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APPLICABILITY ASSESSMENT FOR *IN-SILICO* PATIENT-SPECIFIC TEVAR PROCEDURES

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ABSTRACT

Thoracic Endovascular Aortic Repair (TEVAR) is a minimally invasive technique to treat thoracic aorta pathologies and consists of placing a self-expandable stent-graft into the pathological region to restore the vessel lumen and recreate a more physiological condition. Exhaustive computational models, namely the finite element analysis, can be implemented to reproduce the clinical procedure. In this context, numerical models, if used for clinical applications, must be reliable and the simulation credibility should be proved to predict clinical procedure outcomes or to build *in-silico* clinical trials. This work aims first at applying a previously validated TEVAR methodology to a patient-specific case. Then, defining the TEVAR procedure performed on a patient population as the context of use, the overall applicability of the TEVAR modeling is assessed to demonstrate the reliability of the model itself following a step-by-step method based on the ASME V&V40 protocol. Validation evidence sources are identified for the specific context of use and adopted to demonstrate the applicability of the numerical procedure, thereby answering a question of interest that evaluates the deployed stent-graft configuration in the vessel.

1. INTRODUCTION

In the recent literature (Morrison et al., 2019; Pathmanathan et al., 2017; Viceconti et al., 2021) and regulatory body publications (ASME, 2018, 2006), strong emphasis is given to the role of the credibility and reliability of a computational model. Model credibility can be defined as the capability of a numerical model to address a given question of interest (QOI) or predict a specific context of use (COU), through the collection of evidence (Pathmanathan et al., 2017).

In 2018, the American Society of Mechanical Engineering (ASME, 2018) introduced a verification and validation (V&V) standard for medical device applications to establish the credibility needed to support the use of computational models. Verification and validation are two different aspects both responsible for gaining the accuracy and reliability of the computational results (Oberkampf et al., 2004). Verification is related to the process of determining if the computational simulation is accurate to reproduce the underlying mathematical model. Validation is the process of determining if the mathematical model is accurate in representing the real scenario. A relevant aspect of credibility assessment is the applicability analysis, defined as the use of a computational model in a specific COU supported by validation evidence. A work by Pathmanathan et al., 2017 describes twelve steps for developing the applicability analysis providing a framework for evaluating and justifying the use of an *in-silico* model for a specific COU. In the field of cardiovascular numerical models, few works addressed the applicability analysis following a rigorous framework. Luraghi et al., 2021 applied the credibility process to thrombectomy procedure simulations. Pathmanathan and Gray, 2018 demonstrated the trustworthiness of multiscale models of cardiac electrophysiology. Santiago et al., 2022 assessed the model credibility flow distortion introduced in the left ventricle by the left ventricular assist devices. In Morrison et al., 2019, the credibility assessment framework was applied to haemolysis in centrifugal blood pumps.

The proposed study focuses on the Thoracic Endovascular Aortic Repair (TEVAR) procedure, a minimally invasive technique for treating aortic pathologies in which a self-expandable stent-graft is inserted and deployed in the pathological region to treat the patient and recreate a more physiological

situation (Findeiss and Cody, 2011). The numerical model able to simulate the stent-graft deployment and its interaction with the aortic wall has already been discussed and validated in a previous study of ours (Ramella et al., 2022). This work aims at: (1) presenting and discussing the first patient-specific pilot study based on the validated virtual TEVAR procedure (Ramella et al., 2022); (2) providing an applicability assessment for patient-specific TEVAR procedures following the framework proposed by Pathmanathan et al., 2017.

2. PILOT PATIENT-SPECIFIC *IN-SILICO* TEVAR CASE

2.1. Materials and methods

Clinical patient data. The selected patient was a 63-years-old man, with his first hospital admission due to an asymptomatic Penetrating Aortic Ulceration (PAU) located in his left hemi-aortic arch. The patient had a bovine aortic arch with a common origin of the brachiocephalic trunk and left common carotid artery (LCCA). Diameters of the PAU measured 26 by 32 mm in axial and sagittal sections. TEVAR was performed at the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy. The proximal landing zone was directly distal to the bovine supra-aortic trunk (zone 2) and a 34x34x100 proximal free-flo Valiant Captivia® stent graft (Medtronic, Inc., MN, U.S.A.) was implanted. A 2-month control postoperative CTA (Computed Tomography Angiography) confirmed the thoracic aortic endograft's correct position without complications. Informed consent regarding the specific treatment and data usage was signed by the patient. Approval for this specific study was waived by the local ethical committee.

Numerical models. The 34x34x100 Valiant Captivia (Medtronic, Inc., MN, U.S.A.) stent-graft was modeled following Ramella et al., 2022 (Figure 1.a). The stent was discretized with beam elements (1232 elements with an average size of 1 mm) and the graft with triangular membrane elements (16414 elements with an average size of 1 mm). Nitinol shape memory material formulation for the stent and a fabric material formulation for the graft were adopted. Material parameters can be found in Ramella et al., 2022.

The pre-operative patient-specific aorta lumen was segmented from CTA images using the software VMTK (Orobix s.r.l.) and a constant 1.8 mm of thickness was extruded to create the aorta wall (Choudhury et al., 2009). It was discretized with tetrahedral elements (423891 elements with an average size of 0.75 mm) with three layers of elements through the vessel wall thickness (Figure 1.b). The aorta material was modeled with an isotropic hyperelastic law following the Yeoh constitutive formulation with literature material parameters (Simsek and Kwon, 2015).

The TEVAR simulation follows the steps discussed in our previous work (Ramella et al., 2022). Briefly, the device, which is in a pre-stressed state was crimped and displaced inside the aorta (tracking phase) until the proximal landing zone was reached and then gradually deployed (Figure 1.c). More details on the simulation set-up and vessel geometry post-process can be found in the Supplementary material.

To validate the simulation result, the stent deployed configuration obtained with the simulation was qualitatively and quantitively compared with the stent configuration reconstructed from the post-operative CTA images of the patient, following the framework proposed in Ramella et al., 2022 (Figure 2). The stent was segmented using the software VMTK (Orobix srl.).

2.2. Results

Some of the structural results of the TEVAR simulations are reported in Figure 1.d. The distance between the stent-graft and aorta and Von Mises stress distribution on the aortic wall at the end of deployment are depicted. The struts are mostly in contact with the aortic wall, with the exception of the peaks of the proximal free flow ring due to the vessel anatomy, which presents a low radius of curvature. The anatomy features influence also the von Mises stress distribution: the stress values are maximum in the central region of the stent at the level of the internal aortic curvature and decrease towards the proximal sections.

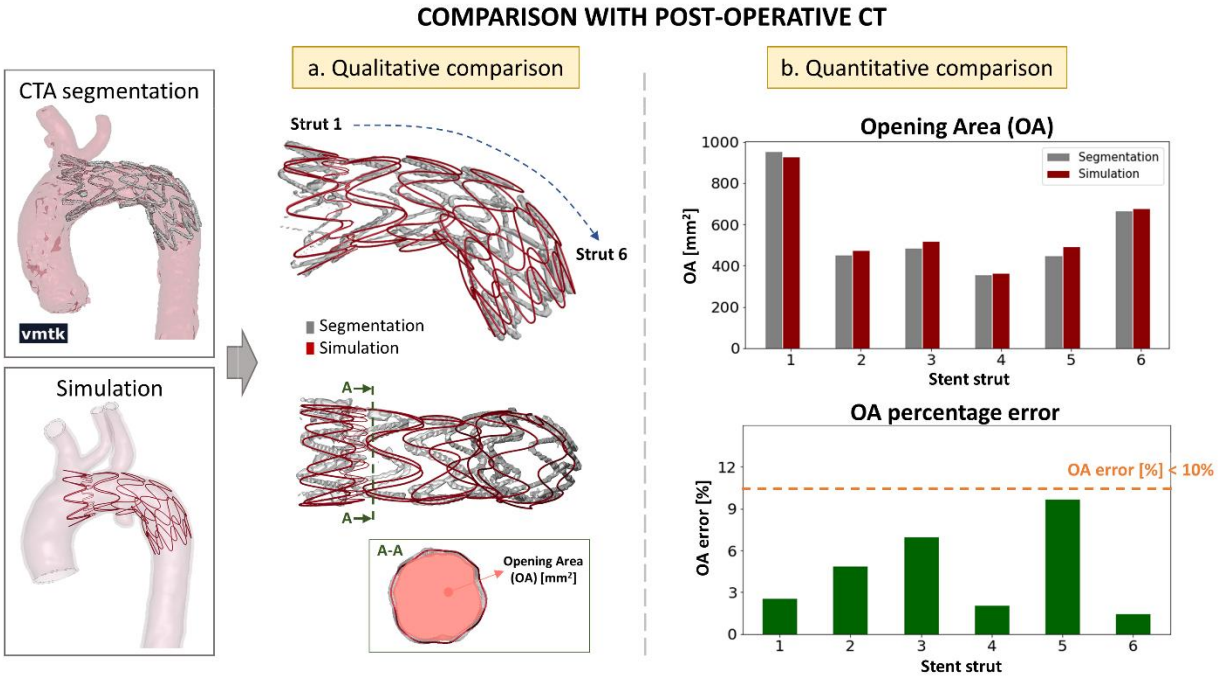

Figure 1. (a.) Finite Element 34x34x100 Valiant Captivia stent-graft model with mesh details. (b.) The patient-specific aortic model with mesh details. (c.) Tracking and deployment steps of the TEVAR simulation. (d.) Simulation results evaluated at the end of stent-graft deployment: distance between the stent struts and the aortic wall (left) and von Mises stress distribution on the aortic wall (right).

In Figure 2, the comparison between the simulation and post-operative CTA stent segmentation is also reported and a good overlap is achieved between the simulated and segmented stent configurations. By evaluating the opening area for each stent strut, the errors between the simulation and CTA reconstruction are below 10%.

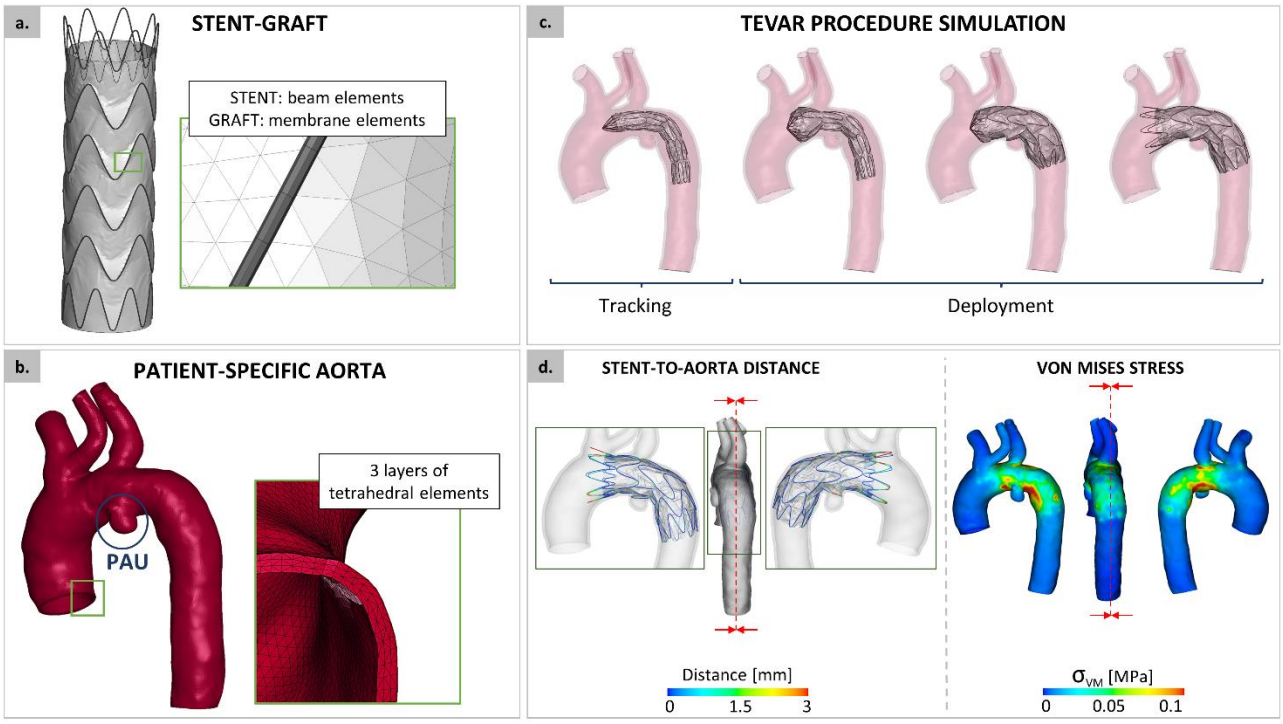

Figure 2. Assessment of stent-graft deployed configuration between the simulation results and CTA segmentation: (a.) Qualitative overlap and example of Opening Area (OA) estimation for a stent strut; (b.) quantitative comparison of the OA for each stent strut and calculation of percentage errors.

3. APPLICABILITY ANALYSIS

The second aim of this work is to discuss and justify the applicability and credibility of patient-specific TEVAR simulation of stent-graft implantation, following the process described in Pathmanathan et al., 2017: three main steps are here proposed as reported in Table 1.

Table 1. Steps of the applicability analysis.

Steps of the applicability analysis	
Step 1.	Description of the real environmental settings and corresponding computational models.
Step 2.	Lists of the equalities and differences between the validation and COU models and reality.

Step 3.	Discussion of the applicability assessment.

3.1. Step 1. Description of the real environmental settings and corresponding computational models.

The main purpose of the computational TEVAR modeling is to replicate the clinical procedure performed with stent-graft models in virtual patients. The computational process can be used to predict the stent-graft deployed configuration after the TEVAR procedure in a virtual population, answering a specific question of interest (QOI). The herewith QOI is "Will a given stent-graft model be successfully deployed in a given patient-specific aorta in a given position with respect to the location of the pathology (e.g., aneurysm, dissection, PAU)?". From a clinical point of view, the stent-graft is successfully deployed if it is completely apposed to the aortic wall at the proximal and distal landing zones (Nation and Wang, 2015). From an engineering perspective, the deployment can be quantitatively evaluated by measuring the distance between the stent-graft and the aorta in relevant regions.

In this analysis, two frameworks (Figure 3) are outlined: the COU and the validation evidence (VAL). Among them, the real-world scenario (R-COU and R-VAL) and the numerical models (M-COU and M-VAL) are identified. The model elements of the context of use (M-) represent the computational models used to replicate the real-world setting scenarios (R-).

In this work, the **R-COU** is related to the clinical TEVAR procedure performed on patients with different pathologies, and with different commercially available stent-grafts, requiring different deployment procedures. On the other hand, the **M-COU** comprises the finite element (FE) models of

the commercial stent-graft and the patient-specific aorta to virtually reproduce the clinical procedure, as shown in the pilot study of the previous paragraph.

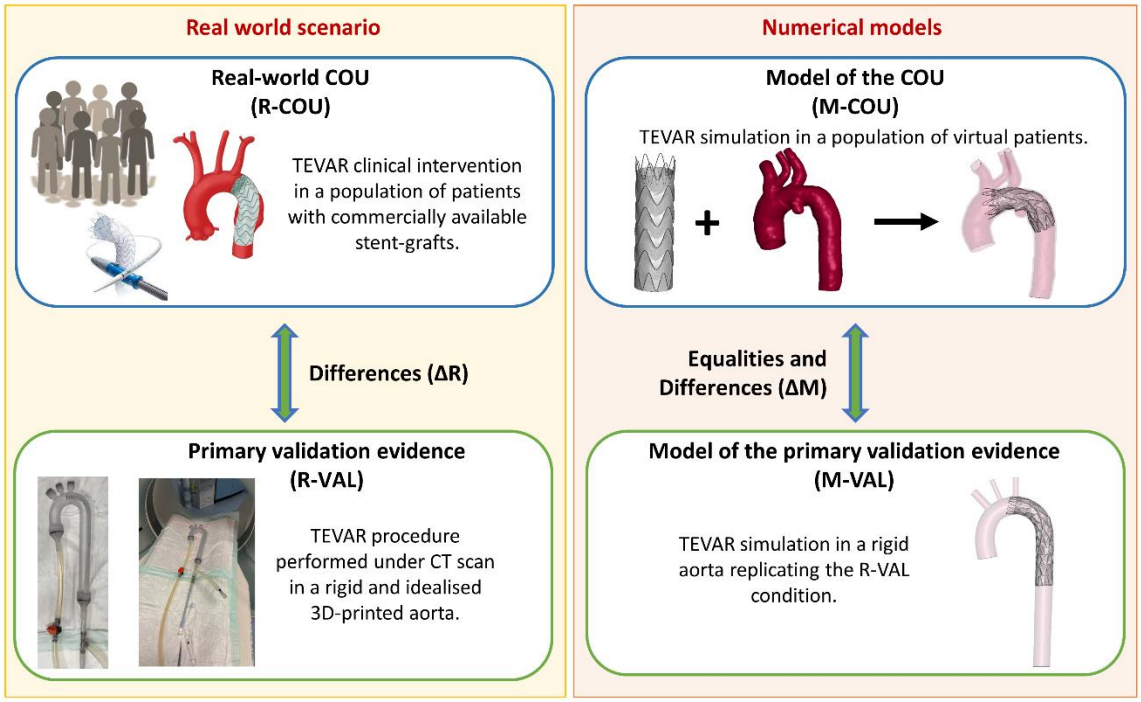

Figure 3. On the left, the real-world scenario of the context of use and validation evidence: the real environment setting (R-COU) and the physical primary validation evidence (R-VAL). On the right, numerical models of the context of use and validation evidence: the COU model adopted to address the QOI (M-COU) and the primary validation computational model (M-VAL).

The adoption of a computational model for predicting the real scenario must be supported by a series of validation results. The following validation evidence sources are available, all of them deeply discussed in Ramella et al., 2022:

1) *Validation of the Nitinol material*. Crimping/release experimental tests on Valiant Captivia stent struts are performed to calibrate and validate the Nitinol material parameters.
2) *Validation of the stent-graft model*. Crimping/release experimental tests on two Valiant Captivia stent-grafts are used to validate the stent-graft models.

3) *Validation of the TEVAR procedure in an idealised rigid aorta*. A rigid 3D-printed idealized aorta is used to experimentally implant a stent-graft under a CT (Computed Tomography) scan. The stent configuration obtained with the experiment is adopted to validate the simulation results.

The validation evidence (3) is considered as the primary validation evidence (VAL) since it involves relevant aspects of the COU.

In this context, **R-VAL** and **M-VAL** refer to the real experimental and computational models of the validation evidence replicating in-vitro and *in-silico* the TEVAR procedure in an idealized aorta. Briefly, in R-VAL, a Valiant Captivia (Medtronic, Inc., MN, U.S.A.) stent-graft is experimentally released into a 3D-printed rigid idealized aorta and inspected in a computed tomography scan at different time points during deployment. The same stent-graft and aorta are modeled for the M-VAL numerical simulation in which the TEVAR procedure steps are replicated. Complete details about the validation evidence are reported in Ramella et al., 2022.

3.2. Step 2. Lists of the equalities and differences between the VAL and COU models and reality.

The identical model aspects in the M-COU and M-VAL are:

a) Stent and graft element formulation. Given a stent-graft model, the stent is discretized with beam elements and the graft with triangular membrane elements. Also, the characteristic dimension of the elements is the same in each model.

b) Material constitutive formulation of the stent-graft. The same shape memory alloy and fabric material formulations are used for all the considered stent-graft.

c) Steps of the TEVAR simulation and software. For each stent-graft, the TEVAR simulation is composed of the same steps (crimping, tracking, deployment). The numerical details (damping and contact friction coefficients, time-step, contact algorithm), explicit solver and

memory requirements (28 CPU and 250 GB of RAM memory) of the simulations are the same.

d) QOIs. In both M-VAL and M-COU, the QOI is related to the estimation of the deployed stent-graft configuration.

On the other hand, the following model aspects are different in the M-COU and M-VAL (ΔM).

a) Aorta geometry. In the M-COU, a patient-specific aorta is involved, while an idealized aorta is used in M-VAL.

b) Aorta element formulation and material properties. In the M-COU tetrahedral elements are used and a deformable hyperelastic material is assigned to the aortic wall, while rigid shell elements are adopted in M-VAL.

c) Stent-graft model, size and materials. In the M-VAL a Valiant Captivia stent-graft (34x34x200 mm size) is implanted with calibrated material parameters. In M-COU, each commercially available stent-graft model and size can be adopted and modelled with its specific material properties. Single parameters of the material modes used in each stent-graft can differ after proper calibration analysis.

d) Position of the stent-graft into the aorta. In M-VAL the stent-graft position reflects the experimental one of R-VAL, in M-COU it can vary depending on the patient's anatomy.

The following model aspects are different in the R-COU and R-VAL (ΔR).

a) Aorta geometry and material. In the R-VAL, the idealized aortic model is realized with physiological dimensions and 3D printed with a rigid transparent isotropic material (Stratasys VeroClear RGD810) with a thickness of 1.5 mm (more details in the Supplementary material). In the R-COU, aortic dimensions, pathologies and material properties (nonlinear, anisotropic, presence of thrombi or calcifications) change among patients.

b) Stent-graft model. In the R-COU, TEVAR can be performed with any commercially available stent-graft. In the R-VAL, a Valiant Captivia stent-graft (34x34x200 mm size) is used.

c) TEVAR procedure. In the R-COU the device location is strictly related to the location of the pathology while an optimal stent-graft positioning is chosen in the R-VAL experiments. In the R-COU the stent-graft is inserted from the femoral artery, in the R-VAL the aortic model is shorter (up to the renal arteries bifurcation).

d) Blood flow. The R-VAL is performed with stationary water at 37°C, while in the R-COU blood is continuously flowing creating a dynamic environment.

3.3. Step 3. Discussion on the applicability assessment.

In this paragraph, the equalities and differences listed above are deeper discussed and justified to demonstrate the overall applicability of the TEVAR model. The key point of the applicability appraisal is the analysis of these identical/dissimilar aspects by answering the question: *"since we assume that it is appropriate to model the R-VAL with the validation results (M-VAL), is it appropriate to use a specific model (M-COU) to predict the R-COU given the differences between R-VAL and R-COU?"*.

First, the identical aspects between M-VAL and M-COU are discussed in light of the differences ΔR of the real settings (Table 2).

Table 2. Identical aspects between M-VAL and M-COU in light of the differences between the R-VAL and R-COU.

<table>
<tr><th rowspan="2">Differences between R-VAL and R-COU (ΔR)</th><th colspan="4">Identical aspects between M-VAL and M-COU</th></tr>
<tr><th>Stent and graft materials</th><th>Element formulations</th><th>Steps of the simulation</th><th>QOIs</th></tr>
<tr><td>a) Aorta geometry and material properties.</td><td></td><td></td><td rowspan="3">(3) Are the simulation steps suitable for modeling the TEVAR procedure of the R-COU?</td><td></td></tr>
<tr><td>b) Stent-graft model.</td><td>(1) Are the stent-graft materials applicable to any stent-graft in the R-COU?</td><td rowspan="2">(2) Are the element formulations acceptable to model the TEVAR procedure of the R-COU?</td><td></td></tr>
<tr><td>c) TEVAR procedure.</td><td></td><td></td></tr>
<tr><td>d) Blood flow.</td><td></td><td></td><td></td><td>(4) Does the presence of the fluid affect the QOI?</td></tr>
</table>

1) Are the stent-graft materials applicable to any stent-graft in the R-COU? The crimping/release tests in the R-VAL are performed with two Valiant Captivia stent-grafts sizes and the material properties are found to be the same for both devices (supporting validation evidence 1 and 2). For this reason, we considered the stent-grafts with the same material properties independently of the sizes (length and diameter). The same rationale stands for other commercial stent-grafts.

2) Are the element formulations acceptable to model the TEVAR procedure of the R-COU? For the same reasons discussed above, all the stent-grafts are discretized in the same way. Modelling the stent with beam elements has been demonstrated (Ramella et al., 2022) to be suitable for correctly describing the stent kinematics during deployment and answering the QOI.

3) Are the simulation steps suitable for modeling the TEVAR procedure of the R-COU? The steps of the simulations (crimping, tracking, deployment) reflect the real TEVAR of R-COU as well as the replication of the experimental procedure of R-VAL. In the simulation, the stent-graft is displaced along the vessel centerline. Differently, in the real scenario, a guidewire is inserted deviating the device trajectory from the centerline. However, this difference is supported by the primary validation evidence. In the R-COU, access to the patient is performed from the femoral artery, while in the R-VAL, a shorter aortic model is considered. This does not affect the results since, in both cases, the stent-graft remained crimped within the catheter until the proximal landing zone is reached. The simulation steps are also tailored to the stent-graft size (e.g., a longer device means higher tracking phase time)

4) Does the presence of the fluid affect the QOI? The main aim of the models is on the stent-graft and aorta interactions, and therefore FE simulations are carried out neglecting the presence of the fluid. The R-VAL is performed under stationary flow water at 37°C. The steadiness of the flow allows the simplification of the model to structural simulation instead of fluid-structure interaction simulation. Since the simulation was validated without modeling blood flow (supporting validation evidence 3.), the stent-graft patient-specific implantation can be performed without fluid as well: as shown in the pilot study, the simulation leads to a reliable deployed stent-graft configuration.

In the light of this analysis, the differences ΔM between M-VAL and M-COU are described to discuss whether modifications of the computational model result in trustworthy predictions for the COU.

a) Vessel geometry. In the M-VAL the aorta is idealized: the goal of the primary validation is to trustily replicate the TEVAR deployment. In the M-COU the patient-specific aorta is

segmented from CTA images. Patient-specific anatomy does not affect the trustworthy prediction of the M-COU as demonstrated by the presented pilot patient-specific analysis. Nevertheless, a change in the vessel anatomy leads to changes in pathology, curvature, and tortuosity which, from the clinical point of view, are factors that affect the outcome of the TEVAR procedure (Findeiss and Cody, 2011; Marrocco-Trischitta et al., 2018; Nation and Wang, 2015; Sweet, 2016; Ueda et al., 2011).

b) Aorta element formulation and material properties. In the M-COU tetrahedral elements are used, while shell elements are adopted in the M-VAL. In the M-VAL the aorta is rigid, thus modeling the vessel with shells or solid elements does not significantly affect the results (shell elements are chosen to reduce the computational time). This material simplification (rigid instead of deformable) was chosen since the M-VAL focused on the device deployment, removing uncertainties related to the aortic wall materials. Differently, the M-COU aortic wall is modeled with a hyperelastic isotropic material to introduce the aortic wall deformations during deployment. The differences between M-COU and M-VAL are overcome given the results obtained with the pilot patient-specific application. In fact, the simulated stent configuration showed a good prediction of reality when compared to the post-operative CTA stent reconstruction (Figure 2).

c) Stent-graft model, size, and materials. In the M-VAL a Valiant Captivia stent-graft (34x34x200 mm size) is implanted with calibrated material parameters. The virtual TEVAR of the M-COU can be performed with any commercial stent-graft. In particular, all the stent-grafts are modeled with the same discretization technique and with material parameters calibrated with the same protocols (supporting validation evidence). Differences in device size are taken into account in the steps of the TEVAR procedure simulation.

d) Position of the stent-graft into the aorta. In M-VAL the stent-graft position reflects the experimental one of R-VAL, in M-COU it can vary depending on the patient's anatomy. The position of the pathology only affects the TEVAR simulation. The ability of the model to

consider these changes is proven by the pilot study which considers patient-specific anatomy instead of an idealized one.

4. DISCUSSION

The model credibility is related to the capability of the model to adequately reproduce an identified context of use and it is of foremost importance if the model will be used for clinical applications. Activities such as verification, validation and evaluation of the applicability of the numerical model must be considered, to establish how reliable the model is, as suggested by the V&V 40 standard introduced by the American Society of Mechanical Engineering (ASME, 2018). In particular, the assessment of the *in-silico* model applicability is a fundamental aspect to demonstrate the reliability of the model itself in a specified COU, as described in the step-by-step framework proposed by Pathmanathan et al., 2017. Among the literature, some studies carried out an exhaustive applicability analysis of the numerical model in different cardiovascular fields such as thrombectomy (Luraghi et al., 2021), cardiac electrophysiology (Pathmanathan and Gray, 2018), left ventricle blood flow after LVAD (Santiago et al., 2022) or haemolysis (Morrison et al., 2019). To the best of the authors' knowledge, this is the first study that investigates the applicability of the TEVAR numerical modeling, following the framework proposed by Pathmanathan et al., 2017.

In this work, the finite element-based TEVAR procedure previously developed (Ramella et al., 2022) is successfully applied to a patient-specific aorta. Comprehensively, the numerical workflow starts with the segmentation of the patient-specific aortic model from pre-operative CTA images, followed by its finite element discretization. Then, once the commercial stent-graft size is selected and discretized, the simulation of the TEVAR procedure is performed. The presented pilot study is a fundamental step in gaining the reliability of the overall TEVAR computational model and it helps in contextualizing the following applicability analysis of the *in-silico* modeling. Although it has some limitations and could be further improved (e.g., the addition of vessel pre-stress, the inclusion of the

blood, the exact position of the guide-wire), it demonstrates the capability to apply a validated methodology to patient-specific anatomies, that could be used to predict clinical outcomes in the future. In fact, with respect to the QOI, the most relevant simulation result is to obtain a reliable stent-graft deployed configuration. In the pilot study, this is proved by the comparison of the simulation result with the post-operative CTA of the patient: in the final deployed configuration, the error between the segmented stent and simulated one is below 10%, coherent with other literature studies (Kan et al., 2021b, 2021a; Perrin et al., 2015). The applicability of this *in-silico* model is assessed by analysing and arguing equalities and differences between the COU (TEVAR procedure in a patient population) and the validation evidence between the real-world settings and the models.

In conclusion, the discussed applicability analysis demonstrated that the developed *in-silico* model is trustworthy for replicating the TEVAR procedure in virtual patients. In particular, the pilot study reports the application of TEVAR to a single patient with one specific commercial stent-graft. A population of aortic anatomies with different pathologies treated with any commercially available device could be embraced in the future, towards an *in-silico* clinical trial.

Conflict of interest statement

Santi Trimarchi is a speaker and consultant for W.L. Gore & Associates, Terumo Aortic, and Medtronic Incorporated.

The other authors declare that they have no conflict of interest.

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