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REVIEW

Models of the human heart for biomedical research: Opportunities and challenges

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Abstract

Model systems that mimic human cardiac structure and function are essential for the development of novel diagnostics and effective treatments for cardiovascular diseases. While non-human vertebrate models, from zebrafish to pig, remain vital to cardiovascular research, the translatability of findings to human patients is often limited. Therefore, animal experiments should be supplemented with human model systems, including human induced pluripotent stem cell-derived cells, 3D engineered constructs, and last but not least, native tissue preparations and isolated primary cardiomyocytes. However, while human myocardium remains the gold standard, human heart tissue – and particularly tissue from control hearts–remains scarce, and its use in research is generally restricted to settings where tissue has been excised from diseased or failing hearts. While it is in principle possible to use tissue from rejected non-failing donor hearts that cannot be transplanted, legal hurdles (e.g., in Germany) can restrict the use of non-transplanted donor organs in research. Given the challenges associated with accessing and using human tissue in biomedical research, an integrated strategy towards combining non-human vertebrate models, in silico models, and human tissue-derived models is recommended, enhancing the chances of successful research and development, and helping bridge the gap between preclinical and clinical research.

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KEYWORDS
animal models, donor tissue, human myocardium, stem cell models, vertebrate models

1 | INTRODUCTION

The development of novel, affordable, and effective treatments for cardiovascular diseases greatly relies on the use of model systems that mimic human cardiac structure and function. While human heart tissue would be the best model for investigating human cardiovascular function and pathology, its limited availability (which is subject to ethical and legal restrictions) means that non-human models play crucial roles in cardiovascular research and development. However, the extent to which cardiovascular diseases can be recapitulated ex vivo is limited, owing to complex aetiologies, the involvement of extra-cardiac influences on the heart (e.g. circulating hormones, immune cells, and nervous system effects), and additional factors such as age, sex, and comorbidities, as well as the progressive nature of structural and functional pathological remodeling (which are all in turn affected by factors such as environmental cues, lifestyle, and medical treatments). This complexity cannot easily be mimicked in vitro, and it may not be well captured in non-human vertebrate models either. As a result, the translatability of basic science findings to patients has remained limited, and the vast majority of candidate drugs that enter human testing fail, often due to a lack of efficacy or unexpected toxicity in spite of prior promising results in non-human models (Austin, 2021; Barter et al., 2007; Harrison, 2016; Ineichen et al., 2024; Morehouse et al., 2007; Perry & Lawrence, 2017; Sun et al., 2022). Combinations of models that mimic human pathophysiological mechanisms more accurately are therefore needed to improve bio-medical translation (Thomas, Desai, & Takahashi, 2022).

This paper is based on discussions at the 5th Translational Workshop of The German Cardiac Society (DGK) and the German Centre for Cardiovascular Research (DZHK) in Hamburg, Germany, September 2024, dedicated to *Models of Human Myocardium in Medical Research*. It reviews existing in vivo, ex vivo, in vitro, and in silico models, and discusses the utility and limitations of using human cells and tissue for clinically motivated research, with special consideration of the research landscape in Germany.

2 | NON-HUMAN VERTEBRATE MODELS OF THE HEART FOR CARDIAC RESEARCH

Non-human vertebrate models allow cardiovascular researchers to perform experiments that cannot be performed on humans, while facilitating the identification of novel therapeutic and treatment approaches, before these are tested in patients (Giacomotto & Ségalat, 2010; Odening et al., 2021). Vertebrate models can be used to mimic complex inter-organ (e.g., metabolic, neurohormonal, or immunological) crosstalk with the heart, while allowing control of factors ranging from genetic background to aging, comorbidities, and treatments. Here, we review some of the more commonly used vertebrate models in cardiac research (see also Table 1). The advantages and disadvantages of each model, as well as examples of research questions for each, are shown in Figure 1 (Tsang et al., 2016; van der Velden et al., 2022; Zaragoza et al., 2011).

2.1 | Zebrafish: An example of non-mammalian model systems

Despite being evolutionarily distant from primates, non-mammalian animal models such as zebrafish and chick embryos (Rees et al., 2026; Wittig & Münsterberg, 2020) have been used to model several human cardiovascular disorders, including congenital heart defects and cardiomyopathies (Asnani & Peterson, 2014; MacRae & Peterson, 2015).

A unique advantage of zebrafish is that their embryos are transparent, allowing for in vivo optical measurements of cardiac structure and function. Additionally, their genome can be manipulated relatively easily, and they possess high regenerative capacities that may provide opportunities to identify novel targets for human cardiac repair, such as following ischaemic injury (Asnani & Peterson, 2014; Cesarovic et al., 2020). Zebrafish have a short breeding cycle and high fecundity, which permits rapid generation of models (Yang et al., 2024).

Crucially, zebrafish have hearts that share electrophysiological properties with human hearts, including conserved fundamentals of excitation–contraction coupling, similar action potential trajectories (both species have a pronounced plateau phase, for example), and comparable major inward and outward current systems, including sodium, calcium, and potassium currents (Vornanen & Hassinen, 2016). However, while useful for biochemical assays such as drug screening, zebrafish hearts differ from human hearts in a host of biophysical properties, including chamber anatomy, size, and haemodynamics, meaning that findings cannot easily be translated to humans.

TABLE 1 Key parameters of selected vertebrate models commonly used in cardiovascular research (other commonly used models include invertebrates, chick embryos, rats, sheep, goats, non-human primates, and historically also cats and dogs).

Parameter	Non-mammalian, e.g. zebrafish	Small mammal, e.g. mouse	Intermediate mammal, e.g. rabbit	Large mammal, e.g. pig	Human
Body weight	0.5 g	20–45 g	1–5 kg	40–90 kg	50–100 kg
Heart weight	0.5 mg	0.15–0.2 g	5–10 g	145–450 g	150–480 g
Resting heart rate	110–170 bpm	450–800 bpm	140–280 bpm	70–120 bpm	60–100 bpm
Cardiac output	0.09–0.172 mL/min	13–15 mL/min	260–420 mL/min	2720–3620 mL/min	3340–9790 mL/min
Ejection fraction	40%–50%	65%–90%	55%–65%	50%–55%	55%–60%
Ventricular action potential duration	150–250 ms	80–180 ms	150–280 ms	180–300 ms	200–400 ms
Conduction velocity	4–10 mm/s	350–600 mm/s	300–500 mm/s	500–800 mm/s	500–900 mm/s
Reentry space factor[a]	0.42	0.34	0.69	1.43	1.5
Approximate cost per animal	€2.00–2.50/tank	€4–7	€250–600	€80–400+	-
Husbandry notes	Swarm fish, density 4–5 animals per liter	Individually ventilated or standard cages	Larger pens	Large facilities or catheterisation laboratories, low volume but translational	-
Anesthesia, and effects on cardiovascular endpoints	Tricaine: bradycardia, decreased heart rate and contractility, effects dose-dependent	Isoflurane and opioids: decreased heart rate and blood pressure	Volatile or injectable anesthetics: altered haemodynamics, effects on heart rhythm	Isoflurane and similar: more frequent arrhythmias, infarct variability, effects on blood pressure effects	-
Typical n per group in cardiovascular studies	30–100+ embryos	8–15	6–10	6–12	-

Note: Color indicates good (green) or satisfactory (yellow) match to human cardiac parameters.

[a]Calculated as maximum ventricular circumference divided by (conduction velocity × action potential duration).

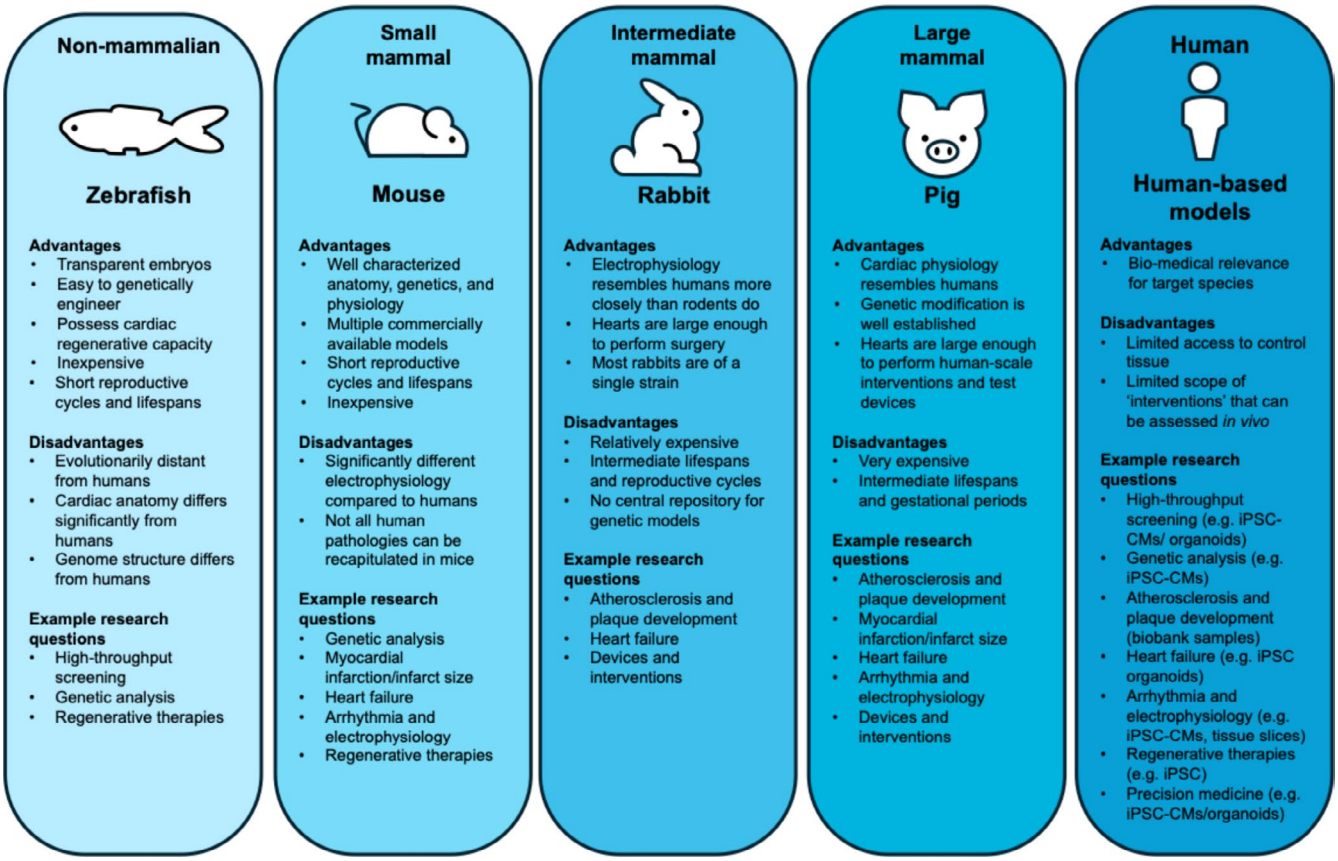

FIGURE 1 Advantages and disadvantages of various vertebrate models used in cardiovascular research (Tsang et al., 2016; van der Velden et al., 2022; Zaragoza et al., 2011).

In conclusion, zebrafish are well-suited for live imaging, genetic and drug screening, as well as developmental and cardiac electrophysiological research. Yet, they differ substantially in size, structure, mechanical activity, and genetic make-up from humans, which can complicate translation of findings (Figure 1).

2.2 | Mice: The most widely used small mammalian model

Mice are the most commonly used animals in biomedical research (Hickman et al., 2017), due in part at least to the availability of standardized recombinatorial lines that allow a level of genetic manipulation unmatched in other vertebrate models (Gurumurthy & Kent Lloyd, 2019). Since the first report of a transgenic mouse (Gordon et al., 1980), the cumulative global production of transgenic founders has reached the millions (Hanahan et al., 2007). Other key advantages of the mouse as a model system are early sexual maturation, short gestational periods, and comparatively short lifespans, allowing for studies over multiple developmental stages of an individual, or even over generations. These features, along with their small size, comparatively low cost of maintenance, and the relative ease of surgical interventions, have contributed to the widespread use of mice in cardiovascular research (Hickman et al., 2017; Justice & Dhillon, 2016).

Given the wide range of ready-to-use models that are commercially available, mice are a convenient choice for experimental investigations. Murine anatomy, genetics, and physiology have been well studied, and reference values are well established. Furthermore, mouse models of a wide variety of diseases and cardiac conditions, including cardiomyopathies, heart failure, and developmental defects, have been established (Chowdhury et al., 2015; Lindsey et al., 2021; Rao et al., 2022; Salerno et al., 2023; Zaragoza et al., 2011). However, due to substantial differences in physiological cardiac function (such as heart rate, action potential shape and duration, calcium dynamics, etc.; Table 1), as well as in responses to pathological stimuli and therapeutic interventions–including resistance to the development of atrial fibrillation (Fu et al., 2022) and atherosclerosis (Emini Veseli et al., 2017)–the translatability of findings in mice to human patients remains limited. In addition, one of the most commonly used mouse strains (C57BL/6J) carries a loss-of-function mutation of the gene encoding

the mitochondrial transhydrogenase, which makes it resistant to a number of common aetiologies of heart failure, such as pressure-overload induced left or right heart failure, hypertrophic cardiomyopathy, and heart failure with a preserved ejection fraction, induced by high fat diet and the vasopressor N(ω)-nitro-L-arginine methyl ester (L-NAME) (Kohlhaas et al., 2024; Müller et al., 2022; Nickel et al., 2015; Pepin et al., 2025; Schiattarella et al., 2019). 'Humanized' mice, which are genetically modified to express functional human genes, have been proposed to extend the utility and translational potential of murine models (Rosshart et al., 1979). In addition, several central repositories for genetic mouse models now contain recently created wild-derived mice that better represent human genetic background diversity (www.mmrrc.org; www.findmice.org (Donahue et al., 2012; Eppig et al., 2015)).

Thus, the mouse is a valuable model for both genetic and epigenetic manipulation, enabling thorough mechanistic studies of various disease conditions and developmental disorders. Limitations include differences in size, genetics, and electro-mechanical function compared to humans (Figure 1).

2.3 | Rabbits: The intermediate size mammalian model

Rabbits (commonly New Zealand white) have been dubbed "the largest of the small mammalian models" in cardiovascular research (Odening & Kohl, 2016). While rabbit hearts are 30 to 40 times smaller than human hearts by weight, they are large enough to allow use of scaled-down instrumentation used in human interventions, including surgical and implantable devices (Pogwizd & Bers, 2008). Rabbit hearts resemble human hearts much more closely than mouse hearts in terms of cellular electrophysiology, including the shape of action potentials and arrhythmia wavelength, as well as their response to ischaemia and pharmacological interventions (Odening et al., 2020; Panfilov, 2006; Pogwizd & Bers, 2008). In contrast to mice and rats, rabbits also display a positive force–frequency relationship with calcium handling properties that are similar to humans (Endoh, 2004; Milani-Nejad & Janssen, 2014). Furthermore, both electrophysiological and mechanical remodeling associated with aging and disease resemble key changes that occur in humans (Alpert et al., 1992; Cooper et al., 2012).

Disadvantages compared to murine models include the later sexual maturity, longer reproductive cycle, and longer lifespan of rabbits, making multi-generational and aging studies more challenging. Rabbit housing and maintenance are also more costly. There are relatively few transgenic rabbit models and, in contrast to mice, these do not allow the easy "mix-and-match" recombination that systems such as the established Cre/LoxP or Flp/FRT lines offer for mice. Regrettably, there is no central repository for genetic rabbit models, leading to duplication of efforts in generating models, and at least occasionally to the loss of transgenic model lines maintained by individual labs (Hornyik et al., 2022). Encouragingly, however, genetic manipulation via point mutations and small insertions can work well, and new genetic techniques using TALEN or CRISPR/Cas9 have simplified the generation of transgenic mammals, including rabbits (Liu et al., 2018; Yang et al., 2019).

Overall, the rabbit is a valuable model for studying cardiac electrophysiology and mechanics in health and disease. Limitations include relatively high demands for time and resources, as well as the limited availability of transgenic models (compared to mice), as well as their somewhat unusual immune system (with one variable heavy chain and an unusually complex immunoglobulin A system) (Figure 1).

2.4 | Pigs: A "human-sized" mammalian model

Several large vertebrate models are used in cardiovascular research, of which non-human primates have the closest phylogenetic relationship to humans. However, other large vertebrate models including goats, sheep, or pigs are also used.

Like humans, pigs are large, omnivorous, diurnal mammals, and the two species share relevant similarities in terms of anatomy, physiology, and biochemistry, with the pig's cardiovascular system being considered a good model for humans (Cesarovic et al., 2020). Pigs and humans have hearts of similar size and mass, and there is overlap in terms of heart rate, cardiac output, and ejection fraction (Table 1). Accordingly, pigs have been used as models for many cardiovascular diseases, including atherosclerosis, hypercholesterolemia, hypertrophic cardiomyopathy, as well as for the exploration of cardiac regeneration and cell therapy (Davis et al., 2014; Huang et al., 2017; Liu et al., 2021; Montag et al., 2018; Sridharan et al., 2023). Genetic modification is well established for the pig, including conditional gene targeting (Fischer & Schnieke, 2023) and blastocyst complementation (Barlabé et al., 2025). Examples of in vivo genome editing of the porcine heart have been published (Moretti et al., 2020; Rieblinger et al., 2021). In view of the high financial and logistic burdens, generation and maintenance of genetically modified pig models is conducted

by few labs worldwide (Prather et al., 2013). Porcine-expanded potential stem cells have also been differentiated into cardiomyocytes, which may provide a useful platform for preclinical testing of cardiac therapies (Gao et al., 2019; Rawat et al., 2023). Given the similarities in size and cardiac anatomy of pigs and humans, pigs are also used for developing and testing cardiovascular devices for diagnosis and intervention (Miller et al., 2016). In addition, research involving pigs also holds promise for xenotransplantation, including the potential to grow humanized hearts in pigs, although significant challenges remain (Cooper & Cozzi, 2024; Garry et al., 2025).

Pigs are comparatively slow to reach sexual maturity (5–6 months) and have long gestational periods (approximately 16 weeks) and lifespans (up to 20 years), making generational and aging studies difficult. In addition, while the possibility of using clinical equipment for research on pigs makes them a favored model for device development and procedure testing, the associated infrastructural demands, such as for operating theater facilities, raise the threshold for wider use.

Therefore, due to similarities between porcine and human hearts, pigs are a valuable translational model for research into pathogenesis, diagnostics, and drug- or device-based therapy. Limitations include their long reproductive cycle and lifespan, often underestimated phylogenetic distance to humans, high costs, and infrastructural demands (Figure 1).

2.5 | Challenges of using non-human vertebrate models of the heart

Vertebrate models of the human heart are vital to cardiovascular research, particularly where experiments cannot be performed on humans. However, it is important that researchers consider interspecies differences that may affect the translatability of results, including mitochondrial function and dynamics (Alibrandi & Lionetti, 2025), ion currents (Horváth et al., 2020; Linz & Meyer, 2000), DNA methylation and gene expression (Pai et al., 2011), as well as cellular (Greiner et al., 2026) and myocardial architecture (Mulbjerg et al., 2025). In addition, researchers should be aware of other model-specific differences, such as in seasonal (different for farm- and laboratory-housed species) and circadian rhythms (especially for nocturnal animals, such as mice, which usually are studied at various points during their rest period, which involves substantial changes, e.g., in cardiomyocyte electrophysiology (Shen et al., 2007)), menstrual cycles (rabbits, for example, do not have a typical oestrous cycle but are induced ovulators, which must be taken into account when exploring sex differences (Giammarino et al., 2025)), and diet (as an example, standard murine chow is soy-based and, as such, high in phytoestrogens, which affects hormone balance and cardiac function in particular in male mice (Stauffer, 2005)).

Regardless of the model chosen, mimicking clinical background therapies, which are one of the central determinants of translational validity in experimental cardiovascular research (van der Velden et al., 2022), is also a crucial consideration. Evaluating new interventions without taking standard-of-care treatments into account can lead to findings that are difficult to interpret or apply in real clinical settings.

The use of living organisms as models of human disease also requires carefully balancing potential benefits for human health that can be gained against the distress, pain, and/or suffering of animals involved. Scientific research is guided by the 3R principles, referring to "replacement" when possible, "reduction" of the number of animals used, and "refinement" of protocols, interventions, and upkeep to minimize animal discomfort while maximizing scientific insight. Implicit in this is a fourth R: responsibility on the part of the investigator for the experimental animal (Hubrecht & Carter, 2019; Lee et al., 2020; Tannenbaum & Bennett, 2015). Computational modeling and simulation can contribute to refined planning of animal experiments, to data integration, and to projection from animal-based data for estimation of effects in humans (Morotti et al., 2021; Viceconti et al., 2021).

The use of non-human vertebrate models in pharmaceutical screening suffers from several principal drawbacks. Both false-positive (when therapies appear effective in animals but fail in human trials) and false-negative observations (when therapies that would perform well in humans perform poorly in animal models and are abandoned prematurely) are common (Perry & Lawrence, 2017; van der Velden et al., 2022). This explains the desire for human models, from in vitro use of patient cells to exploration of tissue and organ explants, and on to clinical data mining approaches. The aim here is to improve the accuracy of testing, and to reduce the percentage of false-negative and false-positive conclusions in pre-clinical development before human trials are commenced. Thus, human wet and dry experimental models are needed to bridge the gap between bench and bedside more effectively.

3 | HUMAN MODELS FOR CARDIAC RESEARCH

3.1 | Human induced pluripotent stem cells and human engineered heart tissue

Cardiomyocytes derived from human induced pluripotent stem cells (hiPSC-CM) provide a sustainable source

of cells that can be maintained in cell culture for months. hiPSC can be differentiated into several cardiomyocyte subtypes, including atrial, ventricular, and pacemaker-like cells (Cyganek et al., 2018; Protze et al., 2017). These cells can be used for basic research in genetics, signaling, biophysics, or regeneration. Genome manipulation, such as introducing mutations, deletions, insertions, knockouts, or knock-ins, enables the creation of disease models, investigation of the consequences of genome alterations and of genetic defect corrections, and the use of reporters and optogenetic actuators to study cell function (Bengel et al., 2021; Haertter et al., 2024; Kime et al., 2016; Stüdemann et al., 2022; Wang, McCain, et al., 2014).

The unique genetic relationship with their donors provides a potential for the exploration of genetic causes of cardiac disorders at a patient-specific level (Cuello et al., 2021; Itzhaki et al., 2011; Moretti et al., 2010; Streckfuss-Bömeke et al., 2017; Wu et al., 2024). This has supported therapy selection for individual patients (Prondzynski et al., 2019) and allowed re-classification of genetic variants of hitherto unknown importance (Ma et al., 2018).

One possibility to improve the functional depth and robustness of readouts, the maturity of hiPSC-CM, and the similarity to native heart muscle is to engineer 3D cardiac tissues and to incorporate other cell types such as fibroblasts, smooth muscle, endothelial or immune cells. These 3D models are not only increasingly being used as a platform for gene and cell therapy studies, drug screening or disease modeling (Borchert et al., 2017; Fomin et al., 2021; Greer-Short et al., 2025; Hinson et al., 1979; Kyriakopoulou et al., 2023; Kyrychenko et al., 2017; Mannhardt et al., 2016; Saleem et al., 2020; Streckfuss-Bömeke et al., 2017), but they are making their way into direct clinical use (Jebran et al., 2025). Combinations of multiple cell types in tissue-engineered heart muscle emerge as a critical precondition for maturing hiPSC-CM. These models allow for cell–cell interaction studies (Landau et al., 2024; Tiburcy et al., 2017), including research in genetically mixed models to determine the contribution of specific cell types to a phenotype or investigations into genome repair for restoration of cardiac function in disease (Long et al., 2018). Novel tissue constructs, such as assembloids composed of atrial, atrioventricular, and ventricular cardiomyocyte spheroids, allow for the study of complex disorders affecting heart rhythm (Li et al., 2024; Mallapaty, 2025). Combining multiple tissue-engineered model systems furthermore opens the door to organ–organ interaction studies (Schneider et al., 2023).

Key limitations of hiPSC-CM include their metabolic, electrophysiological, and structural immaturity, as the cells generally resemble embryonic or neonatal, rather than mature cardiomyocytes. Given this limitation, maturation strategies for iPSC-CM are actively being explored on multiple fronts, including long-term culture (Emanuelli et al., 2022), use of different culture media (Feyen et al., 2020), including protocols to foster metabolic maturation (Emanuelli et al., 2022; Feyen et al., 2020; Li et al., 2025; Rebs et al., 2025; Wickramasinghe et al., 2022), and mechanical or electrical stimulation (Hirt et al., 2014), incorporation into 3D heart organoids, or combinatorial approaches (Tan & Ye, 2018). Thus far, however, the most mature hiPSC-CM remain phenotypically different from adult cardiomyocytes (Yang et al., 2023). Another challenge of working with hiPSC-CM is managing variability that occurs from clone to clone, from differentiation to differentiation, between passages, and from laboratory to laboratory–even when nominally using the same cell lines and protocols (Thomas, Cunningham, et al., 2022). These limitations underscore the need for generally agreed-upon quality assessment routines. Stem cell journals and societies have published relevant guidelines (Selfa Aspiroz et al., 2025) and adopted minimal standards that, for example, require the use of isogenic controls when studying the effects of genetic variants and validation of results in several cell lines, sufficient numbers of replicates, and independent differentiation batches.

3.2 | Human isolated primary cardiomyocytes and non-cardiomyocytes

Unlike hiPSC-CM, primary cardiomyocytes are directly isolated from human myocardial tissue, obtained from different regions of the heart. These cells retain core characteristics of mature cardiomyocytes, including their structural, functional, and epigenetic profile (Zhou et al., 2022), while keeping patient-specific phenotypes (e.g., related to age, sex, comorbidities, medical treatments, and the progressive remodeling associated with cardiac diseases). These native phenotypes make findings more directly translatable. Isolated cardiomyocytes allow for a high degree of experimental control and provide a comparatively inexpensive, convenient pathophysiologically relevant model for evaluating cellular behavior and morphology (Oh et al., 2019; Pitoulis et al., 2020), as well as ion channel function, contraction and electrophysiological characteristics (Odening et al., 2021). Human primary cardiomyocytes have traditionally been used both in basic and translational research, particularly in signaling studies and drug efficacy/toxicity testing (Ahmad et al., 2019; Grammatika Pavlidou et al., 2023; Molina et al., 2018; Odening et al., 2021). More recently, culturing human

primary cardiomyocytes without overt dedifferentiation changes has enabled genetic manipulation, which can in turn be used to study the effects of genome alterations, as proof of concept for gene therapies, to investigate the consequences of tachypacing over time, to analyze biomarker release and function, or to utilize genetically encoded biosensors to study cellular function for example (Aceituno et al., 2024; Beneke & Molina, 2022; Berisha et al., 2021; Grammatika Pavlidou et al., 2023; Pabel et al., 2022).

However, the functional viability of isolated cells is limited to a relatively short period, typically no more than 1 day to 1 week (Aceituno et al., 2024; Beneke & Molina, 2022), before they progressively lose their structural and functional integrity (Banyasz et al., 2008; Beneke & Molina, 2022; Greiner et al., 2022; Guo et al., 2018; Mitcheson et al., 1996; Seidel et al., 2019; Zhou et al., 2022). Cold preservation of mouse hearts and human isolated myocytes can extend the time during which they can be used in functional research without major structural, functional, or transcriptional effects (Aceituno et al., 2024; Pfeilschifter et al., 2025). This time window can also be extended by isolating cells on consecutive days from living cardiac tissue slices (discussed in the next section (Greiner et al., 2022)), as live tissue slices can be maintained for several weeks (Brandenburger et al., 2012). Whether or not even longer-term cryopreservation of cells, with subsequent recovery of key live cell function, is indeed plausible remains to be elucidated (Wang et al., 2026). Although multiple cell types (e.g., cardiomyocytes, fibroblasts, neurons) can be obtained during the isolation process, so that cell–cell interaction studies are possible, cellular models cannot be used to study long-term therapeutic interventions or to replicate in vivo complexity and systemic physiological connections.

3.3 | Myocardial tissue slices

Myocardial tissue slices are living sections of human heart tissue that are usually cut to a thickness of 250–350 μm and kept in culture while mimicking certain physiological conditions. They retain key aspects of the structure (e.g., matrix/cell integration), function (e.g., electrical activity and contractions), and heterocellular signaling of native tissue (Brandenburger et al., 2012; Fischer et al., 2019; Pitoulis et al., 2020; Wang, Terrar, et al., 2014; Watson et al., 2019). Remarkably, myocardial tissue slices can maintain electrophysiological behavior that is close to that of the same tissue-block surface before cutting (as shown in slices from rabbit hearts (Wang, Terrar, et al., 2014)). They also maintain contractility, gene expression profiles and the response to important pharmacological or hormonal stimuli for up to 3 months (Fischer et al., 2019; Klumm et al., 2022; van der Geest et al., 2025). Similar to hiPSC-CM and 3D models, myocardial slices can be used to explore disease mechanisms and can be matched with patient data (Abu-Khousa et al., 2020). They can also be used to evaluate or identify the therapeutic effects of drugs (Amesz et al., 2024; Krammer et al., 2025), and for the study of cardiac contractility modulation (Bierhuizen et al., 2025) and cardiac toxicity screening (Shi et al., 2023). This model can also be used to separate human myocardium from the extracardiac neural innervation that may otherwise confound results in vivo, providing a tissue model with controlled conditions. Direct effects on the myocardium can thus be studied in high detail and with high fidelity. Furthermore, due to the extended viability in culture (Fischer et al., 2019; Habeler et al., 2009), the study of long-term effects, such as of cardiac tissue remodeling, becomes possible. The analysis of the culture medium offers another opportunity, as released metabolic products, cytokines or enzymes, as well as nutrients can be quantified (Baron et al., 2024).

Limitations of myocardial slices include the tissue damage that occurs during slicing, which directly affects near-surface cell layers. Furthermore, given the transmurally varying alignment of cardiac cells relative to the cutting plane, the functional variability from slice to slice, even if cut from the same tissue block, can be significant. Furthermore, although permitting a high level of control, for example, over the diastolic load or the composition of the culture medium, the local biophysical (e.g., stress/strain conditions, electrical source-sink relations) and biochemical environments (e.g., nutrient accessibility, hormonal signaling, oxygen delivery) differ from in vivo conditions (Baron et al., 2024). Slices are also disconnected from the circulation and nervous system, so that the exploration of inter-organ crosstalk, of effects of the immune system, and of response to systemic signals is restricted.

Despite these limitations, myocardial tissue slices represent one of the closest approximations to native human myocardium available in vitro. For myocardial tissue slices to realize their full translational potential, coordinated efforts towards protocol harmonization, inter-laboratory reproducibility assessment, and consensus definition of minimal reporting standards will be essential (Quinn et al., 2011).

3.4 | In silico models

Computational models of the human heart span from single-cell to organ-in-chest levels, with a primary focus on electrophysiology and mechanical function. Mechanistic in silico models are versatile and scalable, allowing researchers to explore various physiological and pathological scenarios

in a well-controlled and cost-effective way, and without the use of animal or human samples (Lai et al., 2025; Niederer et al., 2019; Trayanova et al., 2024; Yamamoto et al., 2026; Zhang et al., 2026). Validated models can predict emergent behavior on different biological levels of integration, to optimize data interpretation, diagnosis, and treatment. In direct iteration with wet-lab research, they can serve as the start (hypothesis-generating) and end (data interpretation) of integrated knowledge development (Loewe et al., 2025), though start and end are arbitrary designations in what is probably more akin to a spiral of knowledge development (Quinn & Kohl, 2013). In combination with artificial intelligence-based data assessment, mechanistic in silico models are becoming increasingly predictive (Corral-Acero et al., 2020; Roney et al., 2022) and are beginning to directly aid personalized cardiac treatment (Lai et al., 2025; Sakata et al., 2024; Sakata et al., 2026; Shade et al., 2021; Waight et al., 2025).

Regulatory acceptance of in silico data is increasing. The Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative, aimed to develop a novel, mechanistic, and model-informed assessment of the pro-arrhythmic potential of new drugs, including the use of in silico computer modeling to calculate pro-arrhythmic risk scores (as well as 2D and 3D hiPSC-CM models), is an example of this development, as it involves regulatory agencies such as the FDA and EMA as stakeholders (Li et al., 2020; Vicente et al., 2018). In April 2025, for example, the FDA announced a phasing out of mandatory animal testing for some drug types, to be replaced with computational models (among other sources of data) (Food and Drug Administration, 2026). The same month, the National Institutes of Health announced a plan to prioritize human-based research technologies, including computational models that "simulate complex human systems, disease pathways, and drug interactions" (National Institutes of Health, 2026). The use of in silico models to assess cardiovascular safety is therefore increasingly embedded within regulatory science and drug development (Ridder et al., 2020). As computational approaches are poised to inform high-consequence decisions, their credibility must be established within structured risk-based frameworks such as V&V40 (Verification & Validation 40) (U.S. Department of Health and Human Services, 2018), and aligned with the emerging principles of Good Simulation Practices (GSP) (Viceconti & Emili, 2024). These frameworks emphasize rigorous verification (ensuring that the computational implementation correctly represents underlying mathematical models), validation (demonstrating that model outputs are consistent with the relevant biological or clinical reality for the defined context of use), and uncertainty quantification (characterizing parametric, structural, and methodological uncertainties and their impact on decision-relevant outputs).

Limitations of in silico models include the fact that their utility depends on the quality and extent of input data, both for mechanistic and probabilistic models. And while computational approaches can help translate insight across species, validation using human data remains paramount.

4 | AVAILABILITY OF HUMAN TISSUE FOR CARDIAC RESEARCH

Human cardiac tissue availability is a bottleneck for basic research. Myocardial tissue cannot be obtained by voluntary live-donation, and while biopsy material or samples from surgical interventions may be collected for certain clinically diagnostic purposes, access to control tissue from non-diseased hearts is not an option, except for post-mortem or (in some countries) non-transplanted donor hearts. The use of human heart tissue for functional and molecular research is therefore generally restricted to settings where it has been excised for medical reasons, such as atrial tissue resected for cardiac bypass surgery, ventricular tissue excised during aortic valve replacement or for ventricular assist device implantation, during septal myectomy in patients with obstructive hypertrophic cardiomyopathy or aortic stenosis, or whole hearts excised from transplant recipients. In all these scenarios, the excised tissue is from diseased hearts, so that "control experiments" compare one medical condition with another (e.g., atrial tissue from patients with atrial fibrillation can be compared to tissue from patients in sinus rhythm–but both groups include patients with cardiac conditions that necessitated cardiac surgery). There is therefore an obvious unmet need for non-failing human heart tissue that can be used as a reference for control investigations. Post-mortem organ donation of non-failing heart tissue for research and teaching is possible, but the suitability of tissue for functional studies is determined by the time taken to access it, as delays of more than a few minutes pose major limitations for studies relying on metabolically competent organs and cells. A realistic source of live non-failing control myocardium would be donor hearts that, for unforeseen reasons, cannot be used for their primary medical purpose–transplantation–but this is not always possible (Iaizzo, 2016).

4.1 | Use of non-failing human heart tissue for scientific research: Challenges and opportunities

Access to non-failing control myocardium in the form of rejected donor hearts is problematic in Germany. While there is a shortage of organ donors in Germany and

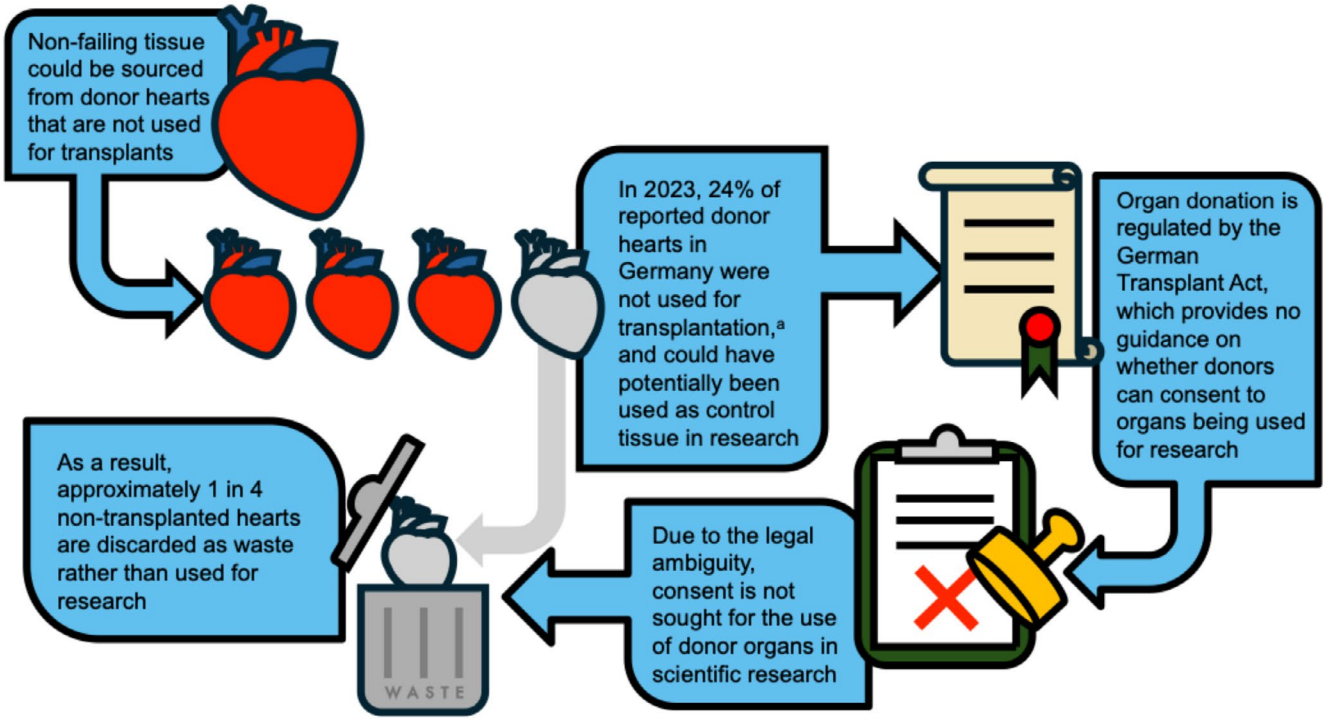

FIGURE 2 Why non-failing hearts are not used as control tissue in scientific research in Germany. [a]Eurotransplant Statistics Report Library 2024 (Library, 2023).

elsewhere anyway (Bunnik, 2023; Eurotransplant, 2024; IRODaT, 2024; Library, 2023; Pick & Krug, 2024; Statista, 2024), not all available organs can be transplanted. For example, 96 of the 399 hearts (24%) that would have been available for transplantation in 2023 were not used (Figure 2). Whatever the reasons for non-transplantation, those donor organs may not be utilized for research in Germany. This means that about one in four donor hearts end up as biological waste, despite the fact that a single donor heart could provide enough human cells and control tissue to support dozens, if not hundreds of research projects utilizing in vitro models, such as live tissue slices, isolated cells, or cultures. This waste occurs because German transplantation legislation does not include (and hence, does not permit) the use of donor organs for any other than medical purposes. Documentation of donor consent is focused exclusively on tissue and organ use for direct therapeutic purposes, and options in case of non-transplantation, including the potential use of donated tissue in research or education, are not included in these forms. This contrasts with the UK, for example, where the donor or the relatives/nominated representatives are consulted, using a clearly structured consent/authorisation form. This is completed by the National Health Service (NHS) staff during consultation and it includes specific tick-box questions covering secondary (non-medical) uses, such as for research, training, or quality assurance. The overall rate of consent for research use of organs found to be unsuitable for transplantation is very high, at 93% for the UK as a whole (Mumford, 2022). The lack of a similar structured approach to consent for secondary uses in Germany, by contrast, means that it is difficult (if not impossible) to even approximate the willingness of patients to consent to their tissue being used for research purposes.

Additional confusion arises around the legal "ownership" of an organ. Once it has been assigned to a recipient by Eurotransplant, for example, 'ownership' is formally transferred to the recipient. But–there is no guidance on whose consent (the donor's or recipient's) would be required for non-medical use if an organ is eventually not transplanted. Due to this legal ambiguity, donor organs which cannot be transplanted are currently discarded (Figure 2).

This situation is part of the patchwork of regulations relating to organ donation across Europe, where the use of donor tissue is generally determined on a national level (Figure 3), and which may add an additional layer of legal complexity around questions of ownership and consent, as organs are regularly shared between countries during the process of donor–recipient matching. This situation contrasts with the USA, where the use of human tissue in research is governed by federal, state, and local laws, regulations, and policies, including the Department of Health and Human Service's "Common Rule" and the Health Insurance Portability and Accountability Act (Bledsoe & Grizzle, 2013; Grizzle, 2019). In practice, human heart

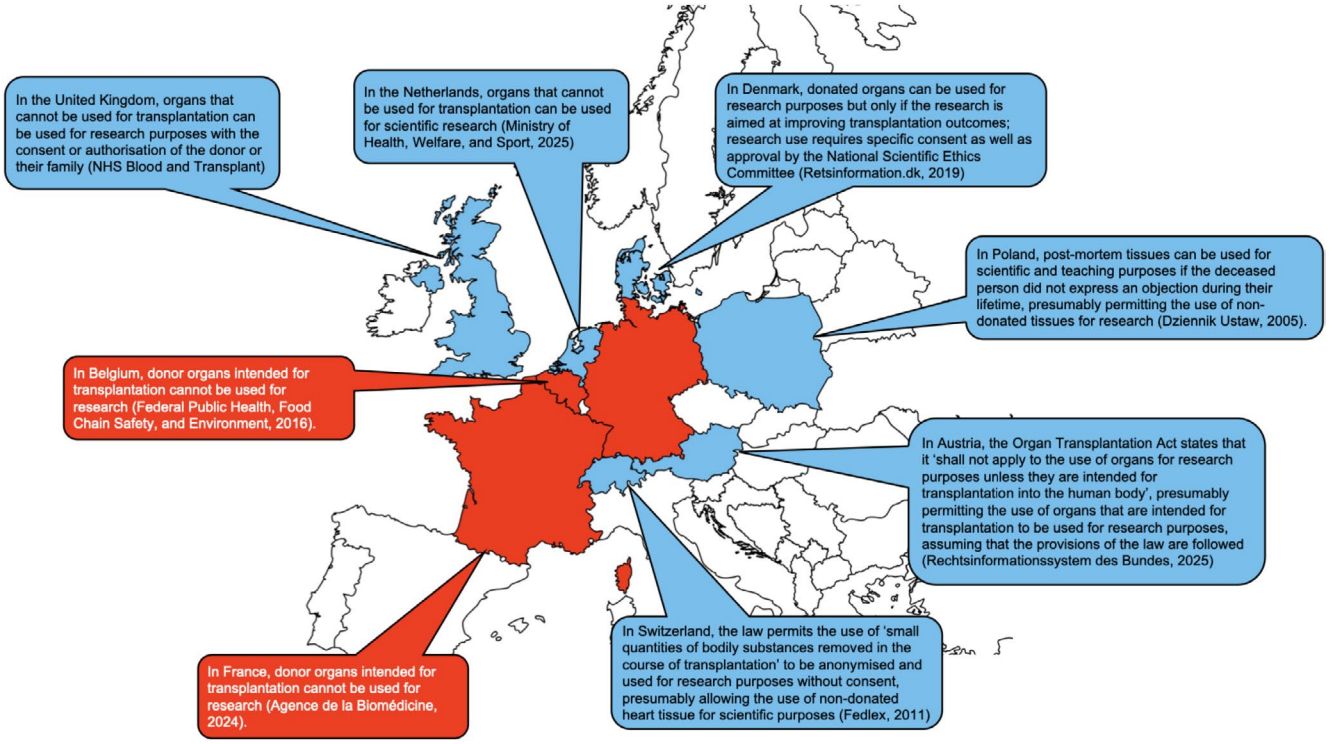

FIGURE 3 Laws and guidelines relating to the use of non-transplanted donor hearts for research in selected European countries (Dossier de presse, 2024; Fedlex. Federal Act, 2011; Health Food Chain Safety Environment, 2016; NHS Blood and Transplant, 2026; Rechtsinformationssystem des Bundes, 2026; Retsinformation.dk, 2026; Scientific Research, 2026; Ustaw, 2026).

tissue can be obtained for scientific research via tissue banks and networks like the National Cancer Institute-funded Cooperative Human Tissue Network (https://chtn.cancer.gov/), Texas Children's Hospital's Heart Center Tissue Bank (https://www.texaschildrens.org/research/find-laboratory/heart-center-tissue-bank), and the International Institute for the Advancement of Medicine (https://iiam.org/researchers/human-tissue-for-research/). These provide non-transplantable organs and tissues (including cardiac tissue) for use in medical research on a national scale.

A key question raised in this context is whether or not it is ethically acceptable (e.g., consistent with donor intentions) for tissue that cannot be used for the originally intended purpose (clinical application) to be used for secondary objectives such as medical research, training, or quality control. It may be assumed that organ donors are altruistic, as they intend their donation to benefit others. Whether this includes the indirect benefits of scientific research into cardiac diseases cannot be assessed retrospectively. However, the high proportion of donors (or their families) who consent to their tissues being used for research purposes when given the option (93% in the UK, 89% in the Netherlands, for example (Lutomski & Manders, 2024; Mumford, 2022)) suggests that donor intentions may be broader than simply supporting direct medical use. This is also evident from the very high proportion of patients who are willing to donate (diseased) tissue for use in scientific research, once it has been excised for medical reasons (Fitzpatrick et al., 2009; Jack & Womack, 2003). This means that, in view of the uniquely relevant roles of control tissue for research, an alternative question should be posed–namely whether it is ethically acceptable for tissue that cannot be transplanted to be simply discarded, instead of being used in secondary applications.

The legislative situation in Germany regarding organ donation seems unlikely to improve soon (Bundestag, 2020; Kappler & Kohl, 2023; Rehsmann, 2023; Welle, 2020), as is evident from the response of the German government (Deutscher Bundestag 20, 2023a) to a formal parliamentary enquiry on this very topic (Deutscher Bundestag 20, 2023b) in 2023. Since the use of organs or tissue, originally intended for transplantation, for research, teaching, or quality control is unaddressed (i.e., neither permitted nor prohibited per se) in Germany, it would seem to be prudent to consider changing the informed consent process, in collaboration with organizations conducting it for organ donation, perhaps to a model similar to that of the UK. This may involve the creation of shared standard operating procedures to ensure that organs which cannot be used for transplantation do not go to waste, as well as the establishment of a coordinated national (or European) procurement network to handle, process,

and share tissue for research, to prevent the current waste of uniquely valuable control tissue.

5 | CONCLUSIONS

There are multiple model systems for human cardiovascular research, including animal tissue, iPSC-derived cells, primary human tissue and cells, and computational models. All these models have inherent benefits and limitations, related to how well they represent specific aspects of human cardiac structure and function, as well as reproducibility, amenability to conducting controlled investigations, cost, and access, to name but a few. While pronounced interspecies differences can be bridged (at least in part) using theoretical models, human heart tissue remains the gold standard for clinically relevant cardiac research. The scarcity of human heart tissue, in particular from non-failing control hearts, is compounded by the fact that donor tissue that cannot be used for its intended primary medical purpose is not yet systematically available for academic research, training, and quality control, with divergent regulations in individual European countries (Figure 3). The UK provides a good example of how consent for primary and secondary uses of organs can be effectively obtained, with very high rates of consent. Conversely, legal ambiguities, such as in Germany, can hinder the use of precious donor tissue for the advancement of medical insight. This calls, on the one hand, for careful combination of multiple model systems leveraging their respective strengths, and on the other hand, for a broader discussion with all stakeholders about the handling of donated tissue for medical progress in the present (i.e., treatment) and future (i.e., research).

AUTHOR CONTRIBUTIONS

Katrin Streckfuss-Bömeke: Conceptualization. **Laura C. Zelarayán:** Conceptualization. **Renate B. Schnabel:** Conceptualization. **Nicolle Kränkel:** Conceptualization. **Christoph Maack:** Conceptualization. **Thomas Eschenhagen:** Conceptualization. **Hannah E. Kappler:** Conceptualization. **Ursula Klingmüller:** Conceptualization. **Rafael Kramann:** Conceptualization. **Axel Loewe:** Conceptualization. **Hendrik Milting:** Conceptualization. **Cristina E. Molina:** Conceptualization. **Daniela Panáková:** Conceptualization. **Bruno K. Podesser:** Conceptualization. **Angelika Schnieke:** Conceptualization. **Katrin Schröder:** Conceptualization. **Thomas Seidel:** Conceptualization. **Samuel Sossalla:** Conceptualization. **Callum Zgierski-Johnston:** Conceptualization. **Wolfram-Hubertus Zimmermann:** Conceptualization. **Eva A. Rog-Zielinska:** Conceptualization. **Peter Kohl:** Conceptualization.

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CONFLICT OF INTEREST STATEMENT

Katrin Streckfuss-Bömeke: speakers' honoraria from Novartis. Christoph Maack: speakers/consulting honoraria from Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Lilly, Novo Nordisk. Thomas Eschenhagen: advisor and member of board of directors of Dinabios AG. Rafael Kramann: founder, equity holder, and advisor Sequantrix GmbH. Bruno K. Podesser: advisor to HeartbeatBio GmbH. Thomas Seidel: equity holder in InVitroSys GmbH. Samuel Sossalla: speakers/consulting honoraria from Astra Zeneca, Novartis, Berlin-Chemie, Daiichi Sankyo, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Lilly. Wolfram-Hubertus Zimmermann: founder of, equity holder in, and advisor to Repairon GmbH and myriamed GmbH. All other authors have no conflicts to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article, as no datasets were generated or analyzed.

ETHICS STATEMENT

There was no ethics approval required for this study.

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