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: WP6
Operation on Study Cohort and Evaluation of DSS

Deliverable: D6.2
Model-based Learning Report

Version: 1v3

Date: 30-Jun-18

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	Carmen LAPLAZA SANTOS (CNECT/H/01)		

Work package	**Number**	6	**Title**	Operation on Study Cohort and Evaluation of DSS
Deliverable	**Number**	6.2	**Title**	Model-based Learning Report

Date of delivery	**Contractual**	31-May-18	**Actual**	30-Jun-18
Status	Version 1v3		Final ☑	
Nature	Prototype ☐ Report ☑ Dissemination ☐ Other ☐			
Dissemination Level	Public (PU) ☑ Restricted to other Programme Participants (PP) ☐ Consortium (CO) ☐ Restricted to specified group (RE) ☐			

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Abstract (for dissemination)	This report provides an update of activities in EurValve relating to acquisition of patient data and presents recent work on machine learning in EurValve. New machine learning algorithms were developed and tested for several target, sensitive input parameters of the computational, mechanistic model used in EurValve.
Keywords	Heart Valve Disease, Reduced Order Model, Heart valves, interventions, clinical decisions, data

Version Log			
Issue Date	**Version**	**Author**	**Change**
28-Mar-18	1v0	PMO	Initial template
22-Jun-18	1v1	HtH	Draft including all parts except summary, conclusions
30-Jun-18	1v2	HtH	Update with summary, conclusions
30-Jun-18	1v3	PMO	Final version

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EXECUTIVE SUMMARY

This report provides an update of activities in EurValve relating to acquisition of patient data and presents recent work on machine learning in EurValve. Improving on our earlier versions of machine learning algorithms, we present the use of clinically validated results from the clinical literature – results that describe influence of patient characteristics and patient comorbidities on key physiological parameters - in construction of multiple, increasingly realistic, simulated patient data sets. Using these data sets for training and independent testing, new machine learning algorithms were developed for four target, sensitive input parameters of the computational, mechanistic model used in EurValve: maximum and minimum left-ventricular elastance, distal systemic resistance, and systemic compliance.

1 INTRODUCTION

In the EurValve project the purpose of the machine-learning module is to infer data on a specific patient that is not available, but is required to execute the computational physiological models being used for making predictions. More specifically, the 0D model used for modelling patient haemodynamics [2] uses as inputs, for example, left ventricular elastance and distal systemic resistance, to compute as outputs clinically relevant parameters such as pressure gradient over the aortic valve or left ventricular work. The target for the machine-learning module is not to be able to determine *all* the input parameters of the 0D model, but rather only the subset identified on the basis of a sensitivity analysis [2].

In this report we present recent work on the machine-learning module and also summarise the status of our actions relating to the acquisition of data for machine learning. See [2] for earlier work on the machine learning module.

2 ACQUISITION OF DATA FOR MACHINE LEARNING

In a later expanded version of EurValve deliverable D3.2, see Section 10 of [2], a plan was described for the acquisition of data for machine learning in EurValve, and a mitigation strategy was described for the situation that no adequate estimation could be obtained of patient-specific input values using machine learning based on data. In this section we provide an update of the part of that section that dealt with data acquisition. More specifically, we consider

- Retrospective data available from the clinical centres within EurValve
- Retrospective data from external clinical centres
- Model-based augmentation of retrospective data
- Prospective data collected within EurValve
- Simulated data based on reported clinical studies.

2.1 Retrospective data from EurValve clinical centres

The following table presents an overview of sources of retrospective patient data for machine learning. An earlier version of this table, together with a more extensive description of these data sets, was presented in [2]. Three data sets are listed, one from each of the clinical centres within EurValve.

Table 1: Sources of retrospective data for machine learning

Source	Period	Number of patients		Availability
		Aortic stenosis	Mitral regurgitation	
Sheffield: STH	2001-2016	3783 surgical patients	1453 surgical patients	Available since Oct-17 Blood pressure data added Nov-17
Eindhoven: Catharina hospital	2015-2018	± 600 TAVI patients	0	2015-16: 280 patients since Oct-17 2017: 200 patients available 2018/1-6: available early 2019
Berlin: DHZB	2011-2016	0	526 minimally invasive surgery patients	Available since Dec-17

Each of the databases listed in this table includes data on patient characteristics, comorbidities, previous interventions, “current” intervention, information derived from ultrasound images, and information on outcomes. As is typical, data on patient characteristics and comorbidities, important for machine learning, is well available based on EMR information. Sufficient information derived from medical images is also essential for the derivation of a machine learning algorithm. However, information derived from medical images is typically present on a relatively sparse level. For the databases from Sheffield and Eindhoven actions were undertaken, in part manually supported by medically trained people, to augment the data derived from medical images – this has not yet been done for the part of the data from 2017.

Data on physiological and laboratory measurements, in particular blood pressure data, are also of considerable importance in connection with machine learning. Blood pressure data are

present only in a very limited extent in the databases from Sheffield and Eindhoven and not available in the database from Berlin. The background of this restricted availability is that blood pressure data is typically collected in paper records and to convert these data to digital form requires manual actions by medically trained people. For the data from Sheffield and Eindhoven such actions have been planned for a period beginning in PM31, subject to the anticipated availability of suitable clinical personnel.

2.2 Retrospective data from external sources

While actions are ongoing to arrive at sufficient retrospective data for machine learning from within EurValve, we have also made efforts to acquire data from clinical centres external to EurValve. As was mentioned in [2], our earlier activities in this direction indicated that it is difficult to obtain comprehensive external data sets on a broad range of data items. We have continued to explore possibilities to obtain a more restricted data set from elsewhere, focusing on specific data items suitable for development of a machine learning algorithm. As will be discussed in the next subsection, such a restricted data set could be useful in connection with a tuning procedure that we have been developing for addition of model inputs to retrospective data.

Based on our work in EurValve we have identified the items that form the minimum dataset needed for development of machine learning algorithms for determination of personalised values of model inputs. We use these items in our interactions with potential external data sources. The data items are listed below:

1. Diagnosis: aortic stenosis or mitral regurgitation
2. Patient characteristics: in particular age, gender, height, weight
3. Information on comorbidities: in particular heart failure, CAD, MI, diabetes, hypertension, chronic kidney disease, COPD, etc.
4. Blood pressure data: diastolic, systolic and mean blood pressure
5. Information derived from medical images: Left-ventricular end diastolic and end systolic volume and diameter, pressure drop across the aortic valve, peak pressure in left ventricle, effective area of aortic valve lumen
6. Information on interventions and outcomes: e.g. complications yes/no, in case of death time to death

Obtaining data from external databases is a time-consuming and often unsuccessful task, but a significant effort is underway to request such data from as many national sources as can be identified. Advantage of this exercise is also being taken in an attempt to obtain additional patient data to populate the Case-Based Reasoning library of patient cases being constructed in WP5.

A summary of the identified data sources is tabulated below. High patient numbers exist in several of the listed sources, including Australia (55k), Canada (500k), Europe (100k+), Poland (500k), USA (6,000k).

Table 2: Identified Sources of Clinical Output Data - European

Nation	Data Name, Topic	Contacts	Comment	EurValve
Europe Centralised				
Europe	Cardiology Audit Registration Data Standards CARDS	http://www.comet-initiative.org/contactus http://www.comet-initiative.org/studies/details/829	Collaborative work by the European Union Department of Health and Children, the European Society of Cardiology, the Irish Cardiac Society, and the European Commission. The goal of this project was to create standardized data variables and definitions for clinical cardiology in an effort to harmonize data collected for local, national, and international registries and audit	Medium
Europe	Expanded Global Registry of Acute Coronary Events GRACE 2	Fred Anderson, University of Massachusetts Keith AA Fox UK: k.a.a.fox@ed.ac.uk	International research collaboration that collected data for patients hospitalized with ACS	Low
Europe	European Registry for ICD and CRT Devices in Paediatrics and Adults with Congenital Heart Disease EURIPEDES	info@kompetenznetz-ahf.de http://www.euripides-registry.eu/	Association for European Paediatric and Congenital Cardiology/ European Society of Cardiology/Competence Network Congenital Heart Defects Congenital	Low
Europe	European Registry for Patients with Mechanical Circulatory Support European Association of Cardio-Thoracic Surgery EUROMACS	Tel.: +44 1753 832166 Email: info@eacts.co.uk EUROMACS Managing Director Tel.: +31653162322 Email: theo.deby@eacts.co.uk Coordinator: Stephanie Halksworth, Tel.: +44 1753838487, Email: Stephanie.halksworth@eacts.co.uk http:// www.euromacs.org	All age patients with durable and temporary mechanical support devices	Low
Europe	International Registry of Mitral Interventions (iRoMi)	National-support@e-dendrite.com +4414191411288 p.punjabi@imperial.ac.uk http://rs2.e-dendrite.com/csp/evrg/FrontPages/index.html	An International registry of surgical and nonsurgical interventions on the Mitral Valve. The aim of the registry is to track activity, assess success rates and analyse outcome of different management strategies for the treatment of primary and secondary mitral valve abnormality.	Medium
EACTS	**European Association for Cardio-Thoracic Surgery EACTS House Madeira Walk Windsor SL4 1EU United Kingdom**	**quip@eacts.co.uk** **Participants**: Austria, Belgium, Croatia, Cyprus, Czech R'pblc, Denmark, France, Italy, Latvia, Lithuania, Luxembourg, Greece, Portugal, Spain, Sweden	**The European Association for Cardio-Thoracic Surgery was founded in 1986 as a European organisation devoted to the practice of cardio-thoracic surgery. Membership has now spread all over the world – 29 countries with 4000 active members including surgeons, perfusionists and allied health professionals. membership is now spread all over the world in all continents representing some 70 countries . The largest contributors were the UK (32.0%), Germany (20.9%) and Belgium (7.3%).**	**Key Source**
Europe by Country (Non-EACTS)				
Bulgaria	The Bulgarian National Cardiac Surgery Registry	National-support@e-dendrite.com +4414191411288		Low
Estonia	Estonian Society of Cardiology		The Estonian Society of Cardiology is a member of the European Society of Cardiology	Low
Finland	Finnish Cardiac Society		The Finnish Cardiac Society is a member of the European Society of Cardiology	Low
Germany	German Society for Thoracic and Cardiovascular Surgery, CTSNet	sesats@abts.org https://www.ctsnet.org/about	Also contributes to: EACTS	High
Germany	German Aortic Valve Registry GARY	Dr. Andreas Beckmann, Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie [DGTHG], Langenbeck-Virchow-Haus Luisenstr. 58-59, Berlin 10117, Germany (e-mail: gf@dgthg.de)	Collects complete data on aortic valve interventions for aortic stenosis across Germany. Patients undergoing invasive treatment for acquired aortic valve stenosis in participating centres were consecutively enrolled	High
Hungary	Hungarian Society of Cardiology		The Hungarian Society of Cardiology is a member of the European Society of Cardiology	Low
Ireland	Irish Transcatheter Aortic Valve Implantation (TAVI) Registry	http://rs2.e-dendrite.com/csp/eiretavi/intellect/login.csp		Medium
Malta	Maltese Cardiac Society		Maltese Cardiac Society is a member of the European Society of Cardiology	Low
Netherlands	The Netherlands Association for Cardio-Thoracic Surgery (Nederlandse Vereniging voor Thoraxchirurgie, NVT)	Dutch Association for Thoracic Surgery, Mercatorlaan 1200, 3528 BL Utrecht , The Netherlands Phone: 31- (0) 30-282 31 75, E-mail: secretariaat@nvtnet.nl http://www.nvtnet.nl/	Also Contributes to: EACTS Completeness of data is excellent and national coverage of all 16 Dutch cardio-thoracic surgery centres has been achieved since the start. The primary goal of the database is to control and maintain the quality of care by evaluation of outcomes. This provides information on survival status, causes of death and readmissions. The dataset comprises demographic factors, type of intervention, in-hospital mortality and 18 risk factors for mortality after cardiac surgery	Low
Poland	European Congenital Heart Surgeons Association Congenital database Now European Association for Cardio-Thoracic Surgery ECHSA Congenital database	Prof. Tjark Ebels, Paediatric and Congenital CardioThoracic Surgeon, ECHSA Treasurer & Chair Database Committee. University Medical Centre Groningen, Netherlands. treasurer@echsa.org t.ebels@umcg.nl telephone: +31 50 361 2750 https://echsacongenitaldb.org/	Also contributes to: EACTS Collects the data from 189 hospitals from 50 countries, while 371 hospitals from 77 countries already registered in the Database and have access to the results of over 235 000 cardiac procedures.	Medium
Romania	Romanian Soc Cardiology		A member of the European Society of Cardiology	Low
Slovakia	Slovak Soc of Cardiology		A member of the European Society of Cardiology	Low
Slovenia	Slovenian Soc Cardiology		A member of the European Society of Cardiology	Low
United Kingdom	**National Institute for Cardiovascular Outcomes Research NICOR**	**T: 020 3765 8542 e: nicor-generalenquiries@bartshealth.nhs.uk http://www.ucl.ac.uk/nicor**	**Collects clinical information from UK hospitals into secure registries established by the cardiovascular specialist societies**	**Key Source Complex process**
United Kingdom	Society of Cardiothoracic Surgery in Great Britain and Ireland SCTS	The Royal College of Surgeons 35-43 Lincoln's Inn Fields London WC2A 3PE	Data from all public hospitals that perform adult cardiac surgery in the UK with some input from private hospitals in Ireland. In addition, the dataset provides long-term mortality data via linkage with the UK Office of National Statistics (ONS)	(Now in EACTS?)

Table 3: Identified Sources of Clinical Output Data - Non-European

Nation	Data Name, Topic	Contacts	Comment	EurValve
Australia and NZ	Australia and New Zealand Congenital Heart Research Centre Fontan Registry	Australia: info@fontanregistry.com NZ: jbarry@adhb.govt.nz http://www.fontan registry.com	All patients in Australia and New Zealand who have undergone a Fontan-type single ventricle Repair Congenital	Low
Australia and NZ	Australian and New Zealand Society of Cardiac and Thoracic Surgeons	info@anzscts.org https://anzscts.org/		Medium
Australia and NZ	Cardiac Society of Australia and New Zealand	AUSTRALIA: info@csanz.edu.au NZ: kayla.kurta@racp.org.nz		Medium
Canada	Congenital Evaluation, Reporting, and Tracking Endeavour Adult Congenital Heart Association/ McGill University, University of Sherbrooke, University of Montreal CONGENERATE	**Dr Ariane Marelli,** Director, McGill Unit for Adult Congenital Heart Disease (Maude Unit), Ariane.Marelli@McGill.ca Silven Rehel, System Coordinator at Collaborative Research For Effective Diagnostics (CRED), Tel.: 1-819-346-1110 #73211, E-mail: Silven.Rehel@Usherbrooke.ca http:// www.congenerate.org	Adult patients with Congenital Heart Disease/Defects	Low
Canada	British Columbia Cardiac Registries BCCR	Website feedback & questions, phsacomm@phsa.ca	Full clinical registry, including diagnostic catheterizations, percutaneous coronary interventions, pacemakers and implantable cardioverter-defibrillator implants. Recently, it has started collection of data on percutaneous heart valves	Medium
Canada	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease APPROACH	http://www.approach.org/contact_pages/contact.html	Collects and evaluates both short-term and long-term patient outcomes, such as mortality, revascularization, and quality of life.	Medium
Canada	Cardiovascular Health Nova Scotia CVHNS	cvhns@nshealth.ca, Tel: 902-473-7834, Fax: 902-425-1752 http://www.cdha.nshealth.ca/cardiovascular-health-nova-scotia	The patient populations of interest were those with acute ischemic syndrome, congestive heart failure or atrial fibrillation.	Low
Canada	National Cardiovascular Data Registries - American College of Cardiology Acute Coronary Syndrome Registry NCDR ACTION	cvquality@acc.org https://cvquality.acc.org/NCDR-Home	The ACS and Cath/PCI databases organized by the National Cardiovascular Data Registries (NCDR)	Medium
Canada	Canadian Outcomes Registry Late After Tetralogy of Fallot Repair CORRELATE	Malini Handa, HUB Program Lead 4168646060 ext 3925]hubresearch@smh.ca http://www.hubresearch. ca/project-profiles/ correlate/	All patients in Canada who have undergone surgical repair of Tetralogy of Fallot, age >12 years	Low
China	Adult Cardiac Surgery Registry			Medium
Japan	Japanese Society for Cardiovascular Surgery	Yuichi Ueda, M.D., Ph.D, President, The Japanese Society for Cardiovascular Surgery 2-26-9 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan Tel: +08-3-5842-2301		Medium
Japan	Japanese Registry for Patients with Mechanical Circulatory Support	Takeshi Nakatani, MD, PhD, Director, Maki Hospital, 7-10-28, Shinmori, Asahi-Ku, Osaka 535-0022, Japan. Telephone: +81-6-6953-0120. Fax: +81-6-6953-7006	All age patients with durable and temporary mechanical support devices	Low
Thailand	Society of Thoracic Surgeons of Thailand	http://thaists.org/contactus.php http://thaists.org/index.php	The registry is participated by 19 government and 2 private hospitals with the valid data of adult cardiac surgery	Medium
USA	Pediatric Cardiac Critical Care Consortium PC4	University of Michigan North Campus Research Complex (NCRC), Building 520, 1600 Huron Parkway, Ann Arbor, MI 48105 (734) 232-3811	Paediatric	Low
USA	Congenital Cardiac Anesthesia Society Database CCAS	209 Dickens Rd, Richmond, VA 23230-2005 Email:ccas@societyhg.com 8042829780 http://www.ccasociety.org/	Congenital	Low
USA	**Society of Thoracic Surgeons, Adult Cardiac Surgery Database STS (ACS)**	**Shelby Kutty, MD, PhD | Cardiology | University of Nebraska Medical Center | Tel: 402.955.4320 | skutty@unmc.edu https://www.sts.org/registries-research-center/sts-national-database/adult-cardiac-surgery-database**	**Database contains more than 6.2 million cardiac surgery procedure records and currently has more than 3,100 participating physicians, including surgeons and anaesthesiologists. The STS Congenital Heart Surgery Database (CHSD) is the largest database in North America dealing with congenital cardiac malformations. The CHSD contains more than 435,000 congenital heart surgery procedure records**	**Key Source Complex Access**
USA	NCDR Cath PCI - National Cardiovascular Data Registries Catheterization and Percutaneous Coronary Intervention NCDR Cath PCI	Email at NCDR@acc.org. By Phone at (800) 257-4737 **Mailing Address** American College of Cardiology NCDR 2400 N Street NW Washington DC 20037-1153 https://www.ncdr.com/webncdr/home/aboutthencdr		Low
USA	Improving Pediatric and Adult Congenital Treatments National Cardiovascular Data Registry/ American College of Cardiology/ Mid-America Heart Institute IMPACT	2400 N St NW Washington DC (800) 2574737 cvquality@acc.org http://cvquality.acc.org/ en/NCDR-Home/ Registries/Hospital-Registries.aspx	Paediatric Congenital	Low
USA	Interagency Registry for Mechanically Assisted Circulatory Support International Society for Heart and Lung Transplantation/ University of Alabama INTERMACS/PediMACS	intermacs@uabmc.edu https://www.uab.edu/ medicine/intermacs/	Patients with durable and temporary mechanical support devices. The STS Intermacs Database became part of the STS National Database™ on January 1, 2018. It represents the next generation of Intermacs, a joint effort among the National Heart, Lung, and Blood Institute, the Food and Drug Administration, the Centers for Medicare & Medicaid Services, and others	Low

2.3 Model-based augmentation of retrospective data

As discussed earlier, no retrospective patient data set on Valvular Heart Disease can be expected to include sensitive 0D model inputs such as total (stressed) blood volume and maximum left ventricular elastance, as these parameters are not measured in clinical practice. To add such model inputs to the retrospective data, and thereby to enable the use of such augmented retrospective data for supervised machine learning, a tuning procedure has been developed as an optimisation algorithm using the 0D model for deriving selected model inputs to match selected model outputs. This work was done as part of Task 3.3 – we cite the following table from [2] which shows the inputs and outputs of the specific tuning procedure that has already been developed for derivation of model inputs. This tuning procedure focuses on several model inputs for which the 0D model was consistently seen to be sensitive according to the analysis in Task 3.4, including maximum left-ventricular elastance and stressed blood volume.

The main bottleneck for our use of this tuning procedure for augmentation of retrospective data is availability of sufficient blood pressure data. As was mentioned, there is an action to convert blood pressure data that is part of the retrospective data from EurValve clinical centres, which are available in paper records, to electronic form. We plan to use this tuning procedure to obtain sufficient data for machine learning once retrospective data is available that includes sufficiently rich blood pressure data.

Model outputs required	Model inputs obtained
Diastolic and mean blood pressure	Maximum left-ventricular elastance
End-diastolic left-ventricular volume	Systemic compliance
End-systolic left-ventricular volume	Distal systemic resistance
At least one of the following parameters describing valve resistance: - Pressure drop across the valve - Peak pressure in the LV - Effective area of the valve lumen	Total (stressed) blood volume
	Aortic valve coefficient

Table 4: Tuning procedure implemented to derive model inputs from selected model outputs

2.4 Model-based augmentation of prospective data collected in EurValve

In line with the original plans, in three clinical studies conducted in EurValve (in Berlin, Sheffield and Eindhoven), prospective data is being collected on in total 120 patients, of which 60 have aortic stenosis and 60 mitral regurgitation. Although these clinical studies are not yet finished, many patients have already been processed. As described in a recent EurValve deliverable on model-based data augmentation [3] the 0D model has been used in an iterative way to augment data for the patients that were already processed with data on model inputs, in particular sensitive model inputs such as maximum left-ventricular elastance and distal systemic resistance. For part of these data, including the data for around 20 patients pre intervention, the image data collected has undergone segmentation, and model-based augmentation has been applied to the combined patient data. It is clear that such augmented data, when available in sufficient quantities, would be useful to form training data and test data

for development of learning algorithms. We are investigating whether these data would also be useful in connection with machine learning even in small quantities.

2.5 Simulated data based on reported clinical studies

In addition to retrospective data or prospective data, it has been recognised from the start of EurValve that literature data could also be useful in connection with our machine learning purposes. With 'literature data' we refer here to published results of clinical studies investigating relationships between inputs of 0D models such as left-ventricular elastance, and patient characteristics and comorbidities such as heart failure that appear frequently among Valvular Heart Disease patients. Such literature has already proved useful as sources for simulated data in our work reported in [1] and, as mentioned in the update to that deliverable [2], we have been investigating more refined possibilities in this direction. In the remainder of this report the main focus is on this approach.[1]

[1] Whilst the project has not yet collected sufficient patient data for machine learning, in addition to our work using simulated data based on clinical studies, we have undertaken one additional approach to data acquisition. As discussed previously, although unplanned at the beginning of EurValve, we have provided the clinical centres with Philips Health Watches, which are used to augment the clinical data collected in the clinical studies with home-based data, both pre and post intervention.

The health watch provides time series data: once per minute, heart rate, respiration rate (at rest) and activity data are collected. See the recent deliverable [D4.6] [I. Craddock, R. Piechocki, R. Santos-Rodriguez, R. McConville, J. Pope, H. ter Horst, M. Kelm, J. Zelis, G. Archer, EurValve D4.6: Activity Monitoring Data Analysis, EurValve deliverable May 2018], where we described extensive work done in EurValve at Philips Research, Eindhoven to develop data retrieval apps and also to develop an automatically generated report that presents watch data to clinicians; this latter work includes an approach to analysis which strongly emphasises the bridging of the gap between the standard outputs of the health watch (a consumer device) and information of a type and level of detail that is of specific interest to clinicians.

In addition to supporting the focused interest of the EurValve clinical centres in these watch data, we are seeking to investigate whether the time series data collected by the health watch could be useful in the computations where the 0D model is used to augment patient data with data on model inputs, in particular in relation to the extension from the rest state to the exercise state.

3 OUTLINE OF RECENT WORK ON THE MACHINE LEARNING MODULE

As was reported in [2], the first version of the machine learning module we developed was based on simulated data. In that work simulated data was generated based on published research that relates sensitive model inputs such as maximum left-ventricular elastance and distal systemic resistance on the one hand and available patient data such as age, gender, BMI and comorbidities on the other hand. That earlier work was based on a relatively quick literature search. The published results that were used included results from clinical studies but also included results from simulation studies. In the remainder of this report we present results of learning from simulated data using data simulations based on a much more extensive literature search than was done for the work reported in [2]. It has become clear that, compared to our earlier activity, we can use much more refined simulated data as a basis for machine learning. In particular, we no longer use results from simulation studies.

Here is a summary of main points in which the new version of the machine learning module is improved compared to the preceding version. These points will be further discussed in the following sections:

- An extensive literature search was done to summarise results from published clinical studies relating sensitive model inputs such as maximum left-ventricular elastance to patient characteristics and comorbidities. These clinically validated results were used as basis for data simulation, we no longer use results from simulation studies.
- Given results found from many published clinical studies, an effort was made to make a selection of results describing baselines and coefficients describing influence of patient characteristics and comorbidities on model inputs, in a way that fits coherently together and that fits well with our patient population.
- New inputs were added to the original inputs of the learning algorithm deriving model inputs. These new inputs help to make the computations of the machine learning module more personalized: BSA, hypertension, chronic kidney disease; for the comorbidity CAD there are now two versions, CAD with normal LVEF and CAD with abnormal LVEF
- Whereas the simulations underlying the earlier version of the machine learning module were based on distribution of age of the general population, the new version of the machine learning module uses data based on improved distributions of age, better corresponding to our patient population
- The simulations of data based on clinical data now incorporate simulation of noise of measurements of the aortic pressure gradient, of arterial pressure, and of end-diastolic and end-systolic left-ventricular volumes.

As in the earlier version, the current version of the machine learning module derives values for the following four inputs of the 0D model being used, the Westkessel model [2]:

- Maximum elastance of the left ventricle,
- Minimum elastance of the left ventricle,
- Distal systemic resistance
- Systemic compliance.

These model inputs were prioritised using sensitivity analysis [2] focusing on cardiac output as model output. In earlier versions of the machine learning module we also derived values for two additional model inputs, valve coefficient and total blood volume, but as there turned out

to be relatively little clinical literature relating these two parameters to patient characteristics these parameters were left out in the work reported here.

To derive these four model input parameters, the machine-learning module makes use of three classes of inputs: patient characteristics, patient diagnoses (comorbidities), and clinical measurements. As mentioned, compared to our earlier work we added one patient characteristic, namely BSA, and two comorbidities: hypertension, chronic kidney disease. Here is the complete, up-to-date list of inputs to the machine learning module:

- Patient characteristics: age, gender, BMI, BSA
- Patient diagnoses (comorbidities): aortic stenosis, MI, heart failure, CAD with normal LVDF, CAD with abnormal LVEF, hypertension, chronic kidney disease
- Clinical measurements: diastolic, systolic and mean arterial pressure together with the following parameters derived from image data: cardiac output, left-ventricular ejection fraction, left-ventricular end systolic volume, and mean and maximum pressure gradient over the aortic valve.

Model parameters were derived based on patient data using simulations exploiting linear relationships of the following form:

$$\text{parameter}_i = \text{baseline}_i + \sum_j \left[a_{i,j} \cdot (\text{personal info})_j\right] + \sum_k \left[b_{i,k} \cdot \text{comorbidity}_k\right] . \quad (1)$$

Here parameter_i denotes the target model input parameters, personal info_j denotes age, gender and BMI, and comorbidity_k denotes the comorbidities already mentioned. The baselines and coefficients used in the simulations are based on clinical literature, as discussed further in the next section. We have defined multiple sets of baselines and coefficients based on clinical literature in order to enable multiple, increasingly realistic simulations as basis for machine learning.

In our earlier work on machine learning [2], for each of the target model input parameters we developed two machine-learning algorithms, which differ in the number of data fields used as input for machine learning. The more restricted version used only data of the type used in generating artificial data. That is, the more restricted version of the machine learning algorithms use only age, gender, BMI and information on comorbidities as input for deriving the target model parameters. The more extended version of the machine learning algorithms use, in addition, also data fields for model outputs / clinical measurements as already mentioned, consisting of blood pressure data and data derived from images such as cardiac output.

As reported in [2], the second version of these machine learning algorithms, which use not only age, gender, BMI and comorbidities but also clinical measurements as input, had much better performance. This provides an interesting connection between machine learning using data and the use of a computational, mechanistic physiological model. As will become clear in this report, we are able to confirm this discovery in the work on machine learning reported here, using simulated data constructed using increasingly realistic simulations as basis. To be able to keep track of influence of different aspects of the setup on performance of machine learning

algorithms obtained, we used increasingly realistic versions of simulated data based on clinical literature to derive multiple machine learning algorithms for each of the target model inputs:

1. A version based on an age distribution of the general population (as in the earlier algorithms presented in [2]) and on the new clinically based baselines and coefficients for simulation, including the same comorbidities as in that earlier work.
2. Same as 1 but based on an age distribution corresponding to our population of VHD patients
3. Same as 2 but with baselines and coefficients indexed to BSA (body surface area).
4. Same as 3 but with additional comorbidities: CAD (abnormal LVEF), hypertension, chronic kidney disease stage 3

For each of these four types of machine learning algorithm we developed a second version based on addition of noise in clinical measurements in the simulations underlying the data for learning.

In the following section, Section 4, we will discuss results of our literature search and present the baselines and coefficients used in these models. Then, in Section 5, we will go into more detail how these models were used to simulate data. In Section 6 we will present the methods used for machine learning and on the results obtained.

4 BASELINES AND COEFFICIENTS FROM PUBLISHED CLINICAL STUDIES

Recall that the machine learning module derives values for four especially sensitive inputs of the 0D model being used in EurValve:

- Maximum left ventricular elastance at end-systole (elvmax)
- Minimum left ventricular elastance at end-diastole (elvmin)
- Distal systemic resistance (sysresdis)
- Systemic compliance (syscom)

In our earlier work [2], simulated patient data was explored as an alternative to the use of retrospective patient data for machine learning. Data for the target model input parameters were generated in accordance with a linear model with the following independent input parameters:

- Age
- Gender
- Body Mass Index (BMI)
- Ischemic heart disease / heart failure (HF)
- Myocardial infarction (MI)
- Coronary artery disease (CAD)
- Aortic stenosis (AS)

In our earlier work, the literature search to determine baselines and coefficients for these linear models was done relatively quickly, and we included results from simulation studies. In order to arrive at refined, more realistic simulated data for machine learning, in the work reported here we performed an extensive literature search including only published clinical studies and no simulation studies. For this purpose, the literature databases Scopus and Medline were searched for appropriate articles using search terms comprising of combinations of one of the six model input parameters and one of the independent input parameters. Also, search terms such as haemodynamics and cardiovascular function were used. Initially, any publication with clinical data on the parameter coefficients were deemed usable, with no restriction on publication date, study size or study population. As will be explained, in a later stage a selection was made from the publications found for actual use in the simulations.

For the target model inputs elvmax, elvmin, sysresdis and syscom, baseline values and parameter coefficients, for the linear model expressing these model inputs as a function of age, gender, BMI and comorbidities, were found in or derived from the clinical literature. These baseline values and coefficients are displayed in the following two tables. These tables contain a column for each of the four target model inputs and rows for the patient characteristics and comorbidities for which clinical studies were found that describe influence on the model inputs. It should be noted that we found many more published studies than the set of clinical studies cited in the following table. We narrowed down the papers found by performing a selection process to arrive at a coherent set of baselines and coefficients, based on several criteria: [2]

[2] Earlier versions of our simulated data sets were based on a much larger set of literature. With these earlier simulations we noted that inconsistencies could be found in simulated data sets: In these earlier simulated data sets (consisting of 30.000 records, as will be discussed in the next section) it was observed that the physical characteristics of a few patients resulted in 0D model parameter values that were not physiological, e.g. negative compliance values were obtained due to the random sampling of a particular patient. Such patients/records were discarded from the data, and replacement patients were created. In the next step, when the 0D model was applied to combine the data to obtain model outputs / clinical

- Baselines used should reflect a healthy population
- Coefficients used should be based on clinical studies into populations relevant for our population of VHD patients, and include controls comparable to a healthy population.
- Studies used should be based on a substantial number of patients

In addition to the four target model input parameters that we considered, in our earlier work [2] we included two additional target model inputs, total blood volume and aortic valve coefficient. Determination of total blood volume, defined as stressed blood volume, requires invasive interventions [4] or is model-based [5] and as such coefficients derived from clinical literature data for total blood volume for the independent inputs parameters could not be found. Also for aortic valve coefficient we could not find useful clinical literature.

Compared to our earlier work, several independent input parameters were added to the list of original parameters based on new literature findings with data on the input parameters:

- Ethnicity
- Hypertension (HTN)
- Chronic kidney disease (CKD)

When data was found to make the distinction between men and women, overweight and obesity, normal left ventricular ejection fraction (LVEF) and abnormal LVEF, these data were added. There are a few situations where the average of the values was taken in case two articles were found with data on the same parameter. Even though we found data on influence of ethnicity on model inputs, we did not yet include this parameter in our simulations.

Since multiple literature sources provided data on baselines and/or parameter coefficients indexed for body surface values (BSA), it was decided to separately create a list of non-indexed values (Table 5) and a list of BSA-indexed values (Table 6). Compared to the table of non-indexed values, the table of indexed values enables more personalised computations. In order to calculate indexed values from non-indexed values, the BSA as mentioned in the article for this particular study population was used or, in the minority of cases where no BSAs were mentioned, an average BSA (1.75 m^2).

The following tables present only the baselines and coefficients from the literature used in our simulations. See the annex for more detailed tables presenting the original results and data from the clinical studies used as input for the baselines and coefficients used.

The clinical literature we studied includes additional information that we didn't yet use in simulations but that could be used to increase the level of realism of simulations of model inputs. For example, multiple papers we used included not only information on baselines and coefficients but also more detailed information on distribution of parameter values among the study group. Moreover, literature information on population characteristics and comorbidities for our patient group could be used to develop further refinements of simulated patient data.

measurements, it turned out that the resulting combination was again not physiological in relatively few cases. In these earlier data sets these patients were also discarded, and a replacement patient created. It is interesting to note that after we narrowed down the clinical papers used as basis for simulation, in the way indicated, such physiological inconsistencies no longer occurred – with the data sets used in the results described here there was no longer any need to discard simulated patients whose data was not physiological from the data.

Table 5: Non-indexed Baselines and Coefficients

	Left ventricular elastance	Left ventricular elastance	Distal systemic resistance	Systemic compliance
	max (end-dystole)	min (end-diastole)		
	elvmax [mmHg.ml-1]	elvmin [mmHg.ml-1]	sysresdis [mmHg.s.ml-1]	syscom [ml.mmHg-1]
Baseline, men and women				1.710 [6,11]
Baseline, men	1.74 [13]	0.145 [14]	0.934 [13]	
Baseline, women	2.13 [13]	0.115 [14]	1.038 [13]	
Age (>55), men and women		0.00250 [15]		0.00500 [15]
Age (>55), men	0.00850 [13]	- *	0.000327 [13]	
Age (>55), women	0.0165 [13]	-	-0.000858 [13]	
Ethnicity, men (0 white, 1 african american)	-	-	0.085 [8]	-0.17 [8]
Ethnicity, women (0 white, 1 african american)			0.060 [8]	-0.04 [8]
BMI (>25), men and women			-	
BMI overweight (25 - 29.9), men and women				-0.05 [a 6]
BMI obese (>= 30), men and women				-0.27 [a 6]
BMI (>25), men	0 # [14]	-0.006 [14]		
BMI (>25), women	0.005 [14]	-0.005 [14]		
Heart Failure	0.43 [9]	-	0.00258 [11]	-0.45 [11]
Myocardial infarction	-	-	-	-
CAD, normal LVEF	-0.14 [7]	-	-	-0.01 [7]
CAD, abnormal LVEF	-0.54 [7]	-	-	0.19 [7]
Aortic stenosis, severe			-0.016 [13]	-0.681 [12]
Hypertension	0.31 [9]	-	0.0515 [11]	-0.41 [11]
CKD stage 3	0.54 [10]	0.05 [10]	-	-

: according to literature no significant difference with baseline
* : no literature found
a : coefficient for BMI (overweight/obese) is viewed as Boolean

Table 6: Indexed Baselines and Coefficients

	Left ventricular elastance	Left ventricular elastance	Distal systemic resistance	Systemic compliance
	max (end-dystole)	min (end-diastole)		
	elvmax [mmHg.ml-1]	elvmin [mmHg.ml-1]	sysresdis [mmHg.s.ml-1]	syscom [ml.mmHg-1]
Baseline, men and women				0.964 [6,11]
Baseline, men	3.463 [13]	0.276 [14]	1.859 [13]	
Baseline, women	3.600 [13]	0.219 [14]	1.754 [13]	
Age (>55), men and women		0.00438 [15]		0.00286 [15]
Age (>55), men	0.0169 [13]	- *	0.000650 [13]	
Age (>55), women	0.0279 [13]	-	-0.00145 [13]	
Ethnicity, men (0 white, 1 african american)	-	-	0.160 [8]	-0.0734 [8]
Ethnicity, women (0 white, 1 african american)			0.195 [8]	-0.0530 [8]
BMI (>25), men and women			-	
BMI overweight (25 - 29.9), men and women				-0.124 [a 6]
BMI obese (>= 30), men and women				-0.291 [a 6]
BMI (>25), men	0 # [14]	-0.0114 [14]		
BMI (>25), women	0.00950 [14]	-0.00950 [14]		
Heart Failure	0.735 [9]	-	0.123 [11]	-0.290 [11]
Myocardial infarction	-	-	-	-
CAD, normal LVEF	-0.245 [7]	-	-	-0.00571 [7]
CAD, abnormal LVEF	-0.945 [7]	-	-	0.109 [7]
Aortic stenosis, severe			-0.0326 [12]	-0.334 [12]
Hypertension	0.543 [9]	-	0.209 [11]	-0.266 [11]
CKD stage 3	0.994 [10]	0.0920 [10]	-	-

: according to literature no significant difference with baseline
* : no literature found
a : coefficient for BMI (overweight/obese) is viewed as Boolean

5 SIMULATION OF PATIENT DATA

Using the clinical data from the literature discussed in the preceding section, we created different virtual populations to realize the multiple versions of machine learning algorithms that were mentioned in Section 3 for the patient-specific tuning of the EurValve 0D model. Each of these populations consisted of 30.000 patients with a 50:50 male to female ratio. Additional general characteristics used for these populations are summarized in the following table.

Table 7: Population characteristics used in simulation

Population	Gender	Age [years]		Height [cm]		BMI [kg/m^2]		Number of possible comorbidities
		Mean	SD	Mean	SD	Mean	SD	
1	Male	56	5	184	7.1	27	4	4
	Female			171	6.3			
2 & 3	Male	71	5	184	7.1	27	4	4
	Female			171	6.3			
4	Male	71	5	184	7.1	27	4	7
	Female			171	6.3			

For each patient in each population the age, gender, height and BMI was randomly sampled from a multi-variate normal distribution with means and SDs as presented in the table. In all of these populations, it was assumed that these variables (age, gender, etc.) were not correlated, i.e. they are independent from each other. A Latin-Hypercube approach was utilised to sample these variables in an attempt to avoid sample clustering.

For each population of 30.000 patients, 10.000 were arbitrarily defined to have no comorbidities, another 10.000 a single comorbidity, and the final 10.000 two comorbidities. In populations 1, 2 and 3, the comorbidities were selected from the following (here the associated ICD9 codes are given in parentheses): myocardial infarction (MI, I21.4), coronary artery disease (CAD) with normal left ventricular ejection fraction (LVEF) (I25.10), heart failure (I11.0) and aortic stenosis (I35.0). For population 4, this was extended with the additional 3 comorbidities: CAD with abnormal LVEF (labelled not with an ICD9 code but as CADa), hypertension (I10) and chronic kidney disease stage 3 (N18.3). Comorbidity combinations where a patient had both CAD related comorbidities were not permitted.

With these populations, key input parameters of the EurValve 0D model - distal systemic resistance, maximum and minimum left ventricular elastances, and systemic compliance - were selected for each patient as a function of their physical characteristics, e.g. age, gender, and BMI.

Using the two tables of coefficients presented in the preceding section (Tables 5 and 6), two different approaches to parameter selection were used - with and without body surface area (BSA) indexing. Populations 1 and 2 utilised parameter selection without BSA indexing, whereas populations 3 and 4 utilised parameter selection with BSA indexing. (Populations 2 and 3 had the same general patient characteristics, as indicated in Table 7, the difference between populations 2 and 3 is that only population 3 uses BSA indexing.) In the creation of populations 3 and 4 BSA was determined (in m^2) from a patient's height (H, in m) and weight (W, in kg) using the commonly used, standard Du Bois - Du Bois formula:

$$\mathrm{BSA} = 0.007184 * W^{0.425} * H^{0.725} \quad (2)$$

For the resulting populations the EurValve 0D model outputs (e.g. pressure, volume, flow, etc.) were collected by running the 0D model for each patient. Furthermore, for each population, these outputs were also corrupted with noise to mimic the noise in clinical measurements. We describe the corruption of the clinical outputs of the EurValve 0D model in more detail in the following paragraphs.

The non-invasive measurement of the aortic pressure gradient is typically obtained using an ultrasound Doppler measurement; however, such measurements are subject to variability when compared to catheter-based measurements. Thus, a bias was added to the aortic pressure gradient output from the EurValve 0D model. This bias was represented as normally distributed, for both maximum and mean ΔP, based upon the mean and variance reported by Baumgartner *et al*. [16]. Here the reported pressure corrected values are utilised.

Non-invasive measurements of mean, systolic and diastolic arterial pressure are typically obtained using a cuff based blood pressure measurement (i.e. sphygmomanometer). Following the standards reported by O'Brien et al., [17], such devices have a margin of error < 5 mmHg for > 60% of all measurements, < 10 mmHg for > 85% of all measurements and < 15 mmHg for > 95% of all measurements. This specification is approximated as a normal distribution with a mean of 0 mmHg and a variance of 7.5 mmHg.

The measurements of end-diastolic and end-systolic left ventricular volumes can be obtained via computed tomography (CT). The resulting ventricular volume are calculated from segmenting the blood volume within the left ventricle. However, such calculations are often subject to an individual's interpretation of anatomical structures; thus, noise was added following the variability in inter-observer measurements as reported by Nicol *et al* [18] Here, only the variance of end-diastolic and end-systolic measurements were used.

Note that as these ventricular volumes are used in clinical practice to calculate derived indices, in particular two of the outputs of the 0D model being used in this work - cardiac output and left-ventricular ejection fraction - the noise in these measurements will also affect such indices. Therefore, these derived indices, cardiac output and LVEF, were recomputed for the simulated data sets that include noise.

6 MACHINE LEARNING

6.1 Method and algorithms

We use the following abbreviations for the four model input parameters used as target parameters for machine learning:

- elvmax, elvmin: maximum and minimum left-ventricular elastance
- sysresdis: distal systemic resistance
- syscom: systemic compliance

For these four target model input parameters, separate machine learning algorithms were developed, and for each of these machine learning algorithms, multiple versions were developed based on increasingly realistic simulated data sets, which were already discussed in the preceding sections. Common to all of these data sets is that data for the four target model input parameters were generated in accordance with a linear model with independent parameters forming a subset or all of the following parameters, among which 7 comorbidities, denoted using common abbreviations and also ICD9 codes:

- Age
- Gender
- BMI
- I11.0: HF, Heart failure/ischemic heart disease
- I21.4: MI, myocardial infarction
- I25.10: CAD, normal LVEF
- I35.0: AS, Aortic stenosis
- I10: HTN, Hypertension
- N18.3: CKD, Chronic kidney disease stage 3
- CADa: CAD, abnormal LVEF

In addition to age, gender and BMI as patient characteristics, we also used BSA (body surface are) as an additional patient characteristic; as was already mentioned some data populations were generated using BSA-indexed clinical data.

After generating values for the target model input parameters, the model was run to also provide model output parameters, which correspond to clinical measurements. These model outputs / clinical measurements, the values of which as indicated were transformed to simulate measurement noise, consisted of data already mentioned: diastolic, systolic and mean arterial pressure together with the following parameters derived from image data: cardiac output, left-ventricular ejection fraction, left-ventricular end systolic volume, and mean and maximum pressure gradient over the aortic valve. To summarise, the generated data set consisted of values for age, gender, BMI, comorbidities as mentioned, target model input parameters as mentioned, and model output parameters (clinical measurements) as mentioned.

To obtain machine-learning algorithms for determining the four target model input parameters, as in our earlier work [2] we randomly selected 20% of the generated data set of 30.000 records as independent test set. As in our earlier work we selected random forests [19] as technique for deriving learning algorithms. Random forests are known to be able to give in many cases a good indication of learning accuracies that can be obtained from a given dataset, are relatively

flexible with respect to feature selection, and have advantages in dealing with missing input data.

6.2 Results

We divided the available data consisting of 30.000 records as mentioned into two independent parts, a training set of 24.000 records and a test set of 6.000 records. We used the machine learning algorithms derived using the training set by testing it on the independent test set. For each of the four populations of simulated data constructed as explained in the preceding sections, the following four tables present results of the use of three versions of the machine learning algorithms:

- The version that uses restricted input data (only age, gender, BMI and comorbidities),
- The version that uses in addition also input data on clinical measurements,
- The version that uses input data on clinical measurements perturbed by noise in the simulations.

In the tables, results for these versions are labelled "Without clinical data," "With clinical data", and "With noisy clinical data," respectively. As the target parameters for machine learning are numerical, we used root mean square error (RMSE) as error measure. To "normalise" error values we also include standard deviations of the test sets and include fractions RMSE/SD in the table.

Table 8 Accuracy of ML algorithm on independent test set: Population 1
Age distribution of general population, 4 comorbidities

Model parameter	Mean of test set	SD of test set	Without clinical data		With clinical data		With noisy clinical data	
			RMSE	RMSE/SD	RMSE	RMSE/SD	RMSE	RMSE/SD
elvmax	1.8370	0.2236	0.00045	0.0020	0.0025	0.0109	0.0172	0.0769
elvmin	0.1347	0.0195	0.0044	0.223	0.0011	0.0586	0.0010	0.0522
sysresdis	0.9311	0.00832	0.0016	0.1877	0.00029	0.035	0.00072	0.087
syscom	1.3358	0.340	0.075	0.188	0.0056	0.014	0.0011	0.0028

Table 9 Accuracy of ML algorithm on independent test set: Population 2
Age distribution of VHD patients, 4 comorbidities

Model parameter	Mean of test set	SD of test set	Without clinical data		With clinical data		With noisy clinical data	
			RMSE	RMSE/SD	RMSE	RMSE/SD	RMSE	RMSE/SD
elvmax	1.9494	0.2254	0.0206	0.092	0.00071	0.0031	0.0376	0.167
elvmin	0.1684	0.0216	0.0024	0.112	0.0017	0.079	0.0032	0.146
sysresdis	0.9354	0.0085	0.0043	0.512	0.0101	0.0157	0.0010	0.118
syscom	1.4045	0.4030	0.0896	0.222	0.0012	0.00294	0.0028	0.007

Table 10 Accuracy of ML algorithm on independent test set: Population 3
Age distribution of VHD patients, 4 comorbidities, BSA indexing

Model parameter	Mean of test set	SD of test set	Without clinical data		With clinical data		With noisy clinical data	
			RMSE	RMSE/SD	RMSE	RMSE/SD	RMSE	RMSE/SD
elvmax	1.9264	0.280	0.0707	0.252	0.01732	0.0618	0.0238	0.0849
elvmin	0.1577	0.0313	0.00528	0.170	0.00187	0.0587	0.00347	0.111
sysresdis	0.9441	0.105	0.0175	0.169	0.00384	0.0356	0.00888	0.0844
syscom	1.4480	0.465	0.1062	0.229	0.00053	0.00115	0.0615	0.133

Table 11 Accuracy of ML algorithm on independent test set: Population 4
Age distribution of VHD patients, 7 comorbidities, BSA indexing

Model parameter	Mean of test set	SD of test set	Without clinical data		With clinical data		With noisy clinical data	
			RMSE	RMSE/SD	RMSE	RMSE/SD	RMSE	RMSE/SD
elvmax	1.9547	0.3785	0.0226	0.0597	0.00460	0.0121	0.0211	0.0558
elvmin	0.1653	0.0363	0.00234	0.0644	0.0031	0.0840	0.00766	0.211
sysresdis	0.9556	0.1110	0.00499	0.0449	0.00955	0.0860	0.000701	0.0063
syscom	1.5554	0.4266	0.0646	0.1513	0.0280	0.0660	0.0809	0.190

The following observations can be made based on these tables:

- When, in addition to patient characteristics and comorbidities, also clinical data is used as input for machine learning, normalised performance (RMSE/SD) typically increases, also when the clinical data is noisy.
- Values of RMSE/SD based on noisy clinical data as part of the input to machine learning are less than 0.15 in all cases considered except two cases, where the values of RMSE/SD are 0.21 and 0.19.

It is interesting to note as in our earlier work [2] but now based on much more refined simulated data that, compared to the use for machine learning only with respect to data that that played a role in data generation (i.e., patient characteristics and comorbidities), the addition of information provided by clinical measurements, as can be derived with the 0D model, leads to improved results for machine learning. Even though these tables support this conclusion not as uniform and clear cut as in the earlier work [2] because we now added noise to the clinical measurements, this seems to be an interesting interaction between learning from data and use of implied data derived using a computational, mechanistic, physiological model.

The following four figures indicate how the machine learning algorithms found use their input variables. For the most refined situation we considered, provided by population 4, where 7 comorbidities as well as BSA indexing and noisy clinical measurements were included in the simulations, these figures show for each target model parameters for learning – elvmax, elvmin, sysresdis, and syscom - how the input variables used for learning are ordered with respect to how often they are used in the random forest. This is quantified with a standard measure called "variable importance". To explain this quantity, note that a random forest consists of trees consisting of nodes at which decisions are made based on values of the input variables to the random forest. The greater the value of variable importance of an input variable for a random forest, the more often that variable is used in this way for decision-making in the nodes in the trees in the random forest.

To facilitate interpretation of the following figures we did not indicate comorbidities by their ICD9 codes but but by commonly used abbreviations: HF (heart failure), HTN (hypertension), MI (myocardial infarction), AS (aortic stenosis), CKD (chronic kidney disease stage 3), CAD (coronary artery disease, where we assume normal LVEF). One uncommon abbreviation is used: CADal (coronary artery disease with abnormal LVEF). Other abbreviations used in the figures: rr_sys, rr_dia, rr_mean (systolic, diastolic, mean arterial blood pressure), ct_seg_co (cardiac output), echo_dpmean, echo_dpmax (mean and maximum pressure drop over the aortic valve), ct_seg_lvef (LVEF), ct_seg_lvves, ct_seg_lvved (left-ventricular volumes, end systolic and end diastolic).

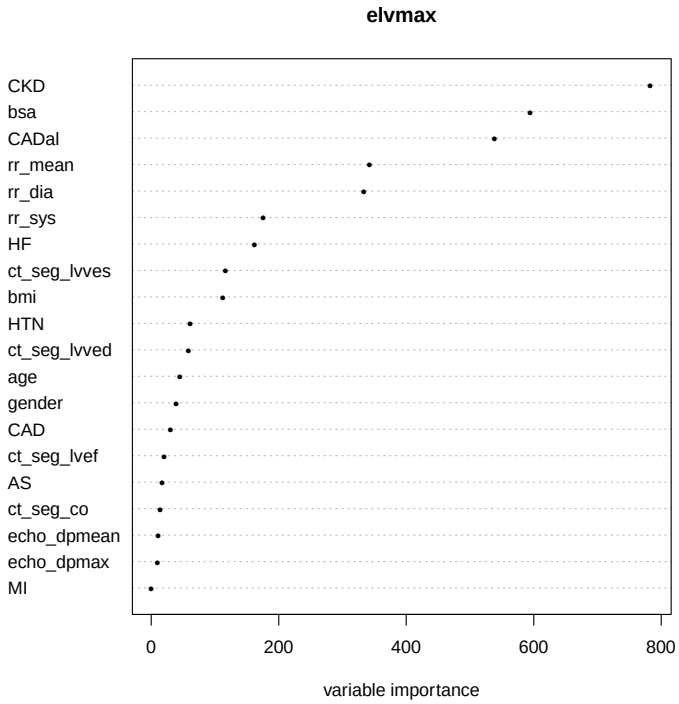

Figure 1: Variable importance for maximum LV elastance

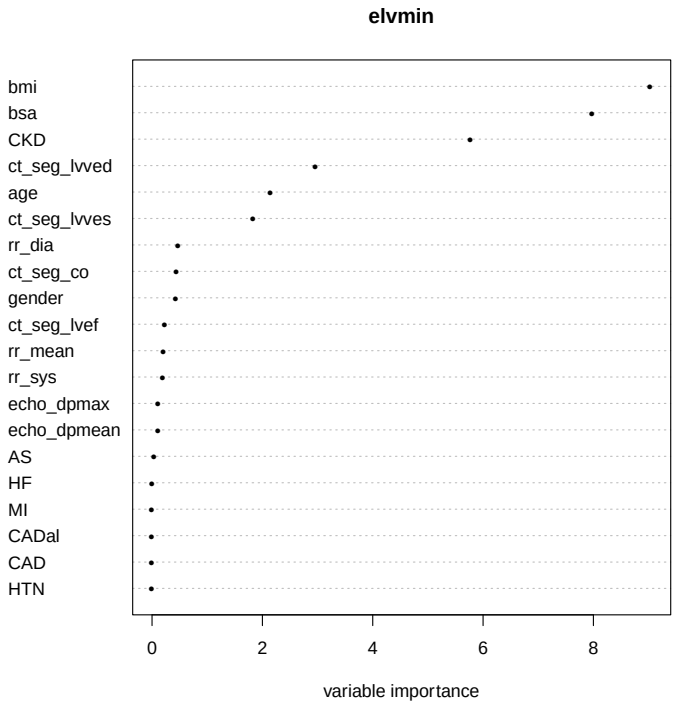

Figure 2: Variable importance for minimum LV elastance

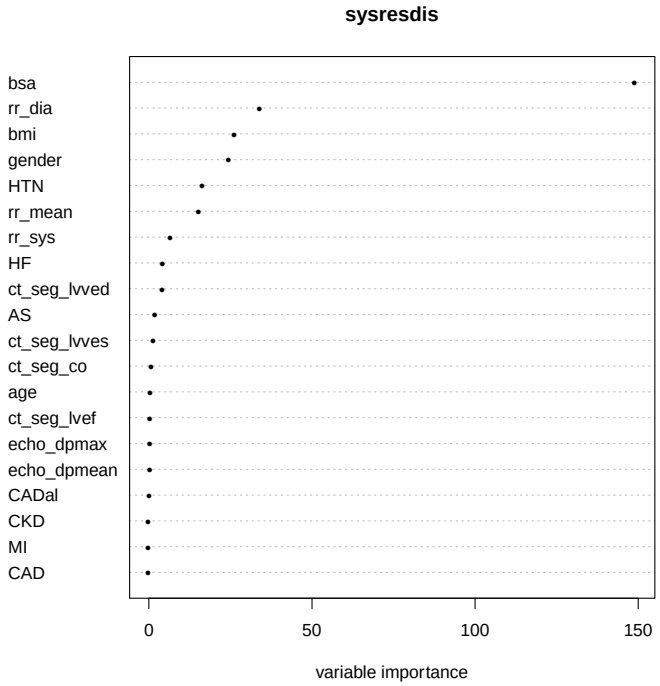

Figure 3: Variable importance for distal systemic resistance

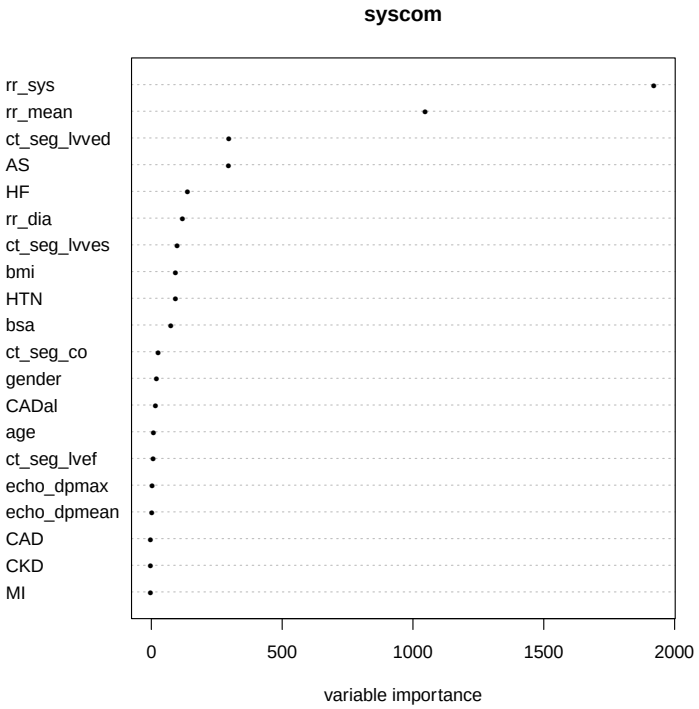

Figure 4: Variable importance for systemic compliance

7 CONCLUDING REMARKS

This report presented an update of activities in EurValve relating to acquisition of patient data and presented recent work on machine learning in EurValve. Improving on our earlier work in EurValve by more deeply exploring the use of clinically validated results from the clinical literature – results that describe influence of patient characteristics and patient comorbidities on key physiological parameters – we constructed multiple, increasingly realistic, simulated patient data sets. Using these data sets for training and independent testing, new machine learning algorithms were developed for four target, sensitive input parameters of the computational, mechanistic model used in EurValve: maximum and minimum left-ventricular elastance, distal systemic resistance, and systemic compliance.

Given that useful patient data for learning – including sufficient blood pressure data and also sufficient data derived from medical images such as end-systolic and end-diastolic left ventricular volumes, left-ventricular ejection fraction, cardiac output, and mean and maximum pressure gradient over the aortic calve – is difficult to obtain in clinical reality, it seems interesting to explore the limits of the use of published, clinically validated results in connection with learning algorithms that can contribute to enable the use of computational, mechanistic models for personalized clinical decision support.

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DEFINITIONS

List of Key Words/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
ML	Machine learning
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

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ANNEX 1

Table 12 Clinical results used on maximum left-ventricular elastance

Lit Ref	Ind'nt param	Source of relationship	Group size	Influence of independent parameter	Result described	Subdiv study cohort #	Baseline [indexed baseline]	Coefficient [indexed coefficient]	Mean BSA, BMI, and age of study cohort
13	Age	population-based study, 45y and older, 96% white	623	Table 3: Effect of age and gender on vascular and ventricular structure and function in those without cardiovascular disease	LV end-systolic elastance (ees) vs gender: age 55y and 75y men 1.74 and 1.91 (mmHg/mL); women 2.13 and 2.46 (mmHg/mL)	M F	1.74 [3.463] 2.13 [3.600]	0.00850 [0.0169] 0.0165 [0.0279]	BSA (M 1.99, W 1.69); BMI (M 26.4, W 24.6); Age (M 56.7, W 57.9)
14	BMI	population-based study, 45y and older	1402	Table 2: Association between obesity measures and changes over time in elastance and ventricular-arterial coupling ratio	end-systole elastance (Ees; mmHg/ml) vs BMI: men beta coeff= -0.002 [p=0.46] and women beta coeff=0.005 [p=0.05]	M F		not significant 0.005 [0.00950]	BSA 1.90; BMI 27.9; age 60
9	HF	population-based study, HF with normal EF and no valvular disease cohort compared to controls * and HTN patients	1580	Table 2: Load, contractility, and ventricular-arterial coupling for all three groups	HF vs HTN vs control patients: ventricular end-systole elastance (mmHg/ml) of 2.42 vs 2.30 vs 1.99	MF	1.99 [3.483]	0.43 [0.753]	BMI 25.4; age 57
7	CAD	clinical study, patients with CAD and abnormal LVEF compared to normal LVEF	50	Table 3: Comparison of resting cardiovascular mechanisms. 38 patients with prior MI	end-systolic left ventricular elastance (Ees), abnormal and normal LVEF (mmHg.ml-1): 1.2 and 1.6 (p<0.01)	N-LVEF AN-LVEF		-0.14 [-0.245] -0.54 [-0.945]	BMI 27; age 57
9	HTN	population-based study, HF with normal EF and no valvular disease cohort compared to controls * and HTN patients	1580	Table 2: Load, contractility, and ventricular-arterial coupling for all three groups	HF vs HTN vs control patients: ventricular end-systole elastance (mmHg/ml) of 2.42 vs 2.30 vs 1.99	MF	1.99 [3.483]	0.31 [0.543]	BMI (C 25.4 HTN 29.8 HF 32.2; Age (C 57, HTN 66, HF 76)
10	CKD	clinical study, patients with stage 2 or 3 CKD compared with controls	157	Table 4. Echocardiographic measures of vascular and ventricular structure and function and haemodynamics in controls and patients with CKD	left ventricular end-systolic elastance (Ees; mmHg/ml) in controls, CKD stage 2 and stage 3: 1.88, 2.43 [p<0.05], and 2.42 [p<0.01]	CKD2 CKD3	1.88 [3.459]	0.55 [1.012] 0.54 [0.994]	BSA (C 1.84, CKD2 1.8, CKD3 1.93; BMI 27; Age (C 50, CKD2 56, CKD3 54)

$: age, gender, and BMI values are expressed as coefficients; HF, CAD, AS, HTN, and CKD values are expressed as booleans

: M: values for men; F: values for women; MF: values for men and women together; N-LVEF: values for patients with normal left ventricular ejection fraction (>=55%); AN-LVEF: values for patients with abnormal left ventricular ejection fraction (<55%); CKD2: values for patients with chronic kidney disease stage 2; CKD3: values for patients with chronic kidney disease stage 3

* : healthy, non-obese, no cardiovascular disease, no diabetes patients

Table 13 Clinical results used on minimum left-ventricular elastance

Lit Ref	Ind'nt param	Source of relationship	Group size	Influence of independent parameter	Result described	Subdiv study cohort #	Baseline [indexed baseline]	Coefficient [indexed coefficient]	Mean BSA, BMI, and age of study cohort
15	Age	population-based study, 45y and older	1402	Table 1: Patient characteristics at study entry and after 4y	end-diastole elastance (Eed; mmHg/ml) 0 vs 4y later: 0.13 vs 0.14 [p <0.001]	MF	0.13 [0.228]	0.00250 [0.0438]	age 60
14	BMI	population-based study, 45y and older	1402	Figure 1: Ea and Eed over time by sex	end-diastole elastance (Eed; mmHg/ml) vs BMI: men beta coeff=-0.006 [p=0.08] and women beta coeff=-0.005 [p=0.001]	M F	0.145 [0.276] 0.115 [0.219]	-0.006 [-0.0114] -0.005 [-0.00950]	BSA 1.90; BMI 27.9; age 60
10	CKD	clinical study, patients with stage 2 or 3 CKD compared with controls	157	Table 4. Echocardio-graphic measures of vascular and ventricular structure and function and haemodyna-mics in controls and patients with CKD	left ventricular end-diastolic elastance (Eed; mmHg/ml) in controls, CKD stage 2 and stage 3: 0.07, 0.11 [p<0.01], and 0.12 [p<0.01]	CKD2 CKD3	0.07 [0.129]	0.04 [0.0736] 0.05 [0.0920]	BSA (C 1.84 CKD2 1.8 CKD3 1.93); BMI 27; Age (C 50 CKD2 56 CKD3 54)

$: age and BMI values are expressed as coefficients; CKD values are expressed as Booleans
: M: values for men; F: values for women; MF: values for men and women together; CKD2: values for patients with chronic kidney disease stage 2; CKD3: values for patients with chronic kidney disease stage 3

Table 14 Clinical results used on distal systemic resistance

Lit Ref	Ind'nt param	Source of relationship	Group size	Influence of independent parameter	Result described	Subdiv study cohort #	Baseline [indexed baseline]	Coefficient [indexed coefficient]	Mean BSA, BMI, and age of study cohort
13	Age	population-based study, 45y and older, 96% white	623	Table 3: Effect of age and gender on vascular and ventricular structure and function in those without cardiovascular disease	resistance index vs gender: at age 55y and 75y men 2479 and 2497 (dyne.s.cm-5.m2); women 2339 and 2301 (dyne.s.cm-5.m2). Conversion to mmHg.s.ml-1.m2: 1.859 and 1.872; 1.754 and 1.725	M F	0.934 [1.859] 1.038 [1.754]	0.000327 [0.00065] -0.000824 [-0.00145]	BSA (M 1.99, W 1.69); BMI (M 26.4, W 24.6); Age (M 56.7, W 57.9)
8	Ethn'ty	longitudinal cohort survey, young adults of 18-44y with BMI 28-31 kg/m^2	800	Table 2. Mean and selected percentiles of arterial compliances, systemic vascular resistance, and vascular impedance by ethnicity and gender	systemic vascular resistance (dyne.sec.cm-5) for white men and women: 1263 and 1327 and African American men and women: 1376 and 1407. Conversion to mmHg.s.ml-1: 0.947 and 0.995; 1.032 and 1.055	Afr Am M Afr Am F	0.947 [2.008] 0.995 [1.831]	0.085 [0.160] 0.060 [0.195]	BSA[&] (W M 2.12 W F 1.84 Afr Am M 2.10, Afr Am F 1.92); BMI (W M 29.1, W F 28.0, Afr Am M 29.3, Afr Am F 31.0); Age (W M 36.4, W F 36.4 Afr Am M 36.4, Afr Am F 36.4)
11	HF	population-based study, HF with normal EF and no valvular disease cohort compared to controls * and HTN patients	244	Table 2: Measures of cardiovascular structure and function	HF vs HTN vs control patients: systemic vascular resistance index (dyne.s.cm-5.m2) of 2588 vs 2703 vs 2424. Conversion to mmHg.s.ml-1.m2: 1.941 vs 2.027 vs 1.818	MF	0.983 [1.818]	0.00258 [0.123]	BSA (C 1.85 HTN 1.96 HF 1.97); BMI (C 25.4 HTN 29.8 HF 32.2); Age (C 57 HTN 66 HF 76)
12	AS	clinical study, undergoing aortic valve replacement with or without CABG	8	Table 2: Hemodynamics and echocardio-graphic parameters	systemic vascular resistance index (dyn.s.cm-5.m-2) before and after aortic valve replacement 600 vs 550. Conversion to mmHg.s.ml-1.m2: 0.450 vs 0.412	MF		-0.0160 [-0.0326]	BSA 2.04 BMI 28.4 age 79
11	HF	population-based study, HF with normal EF and no valvular disease cohort compared to controls * and HTN patients	244	Table 2: Measures of cardiovascular structure and function	HF vs HTN vs control patients: systemic vascular resistance index (dyne.s.cm-5.m2) of 2588 vs 2703 vs 2424. Conversion to mmHg.s.ml-1.m2: 1.941 vs 2.027 vs 1.818	MF	0.983 [1.818]	0.0515 [0.209]	BSA (C 1.85 HTN 1.96 HF 1.97); BMI (C 25.4 HTN 29.8 HF 32.2); Age (C 57 HTN 66 HF 76

$: age and gender values are expressed as coefficients; ethnicity, HF, AS, and HTN values are expressed as booleans

: M: values for men; F: values for women; MF: values for men and women together; white M: values for white men; white F: values for white women; Afr Am M: values for African American men

& : white M: white men; white F: white women; Afr Am M: African American men; Afr Am F: African American women

* : healthy, non-obese, no cardiovascular disease, no diabetes patients

Table 15 Clinical results used on systemic compliance

Lit Ref	Ind'nt param	Source of relationship	Group size	Influence of independent parameter	Result described	Subdiv study cohort #	Baseline [indexed baseline]	Coefficient [indexed coefficient]	Mean BSA, BMI, and age of study cohort
15	Age	population-based study, 45y and older	1402	Table 1: Patient characteristics at study entry and after 4y	compliance (TAC; mL/mmHg) 0 vs 4y later: 1.63 vs 1.65 [p 0.25]	MF		0.00500 [0.00286]	BMI 27.9 age 60
8	Ethn'ty	longitudinal cohort survey, young adults of 18-44y with BMI 28-31 kg/m^2	800	Table 2. Mean and selected percentiles of arterial compliances, systemic vascular resistance, and vascular impedance by ethnicity and gender	large artery compliance (mL/mmHg) for white men and women: 1.69 and 1.42 and African American men and women: 1.52 and 1.38	Afr Am M Afr Am F	1.69 [0.797] 1.42 [0.772]	-0.17 [-0.0734] -0.04 [-0.0530]	BSA& (W M 2.12 W F 1.84 Afr Am M 2.10, Afr Am F 1.92); BMI (W M 29.1, W F 28.0, Afr Am M 29.3, Afr Am F 31.0; Age (W M 36.4 W F 36.4 Afr Am M 36.4 Afr Am F 36.4)
6	BMI	clinical study, 40y and older recruited from the public	134	Table 3: Adjusted values of hemodynamic measures among normal weight, overweight, and obese individuals	normal vs overweight vs obese 15.6 vs 15.1 vs 12.9 (ml/mmHgx10 index, large arterial)	OW OB	1.56 [0.923]	-0.05 [-0.124] -0.27 [-0.291]	BSA (C 1.69 OW 1.89 OB 2.04); BMI (C 22.8 OW 27.4 OB 34.9); Age (C 61 OW 65 OB 60)
11	HF	population-based study, HF with normal EF and no valvular disease cohort compared to controls * and HTN patients	244	Table 2: Measures of cardiovascular structure and function	HF vs HTN vs control patients: arterial compliance (ml/mmHg) of 1.41 vs 1.45 vs 1.86	MF	1.86 [1.005]	-0.45 [-0.290]	BSA (C 1.85 HTN 1.96 HF 1.97); BMI (C 25.4 HTN 29.8 HF 32.2; Age (C 57 HTN 66 HF 76)
7	CAD	clinical study, patients with CAD and abnormal LVEF compared to normal LVEF	50	Table 3: Comparison of resting cardiovascular mechanisms	total arterial compliance (Ca), abnormal and normal LVEF (ml/mmHg): 1.9 and 1.7 (p=0.50)	N-LVEF AN-LVEF		-0.01 [-0.0057] 0.19 [0.109]	BMI 27; age 57
12	AS	clinical study, undergoing aortic valve replacement with or without CABG	8	Table 2: Hemodynamics and echocardio-graphic parameters	systemic arterial compliance (mL/mmHg-1 .m-2) before and after aortic valve replacement of 0.63 vs 0.70 (p=0.315)	MF		-0.681 [-0.334]	BSA 2.04 BMI 28.4 age 79
11	HTN	population-based study, HF with normal EF and no valvular disease cohort compared to controls * and HTN patients	244	Table 2: Measures of cardiovascular structure and function	HF vs HTN vs control patients: arterial compliance (ml/mmHg) of 1.41 vs 1.45 vs 1.86	MF	1.86 [1.050]	-0.41 [-0.266]	BSA (C 1.85 HTN 1.96 HF 1.97; BMI (C 25.4 HTN 29.8 HF 32.2; Age (C 57 HTN 66 HF 76

$: age and gender values are expressed as coefficients; ethnicity, BMI, HF, CAD, AS, and HTN values are expressed as booleans
: M: values for men; F: values for women; MF: values for men and women together; white M: values for white men; white F: values for white women; Afr Am M: values for African American men; OW: overweight (25-29.9 BMI); OB: obese (30 or more BMI); N-LVEF: values for patients with normal left ventricular ejection fraction (>=55%); AN-LVEF: values for patients with abnormal left ventricular ejection fraction (<55%)
& : white M: white men; white F: white women; Afr Am M: African American men; Afr Am F: African American women
* : healthy, non-obese, no cardiovascular disease, no diabetes patients