much more difficult to validate, and will require an appropriately-powered clinical trial with appropriate end-points. There are very many issues to consider. In its clinical cohort EurValve is measuring patient activity data pre-intervention and post-intervention. This has sparked enormous interest in every clinical audience to whom the study has been presented. We believe that this is the first time that such a study has been conducted on a valve patient cohort. It provides potentially important quantitative diagnostic information pre-intervention, and a quantitative measure of change post-intervention. Interpretation is likely, however, to be complex. The spectrum of activity pre-intervention might indeed be a measure of the effect of the disease on the life of an individual, and there is no doubt that the activity levels measured in the EurValve cohort are low compared with those expected in a healthy peer group, but the study numbers are relatively low. Lack of activity might be attributable directly to the disease or to a host of other factors, from co-morbidities through to psychology and inclination. EurValve has produced a rich and deep set of data on its relatively small cohort, and analysis of associations continues and we believe will underpin a substantial number of publications, but the results will remain speculative and direction-pointing until numbers are increased significantly.

It is very interesting to explore the effect that the valve disease has under different physiological conditions. The disease causes high levels of ventricular work during even moderate exercise, and this is quantified by the model. This in turn limits the activity that the patient can undertake, and this might be measured directly by the six minute walk test, so one might expect a correlation with computed cardiac work, or a normalised measure (such as to body surface area). These are acute measures of the capacity of the heart do work, or at least of the capacity to translate this to external work. However all patients spend most of the time in a low activity state, and the propensity to degeneration towards heart failure might be more associated with cardiac work in the rest state than under exertion, although we do not know the balance between acute high load events and long-term mild overload in triggering the progression.

In the post-intervention state we might expect that ventricular work, and/or peak power, reduces for any specific level of external work and that the patient might be able to do more post-intervention than they could do pre-intervention. Whether this will be reflected in measured activity as they go about their lives is yet to be determined, but EurValve is seeking a correlation between computed and measured changes. One of the most important clinical questions is whether the patient will experience positive remodelling and improved cardiac performance as a result of the reduced work. Again, it is unknown whether the rest or the stressed state is most likely to be associated with this phenomenon, but it is not unlikely that the rest state might be dominant. It is interesting to examine whether there is an association directly between pre-intervention measures and outcome. In the EurValve study the focus is on short-term response, measured by increased activity, by increased performance in the six minute walk test or by reduction in ventricular mass based on image data over a short period of months after the intervention. One of the clinical centres has ethical approval and funding to continue the study on its cohort to a twelve month time point, and this will provide interesting follow-up data. EurValve does not have the capacity or the numbers to follow the patients to the harder clinical end points of morbidity and mortality, but this will be an important part of a clinical trial of the DSS.

A major drive over coming months is to publish the associations that EurValve has been able to determine. This work is ongoing, but some positive associations that have already been identified are outlined below. An obvious complication in the seeking of associations is that relationships are not necessarily linear, but the data is sparse to support the establishment of nonlinear associations. As an example, it is not unlikely that if the valve disease does not raise the work or power requirement too much, and there has not been major ventricular remodelling, there might be little immediate benefit from an intervention. If the valve disease does cause significant change then it would be predicted that there would be strong benefit and potential to remodel, but there will come a time when the ventricle is so damaged that, although there might be immediate and acute benefits in relief of symptoms, it is no longer able to see the benefit of a longer-term remodelling process. Under these circumstances there will not be a linear relationship between disease severity, modelled benefit and ultimate prognosis.

The EurValve study was designed to make use of data that could be readily available in clinical practice. In clinical practice there are many technical, operative and patient factors which are largely unpredictable (including procedural complications), and processing of the data for target clinical publication is still under way. Nevertheless a number of interesting and important trends been identified, including the correlation illustrated in Figure 13. Equally interesting from a clinical perspective is the apparent lack of correlation between some parameters which might have been expected to be related.

It is difficult for clinicians to assess the severity of disease based on patient reported symptoms and capacity to exercise. The randomised clinical experiment has confirmed how useful clinicians would find objective data to guide decision making and assessing outcome. In deliverable 1.2 section 1.2.4.6 figure 6 we see how the EurValve Smart Home in a Box can show a trajectory. The project employed a number of ways of assessing patient activity, and one might expect that there is a correlation between them. In the pre and post intervention period there does not appear to be a strong correlation in the aortic stenotic patients.

In the post-operative period, three measures of activity, or activity potential, were compared (six minute walk, watch data, and 'Smart Home in a box' technology from the University of Bristol). The latter was performed in the Sheffield cohort only, for logistical reasons. The six minute walk test is a clinically validated measure and has prognostic significance in valvular heart disease. This test was therefore used as the comparator. Figure 14 illustrates the correlation between the distance walked in the six minute walk test and the measured step count and time spent outside the house (measured using the Bristol device) in the Sheffield aortic valve cohort. It also shows an apparent lack of correlation of the six minute walk test with clinical classification of disease including NYHA class and WHO QoL score. This suggests that these devices may have a role in monitoring patients following their intervention. Not surprisingly a correlation was also noted between step count pre-and post-intervention, indicating that a patient who was more active pre-intervention was also likely to be more active post-intervention.

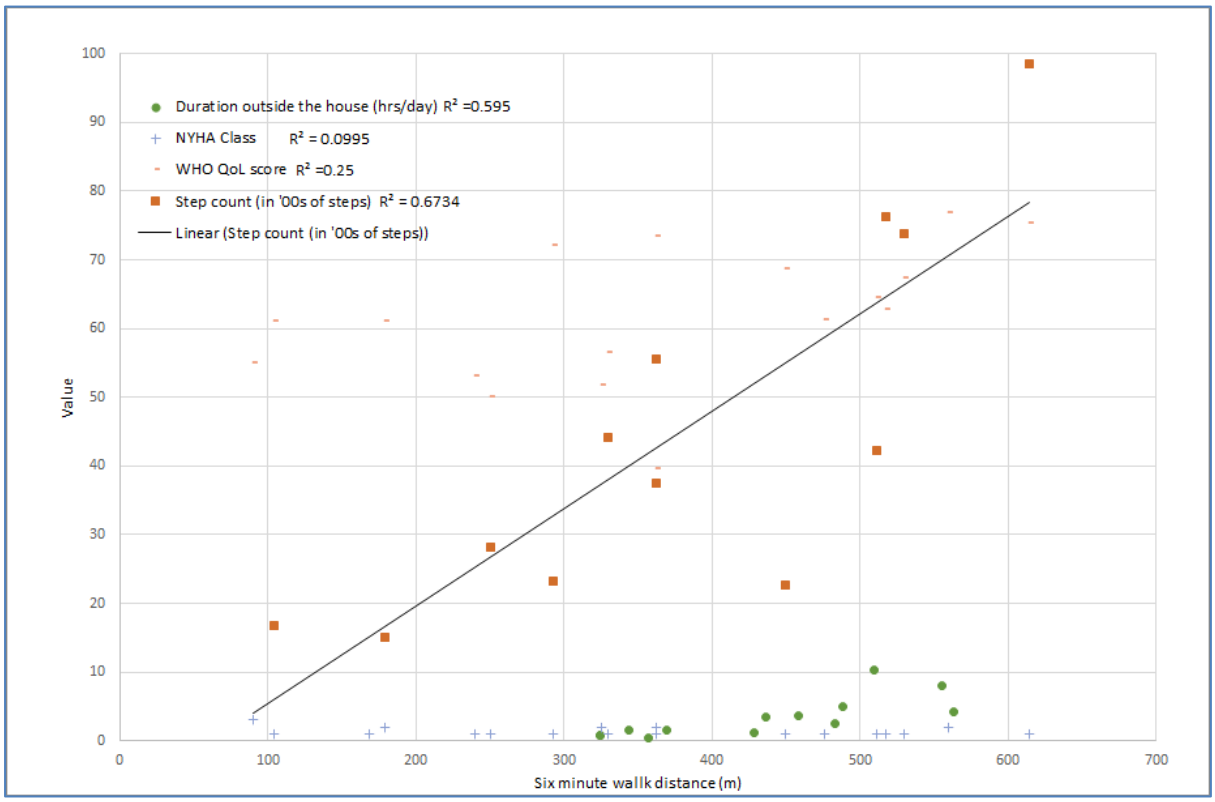


Figure 14: Correlation between measures of disease and exercise capacity
As determined by the six minute walk test

Sleep is an important part of health. EurValve developed a number of ways of assessing sleep quality, efficiency, frequency and duration. Data produced correlated with subjective reports and both the Philips Health watch and the Smart Home in a box produced similar outputs, increasing the confidence in the devices' accuracy. The Pearson correlation coefficient between these measures was statistically significant at an R^2 value of 0.854.

The seeking of correlations between the primary model outputs of left ventricular work and power is still under way, and will continue to the point of publication in target clinical journals. Figure 15 illustrates a promising result in terms of correlation between the predicted change in left ventricular work and the measured increase in step count, as measured by the Philips watch. Unfortunately the numbers are small because the inclusion of the watch data was an opportunistic development in EurValve, not anticipated in the original DoW. This means that pre-intervention watch data is available on only a subset of the recruited cohort because their interventions took place before the device was on stream. Nevertheless, as indicated many times in the EurValve reporting, this is one of the most exciting and clinically-relevant innovations of EurValve and has sparked very strong clinical interest.

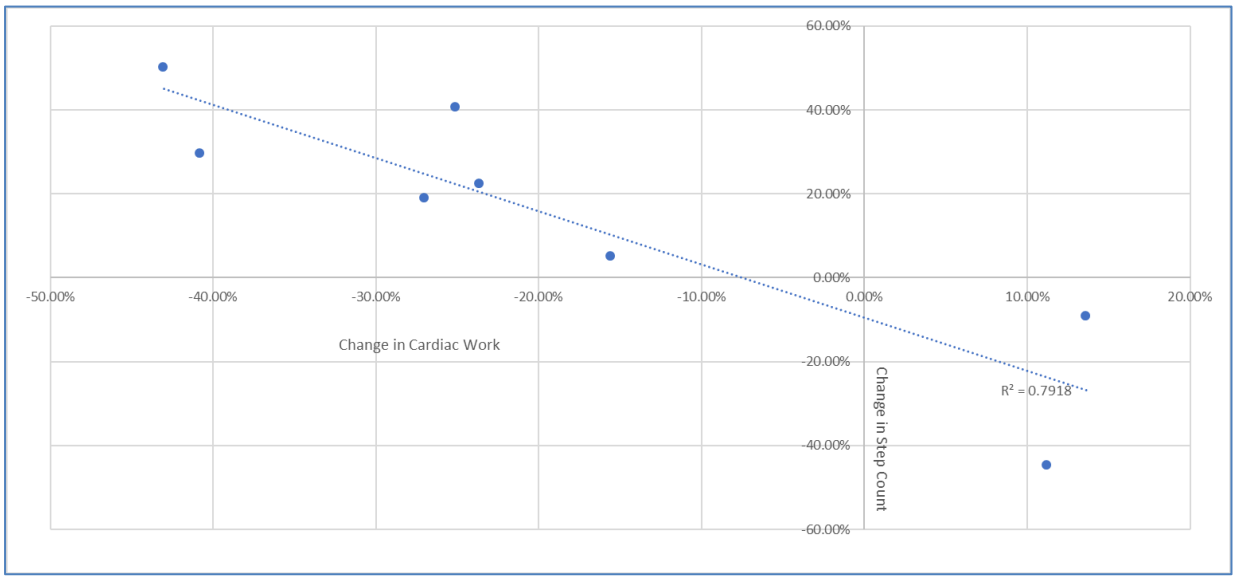


Figure 15: Correlation between computed change in cardiac work Using the valve-image based protocol, and change in step count for a small subset (eight patients) of the aortic valve cohort

9 BIOPSIES

Endo-myocardial biopsies have been obtained at DHZB in Berlin only, in order to allow an analysis of proteomic data by MDC and the parameterisation of a 0d cell model that can be further developed into a detailed biophysical cell model. The details have been reported in D3.2 *Software components Beta Release*. Comprehensive results are reported in D3.4.

Aortic Valve Disease

- 29 left ventricular samples have been analysed.

Mitral Valve Disease the analysis position is as follows:

- 17 left ventricular biopsies have been analysed
- 26 atrial samples have been analysed.

10 MOBILE HEALTH TRACKERS

The clinical sites have significant interest in the additional clinical opportunities to make use of data from mobile health tracker data (Bristol device, and the Philips Health Watch). Specifically, in the process of evaluating a particular treatment strategy, the devices may allow the detection of more subtle changes, which could be of interest in further clinical trial designs. It remains unclear, but worthy of further investigation, the extent to which the acquisition of such data can be of use in a predictive context of benefit to decision support in the future. ***This has been comprehensively reported in D4.6.***

11 GENDER ASPECTS OF CARDIOVASCULAR DISEASE

As gender aspects of cardiovascular disease have been described for several decades, we further investigated how these aspects integrate in individualised patient-specific profiles. Despite a slight recruitment bias towards male patients (58%, in line with prevalence), the size of the cohort can allow useful comparison of gender-specific aspects of valvular heart disease.

DEFINITIONS

List of Key Words and Abbreviations

BMI	Body Mass Index
BSA	Body Surface Area
CABG	Coronary artery bypass grafting
CCS	Canadian Cardiovascular Society grading of Angina
COPD	Chronic obstructive pulmonary disease
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine Standard
dPmax	Max Pressure Drop
dPmean	Mean Pressure Drop
DSS	Decision Support System
eCRF	Electronic Case Report Forms
ED	End diastole
EF	Ejection fraction
ES	End systole
FS	Fractional shortening
ICD	International classification of disease
JSON	Javascript object notation
LV	Left ventricle
LVEDD	Left ventricle end diastolic diameter
LVOT	Left ventricular outflow tract
LVPWD	Left ventricle posterior wall diameter
MR(I)	Magnetic Resonance (Imaging)
NYHA	New York Heart Association Heart Failure Classification
RV	Right ventricle
s/p	Status Post
STL	Stereolithography
STS	Society of Thoracic Surgeons Risk Score
TAVI	Transcatheter aortic valve implantation
WP	Working plan

APPENDIX A: EURVALVE DATA SUMMARY

For completeness we here summarise the acquisition and use of data within EurValve, and the Deliverables in which resulting analyses are reported.

T#	Task Name	Lead	Data	Reporting
WP2	**Data Collection and Sharing Infrastructure**	**CYFRONET**	**Patient-level test data for development**	**D2.x**
2.1	Data warehouse; data collection and publication suite	STHFT	Clinical test data for ArQ	D2.3, D1.3
2.2	Model execution environment	CYFRONET	Clinical and modelling test data	D2.4, D1.3
2.3	Integrated security and data encryption	CYFRONET	Clinical and modelling test data	D2.5, D1.3
2.4	Real-time Multiscale Visualisation	CYFRONET	Results data, imaging and numerical	D2.5, D1.3
2.5	Platform quality assurance	CYFRONET	Clinical test and live data	D2.3, D1.3
WP3	**Software Components**	**PHILIPS**	**Patient-level and population data**	**D3.x**
3.1	Machine learning tools	PEN	Population data; WP6 output data	D3.2, D3.4
3.2	Image segmentation tools	PHILIPS	Patient-level multimodality imaging data	D3.2, D3.4
3.3	Systems models	USFD	EHR, processed images, proteomics	D3.2, D3.4
3.4	Variation and sensitivity analysis tools	TUE	Entire results set, EurValve cohort	D3.2, D3.4
3.5	Proteomics data analysis tools	MDC	Proteomics libraries	D3.2, D3.4
3.6	Reduced-order modelling tools	ANSYS	Parameterised geometries	D3.2, D3.3, D3.4
WP4	**Digital Patient Definition; Data Collection**	**DHZB**	**All clinical data, EurValve cohort**	**D4.x**
4.1	Digital patient definition	DHZB	Example clinical data	D4.1
4.2	Study design; inclusion criteria	DHZB	Example clinical data	D4.2
4.3	Literature data	PEN	(Comprehensive literature review)	D4.3
4.4	Environmental data	UBRIS	EurValve cohort: activity data	D4.5, D4.6, D1.3
4.5	Identification, recruitment, data for clinical cohort	DHZB	EurValve cohort: all clinical data	D4.4, D4.7, D1.3

T#	Task Name	Lead	Data	Reporting
WP5	Decision Support System	THERENVA	Full EurValve clinical data access	D5.x
5.1	CDSS specification	THERENVA	(Data schema)	D5.1
5.2	Integration of CDSS with computational infrastructure	CYFRONET	Example clinical data	D5.2
5.3	CDSS beta version	THERENVA	Live EurValve clinical datasets	D5.2
5.4	Case-based reasoning	LTSI	CBR clinical data libraries	D5.3
5.5	CDSS final version	THERENVA	Access and operation across all data	D5.4, D1.3
WP6	Operation on Study Cohort; Evaluation of CDSS	DHZB	Active operation across EurValve cohort	D6.x
6.1	Operation on study cohort	USFD	Entire EurValve cohort data	D6.1
6.2	Rule set derivation, study cohort	PHILIPS	Entire EurValve cohort data	D6.2
6.3	Evaluation of CDSS on study cohort	DHZB	Entire EurValve cohort data	D6.3
6.4	Evaluation of CDSS against clinical guidelines	DHZB	Entire EurValve cohort data	D6.4
6.5	Evaluation of combined infrastructure/DSS platform	CYFRONET	Entire EurValve cohort data	D6.4

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