Artificial Intelligence, Computational Simulations, and Extended Reality in Cardiovascular Interventions

26 December 2024

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 20, 2023

STATE-OF-THE-ART REVIEW

Artificial Intelligence, Computational Simulations, and Extended Reality in Cardiovascular Interventions

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ABSTRACT

Artificial intelligence, computational simulations, and extended reality, among other 21st century computational technologies, are changing the health care system. To collectively highlight the most recent advances and benefits of artificial intelligence, computational simulations, and extended reality in cardiovascular therapies, we coined the abbreviation AISER. The review particularly focuses on the following applications of AISER: 1) preprocedural planning and clinical decision making; 2) virtual clinical trials, and cardiovascular device research, development, and regulatory approval; and 3) education and training of interventional health care professionals and medical technology innovators. We also discuss the obstacles and constraints associated with the application of AISER technologies, as well as the proposed solutions. Interventional health care professionals, computer scientists, biomedical engineers, experts in bioinformatics and visualization, the device industry, ethics committees, and regulatory agencies are expected to streamline the use of AISER technologies in cardiovascular interventions and medicine in general. (J Am Coll Cardiol Intv 2023;16:2479–2497)

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ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2023.07.022

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

AI = artificial intelligence

AISER = artificial intelligence, computational simulations, and extended reality

AR = augmented reality

CCTA = coronary computed tomography angiography

CFD = computational fluid dynamics

CS = computational simulations

DL = deep learning

ER = extended reality

FDA = Food and Drug Administration

FFR = fractional flow reserve

IVUS = intravascular ultrasound

ML = machine learning

OCT = optical coherence tomography

TAVR = transcatheter aortic valve replacement

VCT = virtual clinical trial

Computational technologies such as artificial intelligence (AI), computational simulations (CS), and extended reality (ER) are changing the medical practice.[1,2] These computational technologies can be used to guide procedures and potentially improve outcomes in the field of cardiovascular interventions.[3] AI algorithms, such as machine learning (ML) and deep learning (DL), make data collection, randomization, and mining easier as well as personalized risk predictions and clinical decision making possible.[4,5] CS of cardiovascular interventions produce patient-specific data related to the diagnosis and treatment of cardiovascular diseases.[6-8] ER technologies improve our understanding of complex cardiovascular anatomy and interventional procedures, and they provide safe and reproducible environments for interventional health care providers and medical technology developers to learn and train.[9]

In this review, we use the acronym AISER to refer to all 3 computational domains: AI, CS, and ER. We investigate AISER's applications in cardiovascular interventions, from preprocedural planning to device research and development, regulatory approval, in silico or virtual clinical trials (VCTs), and education and training (Supplemental Figure 1). **Table 1** contains detailed definitions and terminologies of associated computational technologies. In contrast to previous work that looked at each of the AISER components separately, this paper focuses on the interdependence and synergies between the AISER components.[4,7,9]

ROLE OF AI IN CARDIOVASCULAR INTERVENTIONS

ROLE OF AI IN SEGMENTATION AND ANALYSIS OF CARDIOVASCULAR IMAGES. AI-based tools can automate analysis and the interpretation of invasive (ie, optical coherence tomography [OCT] and intravascular ultrasound [IVUS]) and noninvasive imaging modalities (echocardiography, coronary computed tomography angiography [CCTA], and magnetic resonance angiography) to improve cardiovascular diagnosis and treatment.[5,10,11] AI-facilitated fusion of accurately segmented IVUS or OCT images with invasive angiography or CCTA is the foundation for anatomically correct 3-dimensional (3D) reconstruction of coronary vessels, which in turn enhances the understanding of complex coronary artery anatomies and facilitates preprocedural planning.[12,13] Furthermore, AI-based software facilitates real-time coregistration of fluoroscopy with transesophageal echocardiography to guide structural heart interventions, including left atrial appendage occlusion, transcatheter mitral valve repair, transcatheter aortic valve replacement (TAVR), atrial septal defect

HIGHLIGHTS

- In the era of evidence-based medicine, computational technologies such as artificial intelligence, computational simulations, and extended reality have the potential to reshape the health care systems worldwide.
- This review collectively highlights the latest technological advancements and synergies of artificial intelligence, computational simulations, and extended reality in cardiovascular interventions.
- Artificial intelligence, computational simulations, and extended reality could improve preprocedural planning, real-time decision making, device research and development, device regulatory approval, and education and training of interventional health care providers and medical device innovators.

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H. Vernon "Skip" Anderson, MD, served as Guest Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 3, 2023; revised manuscript received July 11, 2023, accepted July 13, 2023.

TABLE 1 Terminology and Definitions

Term	Definitions
Big data[2]	Large amount of raw data collected from heterogeneous sources, such as electronic health records, clinical imaging, observational registries, demographic biobanks, and atlases
Precision medicine[7]	Customized medical care tailored to each patient's unique characteristics
Artificial intelligence[4]	Computer systems that independently perform a task that usually requires human intelligence. Artificial intelligence includes training (acquisition of information and interpretation of data), reasoning (rules to reach a conclusion), and self-correction
Machine learning[4]	A subset of artificial intelligence that trains algorithms to adapt and improve their performance and outcomes with exposure to more data over time, without active human interference
Deep learning[4]	An advancement of machine learning that requires less structured data to learn simultaneously from large data sets. It is described as a convolute artificial neural network that processes and transmits information
Simulations[7]	Simulation is the recreation of a real-world process or system over time. Three types of simulations have been used in cardiovascular interventions: bench, ex vivo, and computational. • Bench simulations: testing of a device or technique using bench models • Ex vivo simulations: experimental procedures on animal or cadaveric hearts and vessels in a perfusion circuit (eg, Visible Heart [Visible Heart Laboratories] methodologies) combined with imaging[96] • Computational simulations: the process of mathematical modeling performed on a computer, which is designed to predict the behavior or the outcome of a real system.[97] There is a bidirectional relationship between reality and simulations; the experimental results validate and improve the simulation models, and the simulations run endless hypothetical scenarios and generate theoretical outcomes in a time- and cost-efficient manner (Supplemental Figure 2).
Extended reality[9]	Broad term that includes virtual reality, augmented reality, and mixed reality
Virtual reality[9]	A simulated experience wherein the user is fully immersed into the interactive virtual world
Augmented reality[9]	A simulated experience wherein the user can interact with computer-generated virtual objects preserving at the same time the real-world environment
Mixed reality[9]	A state where the augmented and virtual reality coexist and interact in real time

occlusion, and paravalvular leak repair (EchoNavigator, Philips).[14]

ROLE OF AI IN DIAGNOSTIC ASSESSMENT OF CORONARY ARTERY DISEASE AND PREPROCEDURAL PLANNING. AI could improve the diagnosis of coronary artery disease and lead to patient-tailored interventions. AI-guided coronary angiography-based virtual fractional flow reserve (FFR) systems can 3D reconstruct the coronary arteries and assess the hemodynamic significance of stenoses (Supplemental Figure 3A).[15,16] AI algorithms enable CCTA-based 3D reconstruction of coronary arteries with varying degrees of calcification and calculation of FFR (HeartFlow FFR_{CT} and Cleerly [Cleerly Labs]; Supplemental Figure 3B).[17,18] The previously mentioned invasive and noninvasive softwares achieved >90% sensitivity, specificity, positive predictive value, and accuracy compared to invasive FFR.[16,18] IBM has developed an AI system (Medical Sieve) capable of automatically identifying coronary stenoses in coronary angiographies. Initial findings from the CEREBRIA-1 (Machine Learning vs Expert Human Opinion to Determine Physiologically Optimized Coronary Revascularization Strategies) study support the robustness of ML in determining physiologically significant coronary artery stenosis to guide revascularization.[19] ML methods have been used to predict plaque vulnerability by integrating morphologic and biomechanical factors derived from multimodality image-based fluid-structure interaction models.[20] A recently launched software uses DL to automatically segment OCT images in real time and quantify calcium burden, thereby assisting optimal vessel preparation for stent sizing and positioning (Ultreon 1.0, Abbott) (Supplemental Figure 3C).[21,22]

ROLE OF AI IN CARDIOVASCULAR RISK PREDICTION AND OUTCOMES. ML algorithms can identify patients at risk for myocardial infarction who would benefit from early management.[23,24] In a large multicenter observational cohort study, an ML algorithm that combined clinical and computed tomographic variables (including coronary calcium scoring) was found to be superior to standard cardiovascular risk assessment scores, such as atherosclerotic cardiovascular disease risk score or calcium score, in predicting adverse cardiovascular events (Supplemental Figure 4).[25] Traditional scoring systems only include a subset of patient variables, whereas ML methods are exhaustive and can incorporate all available clinical and imaging data to enhance the prognostic accuracy. AI-guided risk assessment models can predict adverse events following acute coronary syndromes as well as

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 20, 2023
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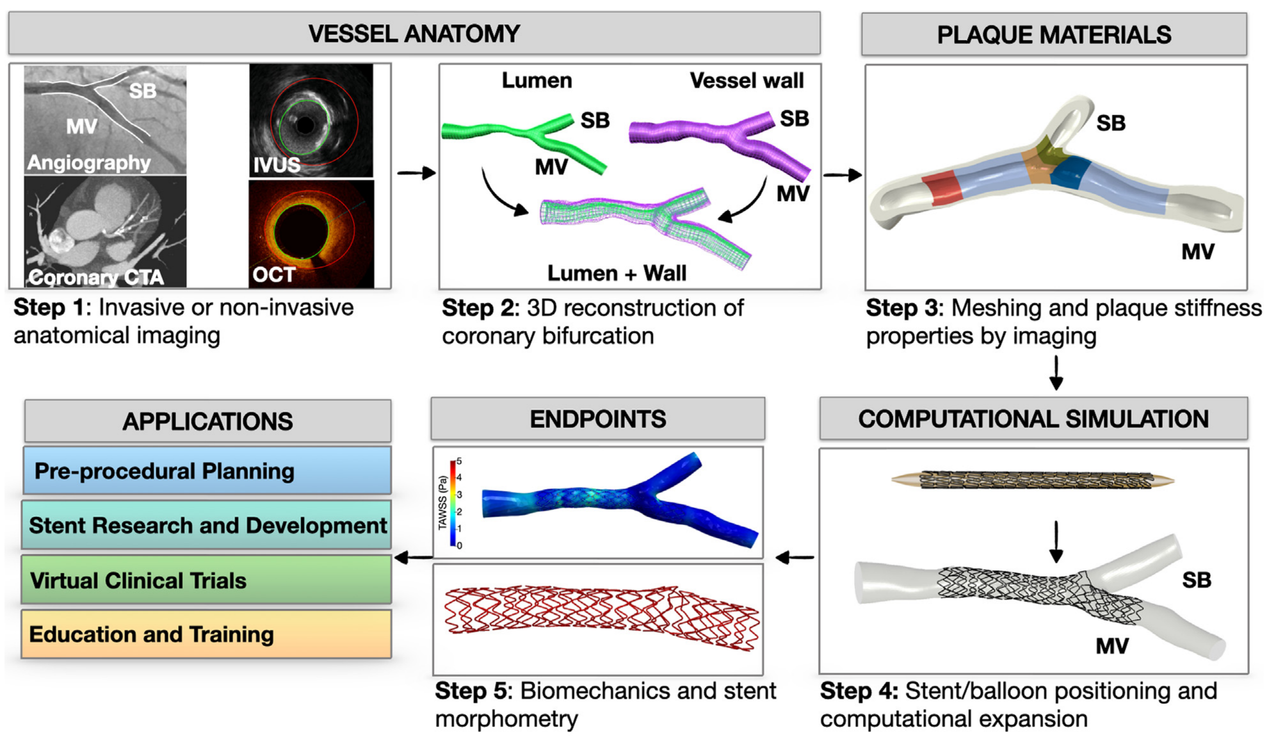
FIGURE 1 Workflow and Applications of the Computational Simulations of Coronary Artery Stenting



 Modified with permission from Zhao et al.[38] CTA = computed tomography angiography; IVUS = intravascular ultrasound; MV = main vessel; OCT = optical coherence tomography; SB = side branch; TAWSS = time-averaged wall shear stress.

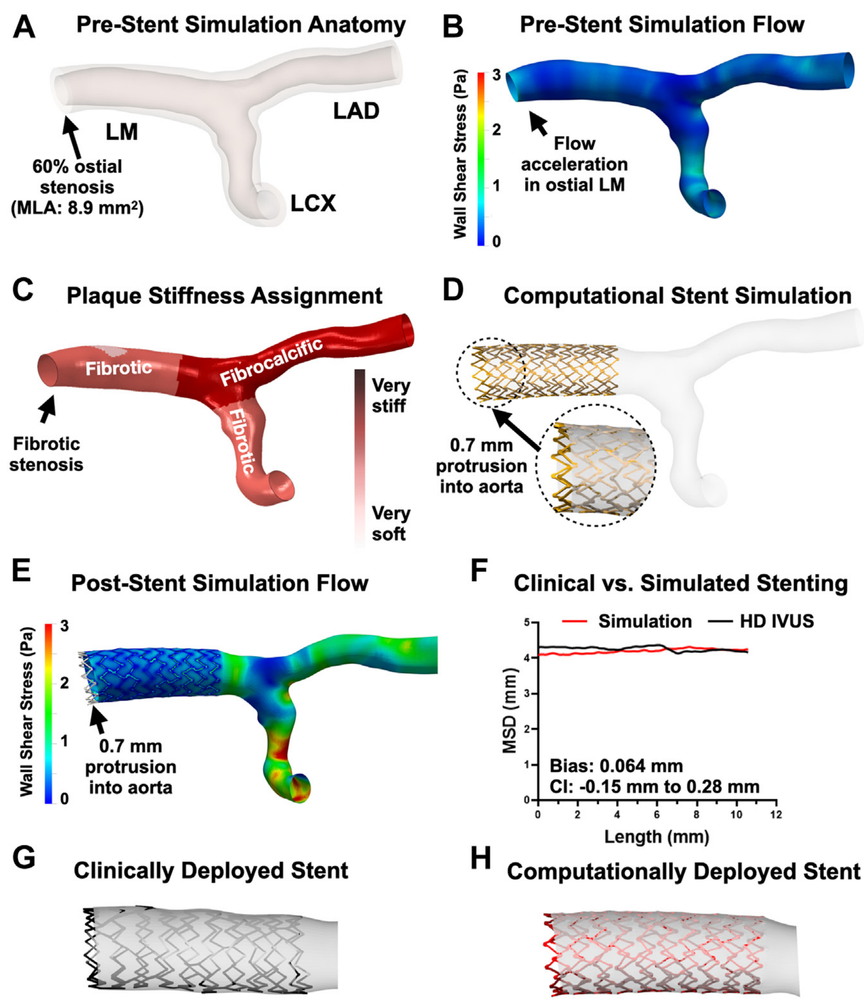
morbidity and mortality post-percutaneous coronary intervention.[26,27] Supervised ML algorithms also predicted in-hospital mortality after TAVR (sensitivity, specificity, and positive and negative predictive values up to 96.3%, 83.9%, 96.5%, and 83.8%, respectively) and transcatheter mitral valve repair (AUC: 0.83).[28,29]

ROLE OF AI IN CORONARY AND STRUCTURAL INTERVENTIONS. AI-driven robotics have the potential to streamline coronary interventions, reduce the duration of procedures, and improve patient outcomes. Small-scale clinical studies have shown that robot-assisted percutaneous interventions in coronary arteries, peripheral lower extremity arteries, and carotid arteries are safe, feasible, and eliminate the radiation exposure and musculoskeletal strain of operators.[30-33] Robotic technologies could enhance procedural precision and efficiency in percutaneous coronary and peripheral interventions.[34] A magnetic resonance-compatible robotic surgical assistant system designed for TAVR deployment has been successfully tested in preclinical swine studies.[35]

ROLE OF CS IN CARDIOVASCULAR INTERVENTIONS

ROLE OF CS IN PREPROCEDURAL PLANNING OF PERCUTANEOUS CORONARY INTERVENTIONS. Patient-specific CS of various stent designs and revascularization strategies could provide detailed information about stent performance and technique optimization.[6] A study showed the ability of invasive angiography-based FFR and virtual stenting to accurately predict the physiological response to actual stenting.[36] A similar approach has been developed using noninvasive CCTA.[37] The Center for Digital Cardiovascular Innovations (University of Miami Miller Medical School) has developed a novel CS platform that combines: 1) anatomical and plaque stiffness information derived from invasive imaging (coronary angiography, IVUS, and OCT) or noninvasive (CCTA) imaging; and 2) finite element analysis and computational fluid dynamics (CFD) to perform patient-specific simulations of coronary bifurcation stenting[38] (Figures 1 and 2) and assess the impact of different stenting techniques on local hemodynamics

FIGURE 2 Preprocedural Computational Planning Using Patient-Specific Coronary Anatomies

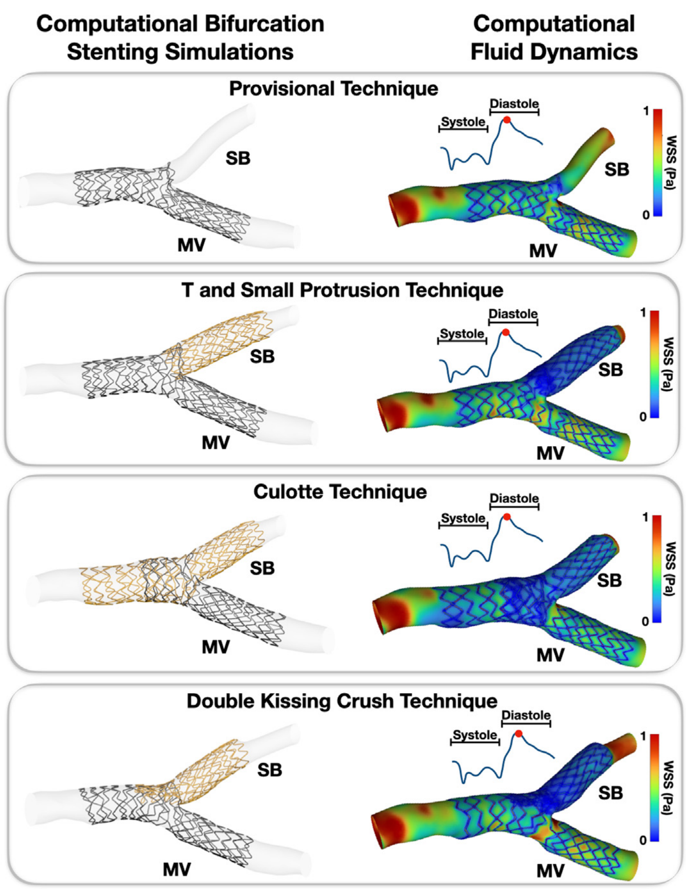


(A) Baseline anatomy; (B) wall shear stress by computational fluid dynamics before computational stenting; (C) plaque stiffness by high-definition intravascular ultrasound (HD IVUS), showing the fibrocalcific ostial left main (LM) coronary artery stenosis; (D) computational stent deployment, (E) wall shear stress by computational fluid dynamics after computational stenting, (F to H) 3-dimensional reconstruction of the clinically deployed stent from HD IVUS and comparison with the computationally deployed stent. Adapted with permission from Chatzizisis et al.[42] LAD = left anterior descending artery; LCX = left circumflex artery; MLA = minimal lumen area.

(Figures 2 and 3).[39-41] This platform generated preliminary clinical data that support the ability of CS-based preprocedural planning to guide left main interventions (Figure 2).[42]

ROLE OF CS IN SURGICAL REVASCULARIZATION OF CORONARY ARTERY DISEASE. Patient-specific CFD studies of coronary artery bypass graft surgery have provided important information on the impact of graft type and competitive flow on graft patency.[43,44] Postoperative calculation of wall shear stress by CFD has predicted the 1-year patency of left internal mammary artery grafts.[45] Consequently, preprocedural planning of bypass surgery using patient-specific CS represents an intriguing concept.[46] The FASTTRACK CABG (Safety and Feasibility Evaluation of Planning and Execution of Surgical Revascularization Solely Based on Coronary CTA and FFR_{CT} in Patients With Complex Coronary Artery Disease) trial investigates the feasibility and safety of noninvasive FFR_{CT} guidance for bypass graft surgery.[47] Similarly, the Center for Digital Cardiovascular Innovations has developed a platform for patient-specific virtual bypass grafting and

FIGURE 3 Patient-Specific Computational Stent Simulations



(Left) Computational stenting of a patient-specific coronary artery bifurcation using 4 different percutaneous coronary intervention techniques. (Right) Wall shear stress (WSS) derived from computational fluid dynamics in the simulated stented bifurcation at peak diastole. Note the potential of computational simulations to guide the operators on the optimal stent sizing, positioning, and technique for any given bifurcation. Abbreviations as in Figure 1.

computational calculation of the flow in native coronary arteries and virtually implanted grafts.[48] This platform could equip the surgeons with a noninvasive tool that would allow them to plan on the number and type of grafts, aiming to improve graft patency and clinical outcomes.

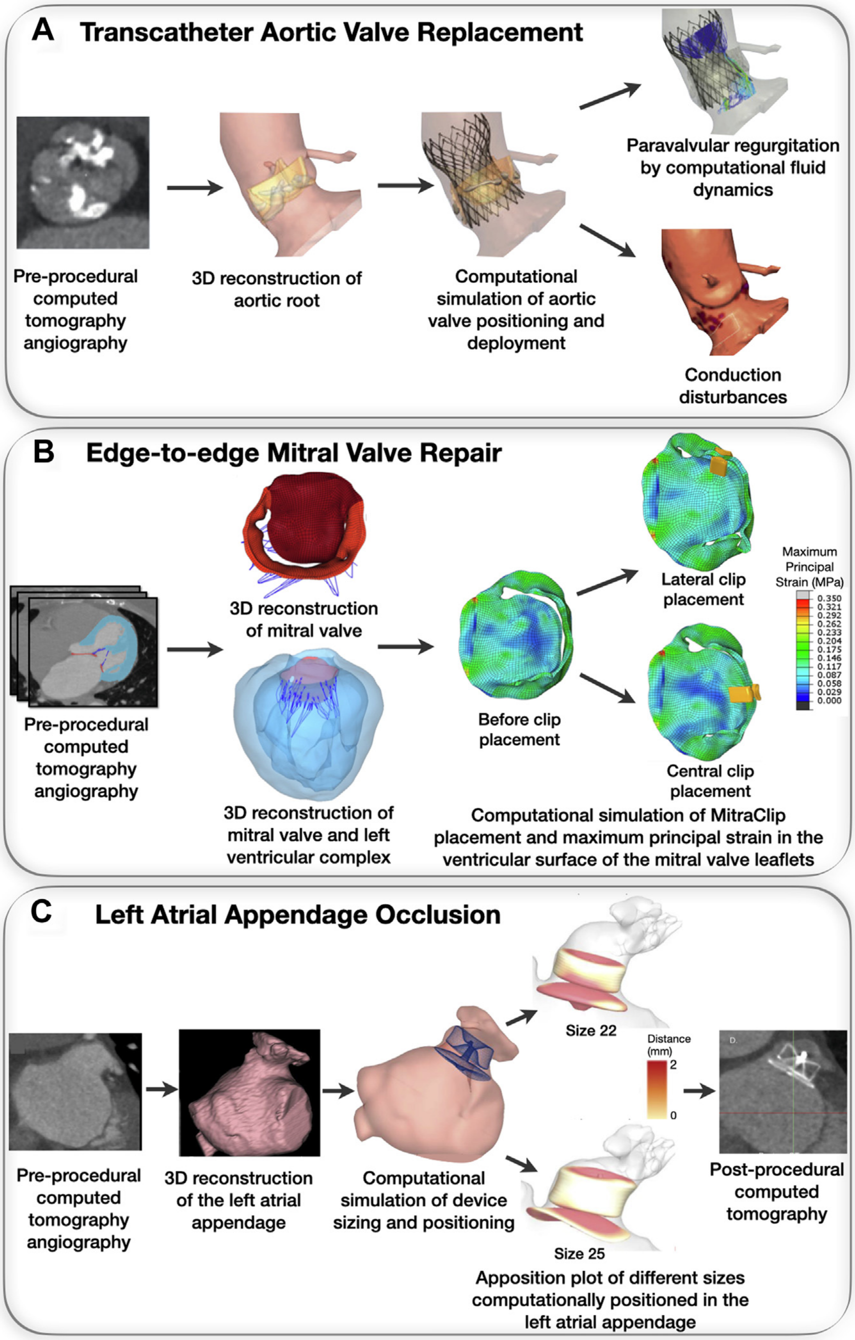
ROLE OF CS IN PREPROCEDURAL PLANNING OF STRUCTURAL INTERVENTIONS. Patient-specific CS of TAVR could guide operators on the optimal aortic valve size and position, thereby minimizing the risk of postprocedural paravalvular aortic regurgitation and conduction abnormalities.[49-52] The feasibility, safety, and efficacy of CS-guided TAVR has been shown in a proof-of-concept case series and in a prospective observational multicenter study using a dedicated computational platform (TAVIguide, FEops NV) (Figure 4A).[52,53] Analogous applications of CS have been deployed for percutaneous edge-to-edge mitral valve repair, mitral valve annuloplasty, and mitral valve replacement procedures.[7,54] Patient-specific CS of edge-to-edge mitral valve repair (MitraClip, Abbott) have used the stress and strain on mitral valve leaflets and mitral valve regurgitation as surrogate endpoints to identify the optimal site for clip placement (Figure 4B).[7,55,56] CS of left atrial appendage occlusion procedures have used simulated device apposition to identify the optimal device size and positioning in patient-specific anatomical models (HEARTguide, FEops) (Figure 4C).[57]

ROLE OF CS IN PERIPHERAL AND CEREBRAL INTERVENTIONS. Patient-specific CS have been used in endovascular aortic aneurysm repair procedures to guide operators on the optimal stent graft size, design, placement, and ultimately improve procedural outcomes.[58-60] CS-guided preprocedural planning of endovascular aneurysm repair led to a reduction in radiation exposure and contrast use.[61] Similarly, patient-specific CS have been used in the cerebral vasculature, studying the effect of vasculature morphology on the outcomes of mechanical thrombectomy with stent retrievers.[62]

ROLE OF CS IN MECHANICAL CIRCULATORY SUPPORT. CS could determine the hemodynamic effects of mechanical circulatory support devices including left ventricular assist devices, intra-aortic balloon pumps, and extracorporeal membrane oxygenation. Patient-specific CS of left ventricular assist devices with realistic pressure-flow rates have elucidated the effects of the device on the free and septal wall stress distribution, identifying the crucial mechanistic role of septal shift to the development of right ventricular dysfunction post-device implantation.[7,63] These studies highlighted the importance of personalizing the optimal rotational speed of the assist device to achieve an equilibrium between effective circulatory support and reduced device-induced wall stress and septal shifting.[7,63] Fluid-structure interaction simulations of an intra-aortic balloon pump and extracorporeal membrane oxygenation were used to study the effect of these devices on end-organ perfusion (ie, heart, brain, and lower extremities), aortic wall stress, and aortic region of blood flow intersection.[64]

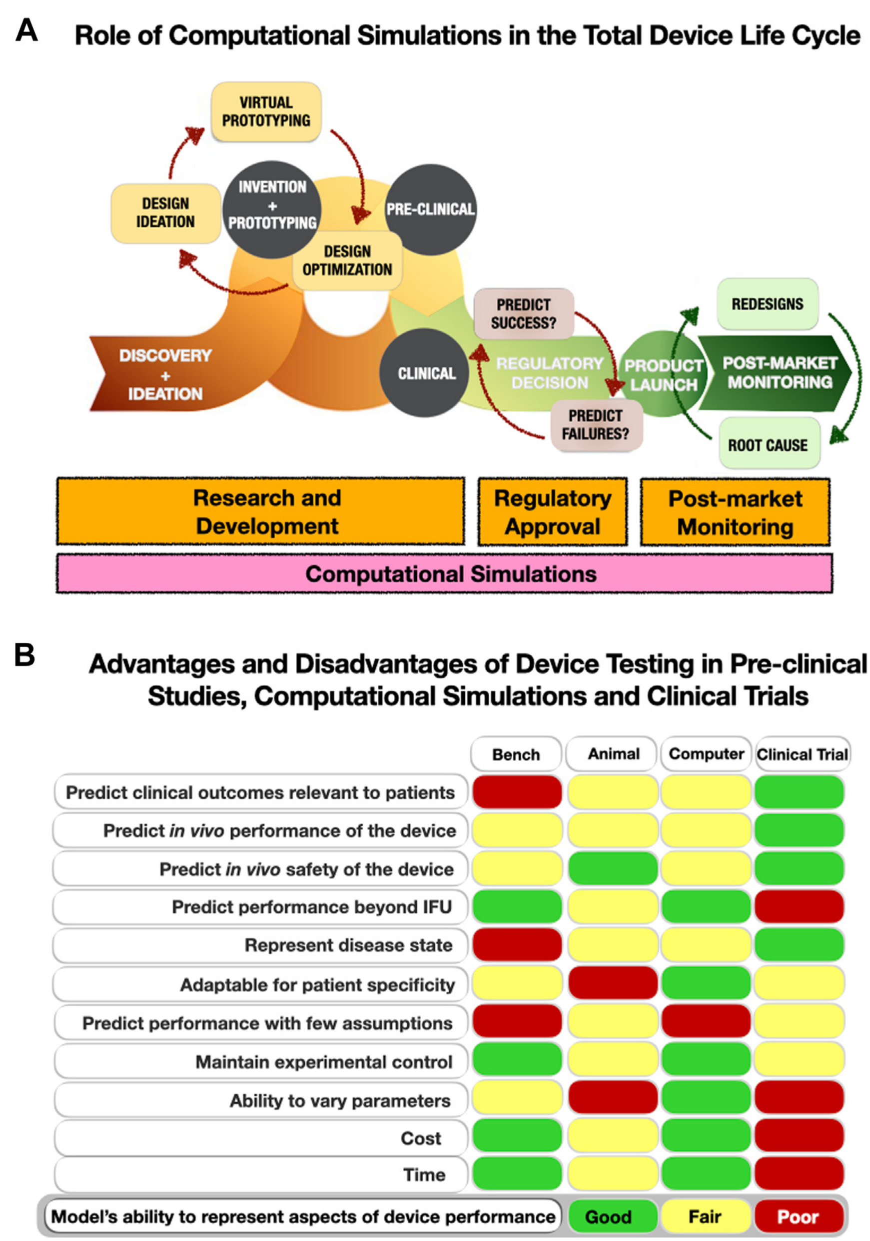
ROLE OF CS IN CARDIOVASCULAR DEVICE LIFE CYCLE. The Food and Drug Administration (FDA) endorses the application of CS throughout the life

FIGURE 4 **Patient-Specific Computational Simulations of Structural Heart Interventions**



(A) Transcatheter aortic valve replacement. Modified with permission from Dowling et al.[52] (B) Percutaneous edge-to-edge mitral valve repair. Modified with permission from Kong et al.[56] (C) Left atrial appendage occlusion device. Modified with permission from Bavo et al.[57] In all illustrated procedures, note the potential of computational simulations to assist the operators with optimal device sizing and positioning.

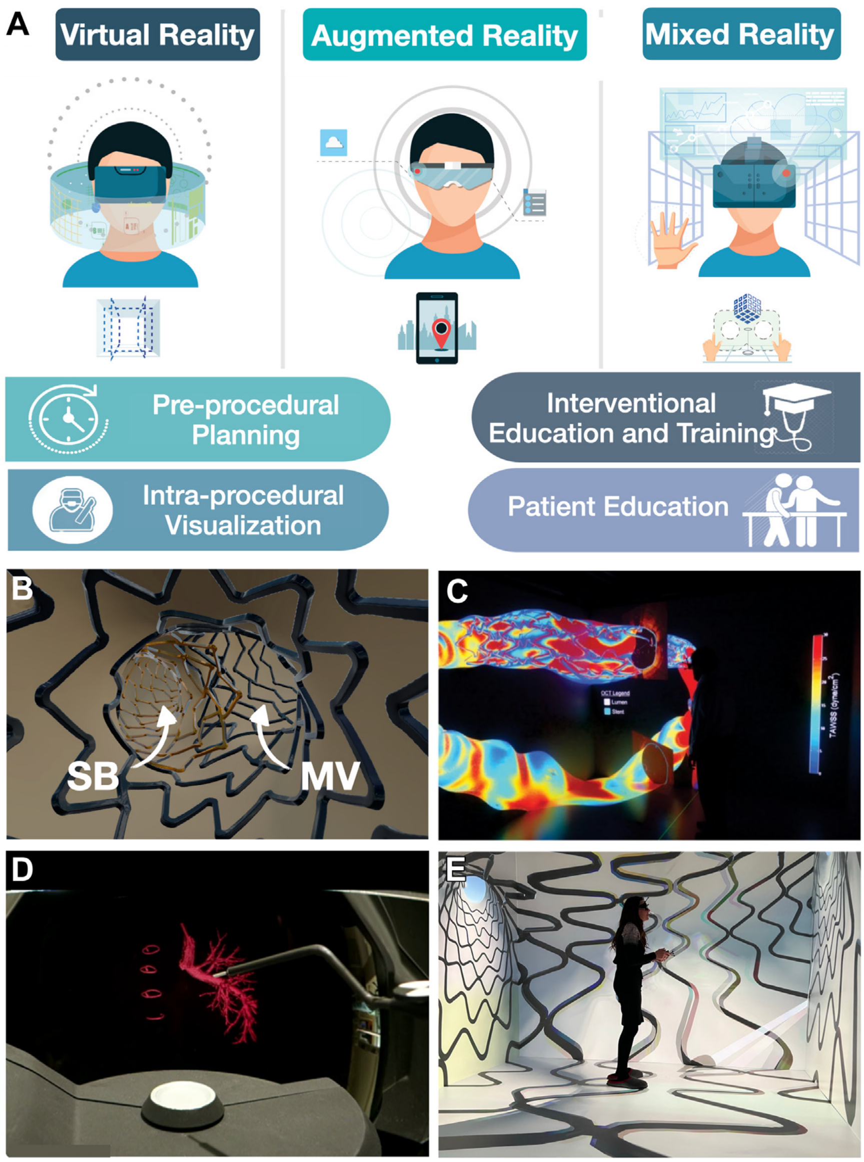
FIGURE 5 **Computational Simulations and Medical Device Development**



(A) Computational simulations play an integral role throughout the entire device life cycle from research and development to regulatory approval and postmarket monitoring. (B) Performance parameters of different testing methods (ie, bench and animal testing, computational simulations, and clinical trials) of cardiovascular devices. Note the higher performance of computational models over preclinical and clinical studies for medical device testing, primarily in terms of patient specificity, cost, time, and ability to cover the whole spectrum of disease complexity. Modified with permission from Morrison et al.[65] IFU = instructions for use.

cycle of a medical device, extending from device prototyping to regulatory approval and postmarket monitoring (**Figure 5A**).[65,66] **Figure 5B** summarizes the performance parameters of different methods for device testing and the improved performance of CS over the presently employed preclinical studies (bench and animal), specifically in terms of patient specificity, time, cost, and ability to cover the entire spectrum of disease complexity. Using patient-specific CS of left main coronary artery bifurcation

FIGURE 6 **Spectrum of Extended Reality and its Applications in Cardiovascular Interventions**



(A) Extended reality is a is a simulated experience wherein the user is fully immersed (virtual reality) or semi-immersed (augmented reality) into the interactive virtual world. Mixed reality is a subtype of extended reality in which the virtual and augmented reality coexist and interact in real time. (B) Fly through in a computational simulation of patient-specific coronary bifurcation with the T and small protrusion technique. (C) Immersive visualization of patient-specific computational fluid dynamics following coronary stenting. Modified with permission from Quam et al.[68] (D) Real-time intraprocedural visualization of a bicaval bidirectional Glenn shunt. Modified with permission from Bruckheimer et al.[71] (E) Real-time interaction of the operator with the angiography machine in a virtual cardiac catheterization laboratory using Inter-professional Experiential Center for Enduring Learning's immersive 5-sided laser-Cave automatic virtual environment (University of Nebraska Medical Center[78]). Abbreviations as in Figure 1.

stenting, we tested the mechanical performance of different prototypes of a novel everolimus-eluting stent (Synergy Megatron, Boston Scientific Inc) and extracted important information on the role of stent design on stent radial strength, stent expansion, lumen scaffolding, and tissue protrusion.[41] The Living Heart Project (SIMULIA, Dassault Systèmes) offers a unique virtual human heart model to perform mechanical, electrical, and hemodynamic simulations and test different cardiovascular devices.[67]

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TABLE 2 Role of ER Technologies in Cardiovascular Interventions

ER Technologies (Ref. #)	Company	Imaging Input	Applications
Ask Angie[98]	Boston Scientific	Live video streaming using Help Lightning's AR platform	Interactive intraoperative virtual support from clinical experts on device setup and troubleshooting during procedures in the cardiac catheterization laboratory
True 3D[99]	EchoPixel	CT, MRI, ultrasound, and fluoroscopy imaging	Preprocedural planning with AR-aided display of patient-specific endovascular structures
Holoscope[71]	RealView Medical Imaging	3D rotational angiography and 3D transesophageal echocardiography imaging	Intraoperative guidance with a computer-generated holographic display during transcatheter atrial septal defect closure
Procedure Rehearsal Studio[100]	Simbionix, 3D Systems	CT angiography	Patient-specific computational models of endovascular anatomy for preprocedural planning

3D = 3-dimensional; AR = augmented reality; CT = computed tomography; ER = extended reality; MRI = magnetic resonance imaging.

ROLE OF ER IN CARDIOVASCULAR INTERVENTIONS

ROLE OF ER IN CORONARY INTERVENTIONS. ER (Table 1) can offer advanced visualization of complex coronary anatomies and assist the planning of complex coronary interventions (Figures 6A and 6B). The Marquette Visualization Lab offers a representative example of a versatile and immersive environment for stereoscopic 3D visualization of patient-specific CFD simulations (Figure 6C).[68]

ROLE OF ER IN STRUCTURAL HEART INTERVENTIONS. ER technologies offer advanced visualization of anatomically complex structural heart defects. The applications of ER technologies in structural heart interventions are summarized in Table 2. Preprocedural planning of transcatheter closure of anatomically complex venous sinus defects using virtual reality technologies resulted in decreased procedural times and radiation exposure.[69] Augmented reality (AR, a type of ER) with an overlay of magnetic resonance imaging on real-time fluoroscopic images enhanced the catheter navigation across the ventricular septal defect, avoiding chordal and trabecular entrapment during percutaneous closure (Figure 6D).[70,71]

ROLE OF ER IN PERIPHERAL INTERVENTIONS. ER technologies provide advanced visualization and intraprocedural guidance during endovascular aortic repair procedures.[72,73] Intraoperative visualization using an AR platform (HoloLens, Microsoft) allowed the operators to overlay virtual angioscopy and computed tomography angiograms on the surgical field and navigate throughout the aorta in real time.[73] Likewise, other AR platforms, including the Fast Method for Virtual Stent-graft Deployment or computer assisted fenestrated endovascular aortic repair and Fiber Optic RealShape (Philips Healthcare), provide real-time intraoperative navigation during endovascular procedures, significantly reducing the fluoroscopy time.[72,74]

ROLE OF ER IN VASCULAR ACCESS. ER technologies can visualize the vascular access sites with precision, thereby minimizing adjacent tissue injury and reducing radiation exposure. AR-assisted retrograde access to the peroneal artery was successfully performed in a patient with critical limb ischemia.[75] 3D visualization of vascular access with a handheld or head-mounted device enabled better bedside visualization of vessel architecture in hemodialysis patients.[76]

ROLE OF ER IN EDUCATION AND TRAINING IN CARDIOVASCULAR INTERVENTIONS. Enhanced visualization of patient-specific CS with ER technologies can assist the operators, staff, trainees, and medical technology innovators to comprehend the complexity of various coronary, structural, and peripheral procedures (Figure 6). Table 3 summarizes many of the available ER tools for education and training of interventional health care providers and patients. Cardiology fellows, who received simulator-based training on transvenous pacing and intra-aortic balloon pump placement, achieved higher skill assessment scores compared to those who did not receive simulator-based training.[77] The Interprofessional Experiential Center for Enduring Learning (University of Nebraska Medical Center) is a multidisciplinary venue with advanced visualization capabilities (eg, 3D CADWalls, 2D interactive digital iWalls, holographic theater, head-mounted displays, and an immersive 5-sided laser-Cave automatic virtual environment) where interventional cardiology trainees and staff can receive experiential learning on cardiac catheterization laboratory operations (Figure 6E, Video 1) and procedures (eg, bifurcation

TABLE 3 Role of ER Technologies in Education and Training

ER Technologies (Ref. #)	Institute	Target Group	Applications
HoloLens[101]	Microsoft	Interventional trainees	AR-guided visualization of structural heart anatomies
The Virtual Heart[9]	Stanford University	Patients and medical students	• Virtual immersion in cardiac anatomy to learn and understand anatomical structures, interventions, and congenital defects • Project Brave Heart: preprocedural VR experience to reduce anxiety and stress in pediatric patients
Vascular Intervention System Training simulator[102]	Mentice	Interventional health care providers (faculty, fellows, and staff)	Virtual training sessions in endovascular procedures in a safe and realistic simulation environment
Interprofessional Experiential Center for Enduring Learning[78]	University of Nebraska Medical Center	Interventional health care providers (faculty, fellows, and staff)	ER visualization hub, which provides an immersive and semi-immersive interactive environment to educate and train providers on cardiovascular interventional procedures
Atlas of Human Cardiac Anatomy[79]	Visible Heart Laboratories (University of Minnesota)	Interventional health care providers (faculty, fellows, and staff)	Educational atlas of patient-specific 3-dimensional anatomies of various structural heart diseases and device implantation procedures

ER = extended reality; VR = virtual reality.

stenting) (Video 2).[78] ER educational tools have also been developed by the Visible Heart Laboratories (University of Minnesota) and are available on the free access website of the Atlas of Human Cardiac Anatomy.[79]

SYNERGIES AMONG AI, CS, AND ER

The feedback loops between each of the AISER components in cardiovascular interventions are summarized in **Figure 7**. CS generates big data, which are analyzed by AI algorithms, whereas AI produces new decision-making algorithms or hypotheses that are further tested in CS. The VCT (described in the following section) is a typical example of synergy between CS and AI.

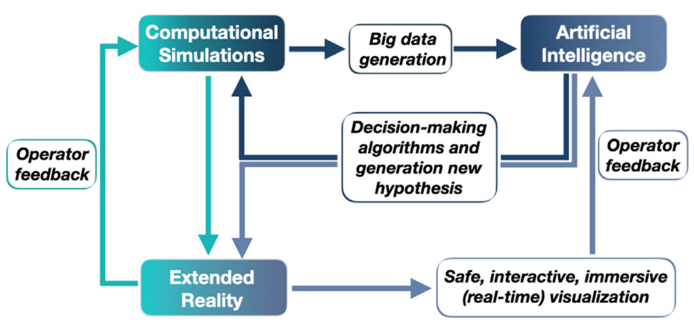
CS provide patient-specific data for ER technologies to visualize cardiovascular interventions in immersive/semi-immersive interactive environments (**Figure 7**). In turn, operators of ER technologies can provide feedback to CS that helps to improve the accuracy of simulations and allows testing of alternate scenarios. The HARVEY platform (Duke University) is a representative example of the cross talk between CS and ER. This platform performs patient-specific CFD in different vascular beds and projects them in immersive/semi-immersive virtual displays.[80] Operators have the ability to model the placement of vascular devices (eg, stents and conduits) and assess their hemodynamic impact.

AI provides decision-making algorithms that can be evaluated in an immersive environment using ER, whereas operators within the ER environment provide continuous feedback to AI decision-making algorithms (**Figure 7**). The FDA has approved the first-ever intraoperative holographic guidance system (CommandEP System, SentiAR) for cardiac ablations.[81] This system uses real-time data from electroanatomic mapping systems and generates an ML-enhanced interactive 3D environment that helps the operator identify arrhythmogenic substrates. Other AI-based electroanatomic mapping technologies have also been introduced.[82,83]

VCTs IN CARDIOVASCULAR INTERVENTIONS

The concept of VCTs was first introduced by the Virtual Physiological Human Institute and transcends traditional computational modeling.[84] VCTs apply CS in large patient-specific data sets to test the efficacy and safety of new drugs, medical devices, or interventional procedures. In recent years, the FDA has become a proponent of VCT approaches to cardiovascular interventions.[65,85] The VCT pathway has 5 integral components (**Figure 8**): 1) collection of a large, randomized data set of patient-specific anatomies representative of different sexes, ethnicities, race, and disease complexities; 2) application of realistic and extensively trained and tested CS methods; 3) use of simulation-derived surrogate endpoints that accurately predict clinical endpoints; 4) use of AI algorithms to collect and mine simulation data; and 5) use of knowledge acquired by the VCT to guide targeted actual clinical trial. The ENRICHMENT

FIGURE 7 Synergies Among Artificial Intelligence, Computational Simulations, and Extended Reality



Feedback loops between artificial intelligence, computational simulations, and extended reality.

(ENRICHMENT *in Silico* Clinical Trial Project) trial, led by the FDA and Dassault Systèmes, constitutes a representative example of a VCT in structural heart interventions.[7] This trial uses patient-specific CS to test different mitral clip prototypes for edge-to-edge mitral valve repair and guide actual clinical trials. In the field of coronary interventions, one could consider a VCT to test the performance of existing or new stent platforms or stent techniques using surrogate endpoints (eg, stent expansion, apposition, and local flow parameters), which are highly predictive of adverse clinical outcomes (eg, revascularization, myocardial infarction, and death). The Center for Digital Cardiovascular Innovations performs a VCT to evaluate the effectiveness of various stenting techniques in coronary bifurcations (Figure 3). This study aims to generate a "bifurcation atlas" of bifurcation anatomies and stent simulations and develop a comprehensive decision-making algorithm for bifurcation interventions. Collectively, the VCT pathway can help the device industry, regulatory bodies, and academia to acquire new knowledge on the performance of different cardiovascular techniques and devices in diverse patient populations in a time- and cost-effective manner.

LIMITATIONS OF AI, CS, AND ER

AISER-related biases, limitations, and considerations, as well as proposed solutions, are summarized in Table 4.

DATA BIASES. Although AISER implementation has the potential to make the health care system more efficient and accessible, it is vulnerable to social, economic, and systemic biases.[86] First, sex, racial, ethnic, and economic biases (eg, underrepresentation of women and minorities) in AI and CS training data sets will lead to inaccurate generalizations.[86] Second, the lack of standardization of data type or the performance metrics, overlapping disease phenotypes, and heterogeneity in the quality of diagnostic studies could make the training of optimal AISER models challenging.[87] Third, small training data sets can result in overfitting of the ML model and lack of generalization, whereas large training data sets with confounding input variables can result in incorrect interpretation and correlation by the AI model. Fourth, data processing for AISER requires regular annotation by trained operators to ensure quality control, potentially leading to annotator biases (eg, contradicting opinions among experts on image segmentation). Finally, there is a paucity of certain categories of data in the scientific literature, and subpar quality of data from electronic medical records may have an effect on the training and accuracy of AI and patient-specific CS.[88] For that reason, AI is currently considered by the FDA as a diagnostic aid in decision making rather than a completely independent tool.[89]

In an effort to minimize the previously mentioned biases and inequalities and promote safe, effective, and good AI practices for medical device development, the FDA, Health Canada, and United Kingdom Healthcare Products Regulatory Agency have jointly identified 10 guiding principles, which are summarized in Table 4.[85] These practices also apply to CS and ER.

LEGAL OBSTACLES. Widespread implementation of AISER requires the exchange of patient data and computational models across multiple institutions and nations, which might challenge patient confidentiality and privacy regulations. The lack of authorities that oversee and govern the AISER standardization is also another regulatory obstacle. AISER-related errors could raise complex ethical and legal queries regarding accountability. For example, legal liability for an unintended fatal complication during a CS-guided cardiovascular intervention could be disseminated between the operator or the software/platform developer. Lastly, the extent to which AISER-assisted interventions devalue the operator's labor represents another challenge that warrants careful consideration.

FINANCIAL BARRIERS. CS requires high-performance computing systems, which could generate an added financial burden for the institutions adopting these

TABLE 4 Limitations of AISER Technologies and Proposed Solutions

	Limitations	Solutions[85]
Data biases	• Limited diversity of the intended population • Limited data standardization • Limited consensus on image segmentation and annotation • Lack of big data for training and testing of AI algorithms	• Clinical study participants and data sets are representative of the intended patient population • Training data sets are independent of testing data sets • Selected reference data sets are based on the best available method • Model design is tailored to the available data and reflects the intended use of the device • Testing demonstrates device performance during clinically relevant conditions • Deployed models are monitored for performance, and retraining risks are managed • Multidisciplinary expertise is leveraged throughout the total product life cycle
Legal obstacles	• Risk to patient confidentiality and privacy • Lack of regulatory authorities to monitor AISER implementation • Questionable accountability in case of patient complications related to AISER-guided interventions • Devalue of operator's labor	• Good software engineering and implementation of security practices • Involvement of regulatory agencies to create a dedicated section to monitor implementation of AISER • Operators are provided clear and essential information • Focus is placed on the performance of the human-AI team
Financial barriers	• High cost of AISER technologies • Lack of wide insurance coverage for AISER technologies • Limited accessibility to AISER technologies across the health care system	• Access to affordable computing power • Wider insurance coverage and accessibility to AISER technologies
Technical considerations	• Limited tactile feedback of computational simulations • Time-consuming process • Limited real-time applicability • Limited incorporation of patient-specific cardiovascular anatomies	• Faster computing (supercomputer clusters, quantum computing)[92] • Big data-trained faster AI algorithms • Statistical emulation[91] • Improved patient specificity (big data, virtual clinical trials) • Large-scale randomized studies to validate the accuracy of AISER technologies

AI = artificial intelligence; AISER = artificial intelligence, computational simulations, and extended reality.

technologies.[89] In addition, the cost-effectiveness and adoption of AISER technologies intended to optimize a cardiovascular intervention could be diminished in the absence of wide insurance coverage and accessibility across the health care systems. On the contrary, AISER has the potential to minimize unnecessary diagnostic testing and clinical decision-making variability among operators, thus streamlining care and decreasing health care costs. For example, AI-facilitated focused cardiac ultrasound (Bay Labs) enables rapid image acquisition, interpretation, and subsequent triaging of patients at the point of care, even by untrained health care providers.[90]

TECHNICAL CONSIDERATIONS. CS does not provide tactile feedback to the operators. Also, patient-specific CS are time-consuming; therefore, their real-time application at the cardiac catheterization laboratory could be challenging. However, the use of supercomputer clusters, quantum computing, and advanced AI and statistical emulation techniques can significantly expedite the simulation process and achieve real-time guidance.[91,92] Current ER technologies appear to lack precise representation of patient-specific cardiovascular anatomies, potentially attenuating their educational value.[93]

FUTURE APPLICATIONS OF AISER IN CARDIOVASCULAR INTERVENTIONS

INDIVIDUALIZED PREPROCEDURAL PLANNING AND REAL-TIME DECISION MAKING. AISER-facilitated preprocedural planning and real-time decision making could transform the daily operations in the cardiac catheterization laboratory of the future (**Central Illustration**). Real-time CS and AI-based predictive analytics could lead to fast and standardized diagnosis of coronary, structural, and peripheral disease and enable operators to devise procedural strategies tailored to individual patients.[94,95] The net gain of this process would include reduced procedure-associated costs, procedural times, complication rates, improved catheterization laboratory efficiency, reduced radiation exposure for patients and operators, reduced health care costs, shorter hospitalization, improved patient satisfaction, and improved

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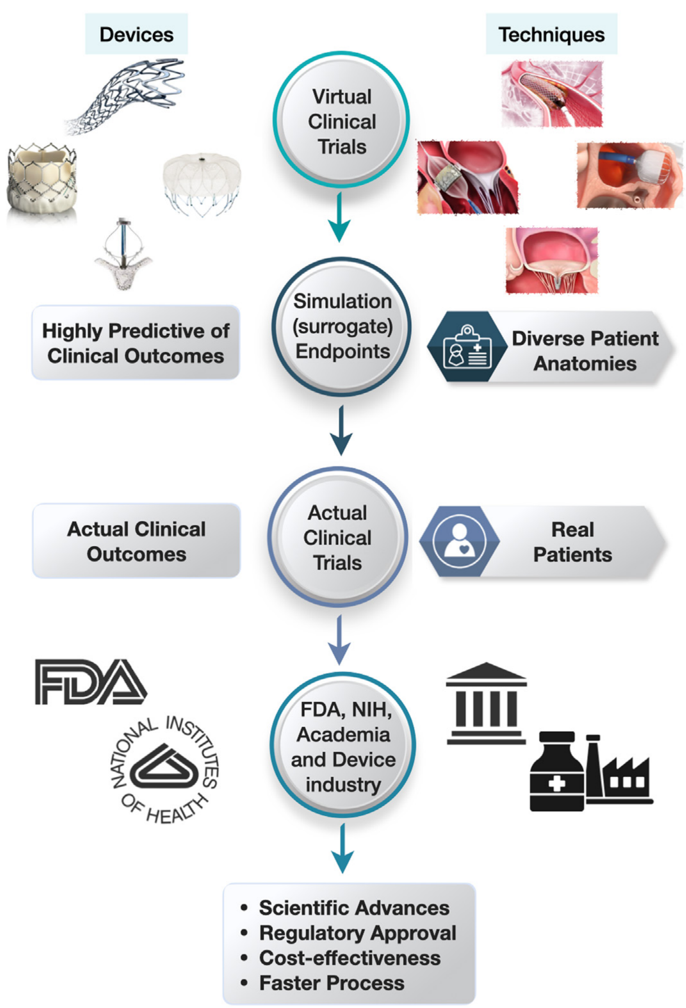
FIGURE 8 **Virtual Clinical Trials Pathway in Cardiovascular Interventions**



A proposed concept on how virtual clinical trials can guide targeted actual clinical trials toward faster and cost-effective testing and regulatory approval of cardiovascular devices and techniques. Note that virtual clinical trials have the potential to be more inclusive of the intended population compared to actual trials.

short- and long-term clinical outcomes. Randomized clinical studies in the years to come are warranted to test the role of AISER technologies in cardiovascular interventions.

DEVICE RESEARCH AND DEVELOPMENT AND REGULATORY APPROVAL. AISER is expected to play a pivotal role in the cardiovascular device industry (Figure 8). In the near future, the device industry and regulatory bodies will engage in statistically powered and representative VCT before assessing the performance of the devices in actual clinical trials. The VCT pathway might change the landscape of clinical research by guiding targeted, faster, and less expensive randomized clinical trials.

EDUCATION AND TRAINING OF INTERVENTIONAL HEALTH CARE PROVIDERS AND MEDICAL DEVICE INNOVATORS. Finally, AISER is expected to play a pivotal role in the education and training of interventional health care providers (faculty, fellows, and staff) and medical device innovators of the future. Using ER technologies, health care providers might have the unique ability to engage all their senses in a radiation- and contrast-free environment and improve the performance of existing or new treatment techniques and strategies (eg, bifurcation stenting techniques and structural heart interventions). This advanced training experience might allow the interventional health care providers to learn "greater, faster, better"; accelerate their learning curves; and minimize the associated procedural risk.

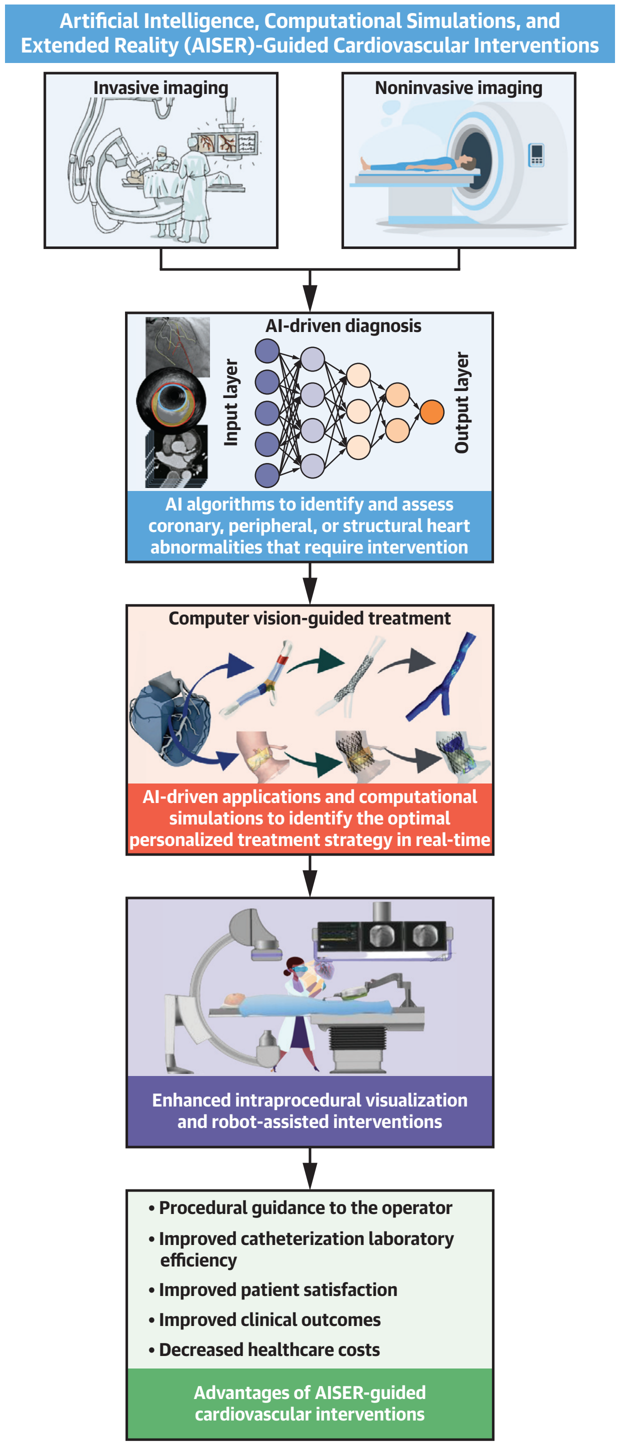
CONCLUSIONS

AISER has the potential to transform the following 3 areas of cardiovascular interventions in the coming years: 1) preprocedural planning and real-time decision making; 2) device innovation, research and development, and regulatory approval; and 3) education and training of interventional health care professionals and technology developers. AISER tools are expected to advance in terms of accuracy and standardization, speed, cost, and accessibility as technology advances. The use of AISER technologies in cardiovascular interventions and medicine in general is anticipated to be streamlined by multidisciplinary synergies between interventional health care providers, computer scientists, biomedical engineers, bioinformatics and visualization experts, device industry, ethical boards, and regulatory agencies.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Supported by the National Institute of Health (R01 HL144690) and Dr Vincent Miscia Cardiovascular Research Fund. Dr Burzotta has received speaker honoraria from Medtronic, Abbott, and Abiomed. Dr Iaizzo is a consultant for Medtronic; and has received a research grant from Medtronic. Dr Bicek is an employee of Boston Scientific. Dr Fontana is an employee of Medtronic. Dr West is an employee and shareholder of Abbott. Dr Mortier is a cofounder of FEops. Dr Jaffer has received sponsored research from Canon, Siemens, Shockwave, Teleflex, and Mercator; is a consultant for Boston Scientific, Abbott

CENTRAL ILLUSTRATION Overview of Computational Technologies in Cardiovascular Interventions



Samant S, et al. J Am Coll Cardiol Intv. 2023;16(20):2479-2497.

A conceptual example of how artificial intelligence, computational simulations, and extended reality can transform the coronary, structural, and peripheral interventions in the cardiac catheterization laboratory of the future. AI = artificial intelligence; AISER = artificial intelligence, computer simulations, and extended reality.

Vascular, Siemens, Asahi Intecc, IMDS, Biotronik, Magenta Medical, and Philips; has equity interest in Intravascular Imaging Incorporated; and DurVena Inc Massachusetts General Hospital has a patent licensing arrangement with Canon, Terumo, and Spectrawave, and Dr Jaffer has the right to receive royalties. Dr Mena-Hurtado is a consultant for Abbott, COOK, Cardinal Health, Medtronic, and Optum Labs. Dr Abbott has received research funding from MicroPort and Boston Scientific; is on the advisory boards of Philips and Medtronic; and is a consultant for Abbott, and Recor. Dr Desai works under contract with the Centers for Medicare and Medicaid Services to develop and maintain performance measures used for public reporting and pay for performance programs. He reports research grants and consulting for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Merck, Novartis, SCPharmaceuticals, and Vifor. Dr Brilakis has received consulting/speaker honoraria from Abbott Vascular, American Heart Association (associate editor *Circulation*), Amgen, Asahi Intecc, Biotronik, Boston Scientific, Cardiovascular Innovations Foundation (board of directors), ControlRad, CSI, Elsevier, GE Healthcare, IMDS, InfraRedx, Medicure, Medtronic, Opsens, Siemens, and Teleflex; has received research support from Boston Scientific and GE Healthcare; is an owner of Hippocrates LLC; and is a shareholder of MHI Ventures, Cleerly Health, and Stallion Medical. Dr Bhatt is on the advisory boards of Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; is on the Board of Directors of Bristol Myers Squibb, Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; is the inaugural chair of the American Heart Association Quality Oversight Committee; is on data monitoring committees for Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards Lifesciences), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Novartis, and Population Health Research Institute; has received honoraria from American College of Cardiology (senior associate editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute. RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim. AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (editor in chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor and associate editor), K2P (cochair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), WebMD (CME steering committees), *Clinical Cardiology* (deputy editor), NCDR-ACTION Registry Steering Committee (chair), and VA CART Research and Publications Committee (chair); has received research funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, and 89Bio; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); is a site coinvestigator for Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, and Svelte; is a trustee for American College of Cardiology; and has performed unfunded research for FlowCo, Merck, and Takeda. Dr Chatzizisis has received speaker honoraria, advisory board fees, and research grants from Boston Scientific; advisory board fees and research grants from Medtronic Inc.; issued U.S. patent (No. 11,026,749) and international patent pending (application No. PCT/US2020/057304) for the invention entitled "Computational simulation platform for the planning of interventional procedures"; Co-founder of ComKardia Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS artificial intelligence, cardiovascular intervention, extended reality, precision medicine, procedural planning, simulations, virtual clinical trials

APPENDIX For supplemental figures and videos, please see the online version of this paper.