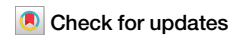




Hematologic complications and design challenges in cardiovascular devices



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In this review, we provide an engineering assessment of prevalent blood-wetted cardiovascular devices, their hematologic complications, and their interconnections to identify key areas for future research. In fact, the incidence of cardiovascular diseases has promoted the development of various devices to treat these conditions, including mechanical circulatory supports (mechanical pumps that assist or replace failing hearts), artificial valves to replace faulty heart valves, stents to relieve obstructions in blood vessels, vascular grafts to repair/reconstruct damaged vessels, patches to reinforce or reconstruct cardiovascular tissues, and other implants. The hemocompatibility of these cardiovascular devices, namely their ability to interact with blood flow without causing adverse reactions, remains unsatisfactory, and recurrent complications include thrombosis, hemolysis, and bleeding. Therefore, the discussion provided herein will support readers approaching cardiovascular technologies in building a solid foundation and provide everyone with an up-to-date overview of ongoing research in this multidisciplinary field.

Cardiovascular diseases encompass a broad class of disorders affecting the heart or blood vessels. These critical conditions include cardiomyopathy, heart failure, valvular heart disease, coronary artery disease, aortic aneurysm, peripheral artery or venous disease, and thrombosis. Cardiovascular diseases are one of the leading causes of mortality worldwide. Heart failure alone impacts millions globally and is associated with a substantial mortality rate, with over 50% of patients not surviving past five years^{1,2}. The incidence of heart failure is on the rise, with predictions of a 46% increase in the United States from 2012 to 2030, accompanied by a 127% increase in the associated healthcare costs². China, with one of the largest populations globally, is experiencing a rising demand for cardiovascular disease treatments due to its aging population. It is estimated that around 330 million people in China suffer from cardiovascular diseases, and about 8.9 million of them are diagnosed with heart failure³.

The frequency and severity of cardiovascular diseases have promoted the development of various devices, specifically designed to treat these conditions. Extensive research is ongoing because state-of-the-art systems are not optimal due to the extreme complexity of the cardiovascular system (the section “The human cardiovascular system” in the supplementary document contextualizes the discussion by briefly describing the cardiovascular system for readers with an engineering background). In particular, popular cardiovascular solutions exposed to blood flow include mechanical circulatory supports (MCSs), artificial heart valves, and implants. They are schematically shown in Fig. 1 and described hereinafter. Additional blood-wetted tools are

respiratory supports like extracorporeal membrane oxygenator equipment, annuloplasty rings to restore the heart valve annulus size, structural occluders to permanently seal a heart defect, atrial flow regulators to establish a controlled shunt between the heart’s upper chambers and manage intracardiac pressure, and pulmonary flow restrictors to limit the amount of blood reaching the lungs. Left atrial assist devices (LAADs) also exist, delivering blood from the left atrium to better fill the left ventricle; they help increase cardiac output, maintaining arterial pulsatility and normal aortic valve function⁴. Dedicated research, not reported here for brevity, is ongoing for these additional instruments because their exposure to blood flow raises hemocompatibility issues similar to those of more studied devices.

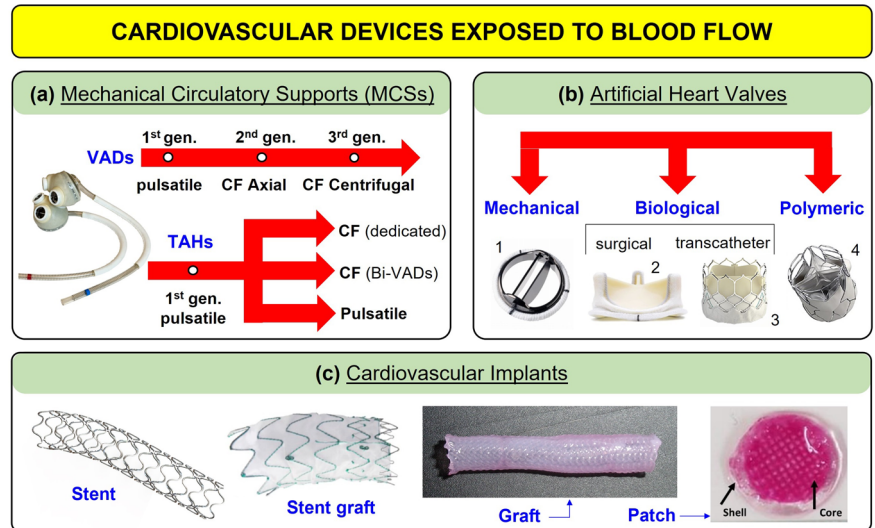
Overall, blood-wetted medical devices, critical for sustaining life or avoiding serious health impairments, undergo rigorous scrutiny because regulatory agencies consider them as “high-risk” devices for clotting, infection, or systemic failure. They typically pertain to the most regulated category, Class III, in the national classifications established by the Food and Drug Administration (FDA) in the USA, the National Medical Products Administration (NMPA) in China, and the Medical Device Regulation (MDR) in the EU. This safety-related demand further complicates their development.

Mechanical circulatory supports

MCSs are pumps equipped with ancillary components that support the heart’s function by assisting with blood circulation. They include ventricular

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Fig. 1 | Overview of commonly used cardiovascular devices exposed to blood flow (images not to scale). **a** Mechanical circulatory supports: evolution of ventricular assist devices (VADs) from pulsatile to continuous-flow (CF), and progress of total artificial hearts (TAHs) showing the CardioWest 70cc (image from https://commons.wikimedia.org/wiki/File:Cuore_artificiale_totale_-_MUSE.jpg). **b** Artificial heart valves: options including mechanical, biological, and polymeric types, with representative examples (images 1–3 from https://commons.wikimedia.org/wiki/File:Implantater_ved_udskiftning_af_hjerteklappen.png, and image 4 adapted from ref. 20: © 2023 Singh et al.). **c** Examples of a stent (image adapted from <https://commons.wikimedia.org/wiki/File:Koronary.png>), a stent graft (image adapted from ref. 187: © 2022 D'Onofrio et al.), an artificial graft (image adapted from <https://commons.wikimedia.org/wiki/File:Gef%C3%A4%C3%9Fprothese.JPG>) and a bio-printed cardiovascular patch (image adapted from ref. 175: © 2022 Bar et al.). Other relevant blood-wetted devices, not explicitly shown in the figure, are in use for temporary support, including extracorporeal membrane oxygenation procedures and intra-aortic balloon pumps, or are in clinical trials, such as left atrial assist devices, atrial flow regulators, and pulmonary flow restrictors.



assist devices (VADs), which are combined with a portion of the human heart to augment its cardiac output, and total artificial hearts (TAHs), which entirely replace the native heart (peristaltic designs for extracorporeal support are not discussed here). Their selection depends on the patient's need, namely, univentricular or biventricular support.

There are two types of VADs based on the heart's supported region: (1) Right ventricular assist devices (RVADs), which are connected to the right ventricle to pump blood into the pulmonary artery; or (2) Left ventricular assist devices (LVADs), which are connected to the left ventricle and supply the aorta. (Combining two VADs into a Bi-VAD solution is considered a TAH and is discussed below.) VADs can also be classified into their therapeutic destinations: (1) bridge-to-transplant (a provisional solution); and (2) destination therapy (a long-term measure, frequently on account of the limited availability of donor organs⁵). Some authors also identify (3) bridge-to-decision and (4) bridge-to-recovery, both short-term measures⁶. Specifically, the first generation of VADs incorporates pulsatile volumetric pumps that mimic the heart's actual functioning (see Fig. 1a and further details in Table S1 in the supplementary document). Although these VADs are relatively bulky and unsuitable for implantation, they are still employed for pediatric patients. The second generation uses continuous-flow axial pumps, suitable for chest implantation. The third generation employs continuous-flow centrifugal pumps with magnetically levitated rotors to eliminate external leakage and reduce mechanical wear for durability.

All VAD generations share three essential components: an inflow cannula connected to either the left or right ventricle, a mechanical pump, and an outflow graft that delivers blood to the arterial (venous) circulation via the aorta (pulmonary artery). The pump is powered using a tunneled driveline coupled to an external controller and power source⁷. Since their introduction in 1962, VADs have improved dramatically: available studies indicate 1- and 5-year survival rates of 86% and 64%, respectively⁸, a 2-year survival rate of 83% in patients with newer-generation devices⁹, and the longest duration of VAD therapy reported to date is 13 years¹⁰. They are, however, still prone to inducing thrombosis, hemolysis, and bleeding, requiring further development. Alternative VADs are available as catheter-delivered pumps, including intra-aortic balloon pumps, axial pumps (e.g., the established Impella models), or a new linear transaortic pulsatile pump¹¹. They are all for temporary short-term use. Some are low-flow devices that

only supplement cardiac output, while others can act as full ventricular support. Lastly, it is worth noting that some non-blood-contacting alternatives are also under investigation. They wrap around the exterior of the heart, ideally helping its functioning without requiring anticoagulation therapies (e.g., direct cardiac compression devices or soft robotic sleeves).

Conversely, TAHs completely replace the human heart. They are expected to autonomously balance the systemic and pulmonary circulations to avoid serious consequences (e.g., respiratory failure or hepatic insufficiency); the output of the left ventricle can, in fact, exceed 1–2% that of the right ventricle¹². A detailed review of TAHs is already available¹³, so we only recall that the SynCardia and Aeson TAHs were recently approved for use as destination therapy. The latter leverages hydraulic pumps to actuate flexible membranes coated with treated bovine pericardium, which increases hemocompatibility. In parallel, research branched off into merging two existing rotary VADs to form a continuous-flow TAH¹⁴, also known as Bi-VAD. These results suggested that a single TAH with continuous flow can ensure an implantable size and function. More modern examples include designs with two impellers on opposing faces of the same rotating element (Cleveland Clinic TAH) or magnetically levitated, disc-shaped rotors (BiVACOR, which received FDA approval in 2023¹⁵). In any case, further investigations are needed, mainly on the durability of pulsatile TAHs and the long-term implications of continuous-flow TAHs¹⁵.

Artificial heart valves

Artificial heart valves (see Fig. 1b and further details in Table S2 in the supplementary document) are designed to replace damaged heart valves, restoring normal blood flow and improving the heart's efficiency. Artificial heart valves can be classified into three main categories: (1) mechanical, (2) biological, and (3) polymeric, based on the materials employed for their realization. Specifically, mechanical valves are made from metal alloys or pyrolytic carbon. Designed for exceptional durability and longevity, mechanical valves require lifelong anticoagulation therapy to prevent blood clots^{16,17}. Biological xenograft, or bioprosthetic, valves are made from animal tissues (such as porcine or bovine pericardium) and thus offer a more natural hemodynamic performance, typically not requiring lifelong anticoagulation therapy¹⁸. The support structure of surgical biological valves, often made of an alloy, is covered with synthetic materials (e.g., Dacron or

PTFE) that surgeons can sew to ensure the valve's correct positioning; transcatheter biological valves, conversely, have an exposed support structure. Valves of the latter type are significantly more expensive than surgical biological valves. Biological homograft (homologous) valves from human donors match the natural anatomy and represent an option, especially for the pediatric population. They can be preserved using freezing techniques (cryopreserved valves), but ethical limitations render their acquisition highly problematic. The Ross procedure represents the only alternative, utilizing the patient's autologous pulmonary valve to substitute for the impaired aortic valve. Then, polymeric valves are made from synthetic materials and designed to offer improved durability and hemocompatibility while reducing the need for long-term anticoagulation therapy. Polymeric valves offer improved fatigue resistance and are expected to have a lifespan of approximately 25 years, which is a significant improvement over biological valves. Their exact durability is still under investigation despite showing promising results in preclinical studies¹⁹. Additionally, polymeric valves can overcome issues related to biocompatibility, common with mechanical valves, and calcification, frequent with biological valves²⁰.

For many years, heart valves have been replaced via open-heart surgery. Older or debilitated patients who cannot endure surgery are increasingly being treated with a minimally invasive procedure known as transcatheter valve replacement, in which the new valve is compressed into a catheter, directed through a blood vessel, and expanded over the defective valve. Transcatheter aortic valve replacement procedures can employ balloon-expandable or self-expandable valves, each with its own advantages in terms of deployment and repositioning capabilities²¹. Mechanical and biological valves are in everyday use, while polymeric valves are generally in clinical trials or still under development, since their long-term *in vivo* durability must be demonstrated^{19,20}.

Cardiovascular implants

Our classification of cardiovascular implants includes stents, stent-grafts, vascular grafts, and patches, namely, tools used to support, bypass, or reconstruct cardiovascular tissues. Stents and stent-grafts (see Fig. 1c and further details in Table S3 in the supplementary document) are metallic or polymeric tubular structures inserted into the lumen of blood vessels to maintain their patency. Although some stents are made of polymers²², most of them are entirely metallic²³; stent-grafts, conversely, have a metallic frame covered by a polymeric skirt²⁴. We label them all as "stents" for simplicity, since the overlapping definitions in the literature might be misleading. Stents offer advantages over other treatments, such as the vascular grafts discussed below, including being less invasive, simpler to implant, and capable of promoting faster healing. Bioresorbable stents are absorbed by the body over time, unlike permanent ones, restoring the vessel's vasomotion and reducing protracted issues²⁵; their long-term vascular patency remains, however, to be further observed. Stents are used in aneurysm treatments (bulging or ballooning of a blood vessel at risk of rupture) and to prevent vessel blockages caused by emboli, thrombi, or plaque formation²⁶. They can be categorized based on their expansion mechanism, design, or materials. Each topology has unique structural and hemodynamic functions for given clinical situations, but they are not without challenges. Associated hemodynamic issues mainly include in-stent restenosis (narrowing of a previously treated vessel) and thrombosis, which may lead to a sudden vessel occlusion. These drawbacks are worsened by stent malposition, migration, edge effects (abnormal hemodynamics due to incomplete coverage of the diseased segment), and mismatch with the vessel size.

Moreover, vascular grafts (see Fig. 1c and further details in Table S4 in the supplementary document) are medical devices designed to replace or bypass segments of damaged or diseased blood vessels. They are used in various surgical procedures, including hemodialysis access, trauma repair, and cardiovascular reconstruction. The success of such grafts depends on several factors: they must resist thrombosis (blood clotting), avoid triggering hyperplasia (excessive cell proliferation), maintain their mechanical integrity, and be compatible with surgical handling requirements, such as being easily suturable. Autologous (from the patient) or allograft (from human

donors) vascular grafts are biological substitutes that avoid the use of foreign artificial surfaces. Allografts are usually cryopreserved and can go through decellularization to leave an immunologically inert matrix. Alternatively, vascular prostheses can be made of expanded Teflon or Dacron cloth (passive, foreign elements) or tissue-engineered vascular grafts (interactive elements promoting the renewal of vascular tissue for seamless integration of the graft²⁷). In terms of size, aortic, iliac, and femoral artery repairs require relatively large-diameter vascular grafts (up to 6–8 mm), but coronary artery replacement requires smaller diameter (1–6 mm) grafting²⁸. The primary failure of artificial grafts is abnormal biomechanical loading; contributing factors include thrombosis, intimal hyperplasia (it narrows the vessel lumen and slows blood flow, increasing the likelihood of clot formation), biocompatibility issues, and mechanical mismatch²⁹. Although the first synthetic vascular grafts were developed over 70 years ago, these issues persist, highlighting the complexity of the engineering-biology-medicine challenge.

Finally, cardiovascular patches are flat biological or synthetic materials that reinforce or reconstruct sections of the heart, including the atrial septum, ventricular septum, valves, and blood vessels. Patches are expected to mimic the compliance of native tissue, a fundamental property for matching the mechanical deformations of surrounding native tissues without altering blood flow (biological patches typically have better compliance). Their biocompatibility has material-related limitations, mainly thrombogenicity, hemolysis, and platelet activation in ePTFE or Dacron patches, calcification in biological patches, and hemostasis in synthetic patches. The long-term efficacy of a patch is also essential to prevent mechanical failure or biological degradation, which might change depending on the exact site of implantation. Even if alternatives exist, there is no one-size-fits-all solution, and efforts in providing specialized versions are anticipated³⁰.

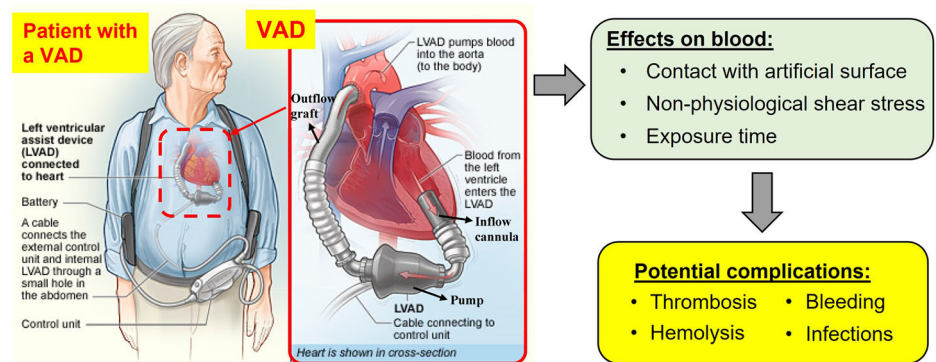
Paper's goal and structure

A common feature of MCSs, artificial heart valves, stents, vascular grafts, and other implants is that they come into direct contact with blood flow. A critical design challenge, therefore, is hemocompatibility. This characteristic is broadly defined as the ability of a device to interact with blood without causing adverse reactions, such as thrombosis (blood clotting), hemolysis (destruction of red blood cells), bleeding, platelet activation, or other blood-related adverse events³¹. It is evident that hemocompatibility is essential for the long-term success of these devices and the associated patient safety³². Despite extensive research documented in the literature, the hemocompatibility of cardiovascular devices remains unsatisfactory, and hematologic complications remain a challenge. For instance, cavitation can happen in blood pumps and artificial valves; while uncommon, it damages blood cells, surrounding tissues, and the device itself³³.

It is also apparent that the technology of cardiovascular devices is a multidisciplinary topic that combines aspects of human physiology and biochemistry with fluid mechanics and deformable solid mechanics at the design stage, and also aspects of mechatronics and materials degradation for the realization and long-term operations (these latter aspects are, for the most part, proprietary information). Existing review studies either approach the subject from a pure engineering perspective by predominantly focusing on the application of numerical simulation models in the development of cardiovascular devices, such as VADs³⁴, artificial heart valves³⁵, stents³⁶, and vascular grafts³⁷, or address the topic from a biomedical angle, focusing on antithrombotic treatments and technological advancements in hemodynamic measurements of blood, including coagulation and thrombosis³⁸, and hemolysis³⁹. More comprehensive descriptions come in the form of bulky books^{40,41}, requiring a long time to absorb the information. What is missing is a concise assessment of this technology that contributes to bridging the gap between medical sciences and engineering, covering the full spectrum of the subject from physiology and biochemistry to mechanical engineering in an accessible way for readers with different backgrounds.

The objectives of the present review are (1) to examine the various issues associated with MCSs, artificial heart valves, stents, vascular grafts, and patches since they share common ground, and (2) to highlight the research approaches aimed at minimizing their hematologic complications.

Fig. 2 | Effects of cardiovascular devices on blood when using a VAD as an example. The potential hematologic complications include bleeding, infections, damage to blood and its constituents, and/or undesired activation of cellular processes (image on the left side adapted from ref. 188: © 2019 Singhvi et al.).



The discussion provided herein will support engineers and, more broadly, readers approaching cardiovascular technologies from a non-medical perspective in building a solid foundation. The scope is restricted to devices directly exposed to blood flow, where hemocompatibility is a key design challenge. Implantable cardiovascular devices not in direct contact with blood flow are beyond the scope, such as pacemakers, cardioverter-defibrillators, loop recorders, and flow-accelerating devices. Finally, the paper is organized as follows. The next section addresses hematological complications linked to device implantation, including hemolysis, thrombosis, bleeding, and infections. The following part discusses recent studies to understand the current advancements and challenges in designing and modeling hemodynamic interactions within cardiovascular devices. Then, the review concludes with a summary of its findings and outlines future research directions.

Complications due to cardiovascular devices

The placement of a cardiovascular device involves the introduction of a foreign body (i.e., non-endothelial surfaces) into the bloodstream, locally altering physiological flow. Thus, blood is exposed to non-physiological shear stress (NPSS), which can differ widely from physiological conditions, and is also affected by protein adhesion to foreign surfaces. These aspects are critical in causing hematologic complications, together with exposure time (the duration of blood exposure to non-physiological flow conditions, such as the residence time in cardiovascular devices). Prolonged exposure can cause damage to cell membranes and membrane-associated intracellular structures, such as red blood cells (RBCs), white blood cells, platelets, coagulation factors (a set of proteins that are part of the coagulation cascade), large plasma proteins, and the von Willebrand Factor (vWF), which facilitates platelet adhesion⁴². The scenario is intricate since blood can be seen as a tissue affected by mechano-biological processes dependent upon physical processes⁴³. Avoiding blood damage is vital since it can lead to clinical complications in patients, including thrombosis, hemolysis, bleeding, and infection (Fig. 2). We briefly address these main issues separately.

Thrombosis

Thrombosis refers to the formation of a blood clot within a blood vessel, which can obstruct blood flow and lead to serious complications if the clot breaks off and travels to other parts of the body, such as the lungs (pulmonary embolism) or brain (stroke)⁴⁴. Thrombosis can be associated with stasis (i.e., the formation of venous or "red" clots, which are fibrin-rich, under low shear stress) or hyper shear (i.e., the creation of arterial or "white" clots that are platelet-rich); these scenarios represent opposite ends of the spectrum⁴⁵. The non-pathophysiology of thrombosis is primarily described in terms of mechanical causes, often relating to external or physical factors that affect blood flow or the vascular system (e.g., the artificial surface of a medical device). A helpful concept for understanding the main contributors to thrombosis is Virchow's triad, which includes stasis (interrupted/stagnant blood flow), endothelial injury (irritation/damage to the blood vessel), and hypercoagulability (alterations in the blood's constitution that tend to

clot). When these factors co-occur, the risk of blood clot formation increases significantly, even if there are limited means of determining the relative significance⁴⁶.

Thrombosis in cardiovascular devices is a complex process involving multiple mechanisms referred to as "mechanochemical signaling"⁴⁷, which is a central phenomenon in the broader field of mechanotransduction⁴⁸ (i.e., it describes how blood's cellular and proteinaceous elements sense and respond to physical forces, for instance, in MCSs⁴⁹). Cells convert mechanical signals into biochemical responses under the influence of two critical elements: shear stress and exposure time⁵⁰. Generally, it is worth highlighting platelet activation and coagulation factor activation. Platelets can be activated by prolonged exposure to high shear forces and by contact with the non-endothelial surface of the cardiovascular device (Fig. 3a). Moreover, the interaction between blood and the medical device leads to the adsorption of plasma proteins onto the device surface⁵¹. Key proteins include fibrinogen, vWF, and components of the contact activation pathway. Fibrinogen provides binding sites for platelets, facilitating the formation of platelet aggregates. Upon binding to the device surface, the contact system proteins trigger the intrinsic coagulation pathway by activating factor IX, which in turn produces thrombin. Thrombin is a critical enzyme that converts fibrinogen into fibrin, the primary structural protein of a blood clot⁵². Studies indicate that shortly after device implantation, there is a significant depletion of contact system proteins, particularly within the first 2 weeks⁵³. This depletion suggests that the initial contact between the blood and the device's surface activates these proteins, leading to their consumption.

Focusing on the broader impact of thrombosis in cardiovascular devices, avoiding it is crucial for both the medical implications already mentioned (e.g., vessel obstruction, pulmonary embolism, or stroke) and device performance. Blood clots can, in fact, lead to obstruction of prosthetic heart valves, interfering with their opening and closing, or pumps, limiting their ability to generate sufficient blood flow. Such complications can become life-threatening due to their potential severity, as shown in Fig. 3b for a VAD impeller removed from a patient. Thus, blood coagulation and thrombus formation must be monitored in cardiovascular devices, as they can serve as primary nucleation sites. The resulting hemodynamic operation, different from the intended design conditions, induces a vicious circle sustained by an improper blood-device interaction⁵⁴.

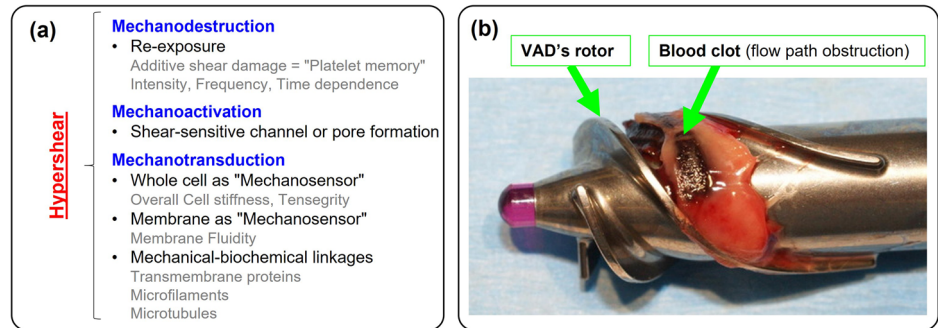
Hemolysis

Other major hematologic complications include hemolysis, characterized by the destruction of RBCs and the subsequent release of free hemoglobin into blood plasma (Fig. 4a), which is a significant concern following the implantation of VADs and other cardiovascular devices.

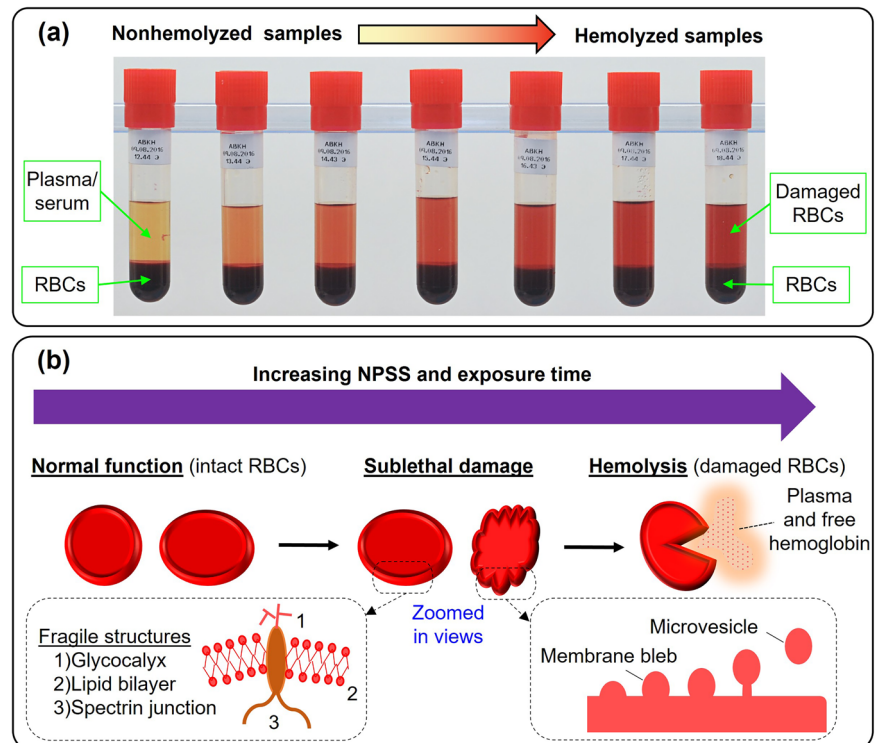
Hemolysis represents a critical aspect of hemocompatibility. It is not an isolated event but a process preceded by sublethal damage to RBCs (even though it is not completely understood, it is well accepted that the level of shear exposure plays a crucial role). There are, in fact, structural and functional alterations that do not immediately lead to the breakdown of cells

Fig. 3 | Thrombosis in cardiovascular devices.

a Schematic diagram of a range of emerging mechanisms for shear-mediated platelet activation, which is central to thrombosis in cardiovascular devices (list adapted from ref. 49): a mechanodestructive pathway (shear damage accumulates, leading to irreversible damage), a mechanoactivation pathway (shear-sensitive elements may open), and a mechanotransduction pathway (shear converts to internal activating signals). **b** A clinical observation of a blood clot (thrombosis) in an axial-flow HeartMate II after the VAD explant from a patient. Image adapted from ref. 189. Reprinted from Journal of the American College of Cardiology, Vol. 60, No. 18, Uriel et al., Development of a Novel Echocardiography Ramp Test for Speed Optimization and Diagnosis of Device Thrombosis in Continuous-Flow Left Ventricular Assist Devices: The Columbia Ramp Study, Page No. 1772, Copyright (2012), with permission from Elsevier.

**Fig. 4 | Hemolysis in cardiovascular devices.**

a Examples of normal and hemolyzed blood samples related to the color changes in the plasma/serum. The transparent, light-yellow color of the non-hemolyzed sample progressively turns into an opaque, dark-red color for elevated levels of hemolysis up to a concentration of plasma-free hemoglobin of about 0.61 g/L (image adapted from ref. 190: © 2022 by Romanova et al.). **b** Diagram of the process leading to hemolysis in response to NPSS during a given exposure time. RBCs deform from their natural shape into an elliptical form with a fragile structure before entering a partially damaged state, releasing microvesicles. Then, the fully damaged state releases free hemoglobin into the plasma.



(cell lysis), resulting in hemolysis under increased NPSS conditions, as illustrated in Fig. 4b. The contact of RBCs with foreign materials and surfaces may also cause hemolysis⁵⁵; for instance, extracorporeal membrane oxygenation devices can cause low pressure in the blood flow, leading to potential cavitation, which can cause hemolysis⁴³. The concept of sublethal damage is particularly relevant in MCSs, where mechanical forces can induce changes in the cytoskeleton of RBCs, emphasizing the importance of considering blood's mechanical properties and interactions with artificial environments in the design of MCSs⁵⁰. The aging of RBCs also favors shear-induced hemolysis, as their reduced deformability makes them more susceptible⁵⁶. This concern is relevant when considering the need for blood transfusions in many patients undergoing cardiovascular surgery.

Moreover, hemolysis can serve as an early marker of thrombosis. Free hemoglobin is frequently used to assess RBC destruction; binding with haptoglobin during hemolysis, lower levels of this protein can be considered

an indicator of hemolysis and thrombosis conditions⁵⁷. In addition, lactate dehydrogenase levels typically increase in the blood during both hemolysis and thrombosis; an increase that exceeds 2.5 times the standard upper limit can signal early device thrombosis⁵⁸. VAD patients may exhibit silent changes in these markers, necessitating appropriate management strategies, including increasing anticoagulation therapy, administering thrombolytics, or proceeding with pump exchange. For instance, the MCS Impella is increasingly used in cardiogenic shock and is associated with a high rate of hemolysis, up to approximately 60% in patients requiring support for more than 24 h⁵⁹. This issue underscores the need for a deeper understanding of the mechanisms that lead to hemolysis and for strategies to mitigate its occurrence.

Hemolysis and thrombosis are, in fact, interconnected processes in cardiovascular devices, where each can contribute to the development of the other. On one side, hemolysis can lead to thrombosis due to the release of

prothrombotic factors from damaged RBCs (i.e., heme capable of activating platelets and the coagulation cascade leading to thrombus formation⁶⁰, and free hemoglobin acting as a strong nitric oxide scavenger and promoting a prothrombotic state⁶¹). Conversely, thrombosis can cause hemolysis through mechanical damage to RBCs as they pass through thrombi (the reduced lumen and subsequent blood flow acceleration can cause the rupture of RBCs, contributing to hemolysis⁶²). The management of the aforementioned aspects requires a comprehensive approach that includes monitoring for early signs of thrombosis, understanding the role of sublethal RBC damage, and considering the blood flow alteration caused by the artificial device.

Bleeding and infections

Bleeding emerges as a significant complication of post-device implantation, notably in the form of gastrointestinal and nasal hemorrhages⁶³. Platelet aggregation impairment, anticoagulation therapy, diminished flow pulsatility (e.g., most VADs are continuous-flow devices that reduce the physiological pulsatility of blood flow in arteries), and NPSS are key contributors to the heightened risk of bleeding. These factors can lead to the development of acquired von Willebrand disease, arteriovenous malformations, and mucosal ischemia. It is estimated that between 15% and 30% of individuals who undergo VAD implantation will face gastrointestinal bleeding⁶⁴. Management of bleeding involves several strategies: using proton pump inhibitors to reduce gastric acidity, administering blood products to counteract anemia or coagulopathy, and carefully adjusting anticoagulation therapy (i.e., modulation/de-escalation of antithrombotic therapy⁶⁵). Specific efforts to contain bleeding are also case-specific, based on the type of cardiovascular device installed, such as LVADs in general⁶⁶, microaxial pumps in particular⁶⁷, or aortic valve replacement⁶⁸.

Infections due to VADs and other cardiovascular devices are also of concern, as they can lead to serious complications. These infections can be classified by their location, such as the pump casing, power supply driveline, or inflow and outflow cannula⁶⁹. The most common type of infection in implantable VADs manifests at the driveline, where a biofilm at the skin-penetration site may form and contain typical pathogens, such as *Staphylococcus* spp. (common skin bacteria) or *Pseudomonas* spp. (versatile bacteria that can cause infections in medical settings)⁷⁰. Also, VAD-induced NPSS can damage white blood cells (leukocytes) and reduce immune response, which may further increase the risk of infections⁷¹. Based on the limited information available on the effects of shear stress on white blood cells, a shear stress of 13 Pa inhibits phagocytosis (ingestion) with an exposure time of roughly 0.1 s, while greater values cause significant damage⁷². In most cases, these infections can be successfully treated without the need for VAD replacement. Infections were once the leading cause of death in pulsatile heart support systems, but today, they mainly force patients to stay in the hospital longer after device implantation⁷³. Despite the advancements in technology, infections remain a critical issue in the management of VAD patients.

Finally, an odd phenomenon involving simultaneous thrombosis and bleeding is frequently observed in patients using implantable cardiovascular therapeutic devices⁷⁴. The paradoxical hemostatic effect is related to mechanochemical signaling acting on vWF multimer modifications and platelets' receptor shedding. High NPSS leads to conformational changes in vWF multimers that affect hemostasis and lead to the formation of platelet thrombi. Simultaneously, the activity of ADAMTS-13 (a vWF-cleaving enzyme) may increase due to high shear stress, triggering excessive cleavage of vWF multimers⁷⁵. This response can reduce platelet adhesion and aggregation, paradoxically increasing the risk of bleeding⁷⁶. (The deficiency of vWF due to excessive cleavage is known as acquired von Willebrand disease, a bleeding disorder often observed in continuous-flow VAD patients⁷⁷.) A high NPSS can also cause shedding of the platelets' surface receptors (GPIIb and GPVI), reducing platelet aggregation and leading to a bleeding tendency. As the mechanism of MCS-related bleeding is not yet fully understood, the concept of platelet dysfunction was proposed. It suggests that the accumulation of supraphysiologic shear stress leads to platelet

degranulation and, mechanistically, limits platelets' aggregatory response⁷⁸. Follow-up analyses by the same authors explained that sheared platelet-derived microparticles impose a bidirectional effect on platelet hemostatic function, but it remains to be defined which mechanism prevails in vivo due to the circumstances⁷⁹.

Summarizing the discussion up to this point, we have provided an overview of the mechanisms by which cardiovascular devices can trigger clot formation (thrombosis), RBC damage (hemolysis), and bleeding. Critical factors are the exposure of blood to an NPSS and the duration of this exposure (residence time). In simple terms, the more pronounced the alteration of the shear stress distribution in the blood flow, and the longer the exposure of blood to such non-physiological flow conditions, the greater the chance for hematologic complications. Clarifying these aspects is paramount to approaching the following section.

Trends in cardiovascular devices

This chapter illustrates available options and future directions in cardiovascular devices, with special consideration of practical needs such as blood compatibility testing and antithrombotic therapies.

Simulations and testing for cardiovascular devices

The complex geometrical structures and mechanical movements within cardiovascular devices can lead to detrimental conditions for blood due to non-physiological hemodynamic conditions. A complete assessment requires combining numerical simulations with experimental tests.

Computational fluid dynamics (CFD) and fluid-structure interaction (FSI) are frequently employed to study cardiovascular devices. Although FSI is more complex and computationally demanding, it offers a more precise representation than CFD because fluid and structure dynamics are interdependent. Thus, FSI better fits the simulation of heart valves⁸⁰ and vascular grafts⁸¹, where the structures undergo significant deformation under flow forces. CFD can, however, predict flow patterns and optimize MCS designs, so FSI simulations are used more selectively for these components (e.g., to understand the MCS impact on adjacent deformable structures, such as the aortic valve⁸²). Achieving high fidelity is challenging since cardiovascular devices often operate in a laminar-to-turbulent transitional flow regime that is difficult to simulate. Various strategies were utilized, but the optimum approach remains controversial. Turbulence-based models are popular choices, namely Reynolds-Averaged Navier-Stokes (RANS) and Large Eddy Simulation (LES) models. RANS models have been preferred for blood pump simulations but struggle with predicting secondary flows and flow separation, leading to deviations in performance predictions⁸³. LES models provide a more detailed estimate of the turbulent flow field (examples include blood pumps⁸⁴, vascular grafts⁸⁵, and prosthetic heart valves⁸⁶), requiring a significantly higher computational cost. Hybrid RANS-LES models are a good trade-off despite their demanding calibration. They use RANS in regions with well-behaved turbulence and LES in areas with separation vortices^{87,88}, offering a promising middle ground between computational efficiency and predictive accuracy⁸⁹. Additionally, it is worth highlighting the emerging field of patient-specific modeling of cardiovascular geometries via non-invasive measurements⁹⁰. These models are used for numerical simulations to extract hemodynamic quantities (e.g., blood flow in the coronary arteries³⁷) or to aid in sizing and positioning heart valves⁹¹, where machine learning techniques can develop fast-running data-driven simulations⁹².

These numerical approaches can be augmented with various blood-damage metrics to predict device hemocompatibility and enable targeted design improvements. The primary metrics currently in use are as follows:

- *Scalar shear stress* experienced by blood elements (high shear stress can damage blood cells and is a primary indicator of potential hemolysis). This approach relies on the shear stress tensor to calculate scalar shear stress^{93,94},
- *Residence time* refers to how long blood elements remain within a specific region of a device (if prolonged, particularly under NPSS, it can

increase the likelihood of blood damage). It helps identify areas where blood may stagnate^{93–95},

- *Hemolysis index* is a measure of RBC damage. It is crucial for understanding the hemocompatibility of a device^{93,94,96},
- *Thrombosis potential* evaluates risk zones for triggering clotting within a device, considering factors such as platelet adhesion and the binding ability of vWF^{93,94,97},
- *General thrombosis prediction* assesses the likelihood of clot formation within a device, considering factors such as platelet adhesion or the transport and reaction of biochemical substances related to clotting^{93,94,97,98},
- *Bleeding probability* evaluates the risk of bleeding complications by considering factors such as the platelet adhesion ability and the activation of platelets^{93,94,97}.

Relying on these numerical considerations, hemolysis has been progressively reduced in current MCSs, but representing thromboembolisms computationally is still a challenge⁴³. Current methodologies have significant limitations^{99–101}, because they primarily focus on the physical factors influencing thrombosis, potentially overlooking the intricate biochemical reactions that are equally pivotal in thrombus formation (e.g., shear stress can initiate biochemical reactions leading to thrombosis but also plays a role in reducing thrombosis risk, increasing the likelihood of bleeding according to the “paradoxical hemostatic effect”¹⁰²). This uncertainty highlights the need for more sophisticated thrombosis risk assessment models to at least integrate the prothrombotic and antithrombotic effects of shear stress.

Due to the extreme complexity of blood-related phenomena (it is a shear-thinning, non-Newtonian fluid as explained in the subsection “Human blood” in the supplementary document), integrating simulations with experimental evidence is critical (e.g., it is recommended to incorporate human blood testing as early as during preclinical approaches with smaller blood loops⁴³). Various thrombosis measuring techniques have correspondingly been developed, including microfluidics methods, fluorescent microscopy, electrochemical sensing, photoacoustic detection, and micro/nano electromechanical systems. Conventional approaches are generally considered in vitro methods, in which measurements are performed in artificial environments, except for the ex vivo Badimon perfusion chamber. Moreover, hemolysis can be measured using spectrophotometric, optical (visual inspection of plasma samples), and electrical methods (Van Buren et al.¹⁰³ recently proposed to monitor hemolysis by measuring blood electrical resistance). Most of these techniques require specialized hardware and trained personnel for execution and data interpretation, limiting their applicability to medical settings. It is therefore apparent that expanding testing opportunities to include simpler methods would benefit research conducted in engineering laboratories. Harmonizing testing methodologies would also help derive definitive conclusions about candidate device designs, as available studies employ in vitro systems or in vivo models that are highly variable.

Regulatory compliance and antithrombotic therapies

The “high-risk” nature of blood-wetted cardiovascular devices requires proof of hemocompatibility to meet regulatory compliance before human use. This process still faces challenges¹⁰⁴ as tests are mainly based on ISO 10993-4 (Biological evaluation of medical devices—Part 4: Selection of tests for interactions with blood), while ISO 14155 governs good practices for clinical investigations and is not applied to hemocompatibility testing. The first mentioned dictates a tailored assessment for each device, redirecting to device-specific standards when possible, and explicitly states that a universal single acceptance threshold is not feasible for all device applications, for instance, for hemolysis. It also does not address the dynamic nature of advanced methods, such as tissue engineering. Thus, significant regulatory gaps, as highlighted by the FDA¹⁰⁵, prevent cardiovascular devices from being fully safe and effective before they reach patients. They mainly include the absence of trustworthy preclinical blood damage assessments to better

predict clinical outcomes, the lack of computational and in vitro test methods accounting for human physiology, and the shortage of confirmed tools to forecast the clinical translation of new devices. As a result, the processes for obtaining regulatory compliance should be further improved through appropriate guidelines to deliver a more reliable gold standard¹⁰⁶, where rigorous standardization and tight controls are invaluable.

Moreover, hemocompatibility paradigms are evolving from inert blood-contact materials to surfaces that actively manage biological responses (e.g., using chemical alterations or coating¹⁰⁷). The underlying goal is to avoid clot formation without using heavy antithrombotic treatments, a process complicated by patient-specific factors¹⁰⁸ and risks of bleeding with life-threatening potential. Traditional medications need conscientious dosing and accurate monitoring (see the abovementioned modulation/de-escalation strategies⁶⁵). Thus, ongoing research focuses on safer drugs to preserve hemostasis¹⁰⁹, including the use of antiplatelet agents and anticoagulants. (Fibrinolytic drugs, or thrombolytics, are not reported here as they are meant to dissolve existing blood clots.)

Conventional antiplatelet drugs tend to suppress signal transduction cascades involved in platelet aggregation¹¹⁰. Since they pose practical challenges, especially an increased bleeding risk, new targets for antiplatelet therapy mainly focus on three areas¹¹¹: a variety of cell-surface receptors, other intracellular signaling molecules, and molecules related to metabolic pathways. Furthermore, current anticoagulants act at the mid-section of the common coagulation pathway (e.g., they target FXa and/or thrombin, which are critical for hemostasis). Newer options address the initiation of coagulation, namely, mechanisms that do not harmfully affect hemostasis. Studies along this line, largely at the preclinical stage, aim to inhibit coagulation targets from both the intrinsic pathway and the common pathway, including factors V, VIII, IX, fibrinogen or fibrin, and FXIII¹¹². More progressed research, which often relies on clinical trials, is on contact pathway inhibition, particularly FXI/FXIa¹¹³ and FXII/FXIIa¹¹⁴. Broadly, exploratory antithrombotic trends revolve around smart nanodrugs, antithrombotic polymers¹¹⁵, and hydrogel coatings¹¹⁶ that go beyond inorganic coatings or simple pharmacological carriers, metal-based complexes¹¹⁷, and drug-free techniques that rely on stimulus-responsive micro/nanosystems¹¹⁸. Even if these approaches hold promise, they typically need further development and verification.

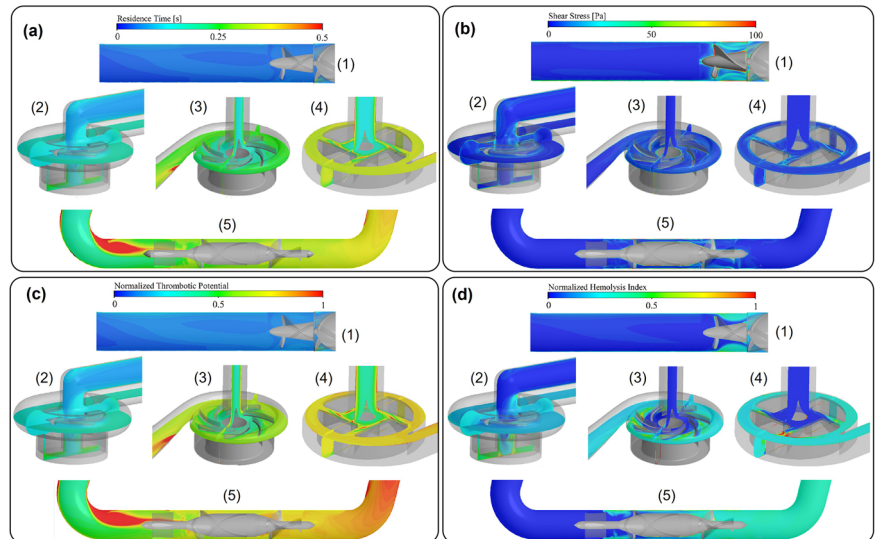
At this point, we can address different cardiovascular devices separately to understand their research trends for hemocompatibility.

Design of mechanical circulatory supports

Research on MCSs focuses primarily on VADs rather than THAs. Generally, two critical factors must be considered: hydraulic performance and hemocompatibility. The latter element is linked to the potential formation of thrombi and blood damage caused by the induced turbulence^{119,120}. Hydraulic performance is operation-related and determined by key indicators such as flow rate, pressure head, and power consumption. The last-mentioned is linked to energy efficiency, simply the proportion of the (hydraulic) power leaving the pump relative to the input (mechanical) power. Efficiency in VADs is typically close to 20–30%³⁴. Enhancing it, for instance, by reducing the gap between the impeller and the pump housing, decreases energy losses and extends the device’s battery duration. However, it remains an open research question to fully understand how efficiency improvements impact hemodynamic performance. A design trade-off between energy efficiency and hemocompatibility is imperative: efficiency is not the sole priority, given the importance of hemolysis and thrombosis.

Three successive generations of VADs have been developed so far (see Table S1 in the supplementary document). The consequence was an evolution from pulsatile to continuous-flow pumps, mainly centrifugal designs. The apparent engineering motivations are constructive simplicity and compactness, even though leveraging a volumetric pump design would appear to be the most natural option for mimicking the human heart. Blood pumps are currently a standard treatment for heart diseases, but they can still cause significant complications, leading to deaths and hospital

Fig. 5 | Numerical analyses of five clinical VADs. The figure includes (1) Impella 5.0, (2) UltraMag, (3) CHVAD, (4) HVAD, and (5) HeartMate II under the same flow conditions. All images are adapted from ref. 94. Reprinted from Computers in Biology and Medicine, vol. 151, no. 106271, Y. Li et al., Multi-indicator analysis of mechanical blood damage with five clinical ventricular assist devices, Pages No. 7, 8, 9, and 10, Copyright (2022), with permission from Elsevier. **a** Residence time, in seconds, of the flow and **b** shear stress in Pa. Evaluations of the corresponding normalized **c** thrombotic potential, and **d** hemolysis index, where values close to 1 indicate detrimental effects on the blood.



readmissions¹²¹. Common issues include bleeding (15–30% of cases¹²²), strokes (15–30% of instances⁶³), and hemolysis (in less than 5% of patients³⁹). Despite the relatively low occurrence of hemolysis, it serves as an important measure of hemocompatibility¹²³. It remains, however, uncertain whether hemolysis alone can fully represent the pump's overall blood compatibility. It is also unclear whether the pump regions at high risk for hemolysis denote a hazard for other complications, such as thrombosis. Therefore, the importance of leveraging numerical simulations becomes apparent.

The aforementioned two-fold interest in hydraulic performance and hemocompatibility is also reflected in some recent studies worth special mention:

- **Main focus on hydraulic performance**

Regarding centrifugal blood pumps, the impeller geometry is of interest. Wu et al.¹²⁴ addressed tip clearance, finding numerically that a 100 μm gap was the most effective at reducing hemolysis. Song et al.¹²⁵ numerically explored blade designs, reporting that backward-curved blades outperformed the others in hemolysis prevention. Ozturk et al.¹²⁶ investigated the effect of the blade wrap angle, discovering that 120° was best in their design. Kannojiya et al.¹²⁷ similarly found that this value balances hydraulic efficiency and hemolysis. Trends presented by Wiegmann et al.¹¹⁹ revealed that a smaller clearance within 50 and 500 μm increases hemolysis, but fewer blades between 4 and 7 reduce the blood stagnation rate and secondary flow regions. These outcomes suggest careful consideration of the pump's design elements. Emphasizing commercial blood pumps, Wu and co-workers¹²⁸ recently simulated the centrifugal maglev HeartMate III and CH-VAD, stressing the importance of impeller design (the first is the most widely implanted pump, while the other is approved for marketing in China). Although evaluated shear stresses in the CH-VAD are well below the hemolysis threshold (i.e., roughly 300–1,000 Pa, even if inconsistent values plague the field⁴³), they would affect platelet activation and damage vWF¹²⁹. In contrast, the HeartMate III has wider clearances (1–2 mm) that reduce stresses, but induce Taylor vortices that increase blood residence time and potentially contribute to blood damage¹³⁰. Again, the importance of balancing hydraulic performance and hemocompatibility stands out, and LES models were recommended for future investigations, as they outperform RANS models^{131,132}.

- **Main focus on hemocompatibility**

Other CFD studies have also been conducted to compare the HeartMate III with the CH-VAD, emphasizing blood damage, flow

detachment, and flow stagnation^{101,133}. Thamsen et al.¹³⁴ found that the flow fields were particularly disrupted under off-design conditions, which aligns with the recent findings in Wu's study¹²⁸. Wu et al.¹³⁵ investigated turbulence and secondary flows in a centrifugal maglev pump. Referring to similar turbulent flows, Huo et al.¹³¹ introduced the “light LES” method, showing improved hydraulic predictions compared to RANS models, which struggle to represent separated flow. Switching to axial designs, Li et al.⁹³ conducted a CFD analysis of the Impella 5.0 and, leveraging these insights, designed their interventional pump, the “Iterative Pump.” Another CFD study⁹⁴ considered five commercial VADs (Fig. 5). High-risk areas for hemolysis and bleeding were similarly distributed, ranking them in the following order for hemocompatibility from lowest to highest: Impella 5.0, UltraMag, CH-VAD, HVAD, and HeartMate II. Finally, even if very few studies address TAHs, particle image velocimetry identified potential thrombogenic regions within Penn State's pediatric TAH¹³⁶. A critical aspect emerged with the right pump, leading to a higher potential for thrombus formation. Then, a combination of in vitro, in vivo, and CFD observations supported design improvements of the Cleveland Clinic's TAH¹³⁷, again to minimize areas of low wall shear stress that favor thrombus formation.

This section has highlighted the dual, and sometimes conflicting, targets of hemocompatibility and hydraulic performance in MCSs. CFD simulations have become instrumental in optimizing pump designs, as they reveal interactions between primary and secondary flow paths and induced turbulence. Nevertheless, MCS parameters should also be interpreted alongside patient history and clinical findings since they are critical for clinical decision-making; routine VAD interrogation is advised in this regard¹³⁸. Furthermore, technological advancements enabled the placement of small, continuous-flow pumps intracardially. Pulsatile (volumetric) pumps may regain interest, particularly for pediatric applications and short-term support, due to their potential to generate low shear stress on blood (pulsatile flow mimics the arterial pulse generated by the heart and is considered “more physiological” by some). Finally, the incorporation of new temporary mechanical circulatory system technologies, including linear cardiac pulsatile pumps, has been reported to be more hemocompatible based on recent preclinical evidence¹¹, but these areas still require follow-up studies. Table 1 condenses the analysis of the more relevant alternatives for MCSs, while Table S5 in the supplementary document covers the older generations of VADs.

Table 1 | Relevant mechanical circulatory supports: critical analysis and forward-looking perspectives

MCSs	Pros	Cons	Risks for patients	Design trade-offs	Translational barriers	Notable research trends
Centrifugal-flow VADs (3rd generation)	• Chest implantation (less invasive). • Prolonged use. • Longer durability (maglev systems). • Room for active speed control (artificial pulsatility). • Lower rotor speeds are feasible (less blood trauma).	• Thoracic surgery. • Lifelong antithrombotic therapy. • Fundamentally continuous flow. • Complex maglev elements. • Percutaneous driveline. • Flow sensitivity to vascular resistance.	• Thrombosis. • Hemolysis. • Bleeding. • Infections (driveline). • Aortic valve fusion and de novo regurgitation (with LVADs). • Right ventricular failure (septum shift).	• Hemodynamics (large impeller gaps to reduce shear stress and stagnation) vs maglev stability and energy efficiency (small gaps for low electromagnetic forces). • Hemodynamic stability (quasi-physiological flow conditions) vs pulsatility (artificial flow transients).	• Poor interpretation of VAD parameters and patient history for optimal clinical decision-making. • Expensive, multi-year regulatory validations for new devices. • Speed up development workflow (modeling and simulation).	• Numerical performance optimization. • Modulation and new antithrombotic therapies. • Entirely transcatheter energy transfer. • Physiologically-smart control adapting to the patient's activity.
Catheter-deployed (axial flow) VADs	• No thoracic surgery (minimally invasive). • Preserved physiology (work with the heart). • Decent scaling.	• Short-term use only. • Blood trauma (very high impeller speed). • Often low output flow (2.5 – 5.5 L/min). • Mobility restrictions. • Positional instability.	• Hemolysis. • Severe access location bleeding. • Aortic valve damage. • Limb ischemia due to catheter obstruction.	• Flow performance (large impeller and inflow area) vs catheter diameter (small impeller) and heart wall stress. • Positional stability (structural stiffness) vs easy deployment (flexibility).	• Hemolysis obstacles for regulatory monitoring. • Tissue-friendly anchoring to prevent intraventricular migration. • Overcome the limits of large-bore catheters.	• Expandable rotors for easier deployment. • Sensing for smart positioning without fluoroscopy. • Redefine procedures for other access locations.
Bi-VADs (continuous flow)	• Complete hemodynamic restoration keeping the native heart. • Outpatient discharge. • Versatile for small-chest implantation.	• Thoracic surgery. • Lifelong antithrombotic therapy (increased). • Demanding left- and right-pump balancing. • More complex emergency protocols.	• Thrombosis (increased in the right pump). • Hemolysis. • Bleeding. • Infections (driveline). • Multi-organ failure.	• Hemodynamics vs maglev stability and efficiency. • Compactness (small impellers) vs vascular health (no normal pressure pulses). • Integrated control (unique and simpler) vs redundancy.	• Stringent boundaries for antithrombotic therapies. • Small market for RVADs, and even smaller for dedicated Bi-VADs, limits costly development.	• Single-rotor devices. • Pulmonary pressure-sensitive speed control. • Improve catheter right pumps to evaluate right ventricle recovery before committing to a Bi-VAD.
THAS ^a (pulsatile flow)	• Availability (no human sources). • Fewer patient restrictions against transplantation. • Instant remedy for ventricular failure.	• Thoracic surgery (irreversible decision). • Size compatibility. • Acoustic/physical discomfort. • Limited options and high costs.	• Thrombosis. • Hemolysis. • Bleeding. • Infections (driveline). • Fitting complications (compression of large thoracic vessels).	• Biomimicry vs durability (see 1st generation VADs). • Flow performance (enough flow and pulmonary/systemic balance) vs anatomical fit. • Power supply (bulky and powerful) vs patient mobility.	• Difficult advancements (limited research compared to VADs) and extremely costly studies. • Impractical approvals as destination therapy.	• Replace polymers with hybrid biomaterials. • Design self-contained power supplies. • Downsize displacement chambers (fit-for-all).
Left atrial assisting devices	• Availability (no animal sources). • Chest implantation. • Physiological flow and pulsatility. • Direct treatment for diastolic dysfunction.	• Strict positioning (mitral plane). • Need for systolic health (good ejection fraction). • Sensitive in diastole. • Overcome high delta pressure in the systole.	• Thrombosis. • Bleeding. • Atrial wall collapse (undue diastole suction). • Flow regurgitation. • Mitral stenosis.	• Centrifugal design (simple) vs backflow prevention. • Robustness (fixed pump speed) vs flow performance. • Pump efficiency (implant at mitral plane) vs practicality (extra-cardiac bypass).	• Lack of accurate models (heart failure with preserved ejection fraction is driven by many human conditions). • Funding competition (priority to VADs).	• Pump's torque-control to match (different) diastole and systole flow demands. • CFD models. • Catheter-delivered pumps. • Integration with a passive atrial shunt.

^a Biological alternatives (transplants) are not considered as "devices" and are not reported.

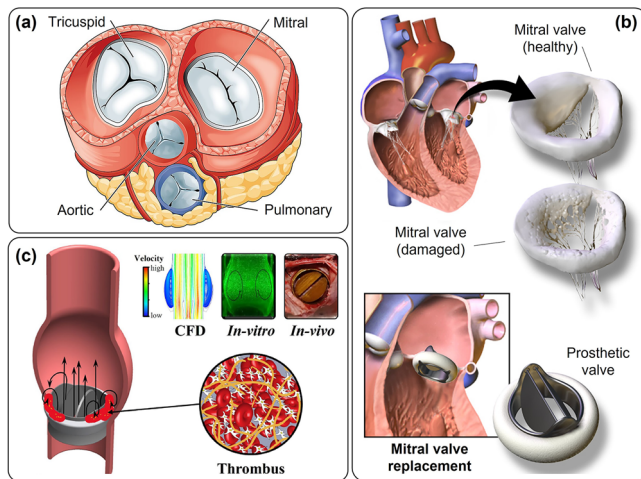


Fig. 6 | Details on heart valves. **a** Illustrative representation of the valves in the human heart (image adapted from Blausen.com staff (2014), “Medical gallery of Blausen Medical 2014”, WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436). **b** Illustrative representation of the mitral valve in both healthy and damaged conditions and its replacement with a prosthetic counterpart (image adapted from Anatomy & Physiology, Connexions. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013.). **c** Visualization of flow recirculating areas around a mechanical aortic valve, which is a condition facilitating thrombus formation (image adapted from ref. 155, <https://link.springer.com/article/10.1007/s10439-024-03480-6>; © 2024 Kreinin et al.).

Design of artificial heart valves

The reasons blood-related issues occur in patients using prosthetic valves are not solely due to direct mechanical degeneration or biodegradation of the implant material. Thrombotic complications, in fact, result from alterations in the hydrodynamics or chemical nature of the valve materials¹³⁹, due to their design and materials (Fig. 6). The high rigidity or inadequate fluid dynamics, particularly in mechanical valves, can lead to non-physiological flow behavior and high shear stresses. Such conditions contribute to cell membrane rupture, hemolysis, platelet activation, and thrombus formation^{139–141}. Additional issues related to valve replacement include bleeding, new-onset conduction disturbances (i.e., problems with the heart’s electrical signaling), and afterload mismatch (i.e., the left ventricle’s workload exceeds its capacity). In response, research on the aortic valve is predominant due to its demanding operations, while studies on the mitral valve significantly outweigh those on the pulmonary valve¹⁴². The mitral valve is more prone to regurgitation and stenosis due to the higher pressure in the left heart. The pulmonary valve, in contrast, has a lower incidence of severe diseases due to lower pressure in the right side of the heart. Lastly, the tricuspid valve also suffers from common valvular disease, and several artificial alternatives for its replacement exist¹⁴³.

In response to the abovementioned complications, the research studies branch off in the following directions:

- **Use of flexible polymer materials or coating**

Bioengineered valves hold promise in reducing immune rejection and thrombogenicity by using decellularized human tissue coated with patient-specific cells. They enhance biocompatibility and promote reendothelialization, potentially minimizing long-term hematologic complications¹⁴⁴. Flexible polymer materials and tricuspid leaflet design are more popular (a recent review of bioprinted valves elaborates on material types¹⁴⁵). Stasiak et al.¹⁴⁶ developed a polymeric valve that underwent extensive in vitro and in vivo testing. The leaflet thickness was optimized so that version J6 demonstrated equivalence to the Carpentier-Edwards Perimount Pericardial Bioprosthesis valve, a benchmark in the field (Fig. 7a). The valve’s durability spans 30 years or over 1.2 billion cycles. Even

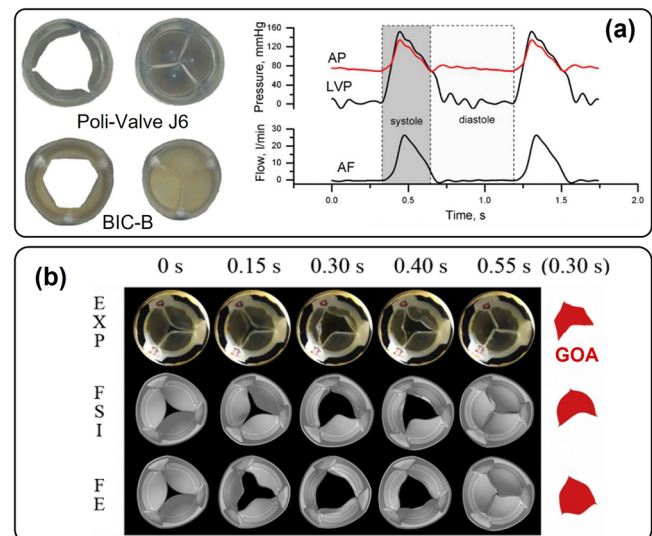


Fig. 7 | Examples of artificial heart valves. **a** Hydrodynamic performance of a polymeric heart valve: valve openings of the prototypes J6 and Carpentier-Edwards BIC-B (21 mm diameter) shown at peak systole (left) and diastole (right), and pressure and flow rates during pulsatile tests of the J6 valve (AP is aortic pressure, LVP left ventricular pressure, and AF aortic flow). All data are prior to fatiguing (image adapted from ref. 146; © 2020 Stasiak et al.). **b** A polymeric heart valve during in vitro tests (EXP) and the corresponding fluid-structure interaction (FSI) and finite element (FE) analyses; the geometric orifice area (GOA) at the maximum opening is highlighted on the right (image adapted from ref. 147; © 2017 Luraghi et al.).

though the study could not quantify thrombosis due to insufficient thrombus formation, optical images showed a thin layer of fibrin and/or red blood cells formed on the samples. Moreover, Luraghi et al.¹⁴⁷ evaluated bio-inspired polymeric valves, concluding that FSI simulations are more appropriate (e.g., they give a closer match to the experiments for leaflet stress). They also emphasized reliability by simulating pulsatile tests (Fig. 7b). The durability of polymeric valves was also confirmed by Rotman et al., since their prototype passed 400 million cycles without failure¹⁴⁸.

In general, the valve’s chemical composition and surface structure significantly influence blood components¹⁴⁹. Blood proteins spontaneously adsorb to the biomaterial surface, depending on many factors¹⁵⁰. Adsorption increases with surface pitting, which provides a larger contact area³¹, or with the presence of chemical substances (e.g., aliphatic compounds, aromatic groups, and perfluorinated groups^{151,152}). Conversely, macromolecules with ionic groups (acidic or basic) and polar chemical groups (ester, ether, and alcohol) reduce protein adsorption on the biomaterial surface^{151,152}. These processes are relevant because adsorption of fibrin stimulates adhesion and platelet activation, initiating the blood clotting cascade on the biomaterial surface¹⁵³. Therefore, the problem of thrombosis in polymeric heart valves remains significant; understanding it is crucial to developing synthetic materials that are less thrombogenic. Tissue-engineered valves are promising because they can enable regenerative properties, but incremental material improvements are insufficient. Successful clinical translation calls for immune modulation and a dynamic response aligned with native tissues¹⁵⁴.

- **Analyses of thrombus formation**

The leaflet restriction is a major cause of failure in mechanical heart valves, originating from uncontrolled thrombus formation at the valve’s periphery and hinge. Kreinin et al.¹⁵⁵ presented an in vitro model of fibrin clot accumulation in prosthetic heart valves under real-time imaging monitoring. Clot accumulation correlated with valve position, with a greater incidence in tilted valves, and was also influenced by local flow features, such as recirculating flows as

indicated by CFD simulations. Furthermore, Laha et al.⁸⁰ used smoothed particle hydrodynamics to model the FSIs of the 25-mm St. Jude bi-leaflet mechanical aortic valve, considering three increasing blockage phenomena. The change in maximum flow velocity from 2.8 to 5 m/s highlights the valve's deteriorating functioning, increasing hemodynamic stress.

• Heart valve fluttering

Heart valve vibration, or fluttering, is an interfering phenomenon that can cause microtrauma to valve tissue, accelerating its degeneration. Chen et al.¹⁵⁶ discussed various detection methods for identifying heart valve fluttering (e.g., particle image velocimetry technology) since it is associated with factors such as thrombi, valve calcification, regurgitation, and hemolysis. The authors suggest fluttering mitigation by optimizing valve design and increasing material strength. Generally, ongoing research aims to understand the FSIs at different levels. The focus can be on specific features (e.g., the optimal height of the valve strut¹⁵⁷) or the overall valve behavior in a channel¹⁵⁸. Such FSI simulations can give reliable results, at least in mechanical aortic valves, and predict the device's life cycle by partially replacing in vitro experimentation in the preclinical and post-market assessments¹⁵⁹.

Summing up this section on artificial valves, it is worth recalling the importance of hemocompatibility (preventing thrombus formation), advanced materials (polymers), and numerical models (simulating FSIs). Table 2 offers an overview of the available options.

Design of cardiovascular implants

We conclude our analysis on cardiovascular devices in contact with blood flow by discussing stents and artificial grafts. Recalling the analogy between the cardiovascular and hydraulic systems, stents and artificial grafts address issues with hydraulic transmission lines, such as bulging or ballooning, vessel blockages, or cardiovascular reconstructions. The illustrative examples in Fig. 8 depict a percutaneous coronary intervention using a stent to treat a blocked artery (the arterial plaque is broken, and the artery diameter is enlarged with an expandable balloon, which deploys and places the stent in the correct location), and the design, manufacturing, and implantation of an artificial graft.

Despite their different nature, stents and grafts share some ongoing research trends. We divide them for convenience into the following broad areas:

• Materials

Enhancing tissue integration to reduce blood-related issues is particularly important for stents, which is achieved via controlled drug release and smart materials that can degrade appropriately¹⁶⁰. Mimicking the nonlinear mechanical behavior of natural blood vessels is crucial for artificial grafts, which is particularly challenging for the small-diameter ones¹⁶¹. Several recent studies addressed these issues, proposing multiple approaches. A move away from metal stents is desirable, embracing polymeric alternatives; however, they pose challenges due to lower mechanical properties (e.g., polymer cracking or detachment is possible), requiring further investigation¹⁶². Surface coatings are explored extensively¹⁶³. Stents can be covered with antithrombotic (heparin) or reendothelialization-promoting materials (they release growth factors or biomimetic molecules). Nanocoating stents and grafts is also possible (e.g., using carbon nanotubes or nanofibers¹⁶⁴) to promote reendothelialization and resist bacterial adhesion, while nanoparticles can be incorporated into stents to efficiently release drugs in situ and reduce side effects. Drug-eluting stents (DESs) address bleeding complications by releasing medications to decrease the duration of post-implantation antiplatelet therapies or encourage vascular repair involving stem cells (mesenchymal stem cells) or gene therapy to promote tissue regeneration¹⁶⁵. (Drug-coated balloons are not discussed since they

represent a temporary alternative.) DESs release antiproliferative agents to suppress excessive neointimal hyperplasia, which is common with bare-metal stents. Everolimus and rapamycin inhibitors, or various rapamycin analogs (rapalogs), are commonplace, while nanoparticle excipients will characterize the next generation of DESs, ensuring targeted delivery of the therapeutic¹⁶⁶. Nevertheless, these drugs facilitate a lipid-driven atherosclerotic process in stented segments (i.e., neoatherosclerosis) that can cause thrombosis long after stent implantation (1–5 years), and no specific solution has been developed to date¹⁶⁷. Additionally, biodegradable and bioabsorbable stents lower the risk of long-term complications by dissolving over time due to their material selection (e.g., magnesium alloys¹⁶⁸). Optimizing the degradation rate and mechanical properties for each patient is also a discussed option.

• Design and manufacturing techniques

Stents and grafts can be tailored to the geometries and mechanical properties of specific patients (i.e., personalized medicine) by combining computed tomography or magnetic resonance imaging reconstruction with 3D-printed realization^{26,169}. To handle the complexity of the stent design procedure, multiple optimization techniques have been leveraged¹⁷⁰. The development of smart stents and grafts equipped with sensors is still in its early stages¹⁶⁰ (e.g., a piezoelectric vascular graft can distinguish between different pulse rates and blood pressures¹⁷¹), as they can potentially detect physiological changes to support patient monitoring post-procedures. (It is worth noticing that general devices for cardiovascular healthcare based on flexible and stretchable electronics are also under development¹⁷².)

Coating is leveraged, particularly in drug-eluting stents. Achieving a challenging uniformity is paramount, and available options include dip, aqueous, and spray coating. The latter technique is the most widely used due to industry-related feasibility metrics, while further advancing coating technologies will benefit this type of stent¹⁷³. Furthermore, tissue-engineered vascular grafts have been intensively investigated using textile manufacturing techniques, such as weaving, knitting, braiding, electrostatic flocking, and electrospinning¹⁷⁴. This approach could reduce the risk of rejection and thrombosis, even if achieving grafts with patency and remodeling (i.e., the adaptive structural changes in response to long-term stress) that mimic natural blood vessels is challenging¹⁶¹. Overall, further research on tissue-engineered vascular grafts is needed in several areas, including hierarchical vascularization, small-diameter grafts, immune response, and long-term stability²⁷.

Regarding cardiac patches, progress has been mostly technology-driven by advancements in design (e.g., bioink's ability to undergo liquid-to-gel phase transition¹⁷⁵) and 3D printing methods such as extrusion, embedded, electrostatic, and light-based printing. They offer specific advantages, so the open challenge is leveraging them complementarily to deliver stable products that favor tissue maturation and actively modulate immune responses¹⁷⁶.

• Hemodynamic studies

In silico and in vitro analyses are complementary approaches to assess the hemodynamics of vascular stents and grafts (Fig. 9). CFD simulations can model device-induced wall shear stress, which adversely affects vascular health, but are computationally expensive when studying complex geometries. The acquisition of similar data experimentally using particle-tracking methods is complicated, particularly at such high resolution, calling for a synergetic effort¹⁷⁷. In particular, a recent meta-analysis on CFD models for stents used to simulate aortic repairs highlighted the marginal credibility of such tools (i.e., collaborative medical and engineering efforts were recommended)³⁶. Several CFD studies were conducted on coronary artery stents³⁶, but fewer on grafts¹⁷⁸. They evaluated the impact of malapposed stents¹⁷⁹, stent-induced deformation effects on aneurysm rupture¹⁸⁰, the use of patient-specific stents to reduce low-velocity and

Table 2 | Available replacements for heart valves: critical analysis and forward-looking perspectives

Valve type	Pros	Cons	Risks for patients	Design trade-offs	Translational barriers	Notable research trends
Mechanical	- High availability (no animal sources). - Best durability (permanent solution). - Virtually no redo surgery.	- Lifelong antithrombotic therapy (frequent tests). - Leaflet restrictions. - Audible noise.	- Thrombosis. - Bleeding (e.g., gastrointestinal). - Afterload mismatch due to an increased (valve) resistance.	Hemodynamic performance (low shear stress, large effective orifice area, etc.) vs thrombogenicity (remove non-physiological flow disturbances).	- Modulate antithrombotic therapy. - Deal with rigid regulations to validate replacements for polylytic carbon leaflets.	- Models for flow in the valve proximity, thrombi formation, fluttering, and valve blockage. - Antithrombotic coatings for leaflets.
Biological xenograft ^a (surgical)	- Availability. - Least antithrombotic therapy. - Better hemodynamics. - Cost-effective.	- Durability (structural degeneration). - Prone to stenosis, calcification, and regurgitation.	- Open-heart surgery. - Surgical redos. - Immune reactions.	- Stented (easier implantation) vs stentless (best hemodynamics). - Bovine pericardium (more strength) vs porcine leaflets (lower transvalvular pressure gradient).	- Eliminate chronic immune responses and antithrombotic therapy. - Deal with complex regulatory pathways. - Perform design informed by native environments.	- Mechanoresponsive (adaptable) scaffolds. - Immuno-related advancements to mask foreign tissues. - Anti-calcification measures.
Biological xenograft (transcatheter)	- Availability. - Minimally invasive (safer) implantation. - Less antithrombotic therapy.	- Durability. - Calcification. - Paravalvular leakage. - Conduction block due to frame expansion. - Coronary artery occlusion. - Higher cost.	- High rates of pacemaker dependency. - Subclinical thrombosis. - Ischemic stroke due to catheter navigation. - Explantation hazards.	- Catheter size (small for easier navigation) vs leaflet integrity (larger design favors durability). - Radial forces (fewer leaks, no valve dislocation) vs conduction injury (pacemaker for excessive compression).	- Overcome design suited to Western anatomies. - Improve predictions of valve expansion inside irregular native rings. - Solve rapid calcification in younger patients. - Integrate novelties into multi-year clinical trials.	- Models for estimating frame deployments. - Emboic protections (filter to catch dislodged debris in the procedure).
Polymeric	- High availability (no animal sources) and customizability. - Less antithrombotics. - Improved durability against calcification and deterioration.	- Actual lifespan (no long-term human data). - Potential fatigue cracking for polymers. - Thrombogenicity for non-treated polymers.	- Potential sudden failure. - Valve stenosis (tissue overgrowth and calcification). - Embolism (polymer particles peeling).	- Mechanical strength (more durability) vs flexibility (less valve's opening effort and catheter implantation). - Polymer biostability (inertness against degradation) vs bioactivity (human cell growth for better integration).	- Complete multi-year validations. - Solve durability mismatches of in vitro and in vivo tests. - Find a feasible way to facilitate customization.	- Less thrombogenic materials and techniques (e.g., endothelialization). - Models to predict durability. - Polymers to avoid calcification.

Polymeric valves are under clinical trials or development, while the other options are in use.
^aOther biological alternatives (homograft heart valves) are not considered as "devices" and are not reported in this table.

Fig. 8 | Examples of cardiovascular implants. **a** Schematic illustration of a percutaneous placement of a stent for treating an artery blocked by plaque formation (image adapted from https://commons.wikimedia.org/wiki/File:Angioplasty_-_Balloon_Inflated_with_Stent.png, Blausen Medical. Retrieved on 22 February 2016). **b** Procedure for obtaining a patient-specific vascular graft using a sheep model. Image adapted from ref. 169. Reprinted from The Journal of Thoracic and Cardiovascular Surgery, vol. 153, no. 4, T. Fukunishi et al., Preclinical study of patient-specific cell-free nano-fiber tissue-engineered vascular grafts using 3-dimensional printing in a sheep model, Page No. 926, Copyright (2017), with permission from Elsevier. The steps A-F include the size reconstruction of the thoracic inferior vena cava, the graft electrospun onto a 3D-printed scaffold, and the graft implantation.

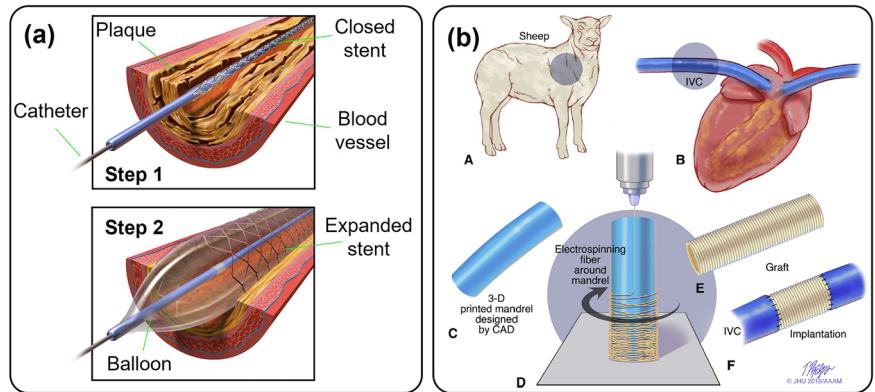
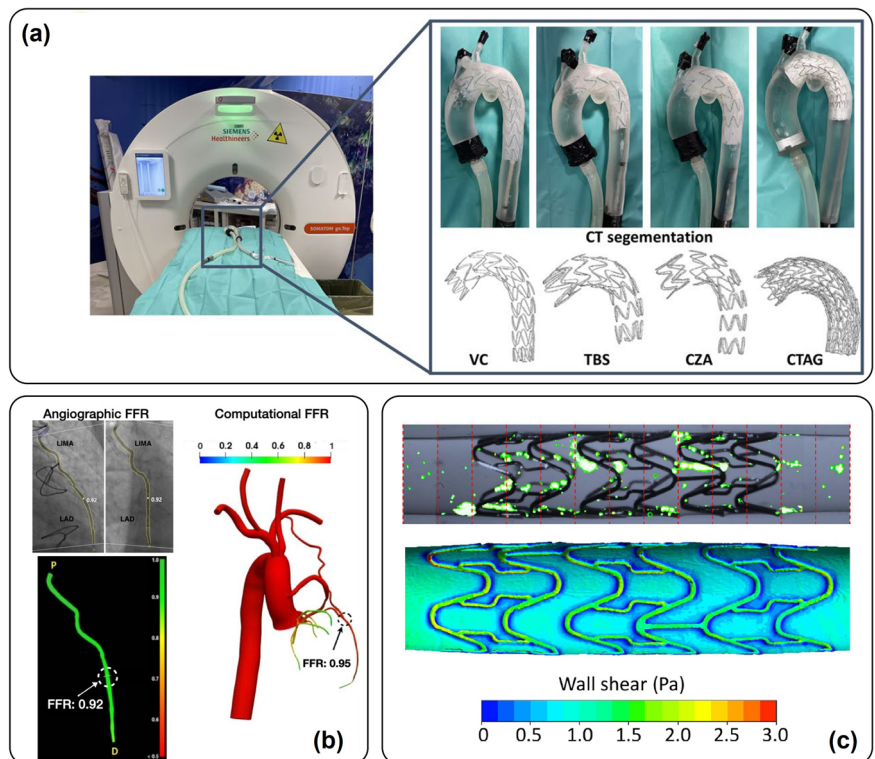


Fig. 9 | Examples of the synergetic use of CFD simulations and experimental measurements in cardiovascular implants. **a** Physical prototypes and stent segmentation from computed tomography images for subsequent numerical simulations (image adapted from ref. 184, <https://doi.org/10.1007/s10439-025-03949-y>; © 2025 Ramella et al.). **b** Comparison of the fractional flow reserve (FFR), which is the gold standard for identifying ischemic lesions, in coronary artery bypass grafting obtained from invasive coronary angiographic (left side) and CFD computations (image adapted from ref. 178, <https://doi.org/10.1371/journal.pone.0281423>. g004; © 2023 Wu et al.). **c** Locations of particle accumulation within a coronary stent deployed in a model vessel on the top (the red segments are 1 mm distant) and corresponding CFD analysis created from a reconstructed scan showing reduced shear stress downstream of struts (images adapted from ref. 177, <https://doi.org/10.1371/journal.pone.0271469.g005> and <https://doi.org/10.1371/journal.pone.0271469.g006>; © 2022 Boldock et al.).



low wall shear stress areas¹⁸¹, and the care required to approximate blood as a Newtonian fluid¹⁸². While CFD provides insights into the effect of stent mesh design on near-wall blood flow and hemodynamics, particle image velocimetry¹⁸³ and particle tracking velocimetry¹⁷⁷ have been used both as standalone measurement methods and as a comparison to validate CFD studies. Additionally, computed tomography was leveraged to reconstruct in vitro stent deployments and enable more accurate CFD simulations^{177,184–186}.

This section has briefly highlighted the critical role of vascular implants in various medical procedures, emphasizing the need for hemodynamic compatibility to prevent complications such as thrombosis and embolism. Computational methods are pivotal for optimizing the design of these devices since multiple studies have shown that implants with improved geometries can enhance hemodynamics. Specifically, integrating CFD in the development process and using patient-specific designs are essential for

creating more effective and safer stents and grafts, ultimately improving patient outcomes. Table 3 summarizes the analysis of the more relevant alternatives.

Conclusions and outlook

In this review, we have discussed various cardiovascular devices in which fluid dynamics plays a dominant role. Our emphasis has been on hemocompatibility (primarily avoiding thrombosis, hemolysis, and bleeding), which is essential for patient safety. Hemodynamic performance is generally unsatisfactory, as hematologic complications remain a challenge for cardiovascular devices. We have, therefore, analyzed and discussed the recent advancements in the field, isolating the following essential conclusions:

- **Mechanical circulatory supports** are vital in managing heart failure, and their design must balance hydraulic performance with hemocompatibility; these two facets reflect the ongoing research trends in

Table 3 | Relevant cardiovascular implants: critical analysis and forward-looking perspectives

Implants	Pros	Cons	Risks for patients	Design trade-offs	Translational barriers	Notable research trends
Permanent stents and stent-grafts	- Minimal surgery. - Instantaneous effect. - Durable vessel patency.	- Lifelong foreign body. - Compulsory antiplatelet therapy. - Complex patient monitoring. - Vessel mismatch.	- Thrombosis. - In-stent restenosis. - Malposition/migration. - Vessel perforation. - Incomplete sealing (stent-grafts only).	- Strength (more metal thickness) vs anatomical conformability and low thrombogenic turbulence. - Anchoring (radial force) vs low wall compression.	- Inaccurate long-term animal models (vastly different responses). - Multi-year evidence for regulatory approvals.	- Mimic natural blood vessel behavior. - Coating with drugs. - Tissue-engineered grafts. - Patient-specific design. - Numerical simulations.
Bioresorbable stents	- Minimal surgery. - Interim foreign body (no late thrombosis). - Restoration of the vessel's physiological flexibility. - No material-related long-term inflammation.	- Lower mechanical properties. - Thicker geometry to match metal strength. - Complex deployment. - Restrictions of use.	- Thrombosis (if shortened antiplatelet therapy). - In-stent restenosis. - Malposition/migration. - Delayed resorption. - Early scaffold fracture and fragment release.	- Strength vs turbulence (see above). - Quick resorption vs full vessel restoration. - Visibility (radiopaque markers) vs structural integrity.	- Skeptical environment (undesired performance of early versions). - Consistent resorption dynamics in all patients. - Manufacturing (3D print still undeveloped).	- Tailored 3D printing. - Bioresorbable metallic alloys (more strength). - Bioactive additives and adaptive resorption. - Risk stratification models.
Artificial vascular grafts ^a	- Availability (quantity and sizes/shapes). - Effective (large size). - Mechanical strength.	- No bio-response. - Mechanical mismatch. - Failure (small size). - Antithrombotic or antiplatelet therapy (many patients).	- Thrombosis. - Vessel hyperplasia. - Pseudo-aneurysm. - Infections.	- Tissue growth (graft porosity) vs sealing. - Flexibility (low thickness) vs strength. - Biocompatibility (coatings) vs localized immune response.	- Dealing with slow vessel endothelialization. - Unsolved small-diameter non-thrombogenic design. - Multi-year evidence for regulatory approvals.	- Tissue-engineered vascular grafts. - Coating with drugs. - Patient-specific design.
Biological vascular patches ^b	- Best compliance and biocompatibility. - Handling and suturing characteristics. - Low thrombogenicity.	- Long-term biological degradation. - Calcification. - Unpredictable variability (strength). - Finite availability.	- Rupture/dilatation. - Late-stage restenosis. - Immune rejection. - Infections. - Harvest trauma (autographs only).	- Immune tolerance (deep "cleaning") vs remodeling abilities and strength. - Anti-calcification (coatings) vs biocompatibility.	- Complex regulatory approvals for biological tissue derivatives. - Sterilize and preserve mechanical properties. - Pediatric growth limits.	- Alternative (stabilizing) cross-linking agents. 3D bioprinted patches layered with patient cells. - Plant-derived structures to avoid disease risks.
Artificial vascular patches	- No harvest trauma. - Availability (quantity). - Predictable response. - Durability.	- Limited compliance. - No bio-response. - Difficult suturability.	- Rupture/dilatation. - Thrombosis. - Late-stage restenosis. - Infections.	- Conformability (thin patch) vs edge forces. - Packed polymer (sealing and resistance) vs knitted. - Inertness (coatings) vs healthy cell attachment.	- Dealing with slow human endothelialization. - Polymer alterations induced by sterilization. - Pediatric growth limits. - Multi-year evidence for regulatory approvals.	- Tissue engineering to recruit patient cells. - Biodegradable patches. - Antithrombotic surface functionalization. - Development of 3D printing techniques.

^aBiological alternatives (autologous and allografts) are not considered as "devices" and are not reported in this table. Autologous grafts are often used for small-diameter (<6 mm) applications.

^bBiological vascular patches comprise materials derived from the patient's own tissue (autographs), human tissues (allografts), and animal tissues (xenografts).

this area (see Table 1). Developing more compact designs (mainly magnetically-levitated centrifugal pumps for continuous flow) allowed for intracardiac placement, improving patient comfort and reducing infection risk. However, volumetric pumps for pulsatile flow could regain interest. They generate lower shear stresses on blood, being more hemocompatible, and mimic the physiological arterial pulse of the heart. There is also a need for fit-for-all devices, expandable (catheter-delivered) pumps, and physiologically smart control. Improving the interpretation of MCS parameters alongside patient history is also advised for optimal clinical decision-making, so dedicated studies are required. Lastly, CFD and FSI analyses have become instrumental in refining the MCS geometry, given the influence of many design parameters; extensive experimental data are still needed to validate accurate simulation models.

- **Artificial heart valves** restore normal blood flow in the heart and face challenges such as ensuring sufficient durability and minimizing the need for anticoagulation therapies in patients. In response, the current research focuses on using antithrombotic polymers or coatings, understanding thrombus formation due to the induced fluid dynamics, and studying valve fluttering and FSIs (see Table 2). Technology has advanced from mechanical to biological and polymeric valves. This evolution improved hemodynamic compatibility by returning to a more natural hemodynamic performance and reduced material fatigue by leading to an expected lifespan of about 25 years, which still requires extensive confirmation. Further improvements call for advances in materials science (e.g., flexible polymers with anti-calcification properties) and numerical modeling (e.g., simulating FSIs and assessing the impact of leaflet blockage).
- **Cardiovascular implants** maintain the proper shape of obstructed blood vessels or replace/bypass damaged vessel segments. Despite the different functions, they must ensure appropriate integration with biological tissues without immune rejection, minimize thrombosis, and sustain biomechanical loading over time. Recent research trends revolve around using advanced materials and tissue-engineered artifacts, improving manufacturing techniques, and studying their impact on hemodynamic parameters (see Table 3). Additive manufacturing has emerged, and thin polymer membranes have been used, but they are still in early development. Further, combining computational methods (CFD and FSI simulations) with patient-specific studies optimizes the device's hemodynamic performance, which requires enhancing reconstruction techniques, such as micro-computed tomography.

Due to the complexity of the topic, it is apparent that cutting-edge research on cardiovascular devices should combine numerical methods with experimental trials, which are also mandatory for approved medical products. This integration offers a comprehensive hemocompatibility assessment, which is vital for developing the next generation of cardiovascular devices. Considering the multidisciplinary nature of this field (human physiology, surgery, biochemistry, fluid mechanics, deformable solid mechanics, materials science, manufacturing, and mechatronics all play a role), the future of patient care is also significantly influenced by collaboration among researchers with different backgrounds, clinicians, and industry. Such a broad partnership is ineluctable and should be facilitated to the greatest extent possible. Therefore, creating a link to enable an adequate flow of information and data exchange is paramount.

Further elaborating on these aspects, we now propose our outlook, in random order, on the predominant topics that call for future research efforts:

- **Modeling blood, blood vessels, and cardiovascular devices.** Developing CFD and FSI simulations to predict blood flow and blood-device interactions can improve hemocompatibility and hydraulic performance. Numerical approaches also facilitate patient-specific treatments, which are game-changers for long-term patient well-being.

Fully leveraging these opportunities requires creating extensive, high-quality data banks for model validation and improving models to predict blood damage over time.

- **Design and optimization.** High-fidelity simulation tools enable optimization processes to identify the best design parameters (shape optimization) and deployment methods for cardiovascular devices. Conventional techniques, such as gradient-based and derivative-free methods, can be used to optimize a cost function despite the need for complex, time-consuming simulations. Thus, AI-driven design solutions should be considered for faster outcomes, especially if wide-ranging data banks are available.
- **Innovative materials and medicaments.** Engineered materials have the potential to revolutionize many fields of science, and cardiovascular devices are no exception. Using polymers and nanomaterials has already opened up new hemocompatibility paradigms. Still, more action is needed to ensure complete hemocompatibility and tissue integration, and promote long-term durability with consistent mechanical properties. More effort is also required for antithrombotic therapies that do not harmfully affect hemostasis and, possibly, on (drug-free) stimulus-responsive techniques.
- **Manufacturing and prototyping.** Additive manufacturing offers unique capabilities to realize complex structures, including soft ones. This approach should be exploited intensively since it can create complex geometries to improve hemodynamics (e.g., pump impellers), easily apply personalized design features for patient-specific treatments, and quickly generate prototypes to obtain extensive data banks (e.g., prototyping and testing a blood pump takes a few hours and can be faster than simulating it, particularly when high-fidelity numerical models are employed).
- **Sensing and monitoring.** There is a generalized tendency to equip almost every engineering product with embedded sensors. The same approach should be considered for cardiovascular devices, particularly MCSs, to detect undesired changes and collect relevant real-time data for long-term monitoring. Then, specific protocols should be developed to process the measurements, ideally using machine learning or AI-driven analytics, so that appropriate decisions can be made to perform proactive action.
- **Blood measuring and monitoring techniques.** Enabling real-time techniques for ex vivo tracking of blood damage without advanced setups or medical personnel will facilitate experimental validations. These methods are valuable in medical settings and, most importantly, in engineering research laboratories where large-scale data collection is required. Defining in vitro tests that account for human physiology and enable trustworthy preclinical assessments of blood damage is paramount for the efficient development of new devices. Lastly, a more reliable gold standard for obtaining regulatory compliance is also needed.

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References

1. Martin, S. S. et al. 2024 heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation* **149**, E347–E913 <https://doi.org/10.1161/CIR.0000000000001209> (2024). This recent medical article puts into context the extremely serious consequences of heart disease with a special focus on the USA.
2. Shahim, B., Kapelios, C. J., Savarese, G. & Lund, L. H. Global public health burden of heart failure: an updated review. *Card. Fail. Rev.* **9**, e11 <https://doi.org/10.15420/cfr.2023.05> (2023).
3. Mingbo, L., Xinye, H., Xiaohong, Y. & Zengwu, W. Interpretation of report on cardiovascular health and diseases in China 2023. *Chin. Gen. Pract.* **28**, 20–38 <https://doi.org/10.12114/j.issn.1007-9572>.

- 2024.0293. This recent medical article puts into context the extremely serious consequences of heart disease with a special focus on China.
4. Fukamachi, K. et al. Left atrial assist device to treat patients with heart failure with preserved ejection fraction: initial in vitro study. *J. Thorac. Cardiovasc. Surg.* **162**, 120–126 <https://doi.org/10.1016/j.jtcvs.2019.12.110> (2021).
 5. Sapna, F. et al. Advancements in heart failure management: a comprehensive narrative review of emerging therapies. *Cureus* **15**, 1–13 <https://doi.org/10.7759/cureus.46486> (2023).
 6. Köhne, I. Review and reflections about pulsatile ventricular assist devices from history to future: concerning safety and low haemolysis—still needed. *J. Artif. Organs* **23**, 303–314 <https://doi.org/10.1007/s10047-020-01170-3> (2020).
 7. Levine, A. & Gass, A. Third-generation LVADs. *Cardiol. Rev.* **27**, 293–301 <https://doi.org/10.1097/CRD.0000000000000268> (2019).
 8. Kozakov, K., Provaznik, Z., Schmid, C. & Camboni, D. Advancing LVAD technology: overcoming challenges and shaping the future of mechanical circulatory support. *J. Clin. Med.* **13**, 7813 <https://doi.org/10.3390/jcm13247813> (2024).
 9. Al Khoufi, E. A. Outcomes of left ventricular assist devices as destination therapy: a systematic review with meta-analysis. *Life* **15**, 53 <https://doi.org/10.3390/life15010053> (2025).
 10. Potapov, E. V., Kaufmann, F., Müller, M., Mulzer, J. & Falk, V. Longest ongoing support (13 Years) with magnetically levitated left ventricular assist device. *ASAIO J.* **66**, E121–E122 <https://doi.org/10.1097/MAT.0000000000001131> (2020).
 11. Kim, J. et al. A novel transaortic pulsatile pump to unload the left ventricle. *JACC Basic Transl. Sci.* **10**, 270–272 <https://doi.org/10.1016/j.jacbts.2025.01.012> (2025).
 12. Hall, J. E. & Guyton A. C. *Guyton and Hall Textbook of Medical Physiology* 12th edn (Saunders/Elsevier, 2011).
 13. Vis, A. et al. The ongoing quest for the first total artificial heart as destination therapy. *Nat. Rev. Cardiol.* **19**, 813–828 <https://doi.org/10.1038/s41569-022-00723-8> (2022). This article offers a complete and relatively recent overview of total artificial hearts.
 14. Lavee, J. et al. An international multicenter experience of biventricular support with HeartMate 3 ventricular assist systems. *J. Heart Lung Transpl.* **37**, 1399–1402 <https://doi.org/10.1016/j.healun.2018.08.008> (2018).
 15. Perkins, I. L., Jansen, P., Smith, P. A., Cohn, W. E. & Frazier, O. H. Total artificial hearts. in *Mechanical Circulatory and Respiratory Support* 2nd edn, Ch. 6, 171–198 <https://doi.org/10.1016/B978-0-443-22148-4.00006-X> (Elsevier, 2025).
 16. Tillquist, M. & Maddox, T. Cardiac crossroads: deciding between mechanical or bioprosthetic heart valve replacement. *Patient Prefer. Adherence* **5**, 91 <https://doi.org/10.2147/PPA.S16420> (2011).
 17. Wang, Y. et al. Recent advancements in polymeric heart valves: from basic research to clinical trials. *Mater. Today Bio.* **28**, 101194 <https://doi.org/10.1016/j.mtbio.2024.101194> (2024).
 18. Kueri, S. et al. The use of biological heart valves—types of prosthesis, durability and complications. *Dtsch. Arztebl. Int.* **116**, 423–430 <https://doi.org/10.3238/arztebl.2019.0423> (2019).
 19. Todesco, M., Lezziero, G., Gerosa, G. & Bagnò, A. Polymeric heart valves: do they represent a reliable alternative to current prosthetic devices?. *Polymers* **17**, 1–45 <https://doi.org/10.3390/polym17050557> (2025). This recent medical review article provides a deep understanding of the current issues and future research trends for polymeric heart valves.
 20. Singh, S. K. et al. Polymeric prosthetic heart valves: a review of current technologies and future directions. *Front. Cardiovasc. Med.* **10** <https://doi.org/10.3389/fcvm.2023.1137827> (2023).
 21. Ando, T., Briasoulis, A. & Panaich, S. Advances in transcatheter aortic valve replacement. *Sci. Press* <https://doi.org/10.11909/j.issn.1671-5411.2019.09.002> (2019).
 22. Ullah, M. et al. Stent as a novel technology for coronary artery disease and their clinical manifestation. *Curr. Probl. Cardiol.* **48** <https://doi.org/10.1016/j.cpcardiol.2022.101415> (2023).
 23. Korei, N., Solouk, A., Hagbin Nazarpak, M. & Nouri, A. A review on design characteristics and fabrication methods of metallic cardiovascular stents. *Mater. Today Commun.* **31**, 103467 <https://doi.org/10.1016/j.mtcomm.2022.103467> (2022).
 24. Auricchio, F., Boatti, E. & Conti, M. SMA cardiovascular applications and computer-based design. in *Shape Memory Alloy Engineering*, (eds Lecce, L. & Concilio, A.) Ch. 12, 343–367 <https://doi.org/10.1016/B978-0-08-099920-3.00012-7> (Elsevier, 2015).
 25. Farhan, M. et al. Bioresorbable scaffolds advances, challenges, and future directions. *Ann. Med. Surg.* **87**, 4173–4183 <https://doi.org/10.1097/MS9.00000000000003424> (2025).
 26. Li, Y. et al. Additive manufacturing of vascular stents. *Acta Biomater.* **167**, 16–37 <https://doi.org/10.1016/j.actbio.2023.06.014> (2023).
 27. Das, K. K., Tiwari, R. M., Shankar, O., Maiti, P. & Dubey, A. K. Tissue-engineered vascular grafts for cardiovascular disease management: current strategies, challenges, and future perspectives. *MedComm—Biomater. Appl.* **3** <https://doi.org/10.1002/mba2.88> (2024).
 28. Chen, J., Zhang, D., Wu, L. P. & Zhao, M. Current strategies for engineered vascular grafts and vascularized tissue engineering. *Polymers* **15**, 1–35 <https://doi.org/10.3390/polym15092015> (2023).
 29. Szafron, J. M., Heng, E. E., Boyd, J., Humphrey, J. D. & Marsden, A. L. Hemodynamics and wall mechanics of vascular graft failure. *Arterioscler. Thromb. Vasc. Biol.* **44**, 1065–1085 <https://doi.org/10.1161/ATVBAHA.123.318239> (2024).
 30. Sun, M. et al. Cardiovascular patches applied in congenital cardiac surgery: Current materials and prospects. *Bioeng. Transl. Med.* **10** <https://doi.org/10.1002/btm2.10706> (2025). This article offers a complete and recent overview of total cardiovascular patches.
 31. Weber, M. et al. Blood-contacting biomaterials: In vitro evaluation of the hemocompatibility. *Front. Bioeng. Biotechnol.* **6**, 99 <https://doi.org/10.3389/fbioe.2018.00099> (2018).
 32. Nalezinková, M. In vitro hemocompatibility testing of medical devices. *Thromb. Res.* **195**, 146–150 <https://doi.org/10.1016/j.thromres.2020.07.027> (2020).
 33. Wang, C. Simmonds, M. J., An, H. & McNamee, A. P. Cavitation in blood-contacting biomedical devices. *Biophys. Rev.* **7** <https://doi.org/10.1063/5.0300934> (2026).
 34. Fraser, K. H., Taskin, M. E., Griffith, B. P. & Wu, Z. J. The use of computational fluid dynamics in the development of ventricular assist devices. *Med. Eng. Phys.* **33**, 263–280 <https://doi.org/10.1016/j.medengphy.2010.10.014> (2011).
 35. Le, T. B., Usta, M., Aidun, C., Yoganathan, A. & Sotiropoulos, F. Computational methods for fluid-structure interaction simulation of heart valves in patient-specific left heart anatomies. *Fluids* **7**, 94 <https://doi.org/10.3390/fluids7030094> (2022).
 36. Valentim, M. X. G., Zinani, F. S. F., da Fonseca, C. E. & Wermuth, D. P. Systematic review on the application of computational fluid dynamics as a tool for the design of coronary artery stents. *Beni. Suef. Univ. J. Basic Appl. Sci.* **12**, 49 <https://doi.org/10.1186/s43088-023-00382-9> (2023).
 37. Candrea, A. et al. Current and future applications of computational fluid dynamics in coronary artery disease. *Rev. Cardiovasc. Med.* **23**, 1–18 <https://doi.org/10.31083/j.rcm2311377> (2022).
 38. Kuchinka, J., Willems, C., Telyshev, D. V. & Groth, T. Control of blood coagulation by hemocompatible material surfaces—a review. *Bioengineering* **8**, 1–26 <https://doi.org/10.3390/bioengineering8120215> (2021).
 39. Yu, H., Engel, S., Janiga, G. & Thévenin, D. A review of hemolysis prediction models for computational fluid dynamics. *Artif. Organs* **41**, 603–621 <https://doi.org/10.1111/aor.12871> (2017).
 40. Gregory, S. D., Stephens, A. F., Heinsar, S., Arens, J. & Fraser, J. F. *Mechanical Circulatory And Respiratory Support* 2nd edn (Academic

- Press, 2024). This recent textbook provides an overview of all the essential aspects of cardiovascular devices, with a focus on medical sciences.
41. Arabía, F. A. *Mechanical circulatory support* (Springer, 2025). This recent textbook provides an overview of all the essential aspects of cardiovascular devices, with a focus on medical sciences.
 42. Hilal, T., Mudd, J. & DeLoughery, T. G. Hemostatic complications associated with ventricular assist devices. *Res. Pract. Thromb. Haemost.* **3**, 589–598 <https://doi.org/10.1002/rth2.12226> (2019).
 43. Simmonds, M. J., Watanabe, N., McNamee, A. P. & Clauser, J. C. Blood–device interactions. in *Mechanical Circulatory and Respiratory Support* 2nd edn. Ch. 20, 611–640 <https://doi.org/10.1016/B978-0-443-22148-4.00020-4> (Elsevier, 2025).
 44. Cardenas, J. C. Thrombin generation following severe trauma: mechanisms, modulators, and implications for hemostasis and thrombosis. *Shock* **56**, 682–690 <https://doi.org/10.1097/SHK.0000000000001773> (2021).
 45. Casa, L. D. C., Deaton, D. H. & Ku, D. N. Role of high shear rate in thrombosis. *J. Vasc. Surg.* **61**, 1068–1080 <https://doi.org/10.1016/j.jvs.2014.12.050> (2015).
 46. Slepian, M. J., Italiano, J., Bluestein, D., Sheriff, J. & Roka-Moia, Y. Evolving perspectives on mechanical circulatory support biocompatibility and interfaces. *Ann. Cardiothorac. Surg.* **10**, 396–398 <https://doi.org/10.21037/acs-2020-cfmcs-247> (2021).
 47. Berdiaki, A. et al. Extracellular matrix components and mechanosensing pathways in health and disease. *Biomolecules* **14**, 1186 <https://doi.org/10.3390/biom14091186> (2024).
 48. Davis, M. J., Earley, S., Li, Y.-S. & Chien, S. Vascular mechanotransduction. *Physiol. Rev.* **103**, 1247–1421 <https://doi.org/10.1152/physrev.00053.2021> (2023).
 49. Slepian, M. J. et al. Shear-mediated platelet activation in the free flow: perspectives on the emerging spectrum of cell mechanobiological mechanisms mediating cardiovascular implant thrombosis. *J. Biomech.* **50**, 20–25 <https://doi.org/10.1016/j.jbiomech.2016.11.016> (2017). This biomedical article provides a deep understanding of advanced mechanisms central to thrombosis in cardiovascular devices.
 50. McNamee, A. P. & Simmonds, M. J. Red blood cell sublethal damage: hemocompatibility is not the absence of hemolysis. *Transfus. Med. Rev.* **37**, 150723 <https://doi.org/10.1016/j.tmr.2023.03.001> (2023).
 51. Annich, G. M. Extracorporeal life support: the precarious balance of hemostasis. *J. Thromb. Haemost.* **13**, S336–S342 <https://doi.org/10.1111/jth.12963> (2015).
 52. Al-Koussa H., Al-Zaim I., and El-Sabban M. E., Pathophysiology of coagulation and emerging roles for extracellular vesicles in coagulation cascades and disorders. *J. Clin. Med.* <https://doi.org/10.3390/jcm11164932> (2022).
 53. Rohmann, J. L. et al. Coagulation factor XII, XI, and VIII activity levels and secondary events after first ischemic stroke. *J. Thromb. Haemost.* **18**, 3316–3324 <https://doi.org/10.1111/jth.15092> (2020).
 54. Schöps, M. et al. Hemolysis at low blood flow rates: in-vitro and in-silico evaluation of a centrifugal blood pump. *J. Transl. Med.* **19**, 2 <https://doi.org/10.1186/s12967-020-02599-z> (2021).
 55. Goldsmith, H. L., Turitto, V. T. Rheological aspects of thrombosis and haemostasis: basic principles and applications. ICH-report-Subcommittee on rheology of the international committee on thrombosis and haemostasis. *Thromb. Haemostat.* **55**, 415–435 (1986).
 56. McNamee, A. P., Richardson, K., Horobin, J., Kuck, L. & Simmonds, M. J. Susceptibility of density-fractionated erythrocytes to subhaemolytic mechanical shear stress. *Int. J. Artif. Organs* **42**, 151–157 <https://doi.org/10.1177/0391398818790334> (2019).
 57. Heilmann, C. et al. Haemolysis in patients with ventricular assist devices: major differences between systems. *EJCTS* **36**, 580–584 <https://doi.org/10.1016/j.ejcts.2009.04.015> (2009).
 58. Starling, R. C. et al. Unexpected abrupt increase in left ventricular assist device thrombosis. *N. Eng. J. Med.* **370**, 33–40 <https://doi.org/10.1056/nejmoa1313385> (2014).
 59. Badiye, A. P., Hernandez, G. A., Novoa, I. & Chaparro, S. V. Incidence of hemolysis in patients with cardiogenic shock treated with Impella percutaneous left ventricular assist device. *ASAIO J.* **62**, 11–14 <https://doi.org/10.1097/MAT.0000000000000290> (2016).
 60. Dimitrov, J. D., Roumenina, L. T., Perrella, G. & Rayes, J. Basic mechanisms of hemolysis-associated thrombo-inflammation and immune dysregulation. *Arterioscler. Thromb. Vasc. Biol.* **43**, 1349–1361 <https://doi.org/10.1161/ATVBAHA.123.318780> (2023).
 61. Capecci, M., Ciavarella, A., Artoni, A., Abbattista, M. & Martinelli, I. Thrombotic complications in patients with immune-mediated hemolysis. *J. Clin. Med.* **10**, 1–18 <https://doi.org/10.3390/jcm10081764> (2021).
 62. Luo, S., Hu, D., Wang, M., Zipfel, P. F. & Hu, Y. Complement in hemolysis- and thrombosis- related diseases. *Front. Immunol.* **11**, 1–10 <https://doi.org/10.3389/fimmu.2020.01212> (2020).
 63. Han, J. J., Acker, M. A. & Atluri, P. Left ventricular assist devices synergistic model between technology and medicine. *Circulation* **138**, 2841–2851 <https://doi.org/10.1161/CIRCULATIONAHA.118.035566> (2018).
 64. Goldstein, D. J. et al. Gastrointestinal bleeding in recipients of the HeartWare ventricular assist system. *Jacc. Heart Fail.* **3**, 303–313 <https://doi.org/10.1016/j.jchf.2014.11.008> (2015).
 65. Galli, M. et al. Antithrombotic therapy in high bleeding risk, Part I. *JACC Cardiovasc. Interv.* **17**, 2197–2215 <https://doi.org/10.1016/j.jcin.2024.08.022> (2024).
 66. Del Rio-Pertuz, G. & Nair, N. Gastrointestinal bleeding in patients with continuous-flow left ventricular assist devices: a comprehensive review. *Artif. Organs* **47**, 12–23 <https://doi.org/10.1111/aor.14432> (2023).
 67. Van Edom, C. J. et al. Management of bleeding and hemolysis during percutaneous microaxial flow pump support. *JACC Cardiovasc. Interv.* **16**, 1707–1720 <https://doi.org/10.1016/j.jcin.2023.05.043> (2023).
 68. van Nieuwkerk, A. C. et al. Bleeding in patients undergoing transfemoral transcatheter aortic valve replacement. *JACC Cardiovasc. Interv.* **16**, 2951–2962 <https://doi.org/10.1016/j.jcin.2023.10.011> (2023).
 69. Nienaber, J., Wilhelm, M. P. & Sohail, M. R., Current concepts in the diagnosis and management of left ventricular assist device infections. <https://doi.org/10.1586/eri.12.163> (2013).
 70. O'Horo, J. C. et al. Left ventricular assist device infections: a systematic review. *ASAIO J.* **64**, 287–294 <https://doi.org/10.1097/MAT.0000000000000684> (2018).
 71. Chen, Z., Sun, A., Wang, H., Fan, Y. & Deng, X. Non-physiological shear stress-induced blood damage in ventricular assist device. *Med. Nov. Technol. Devices* **3**, 1–7 <https://doi.org/10.1016/j.medntd.2019.100024> (2019).
 72. Carter, J., Hristova, K., Harasaki, H. & Smith, W. A. Short exposure time sensitivity of white cells to shear stress. *ASAIO J.* **49**, 687–691 <https://doi.org/10.1097/01.MAT.0000094194.93742.A7> (2003).
 73. Rose, E. A. et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N. Eng. J. Med.* **345**, 1435–1443 <https://doi.org/10.1056/NEJMoa012175> (2001).
 74. Atti, V. et al. A comprehensive review of mechanical circulatory support devices. *Heart Int.* **16**, 37–48 <https://doi.org/10.17925/HI.2022.16.1.37> (2022). This review article provides an overview of mechanical circulatory support devices.

75. DeYoung, V., Singh, K. & Kretz, C. A. Mechanisms of ADAMTS13 regulation. *J. Thromb. Haemost.* **20**, 2722–2732, <https://doi.org/10.1111/jth.15873> (2022).
76. South, K. & Lane, D. A. ADAMTS-13 and von Willebrand factor: a dynamic duo. *J. Thromb. Haemost.* **16**, 6–18, <https://doi.org/10.1111/jth.13898> (2018).
77. Ito, T. et al. Optimization of anti-ADAMTS13 antibodies for the treatment of ADAMTS13-related bleeding disorder in patients receiving circulatory assist device support. *Sci. Rep.* **11**, 1–11 <https://doi.org/10.1038/s41598-021-01696-3> (2021).
78. Roka-Moiia, Y. et al. Platelet dysfunction during mechanical circulatory support. *Arterioscler. Thromb. Vasc. Biol.* **41**, 1319–1336 <https://doi.org/10.1161/ATVBAHA.120.315583> (2021).
79. Roka-Moiia, Y. et al. Shear-mediated platelet microparticles demonstrate phenotypic heterogeneity as to morphology, receptor distribution, and hemostatic function. *Int. J. Mol. Sci.* **24**, 7386 <https://doi.org/10.3390/ijms24087386> (2023).
80. Laha, S., Fourtakas, G., Das, P. K. & Keshmiri, A. Fluid–structure interaction modeling of bi-leaflet mechanical heart valves using smoothed particle hydrodynamics. *Phys. Fluids* **35**, 1–15 <https://doi.org/10.1063/5.0172043> (2023).
81. Fandaros, M., Kwok, C., Wolf, Z., Labropoulos, N. & Yin, W. Patient-specific numerical simulations of coronary artery hemodynamics and biomechanics: a pathway to clinical use. *Cardiovasc. Eng. Technol.* **15**, 503–521 <https://doi.org/10.1007/s13239-024-00731-4> (2024).
82. Wang, Y., He, F., Hao, P. & Zhang, X. A fluid–structure interaction simulation on the impact of transcatheter micro ventricular assist devices on aortic valves. *Comput. Methods Prog. Biomed.* **254**, 108270 <https://doi.org/10.1016/j.cmpb.2024.108270> (2024).
83. Lopes, G., Bock, E. & Gómez, L., Numerical analyses for low Reynolds flow in a ventricular assist device. *Artif. Organs* **41** <https://doi.org/10.1111/aor.12776> (2017).
84. Huang, X. et al. Large-eddy simulation of the FDA benchmark blood pump: validation against experiments and implications for turbulent flow mechanisms. *Artif. Organs* <https://doi.org/10.1111/aor.70190> (2026).
85. Lopes, D. et al. Comparison of RANS and LES turbulent flow models in a real stenosis. *Int. J. Heat Fluid Flow* **107** <https://doi.org/10.1016/j.ijheatfluidflow.2024.109340> (2024).
86. Becsek, B., Pietrasanta, L. & Obrist, D. Turbulent systolic flow downstream of a bioprosthetic aortic valve: Velocity spectra, wall shear stresses, and turbulent dissipation rates. *Front. Physiol.* **11** <https://doi.org/10.3389/fphys.2020.577188> (2020).
87. Menter, F., Hüppe, A., Matyushenko, A., & Kolmogorov, D. An overview of hybrid RANS–LES models developed for industrial CFD. *Appl. Sci.* **11** <https://doi.org/10.3390/app11062459> (2021).
88. Haering, S. W., Oliver, T. A. & Moser, R. D. Active model split hybrid RANS/LES. *Phys. Rev. Fluids* **7** <https://doi.org/10.1103/PhysRevFluids.7.014603> (2022).
89. Drešar, P. & Duhovnik, J. A hybrid RANS–LES computational fluid dynamics simulation of an FDA medical device benchmark. *Mechanics* **25**, 291–298 <https://doi.org/10.5755/j01.mech.25.4.20105> (2019).
90. Redaelli, A. & Votta, E. Cardiovascular patient-specific modeling: where are we now and what does the future look like? *APL Bioeng.* <https://doi.org/10.1063/5.0031452> (2020).
91. Ghosh, R. P. et al. Numerical evaluation of transcatheter aortic valve performance during heart beating and its post-deployment fluid–structure interaction analysis. *Biomech. Model. Mechanobiol.* **19**, 1725–1740 <https://doi.org/10.1007/s10237-020-01304-9> (2020).
92. Caron, C., Lauret, P. & Bastide, A. Machine learning to speed up computational fluid dynamics engineering simulations for built environments: a review. <https://doi.org/10.1016/j.buildenv.2024.112229> (2025).
93. Li, Y. et al. Evaluation and optimization of interventional blood pump based on hydraulic performances and hemocompatibility performances. *Phys. Fluids* **36**, 1–14 <https://doi.org/10.1063/5.0238874> (2024).
94. Li, Y. et al. Multi-indicator analysis of mechanical blood damage with five clinical ventricular assist devices. *Comput. Biol. Med.* **151**, 106271 <https://doi.org/10.1016/j.combiomed.2022.106271> (2022).
95. Chen, Z. et al. Flow features and device-induced blood trauma in CF-VADs under a pulsatile blood flow condition: A CFD comparative study. *Int. J. Numer. Method. Biomed. Eng.* **34**, 1–21 <https://doi.org/10.1002/cnm.2924> (2018).
96. Wu, P. Recent advances in the application of computational fluid dynamics in the development of rotary blood pumps. *Med. Nov. Technol. Devices* **16**, 100177 <https://doi.org/10.1016/j.medntd.2022.100177> (2022).
97. Menichini, C. & Xu, X. Y. Mathematical modeling of thrombus formation in idealized models of aortic dissection: initial findings and potential applications. *J. Math. Biol.* **73**, 1205–1226 <https://doi.org/10.1007/s00285-016-0986-4> (2016).
98. Laha, S., Fourtakas, G., Das, P. K. & Keshmiri, A., Graphics processing unit accelerated modeling of thrombus formation in cardiovascular systems using smoothed particle hydrodynamics. *Phys. Fluids* **37** <https://doi.org/10.1063/5.0250640> (2025).
99. Dai, W.-F., Wu, P. & Liu, G.-M. A two-phase flow approach for modeling blood stasis and estimating the thrombosis potential of a ventricular assist device. *Int. J. Artif. Organs* **44**, 471–480 <https://doi.org/10.1177/0391398820975405> (2020).
100. Liao, S. et al. The influence of rotary blood pump speed modulation on the risk of intraventricular thrombosis. *Artif. Organs* **42**, 943–953 <https://doi.org/10.1111/aor.13330> (2018).
101. Zhang, J., Chen, Z., Griffith, B. P. & Wu, Z. J. Computational characterization of flow and blood damage potential of the new maglev CH-VAD pump versus the HVAD and HeartMate II pumps. *Int. J. Artif. Organs* **43**, 653–662 <https://doi.org/10.1177/0391398820903734> (2020).
102. Chen, Z. et al. High shear induces platelet dysfunction leading to enhanced thrombotic propensity and diminished hemostatic capacity. *Platelets* **30**, 112–119 <https://doi.org/10.1080/09537104.2017.1384542> (2019).
103. Van Buren, T., Arwatz, G. & Smits, A. J. A simple method to monitor hemolysis in real time. *Sci. Rep.* **10** <https://doi.org/10.1038/s41598-020-62041-8> (2020).
104. van Oeveren, W. Obstacles in haemocompatibility testing. *Scientifica* **2013**, 1–14 <https://doi.org/10.1155/2013/392584> (2013).
105. U.S. Food and Drug Administration, Cardiovascular program: Research on cardiovascular medical devices.” Accessed 12 May 2026. [Online]. Available: <https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/cardiovascular-program-research-cardiovascular-medical-devices>
106. Jurczak, K. M. et al. Recent regulatory developments in EU Medical Device Regulation and their impact on biomaterials translation. *Bioeng. Transl. Med.* **10** <https://doi.org/10.1002/btm2.10721> (2025).
107. Gillot, C. et al. Device-induced thrombosis in blood-contacting medical devices: mechanisms and emerging prevention strategies. *Adv. Healthc. Mater.* <https://doi.org/10.1002/adhm.202505409> (2026).
108. Isath, A., Pfeffer, M. & Mehra, M. R. Advancing antithrombotic therapies for left ventricular assist devices: challenges, innovations, and future perspectives. *Future Cardiol.* **21**, 411–413 <https://doi.org/10.1080/14796678.2025.2491196> (2025).

109. Sim, M. M. S., Shiferawe, S. & Wood, J. P., Novel strategies in antithrombotic therapy: Targeting thrombosis while preserving hemostasis. *Front. Cardiovasc. Med.* **10** <https://doi.org/10.3389/fcvm.2023.1272971> (2023).
110. Jourdi, G., Lordkipanidzé, M., Philippe, A., Bachelot-Loza, C. & Gaussem, P. Current and novel antiplatelet therapies for the treatment of cardiovascular diseases. *Int. J. Mol. Sci.* **22**, 13079 <https://doi.org/10.3390/ijms222313079> (2021).
111. Zhang W. et al. Emerging targets, novel directions, and innovative approaches in thrombosis therapy. *Aging Dis.* **0** <https://doi.org/10.14336/AD.2024.1688> (2025).
112. Dobbing, H. C., Webb, K. L. & Ariëns, R. A. S. Novel and experimental anticoagulant strategies beyond current direct oral anticoagulants. *J. Thromb. Haemost.* **24**, 1213–1229 <https://doi.org/10.1016/j.jtha.2025.11.033> (2026).
113. Bernardi, F. F. et al. Direct oral anti-Xa anticoagulants and the future of factor XI/FXIIa inhibition: a new paradigm in thrombosis prevention. *Pharmacy* **14**, 19 <https://doi.org/10.3390/pharmacy14010019> (2026).
114. Kalinin, D. V. Recent advances in factor XII(a) inhibitors: an updated patent landscape (2020-present). *Expert Opin. Ther. Pat.* **36**, 333–361 <https://doi.org/10.1080/13543776.2026.2627911> (2026).
115. Smola-Dmochowska, A. et al. Antithrombotic polymers: a narrative review on current and future strategies for their design, synthesis, and application. *Int. J. Mol. Sci.* **27**, 1026 <https://doi.org/10.3390/ijms27021026> (2026).
116. Zhang, S., Deng, Z., Wang, Y. & Zhao, C. A review of anticoagulant surface modification strategies for blood-contacting materials: from inertness to bioinspired and biointegration, *Coatings* **15** <https://doi.org/10.3390/coatings15121486> (2025).
117. Sheu, J.-R. et al. Metal-based complexes as emerging antiplatelet and antithrombotic agents: mechanistic insights and therapeutic perspective. *Inorg. Chem. Commun.* **189**, 116707 <https://doi.org/10.1016/j.inoche.2026.116707> (2026).
118. Sarfati, P., Lalatonne, Y. & Chauvierre C. Drug-free thrombolysis mediated by physically activated micro/nanoparticles. *Adv. Funct. Mater.* **36** <https://doi.org/10.1002/adfm.202528440> (2026).
119. Wiegmann, L. et al. Blood pump design variations and their influence on hydraulic performance and indicators of hemocompatibility. *Ann. Biomed. Eng.* **46**, 417–428 <https://doi.org/10.1007/s10439-017-1951-0> (2018). pp.
120. Avci, M., Heck, M., O'Rear, E. A. & Papavassiliou, D. V. Hemolysis estimation in turbulent flow for the FDA critical path initiative centrifugal blood pump. *Biomech. Model. Mechanobiol.* **20**, 1709–1722 <https://doi.org/10.1007/s10237-021-01471-3> (2021).
121. Agrawal, S. et al. Thirty-day readmissions after left ventricular assist device implantation in the United States. *Circ. Heart Fail.* **11**, 1–9 <https://doi.org/10.1161/CIRCHEARTFAILURE.117.004628> (2018).
122. Maltais, S. et al. PREVENTion of HeartMate II pump thrombosis through clinical management: the PREVENT multi-center study. *J. Heart Lung Transpl.* **36**, 1–12 <https://doi.org/10.1016/j.healun.2016.10.001> (2017).
123. Ray, P. K., Das, A. K. & Das, P. K. Numerical assessment of hemodynamic perspectives of a left ventricular assist device and subsequent proposal for improvisation. *Comput. Biol. Med.* **151**, 106309, <https://doi.org/10.1016/j.combiomed.2022.106309> (2022).
124. Wu, J., Paden, B. E., Borovetz, H. S. & Antaki, J. F. Computational fluid dynamics analysis of blade tip clearances on hemodynamic performance and blood damage in a centrifugal ventricular assist device. *Artif. Organs* **34**, 402–411 <https://doi.org/10.1111/j.1525-1594.2009.00875.x> (2010).
125. Song, G., Chua, L. P. & Lim, T. M. Numerical study of a bio-centrifugal blood pump with straight impeller blade profiles. *Artif. Organs* **34**, 98–104 <https://doi.org/10.1111/j.1525-1594.2009.00756.x> (2010).
126. Ozturk, C., Aka, I. B. & Lazoglu, I. Effect of blade curvature on the hemolytic and hydraulic characteristics of a centrifugal blood pump. *Int. J. Artif. Organs* **41**, 730–737 <https://doi.org/10.1177/0391398818785558> (2018).
127. Kannojiya, V., Das, A. K. & Das, P. K. Numerical simulation of centrifugal and hemodynamically levitated LVAD for performance improvement. *Artif. Organs* **44**, E1–E19 <https://doi.org/10.1111/aor.13533> (2020).
128. Wu, P., Zhang, K. J., Xiang, W. J. & Du, G. T. Turbulent flow field in maglev centrifugal blood pumps of CH-VAD and HeartMate III: secondary flow and its effects on pump performance. *Biomech. Model. Mechanobiol.* **23**, 1571–1589 <https://doi.org/10.1007/s10237-024-01855-1> (2024).
129. Tompkins, L. H. et al. Development of inspired therapeutics pediatric VAD: computational analysis and characterization of VAD V3. *Cardiovasc. Eng. Technol.* **13**, 624–637 <https://doi.org/10.1007/s13239-021-00602-2> (2022).
130. Fiusco, F., Broman, L. M. & Wittberg, L. P. Blood pumps for extracorporeal membrane oxygenation: platelet activation during different operating conditions. *ASAIO J.* **68**, 79–86 <https://doi.org/10.1097/MAT.0000000000001493> (2022).
131. Huo, J.-D., Wu, P., Zhang, L. & Wu, W.-T. Large eddy simulation as a fast and accurate engineering approach for the simulation of rotary blood pumps. *Int. J. Artif. Organs* **44**, 887–899 <https://doi.org/10.1177/03913988211041636> (2021).
132. Wu, P., Huo, J., Zhang, Z. & Wang, C. The influence of non-conformal grid interfaces on the results of large eddy simulation of centrifugal blood pumps. *Artif. Organs* **46**, 1804–1816 <https://doi.org/10.1111/aor.14263> (2022).
133. Wiegmann, L. et al. Fluid Dynamics in the HeartMate 3: influence of the artificial pulse feature and residual cardiac pulsation. *Artif. Organs* **43**, 363–376 <https://doi.org/10.1111/aor.13346> (2019).
134. Thamsen, B. et al. Assessment of the flow field in the HeartMate 3 using three-dimensional particle tracking velocimetry and comparison to computational fluid dynamics. *ASAIO J.* **66**, 173–182 <https://doi.org/10.1097/MAT.0000000000000987> (2020).
135. Wu, P. et al. On the optimization of a centrifugal maglev blood pump through design variations. *Front. Physiol.* **12**, 699891 <https://doi.org/10.3389/fphys.2021.699891> (2021).
136. Kubicki, C. et al. Fluid dynamic study of the Penn State pediatric total artificial heart. *J. Biomech. Eng.* **146** <https://doi.org/10.1115/1.4065377> (2024).
137. Kuroda, T. et al. Cleveland Clinic continuous-flow total artificial heart: progress report and technology update. *ASAIO J.* **70**, 116–123, <https://doi.org/10.1097/MAT.0000000000002076> (2024).
138. Belkin, M. N., Kagan, V., Labuhn, C., Pinney, S. P. & Grinstein, J. Physiology and clinical utility of HeartMate pump parameters. *J. Card. Fail.* <https://doi.org/10.1016/j.cardfail.2021.11.016> (2022).
139. Dangas, G. D., Weitz, J. I., Giustino, G., Makkar, R. & Mehran, R. Prosthetic heart valve thrombosis. *J. Am. Coll. Cardiol.* **68**, 2670–2689 <https://doi.org/10.1016/j.jacc.2016.09.958> (2016).
140. Zhu, G. et al. In vitro assessment of the impacts of leaflet design on the hemodynamic characteristics of ePTFE pulmonary prosthetic valves. *Front. Bioeng. Biotechnol.* **7**, 1–11 <https://doi.org/10.3389/fbioe.2019.00477> (2020).
141. Piatti, F. et al. Hemodynamic and thrombogenic analysis of a trileaflet polymeric valve using a fluid-structure interaction approach. *J. Biomech.* **48**, 3641–3649 <https://doi.org/10.1016/j.jbiomech.2015.08.009> (2015).
142. Toma, M., Singh-Gryzbon, S., Frankini, E., Wei, Z. & Yoganathan, A. P. Clinical impact of computational heart valve models. *Materials* **15**, 1–21 <https://doi.org/10.3390/ma15093302> (2022).

143. Hausleiter, J. et al. Transcatheter tricuspid valve replacement. *J. Am. Coll. Cardiol.* **85**, 265–291 <https://doi.org/10.1016/j.jacc.2024.10.071> (2025).
144. Sanders, B. et al. Improved geometry of decellularized tissue engineered heart valves to prevent leaflet retraction. *Ann. Biomed. Eng.* **44**, 1061–1071 <https://doi.org/10.1007/s10439-015-1386-4> (2016).
145. Haddad, S. et al. Next-gen heart solutions: 3D bioprinting and AI in valve replacement therapy. *Ann. 3D Print. Med.* **20**, 100219 <https://doi.org/10.1016/j.stlm.2025.100219> (2025).
146. Stasiak, J. R. et al. Design, development, testing at ISO standards and in vivo feasibility study of a novel polymeric heart valve prosthesis. *Biomater. Sci.* **8**, 4467–4480 <https://doi.org/10.1039/D0BM00412J> (2020).
147. Luraghi, G. et al. Evaluation of an aortic valve prosthesis: fluid-structure interaction or structural simulation. *J. Biomech.* **58**, 45–51 <https://doi.org/10.1016/j.jbiomech.2017.04.004> (2017).
148. Rotman, O. M., Kovarovic, B., Bianchi, M., Slepian, M. J. & Bluestein, D. In vitro durability and stability testing of a novel polymeric transcatheter aortic valve. *ASAIO J.* **66**, 190–198 <https://doi.org/10.1097/MAT.0000000000000980> (2020).
149. Yousefi, S., Borna, H., Rohani Shirvan, A., Wen, C. & Nouri, A. Surface modification of mechanical heart valves: a review. *Eur. Polym. J.* **205**, 112726 <https://doi.org/10.1016/j.eurpolymj.2023.112726> (2024). This review article describes recent approaches under consideration to improve mechanical heart valves.
150. Rahmati, M. & Mozafari, M. Protein adsorption on polymers. *Mater. Today Commun.* **17**, 527–540 <https://doi.org/10.1016/j.mtcomm.2018.10.024> (2018).
151. Ngo, B. K. D. & Grunlan, M. A. Protein resistant polymeric biomaterials. *ACS Macro Lett.* **6**, 992–1000 <https://doi.org/10.1021/acsmacrolett.7b00448> (2017).
152. Recek, N. et al. Adsorption of proteins and cell adhesion to plasma treated polymer substrates. *Int. J. Polym. Mater.* **63**, 685–691, <https://doi.org/10.1080/00914037.2013.854243> (2014).
153. Labarrere, C. A., Dabiri, A. E. & Kassab, G. S. Thrombogenic and inflammatory reactions to biomaterials in medical devices. *Front. Bioeng. Biotechnol.* **8**, 1–18, <https://doi.org/10.3389/fbioe.2020.00123> (2020).
154. Guidi, L., Rosellini, E., Riccio, G. & Cascone, M. G. Advancements and challenges in tissue-engineered heart valves: integrating biomechanics, biomaterials, and biomimetic design for functional maturity. *Biomimetics* **11**, 185, <https://doi.org/10.3390/biomimetics11030185> (2026).
155. Kreinin, Y. et al. A fibrin-thrombin based in vitro perfusion system to study flow-related prosthetic heart valves thrombosis. *Ann. Biomed. Eng.* **52**, 1665–1677 <https://doi.org/10.1007/s10439-024-03480-6> (2024).
156. Chen, L., Zhang, Z., Li, T. & Chen, Y. A review of biomechanical studies of heart valve flutter. *Fluids* **9**, 1–15 <https://doi.org/10.3390/fluids9110254> (2024).
157. Kim, Y. et al. A parametric study regarding structural design of a bioprosthetic aortic valve by 3D fluid-structure interaction simulations. *Heliyon* **10**, e27310 <https://doi.org/10.1016/j.heliyon.2024.e27310> (2024).
158. Yang, J. Fluid-structure interaction for mechanical filament valve mimicking a biological leaflet valve. *Phys. Fluids* **36**, 031904 <https://doi.org/10.1063/5.0196671> (2024).
159. Arminio, M., Carbonaro, D., Morbiducci, U., Gallo, D. & Chiastra, C. Fluid-structure interaction simulation of mechanical aortic valves: a narrative review exploring its role in total product life cycle. *Front. Med. Technol.* **6**, 1–22 <https://doi.org/10.3389/fmedt.2024.1399729> (2024). This recent review article focuses on a subtopic of cardiovascular devices that stresses the importance of arranging multidisciplinary research teams.
160. Zhang, K., Liang, W., Chen, X.-B. & Mang, J., Smart materials strategy for vascular challenges targeting in-stent restenosis: a critical review. *Regen. Biomater.* **12** <https://doi.org/10.1093/rb/rbaf020> (2025).
161. Wang, X. et al. Nonlinear elasticity of blood vessels and vascular grafts. *ACS Biomater. Sci. Eng.* **10**, 3631–3654 <https://doi.org/10.1021/acsbomaterials.4c00326> (2024).
162. Yasmin, F., Vafadar, A. & Tolouei-Rad, M. Application of additive manufacturing in the development of polymeric bioresorbable cardiovascular stents: a review. *Adv. Mater. Technol.* **10** <https://doi.org/10.1002/admt.202400210>. (2025).
163. Li, J. et al. Review of recent progress in vascular stents: from conventional to functional vascular stents. *Chin. Chem. Lett.* **36**, 110492 <https://doi.org/10.1016/j.cclet.2024.110492> (2025). This recent review article pinpoints the great potential of changing an apparently simple cardiovascular device by using a new approach.
164. D'Ambrogio, G. et al. Piezoelectric biosensor for smart cardiovascular grafts based on NaNbO₃ fibers/PDMS structured composite. *Mater. Des.* **223**, 111195 <https://doi.org/10.1016/j.matdes.2022.111195> (2022). Nov.
165. Wang, C. et al. Recent advances in surface functionalization of cardiovascular stents. *Bioact. Mater.* **44**, 389–410 <https://doi.org/10.1016/j.bioactmat.2024.10.025> (2025).
166. Cho, L. D. & Parikh, S. A. Next-generation drug delivery systems and drugs for vascular intervention. *Interv. Cardiol. Clin.* **15**, 307–318 <https://doi.org/10.1016/j.iccl.2025.12.010> (2026).
167. Liu, J. & Bursill, C. When stents become plaques: in-stent neoatherosclerosis. *Nat. Rev. Cardiol.* **23**, 85–85 <https://doi.org/10.1038/s41569-025-01241-z> (2026).
168. Wang, Z., Song, J. & Peng, Y. New insights and perspectives into biodegradable metals in cardiovascular stents: a mini review. *J. Alloy. Compd.* **1002**, 175313, <https://doi.org/10.1016/j.jallcom.2024.175313> (2024).
169. Fukunishi, T. et al. Preclinical study of patient-specific cell-free nanofiber tissue-engineered vascular grafts using 3-dimensional printing in a sheep model. *J. Thorac. Cardiovasc. Surg.* **153**, 924–932 <https://doi.org/10.1016/j.jtcvs.2016.10.066> (2017).
170. Kapoor, A. et al. The road to the ideal stent: a review of stent design optimisation methods, findings, and opportunities. *Mater. Des.* **237**, 112556 <https://doi.org/10.1016/j.matdes.2023.112556> (2024).
171. Ma, Z. et al. Integrated piezoelectric vascular graft for continuous real-time hemodynamics monitoring. *Adv. Funct. Mater.* **34** <https://doi.org/10.1002/adfm.202409874> (2024).
172. Hong, Y. J., Jeong, H., Cho, K. W., Lu, N. & Kim, D. Wearable and implantable devices for cardiovascular healthcare: from monitoring to therapy based on flexible and stretchable electronics. *Adv. Funct. Mater.* **29**, 19 <https://doi.org/10.1002/adfm.201808247> (2019).
173. Jadhav, S. A., Raval, A. J. & Patravale, V. B. Drug delivery, development, and technological aspects for peripheral drug eluting stents. *Adv. Drug Deliv. Rev.* **226**, 115678 <https://doi.org/10.1016/j.addr.2025.115678> (2025).
174. Bakare, A. et al. Advancements in textile techniques for cardiovascular tissue replacement and repair. *APL Bioeng.* **8** <https://doi.org/10.1063/5.0231856> (2024).
175. Bar, A., Kryukov, O. & Cohen, S. Three-dimensional bio-printed cardiac patch for sustained delivery of extracellular vesicles from the interface. *Gels* **8**, 769 <https://doi.org/10.3390/gels8120769> (2022).
176. Shen, D. et al. The application of 3D printing in cardiac patch manufacture. *Adv. Healthc. Mater.* <https://doi.org/10.1002/adhm.202504250> (2026).
177. Boldock, L. et al. Integrating particle tracking with computational fluid dynamics to assess haemodynamic perturbation by coronary artery stents. *PLoS ONE* **17**, 1–18 <https://doi.org/10.1371/journal.pone.0271469> (2022).

178. Wu, W. et al. Patient-specific computational simulation of coronary artery bypass grafting. *PLoS ONE* **18**, e0281423 <https://doi.org/10.1371/journal.pone.0281423> (2023).
179. Lagache, M. et al. Impact of malapposed and overlapping stents on hemodynamics: A 2D parametric computational fluid dynamics study. *Mathematics* **9**, 1–19 <https://doi.org/10.3390/math9080795> (2021).
180. Salavatidezfouli, S. et al. Investigation of the stent induced deformation on hemodynamic of internal carotid aneurysms by computational fluid dynamics. *Sci. Rep.* **13**, 1–14 <https://doi.org/10.1038/s41598-023-34383-6> (2023).
181. Bologna, E. et al. Computational fluid dynamics (CFD) and finite element analysis (FEM) of a customized stent-graft for endovascular (EVAR) treatment of abdominal aortic aneurism (AAA). *Appl. Sci.* **13**, 1–16 <https://doi.org/10.3390/app13095712> (2023).
182. Ahadi, F., Biglari, M., Azadi, M. & Bodaghi, M. Computational fluid dynamics of coronary arteries with implanted stents: effects of Newtonian and non-Newtonian blood flows. *Eng. Rep.* **6**, 1–27, <https://doi.org/10.1002/eng2.12779> (2024).
183. Williamson, P. N. et al. Review of the development of hemodynamic modeling techniques to capture flow behavior in arteries affected by aneurysm, atherosclerosis, and stenting. *NLM (Medline)*. <https://doi.org/10.1115/1.4053082> (2022).
184. Ramella, A. et al. Mechanical performance of thoracic aortic stent-grafts: an in vitro and in silico study. *Ann. Biomed. Eng.* <https://doi.org/10.1007/s10439-025-03949-y> (2025).
185. Raymond, P. et al. A novel method for brain aneurysms computed fluid dynamics analysis after flow diverter stent implantation based on micro-computed tomography reconstruction. *J. Biomech.* **186**, 1–7 <https://doi.org/10.1016/j.jbiomech.2025.112634> (2025). This paper presents an example of the potential related to patient-specific medicine.
186. Fan, Z. et al. Insights from computational fluid dynamics and in vitro studies for stent protrusion in iliac vein: how far shall we go. *Cardiovasc. Eng. Technol.* **16**, 79–90 <https://doi.org/10.1007/s13239-024-00758-7> (2025).
187. D'Onofrio, A., Caraffa, R., Cibin, G., Antonello, M. & Gerosa, G. Total endovascular aortic arch repair: from dream to reality. *Medicina* **58**, 372 <https://doi.org/10.3390/medicina58030372> (2022).
188. Singhvi, A. & Trachtenberg, B. Left ventricular assist devices 101: shared care for general cardiologists and primary care. *J. Clin. Med.* **8**, 1720 <https://doi.org/10.3390/jcm8101720> (2019).
189. Uriel, N. et al. Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices. *J. Am. Coll. Cardiol.* **60**, 1764–1775 <https://doi.org/10.1016/j.jacc.2012.07.052> (2012).
190. Romanova, A. N. et al. Hemolytic performance in two generations of the sputnik left ventricular assist device: a combined numerical and experimental study. *J. Funct. Biomater.* **13**, 7 <https://doi.org/10.3390/jfb13010007> (2022).

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Competing interests

The authors declare no competing interests.

Additional information

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