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Citation for published version (APA):

Visser, V. L., Zaytseva, P., Motta, S. E., Loerakker, S., Hoerstrup, S. P., & Emmert, M. Y. (2021). Computational modelling to reduce outcome variability in tissue-engineered heart valves: Could computational models become a pre-requisite for the broad clinical translation of tissue-engineered heart valves? . *European Heart Journal*, 42(23), 2225-2229. <https://doi.org/10.1093/eurheartj/ehab034>

DOI:

[10.1093/eurheartj/ehab034](https://doi.org/10.1093/eurheartj/ehab034)

Document status and date:

Published: 14/06/2021

Document Version:

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Computational modelling to reduce outcome variability in tissue-engineered heart valves

Could computational models become a pre-requisite for the broad clinical translation of tissue-engineered heart valves?

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Clinical problem

Replacement of a severely dysfunctional heart valve remains the only viable option for the majority of patients with valvular heart disease, and the choice of the best suitable prosthesis is based on the patient's anatomy, pathology, and comorbidities.¹ Heart valve replacement via open-heart surgery with temporary cardiac arrest has been the standard of care for decades but is not always applicable to elderly or high-risk patients. In this context, transcatheter valve replacement (TVR) strategies have evolved in recent years and provide an alternative treatment option for inoperable, high-risk, but now also intermediate- and low-risk patients.¹ However, despite this tremendous evolution in the field, the heart valve prostheses currently utilized in TVR approaches (i.e. bioprostheses) are prone to continuous degeneration and still lack the ability to grow, self-repair, and regenerate, thus making them not suitable for younger patients.¹ Hence, the combination of TVR with tissue-engineered heart valves (TEHVs) with self-repair and remodelling properties may provide a next-generation solution that can be implanted via minimally invasive techniques and will subsequently integrate in the heart of the patients.¹ These intrinsic regeneration properties will allow TEHVs to grow with the patient, adjust to the dynamic environment, and eliminate the reoperation risks, thus providing a lifelong, durable solution for paediatric and elderly patients.

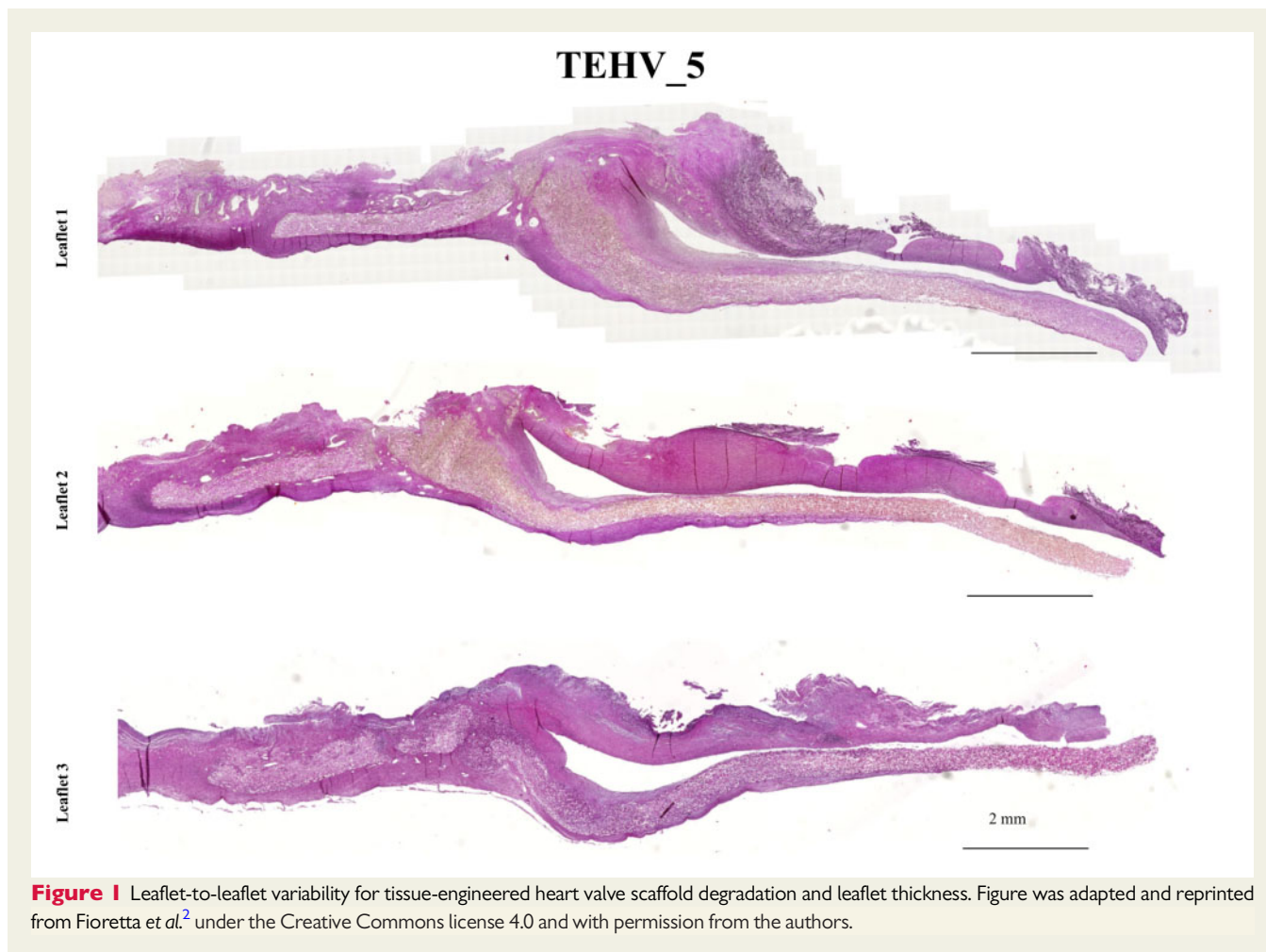
Large heterogeneity of the implanted tissue and subsequent remodelling response

Despite the huge potential of such next-generation valve substitutes, the technical and regulatory complexity, as well as the control of the *in vivo* remodelling processes remain major translational challenges limiting TEHVs clinical translation. Additionally, it has recently been shown that there is a large variability in the preclinical outcomes of

TEHV remodelling.¹ Factors like the *in vitro* culture method, the use of xenogeneic material, cell seeding, scaffold type, valve design, and implantation method lead to heterogeneity of the implanted tissue.¹ Other factors such as inter- and intra-subject differences in the growth and remodelling response between animals and ultimately patients, also contribute to the observed variability in the (pre)clinical outcomes. One study demonstrated that substantial leaflet-to-leaflet variability is observed in regard to the degree of scaffold degradation and leaflet thickness, as can be seen in *Figure 1*.² Given that the differences in (epi)genetic and environmental factors are rather small in pre-clinical studies, the variability in outcome is expected to be even larger in the clinical setting. Therefore, an in-depth mechanistic understanding of how such differences arise is mandatory in order to reliably develop TEHVs that are predictable with regard to remodelling outcomes and the associated functionality.

Solution: computational modelling and the rise of personalized medicine

To successfully translate TEHVs to the clinic, a systematic approach is needed to identify TEHV design criteria. The integration of *in silico* computational modelling (CM) tools with experimental studies is crucial to obtain a mechanistic understanding of the multi-level phenomena that occur after TEHVs implantation.³ Only when the *in vivo* remodelling process of TEHVs is understood from a mechanistic point of view, the currently observed variability can be reduced or even eliminated.³ It is important to note that the optimal TEHV is not defined only by its design but also by the anatomical correspondence, adaptation to patient-specific haemodynamic loading, and anticipation of the presence of comorbidities in the patient which might affect the regenerative capacity. To this end, patient-specific therapies are becoming increasingly popular (i.e. personalized medicine), as new



inter-patient differences that might affect functional remodelling of TEHVs are discovered on a regular basis.⁴ Nevertheless, CM has the potential to explain their influence, adjust for these differences and may therefore play a central role in the development of patient-specific TEHVs.

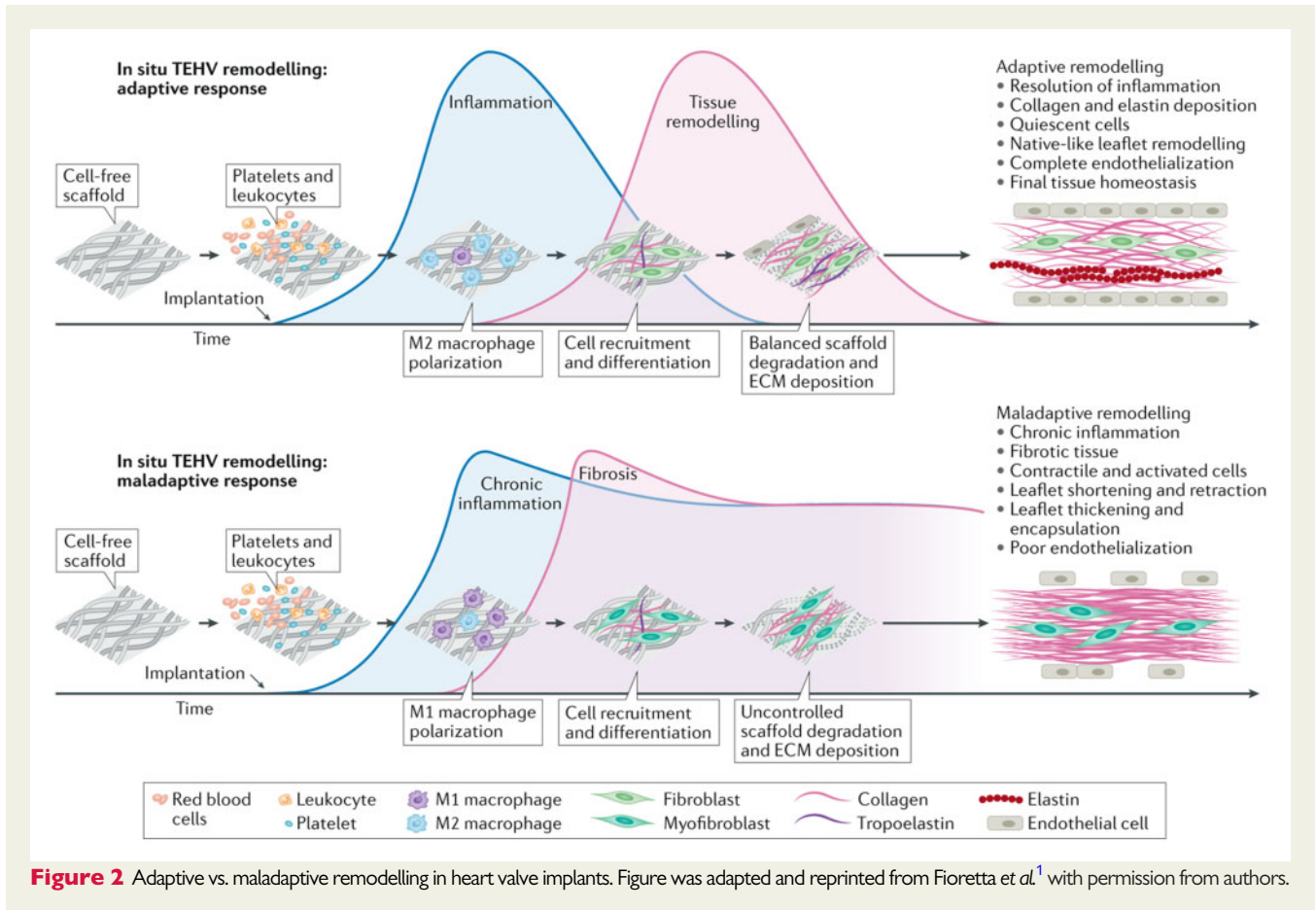
Mechanical factors heavily influence tissue-engineered heart valve functionality and remodelling

Mechanical factors have a large influence on the performance, integration, and adaptation of TEHVs in the host.⁵ Cells repopulating the heart valves after implantation are subjected to haemodynamic parameters such as pressure, shear forces, and stretch and are known to respond and adapt to these forces to maintain homeostasis in healthy valve tissues.⁵ These cellular responses are also crucial for functional remodelling of TEHVs towards native-like valve tissue as they, for example, control extracellular matrix remodelling, tissue compaction and growth factor excretion and inhibition.^{3,6} On the other hand, cells can also transform into pathologically activated phenotypes (e.g. M1 macrophages and myofibroblasts), under non-physiological (mechanical) conditions,⁵ like hypertension or aberrant tissue stretch.⁵ These pathological stimuli may induce a chronic inflammatory state, which causes

maladaptive remodelling of TEHVs for example leading to excessive leaflet thickening and calcification (Figure 2). Understanding of how mechanical stimuli affect the remodelling response of cells and tissues is therefore crucial to understand how functional (adaptive) remodelling of TEHVs may be established.

Inter- and intra-patient differences influence remodelling of tissue-engineered heart valves

Mechanical parameters can vary between patients or even between different heart valve leaflets. Inter-patient variability is often observed in blood pressure, annulus size, and stiffness.⁷ Intra-patient variabilities are also found in heart valves such as asymmetry in the leaflet size and composition.⁸ Inter- and intra-patient variations affect the mechanical behaviour of heart valve leaflets and may induce a heterogeneous spatial distribution of stresses and strains.⁸ These mechanical stimuli evoke a response from the valvular interstitial cells, and subsequently either physiological homeostasis or a maladaptive inflammatory state is reached.¹ Therefore, mechanistic understanding of how inter- and intra-patient differences affect remodelling could indicate how TEHVs adopt a functional remodelling response instead of maladaptive remodelling (Figure 2).



In addition to mechanical parameters, there are also systemic effects which might affect TEHV remodelling in patients, such as comorbidities which may significantly affect the remodelling capacity of the cells in TEHVs.⁸

Computational modelling can be used to rationally optimize tissue-engineered heart valve design

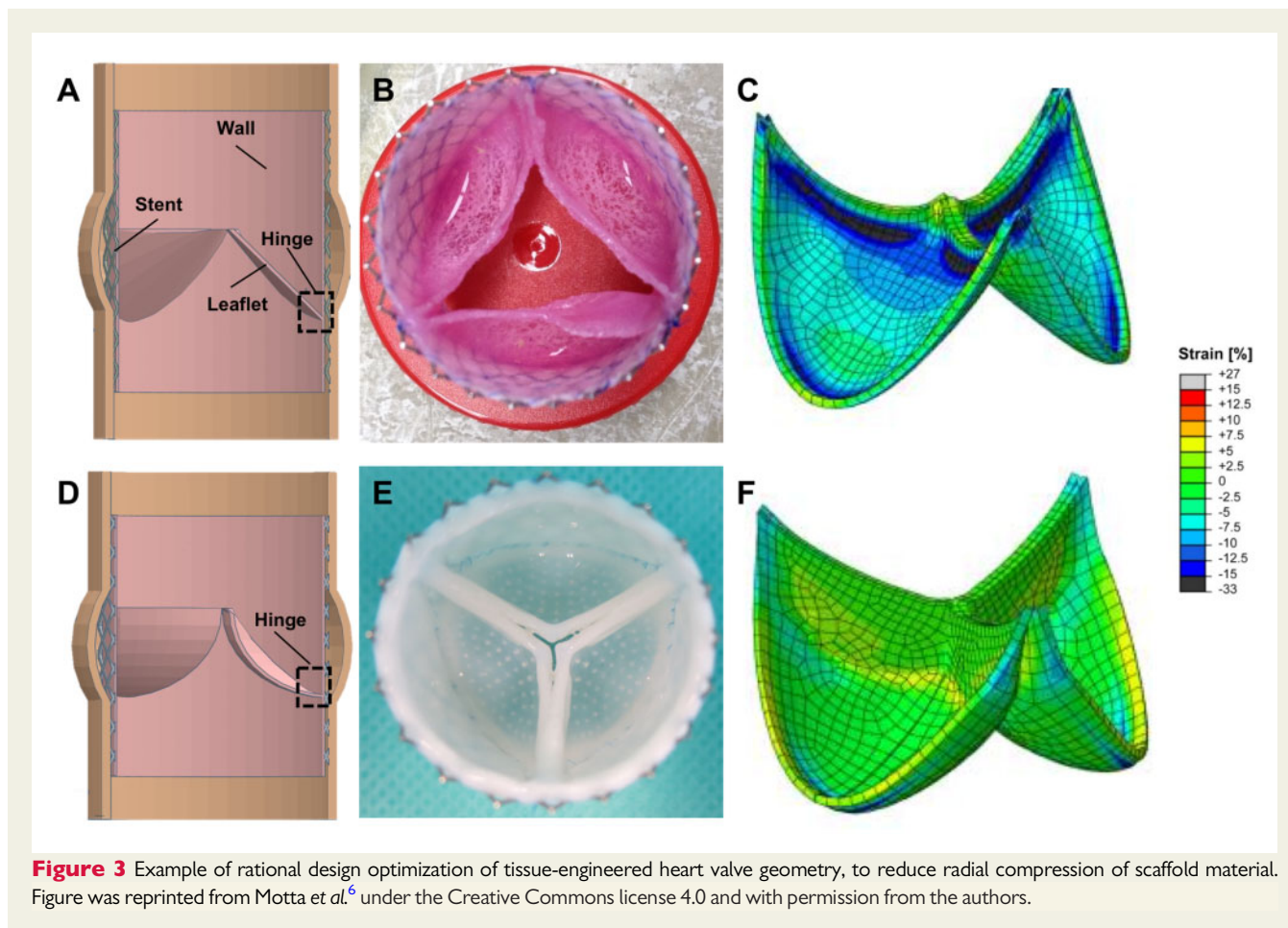
CM is utilized to optimize the design of TEHVs in all steps of the clinical translation from bench to bedside, as visualized in Figure 4. First, models are used to study how (mechanical) stimuli affect the remodelling response of (single) cells *in vitro*.⁹ This can be expanded to understand how a functional remodelling response can be provoked in a tissue *in vitro* in either a static condition or a bioreactor, where the tissue is often subjected to multiple stimuli in concert.⁹ Finally, models are used in *in vivo* studies, to predict the remodelling potential of a TEHV towards native-like tissue.³ As it often occurs that several pathways or stimuli will have competing or synergistic influences on cell or tissue behaviour, models can aid in understanding how these processes cooperate to define the final remodelling response of a cell or tissue.⁹

For all steps from bench to bedside, a model could be made prior to the experiment, which aids to define hypotheses or defines how the TEHV should be designed. Besides this, retrospective models can be made, to explain unexpected findings.

Both the simulations prior and after an experiment can be used to optimize the design of the TEHV, as for example done previously by Emmert *et al.* where the geometry of TEHV was substantially improved as visualized in Figure 3.^{3,6} Optimization algorithms should therefore be developed to enable the improvement of the valve design within a predefined set of suitable parameter ranges.

Computational modelling can analyse the effect of inter- and intra-patient differences on the remodelling of tissue-engineered heart valves

Computational models, which describe the remodelling response of a TEHV, are often able to incorporate patient-specific input parameters. If a maladaptive remodelling response is predicted to arise, either the design of the TEHV could be optimized or patients with these specific conditions are not recommended to use this TEHV. It is possible that there is no design that will suit the majority of the patients, or that a patient has an exceptional cardiovascular signature. In that case, patient-specific treatments could be developed, where the TEHV is tailored to each specific case. Initiatives like the digital patient roadmap and the Virtual Physiological Human provide frameworks to integrate multiple



computational models to study the human body and are of great importance for the development of these patient-specific treatments.⁴

Using computational modelling reduces trial and error in pre-clinical and clinical studies

CM would enable investigators to scale down the trial and error phase in preclinical studies, obtaining scientific results at reduced labour cost and animal sacrifice. *In silico* designed TEHVs have shown sustainable long-term performance in a translational sheep model as predicted by computational solutions,³ indicating the relevance of an integrated bioengineering approach. CM can be implemented at any stage of clinical translation—from TE implant design and parameter evaluation to predicting therapy outcomes in (pre)clinical trials and beyond.

Recently, a clinical trial in Japan showed promising results following implantation of tissue-engineered vascular grafts as cardiac conduits in children.¹⁰ However, a follow-up trial in the USA was halted, after evidence of stenosis was observed within 8 months of implantation. By simulating the adaptation of the graft *in silico*, CM could explain the development of stenosis observed in the trials, as well as predict its spontaneous resolution via inflammation-driven graft remodelling—which

was later confirmed experimentally. This evidence substantiates the importance of CM in cardiovascular tissue engineering and its ability to reduce trial and error within the preclinical development and validation of such technologies.

How computational modelling should be incorporated in ISO guidelines

Current regulatory requirements for cardiovascular implants outlined by ISO 5840 guidelines are suboptimal for tissue-engineered devices, as they do not consider their regenerative and growth potential.¹ The regulations are set to be revised, once the clinical translation of TEHV is achieved. Including *in silico* clinical trials as part of the updated guidelines would support the evaluation of the devices and facilitate quality assurance. Importantly, models should be properly validated in order to contribute successfully to clinical translation.⁴

Implementing CM as a pre-requisite in the ISO testing standards to study maladaptive remodelling responses could systematically raise clinical performance of next-generation TEHV. On top of that, by implementing CM the safety of TEHV will be increased significantly, as suboptimal TEHV designs are avoided by predicting success or failure.

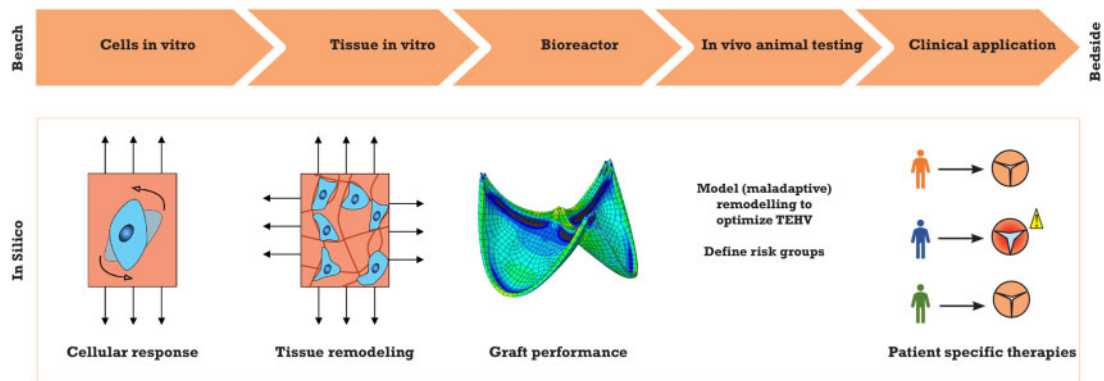


Figure 4 Examples of added value of computational modelling in each step of clinical translation of tissue-engineered heart valve (TEHV) from bench to bedside. *In silico* models can attribute to mechanistic understanding of *in vitro* and *in vivo* studies. Subfigure of TEHV performance was reprinted from Motta *et al.*⁶ under the Creative Commons license 4.0 and with permission from the authors.

Models as pre-requisite for clinical translation would improve treatment efficacy

In summary, next-generation TEHVs are eagerly awaited in the field, and provide hope for future heart valve replacement therapies, in particular for the young and children. To date, efficient clinical translation has been slower than anticipated due to several technical challenges.¹ Advancements in CM have consolidated it as an increasingly valuable tool with great potential to revolutionize TEHV design and evaluation. *In silico* strategies could help to carry out safe clinical translation of TE cardiovascular implants, as well as improve treatment efficacy and long-term performance through the simulation of treatment outcomes.

Funding

M.Y.E. and S.L. have received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme, grant agreement no. 852814 (TAVI4Life) and grant agreement no. 802967 (MechanoSignaling). V.V., P.Z., and S.E.M. are supported by the ERC grant TAVI4Life.

Conflict of interest: S.P.H. is a shareholder at Xeltis BV and LifeMatrix Technologies AG. M.Y.E. is a shareholder at LifeMatrix Technologies AG.

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