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Review article

Recent developments in next-generation occlusion devices

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ABSTRACT

Transcatheter closure has been widely accepted as a highly effective way to treat abnormal blood flows and/or embolization of thrombus in the heart. It allows the closure of four types of congenital heart defects (CHDs) and stroke-associated left atrial appendage (LAA). The four types of CHDs include atrial septal defect (ASD), patent foramen ovale (PFO), patent ductus arteriosus (PDA), and ventricular septal defect (VSD). Advancements in the materials and configurations of occlusion devices have spurred the transition from open-heart surgery with high complexity and morbidity, or lifelong medication with a high risk of bleeding, to minimally invasive deployment. A variety of occlusion devices have been developed over the past few decades, particularly novel ones represented by biodegradable and 3D-printed occlusion devices, which are considered as next-generation alternatives to conventional Nitinol-based occlusion devices due to biodegradability, customization, and improved biocompatibility. The aim here is to comprehensively review the next-generation occlusion devices in terms of materials, configurations, manufacturing methods, deployment strategies, and (if available) experimental results or clinical data. The current challenges and the direction of future work are also proposed.

Statement of significance

Implantation of occlusion devices has become a widely accepted and highly effective treatment for occluding abnormal blood/thrombus flow within the heart. Due to the serious complications such as erosion and displacement of conventional Nitinol-based occluders, next-generation occluders with reduced risk of complications and improved biocompatibility has emerged. Here, we comprehensively review the next-generation occluders developed for atrial septal defect (ASD), patent foramen ovale (PFO), patent ductus arteriosus (PDA), ventricular septal defect (VSD), and left atrial appendage (LAA), with special emphasis on biodegradable occluders. Besides, intelligent materials (e.g., automatically deployable shape memory polymers) and rapid customized manufacturing methods (3D/4D printing) for the fabrication of occluders are also introduced. Lastly, the directions of future work are highlighted.

1. Introduction

Great advances in transcatheter and imaging techniques have expedited the expansion of the treatment scope of interventional therapy [1]. Due to the low trauma, high safety, easy operation, and few complications, transcatheter closure has been considered as an effective alternative to congenital heart defects (CHDs), as well as the stroke-associated left atrial appendage (LAA) [2–6]. CHD refers to the general structural abnormality of the heart or thoracic great vessels at birth, with an incidence of 4–50 per 1000 live births [7]. There are four main types of CHDs treated with transcatheter closure, including atrial septal defect (ASD), patent foramen ovale (PFO), patent ductus arteriosus (PDA), and ventricular septal defect (VSD) [8]. The LAA is a tubular hook-like structure protruding from the left atrium. The definitions and symptoms of the four types of CHDs will be discussed in detail as follows, and the strong association between LAA and stroke will also be elaborated.

The heart is composed of four chambers (Fig. 1a), including two upper atria (left and right atria) and two lower ventricles (left and right ventricles). Fig. 1b shows the heart with various defects. ASD caused by abnormal embryonic development is a residual hole in

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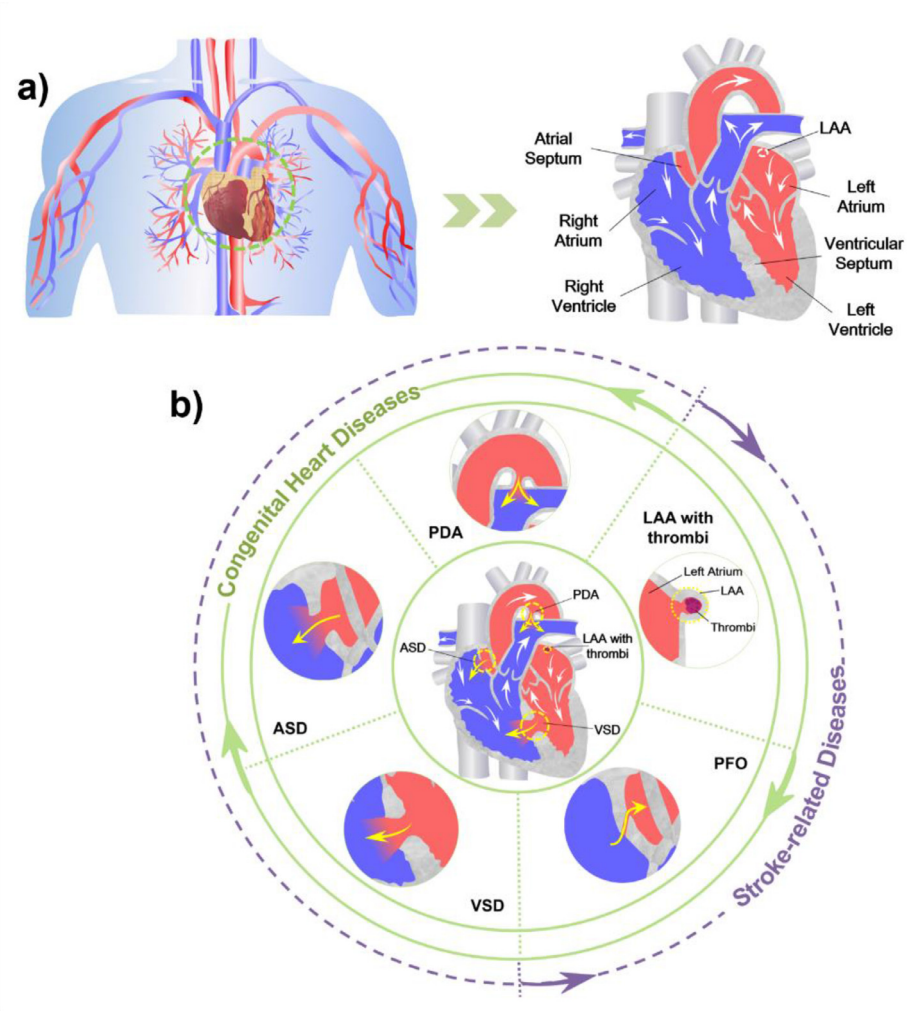

Fig. 1. Anatomies and blood flow directions of (a) normal heart, and (b) heart with various defects.

the septum between two atria, allowing abnormal blood flow. This will cause an overload of the right heart and excessive circulation of the lung, further leading to atrial arrhythmias, pulmonary hypertension, and even heart failure. ASD is a typical CHD, occurring in 1 out of 2000 newborns [8,9]. Ostium secundum ASD accounts for 75% of ASDs, while other types of ASDs, such as sinus venosus ASD, are uncommon. Since King and Mills first conducted transcatheter ASD closure in 1974, transcatheter closure has become the preferred treatment for most cases of secondary ASD. It has been proven that transcatheter closure ASD outperformed the surgical repair with a lower rate of complications [10]. Among the five defects discussed in this work, transcatheter closure of ASD is the most widely used and well-developed transcatheter closure technique, in part because ASD is in a location where the interventional catheter is easily accessible via the inferior vena cava, thus there is little damage to the heart [8].

Another type of defect in the septum between the left and right atria is PFO. It is a flap-like opening without any loss of septal tissue, which is the biggest difference from ASD (Fig. 1b). During the embryonic period, PFO is part of the normal fetal circulatory system. It is an open part at the junction of the septum primum and septum secundum that allows the normal flow of blood from right to left. After birth, the septum primum and septum secundum merge to form a permanent atrial septum. If this process is not carried out normally, PFO will be formed with an incidence of 25–30%. Although most PFO patients are asymptomatic, it is widely believed that PFO-induced paradoxical embolism is the most common cause of cryptogenic stroke. The PFO provides a pathway for the paradoxical embolism that occurs when an embolus (e.g., a blood clot, fat, air, amniotic fluid, or tumor) in the venous system enters the systemic circulation through an intracardiac defect [11–14]. Long-term warfarin anticoagulation can prevent recurrent embolism, but oral anticoagulation may lead to high-risk bleeding. As a minimally invasive alternative, transcatheter PFO closure has demonstrated its safety and effectiveness in preventing stroke recurrence after cryptogenic stroke [13–15].

If this residual hole is in the septum of the left and right ventricles, it is defined as VSD, which is the most common CHD and accounts for about 40% of all CHDs [16]. VSD mainly includes perimembranous VSD (pmVSD) and muscular VSD (mVSD), and pmVSD accounts for more than 80% of VSD cases [17]. Compared with non-VSDs, transcatheter closure of VSD is more challenging because it involves repairing the wall with significant motion. Besides, the occluder may affect the aortic valve and interfere with the conduction system when performing pmVSD closure [1,18]. Complete atrioventricular (AV) block is the most severe complication, thus surgical closure of VSD has long been regarded as the gold standard treatment [19]. However, the advancements in occlusion devices (i.e., occluders) and intervention techniques in recent years have expanded the qualified population, allowing transcatheter closure not only to close mVSD but also to achieve positive results in closing pmVSD [16,19–21].

PDA is a persistent opening between the descending aorta and the pulmonary artery, which occurs in 5–10% of CHDs. This opening is also part of the fetal circulation and is usually closed shortly after birth [22]. Since PDA allows the oxygen-poor blood to flow in the wrong direction, which may be related to endarteritis, heart failure, and even pulmonary hypertension, it is recommended to close moderate-to-large PDAs and small audible PDAs [23]. Transcatheter closure of PDA has been shown to be less risky than surgical closure, especially in adults [17].

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its most serious complication is stroke. The risk of stroke in AF patients is fivefold higher than that in the general population, and the risk of stroke in AF patients aged 80–89 years is as high as 23.5% [24]. AF-induced stroke is usually caused by cardiac thromboembolism, and over 90% of intracardiac thrombi in patients with nonvalvular AF originate from LAA [25]. As mentioned above, LAA, originating from the left atrium of the primitive embryo, is a tubular hook-like structure protruding from the left atrium. There are pectinate muscles on the inner wall to form a trabecular structure. The individual anatomy of LAA varies greatly, and its typical shapes are chicken wings, cactus, and cauliflower. When the atrium in AF patients fails to contract properly, the shape and internal structure of LAA may cause blood stagnation and thrombosis, which will lead to stroke when the thrombus escapes and embolizes the brain [26]. The standard treatment for preventing stroke in AF patients is oral anticoagulants (OACs), including warfarin and novel OACs. However, complicated drug interactions, as well as life-threatening bleeding risk, result in approximately 40% of high-risk stroke patients not eligible for OAC treatment [6,27]. Therefore, LAA closure is an effective treatment to prevent a stroke from the source and provides a new treatment strategy for people who are not suitable for drug anticoagulation [28]. More importantly, the efficacy of LAA occlusion in the prevention of stroke in patients with nonvalvular AF has been proven to be no less than traditional drug therapy [29,30].

Based on the above five types of defects, a variety of Nitinol-based occlusion devices have been designed and developed over the past few decades, such as Amplatzer septal occluder (ASO, Abbott, Abbott Park, IL, USA), Gore Cardioform septal occluder (W. L. Gore & Associates, Inc., AZ, USA), and Cera ASD/PFO occluder (Lifetech Scientific, Shenzhen, China). The basic information and features of non-degradable occlusion devices are listed in Tables 1–4, including septal (ASD and PFO), PDA, VSD, and LAA occlusion devices, and details are provided in *Supplementary information*.

Although these Nitinol occluders can effectively seal the defect and have been widely used clinically, the long-term presence of Nitinol in the heart still poses some problems, such as (1) Nickel ion precipitation and nickel allergy; (2) Mechanical complications related to long-term wear (e.g., erosion, perforation, and pericardial tamponade); (3) Long-term displacement and embolization; (4) Delayed endothelialization; (5) Permanent ASD occlusion devices hinder interventions that enter the left part of the heart via septum (e.g., LAA closure and mitral valve repair), etc. [31–38]. Therefore, there is an urgent need to develop next-generation occlusion devices to minimize the risk of device-associated short- or long-term complications. Recently, a wide range of next-generation occlusion devices have emerged, some of which have been clinically tested and initially showed favorable outcomes [36].

This review aims to provide a comprehensive overview of the next-generation occlusion devices developed for ASD, PFO, PDA, VSD, and LAA closures. The overview of the next-generation occlusion devices is presented in Fig. 2. We start with the materials for next-generation occlusion devices, including frame materials and membrane materials (Section 2.1). Then, partially/completely biodegradable occlusion devices and 3D/4D printed occlusion devices are detailed with respect to materials, configurations, manufacturing methods, deployment strategies, and experimental/clinical results (Sections 2.2 and 2.3). The features of various next-generation occlusion devices are summarized in Table 5. In addition, information and characteristics of various conventional non-degradable occluders are also provided for comparison (Tables 1–4, **Supplementary Information**). Finally, current challenges and future directions of occlusion devices are highlighted.

2. Next-generation occlusion devices

Ideally, the occluder provides a temporary bridge for the self-repair of the heart. Once the defect is completely endothelialized and firmly covered by the newly formed autologous tissues, the "mission" of the occluder is completed. Studies have shown that it takes 1–3 months for the fibrous granulation tissue to fully encapsulate the polymer membrane, while the endothelialization time of the frame, especially the protruding parts such as the central hub, is longer, approximately 3–6 months [8,39,40]. That is, the occluder is no longer needed after 6 months. Therefore, the ideal occlusion device should be biodegradable, and the degradation products are non-toxic and can be fully absorbed [41]. The degradability of the occlusion device is critical for young patients, especially for infants with CHD. Implanting biodegradable occlusion devices can not only prevent permanent metal occlusion devices from remaining in these young patients for a long time but also avoid complications such as accelerated wear of the device to the tissue due to the physiological growth of the heart. The evolution of biodegradable occluder has experienced a process from "partially biodegradable" to "completely biodegradable". The first occlusion device that introduced the concept of "biodegradable" was the BioSTAR occluder, which consisted of a non-degradable frame and absorbable collagen membranes [35]. Subsequently, other partially biodegradable occluders such as Carag bioresorbable septal occluder and Double BioDisk were designed [42,43]. To fully serve as a "temporary bridge", completely biodegradable occlusion devices were finally developed. At present, there is a wide range of completely biodegradable occluders, such as Chinese lantern occluder, 4D printed shape memory polymer (SMP) occluder, Lifetech Absnow PLLA occluder, etc., which will be described in detail below [31,44,45].

2.1. Materials for next-generation occlusion devices

The occlusion device is mainly composed of a supporting frame and membranes. The materials of these two parts are supposed to have the following characteristics: (1) The frame material can self-expand or deploy from the small-diameter state in the delivery sheath (i.e., catheter) to the large-diameter state at the defect site with the assistance of the locking mechanism; (2) The frame material and membrane material should provide sufficient mechanical support for the defect until endothelialization; (3) The frame material and the membrane material are biocompatible; (4) The membrane can be deformed with the frame; (5) The membrane with proper porosity can occlude blood flow and facilitate endothelialization; (6) The degradation products of the biodegradable materials are non-toxic and are eventually excreted from the body. The evolution of occlusion devices from non-degradable to biodegradable depends on the evolution of frame materials and membrane materials. The frame materials evolved from non-degradable stainless steel, cobalt-based alloy, and Nitinol to biodegradable polylactide (PLA), polydioxanone (PDO), polycaprolactone (PCL), etc; The membrane materials evolved from non-degradable polyethylene terephthalate (PET), polytetrafluoroethylene (PTFE), and expanded polytetrafluoroethylene (ePTFE) to biodegradable porcine intestinal collagen, PLA, etc.

Table 1
Representative non-degradable septal occlusion devices.

Device	Institution	Frame	Membrane	Sheath [F]	Approval Status	Features
Amplatzer septal occluder [2]	Abbott, Abbott Park, IL, USA	Nitinol	Polyester	6–12	FDA; CE mark	(1) Waist diameter matches defect diameter to fill the defect; (2) Innovative design; (3) Highly operable deployment technique; (4) Self-centering; (5) Recapturable and repositionable
Amplatzer Cribriform Multifenestrated septal occluder [100]	Abbott, Abbott Park, IL, USA	Nitinol	Polyester	8–9		(1) Thin waist; (2) Effective for the treatment of multifenestrated atrial septum
Amplatzer PFO occluder [15]	Abbott, Abbott Park, IL, USA	Nitinol	Polyester	8-9	FDA; CE mark	(1) Minimized materials in the left atrium; (2) Intagio wire treatment to reduce nickel leaching
Occlutech Figulla Flex II ASD occluder [101]	Occlutech International AB, Helsingborg, Sweden	Titanium oxide-coated Nitinol	PET	7–12	(1) Can be automatically centered and repositioned; (2) No stainless steel hub on the left disc; (3) Titanium oxide-coated Nitinol improves biocompatibility	Further improvements to the delivery system, allowing 360-degree rotation
Occlutech Figulla Flex II PFO occluder [102]	Occlutech International AB, Helsingborg, Sweden	Titanium oxide-coated Nitinol	PET	7–11		Ball-forceps connection allows a maximum angle of 50 degrees
Gore Helex septal occluder [103]	W. L. Gore & Associates, Inc., AZ, USA	Nitinol	ePTFE	9	FDA for ASD closure; discontinued	(1) A spiral single-stranded Nitinol wire frame; (2) Not a self-centering occluder; (3) Applicable for defects up to 18 mm in diameter
Gore Cardioform septal occluder [104]	W. L. Gore & Associates, Inc., AZ, USA	Platinum-filled Nitinol	ePTFE	10	FDA for PFO closure	(1) Improved stability. The frame is woven from five Nitinol wires filled with platinum; (2) Improved compliance with cardiac anatomy; (3) More porous ePTFE membrane; (4) Suitable for ASDs and PFOs up to 17 mm in diameter
Gore Cardioform ASD occluder [105]	W. L. Gore & Associates, Inc., AZ, USA	Platinum-filled Nitinol	ePTFE	10–14	FDA; CE mark	(1) Anatomically adaptable waist; (2) Applicable to a wider range of ASD patients
Heart^{R} ASD occluder	Lifetech Scientific, Shenzhen, China	Nitinol	PET	7–14	CE mark; CFDA	Fatigue-resistance
Cera ASD occluder [106]	Lifetech Scientific, Shenzhen, China	TiN-coated Nitinol	PET	7-14	CE mark; CFDA	TiN-coated Nitinol frame improves biocompatibility
CeraFlex ASD occluder [107,108]	Lifetech Scientific, Shenzhen, China	TiN-coated Nitinol	PET	8–14	CE mark; CFDA	(1) Improved biocompatibility; (2) 360-degree flexible rotation; (3) New lock/release mechanism
CardioSEAL device	NMT Medical, Boston, MA, USA	MP35N	Dacron	10		MP35N skeleton (instead of stainless steel) improves MRI compatibility
STARFlex device [109]		Nitinol	Dacron			Self-centered
Ultrasept ASD occluder [110]	Cardia Inc., Eagan, MN, USA	Nitinol	PVA	9–11	CE mark	(1) Low-profile; (2) Patented self-centering mechanism; (3) Integral locking delivery and retrieval mechanism; (4) Dual articulating sails
Ultrasept PFO occluder	Cardia Inc., Eagan, MN, USA	Nitinol	PVA	10, 11		
Cocoon ASD occluder [111]	Vascular Innovations Co., Nonthaburi, Thailand	Nitinol with nano platinum coating	PP	6–14	CE mark	(1) The platinum coating improves biocompatibility and provides radio opacity for positioning; (2) Economical
Cocoon PFO occluder [112]	Vascular Innovations Co., Nonthaburi, Thailand	Nitinol with nano platinum coating	PP	6, 8		
Nit-Occlud ASD-R occluder [113,114]	PFM Medical, Cologne, Germany	Nitinol	Polyester	7–14	CE mark	(1) Woven by a single Nitinol wire; (2) Metal content in the left atrial disc is decreased by about 50%
Nit-Occlud PFO occluder [115,116]	PFM Medical, Cologne, Germany	Nitinol	Dacron	9, 10	CE mark	(1) Concave single-layer left atrial disc; (2) Reduced Nitinol content; (3) Highly operable delivery system; (4) Woven from a single Nitinol wire; (5) Soft atraumatic rim
Solysafe septal occluder [117–119]	Swissimplant AG, Solothurn, Switzerland	Phynox	Polyester	10	CE mark; discontinued	Easy to be shaped for sheath loading
Premere PFO closure system [120]	Velocimed Inc.; acquired by St. Jude Medical, Inc.; now Abbott	Nitinol	Polyester	9, 11		(1) Flexible Nitinol anchors; (2) Variable tether length enables the device to adapt to various PFO lengths; (3) The low surface area of the left atrial anchor leads to a low risk of thrombosis
SeptRx Intrapocket PFO occluder [11]	SeptRx, Inc., Fremont, CA, USA	Nitinol	Woven Nitinol mesh	9		The longer anchor struts are designed to conform to various PFO tunnel lengths by changing the shape

CFDA is the abbreviation of the China Food and Drug Administration.
Details of each occlusion device are provided in the **Supplementary Information**.

Table 2
Representative non-degradable PDA occlusion devices.

Device	Institution	Frame	Membrane	Sheath [F]	Approval Status	Features
Amplatzer duct occluder	Abbott, Abbott Park, IL, USA	Nitinol	Polyester	5–7	FDA	(1) Can adapt to large-sized PDAs with a single device; (2) Cone shape device helps conform to tapering ducts
Amplatzer duct occluder II [3]	Abbott, Abbott Park, IL, USA	Nitinol	Membrane-free	4–5		(1) Conforms to most classifications of PDAs; (2) Can be delivered via an arterial or venous route; (3) Can be delivered by a low-profile sheath
Occlutech duct occluder [121]	Occlutech International AB, Helsingborg, Sweden	Titanium oxide coated Nitinol	PET	6–9	CE mark	(1) No protruding hub on the left disc; (2) Low risk of protrusion and embolism to the aortic side; (3) Provides two options for shank length (standard and long)
Nit-Occlud PDA occluder [22,23]	PFM Medical, Cologne, Germany	Nitinol	Membrane-free	4–5	FDA premarket approval; CE mark	(1) Increased stiffness gradient from the lung side to the aortic side; (2) Suitable for PDAs up to 6 mm in diameter; (3) Provides devices with various stiffness (Flex, Medium, and Stiff)
Nit-Occlud PDA-R occluder [122]	PFM Medical, Cologne, Germany	Nitinol	Polyester			(1) Braided by a Nitinol wire without any welding or hub; (2) Suitable for PDAs between 2 mm and 8 mm in diameter; (3) "Snare-like" release mechanism
Heart^{R} PDA occluder	Lifetech Scientific, Shenzhen, China	Nitinol	PTFE	5–12		Retrievable, repositionable, and fatigue-resistance.
Cera PDA occluder [123]	Lifetech Scientific, Shenzhen, China	TiN-coated Nitinol	PTFE	5–12	CE mark; CFDA	TiN-coated Nitinol frame improves biocompatibility
CeraFlex PDA occluder	Lifetech Scientific, Shenzhen, China	TiN-coated Nitinol	PTFE	6–14		(1) Improved biocompatibility; (2) 360-degree flexible rotation; (3) New lock/release mechanism; (4) Premounted delivery system for easy operation
Cocoon duct occluder [124]	Vascular Innovations Co., Nonthaburi, Thailand	Platinum-coated Nitinol	PP	6–10		(1) The platinum coating enables radio opacity; (2) Improved biocompatibility; (3) Economical

Details of each occlusion device are provided in the **Supplementary Information**.

2.1.1. PLA

PLA, with lactide as the main monomer, is an aliphatic polyester derived from lactic acid (2-hydroxypropionic acid). It is a semi-crystalline polymer with a glass transition temperature (T_g) of approximately 65 °C and a melting temperature (T_m) of approximately 178 °C [49]. PLA can be obtained through direct polycondensation of lactic acid and ring-opening polymerization of lactide (the dimer of lactic acid). Lactic acid is used as a raw material in both synthetic routes. By extracting starch from renewable resources (e.g., corn and wheat), and enzymatically decomposing the starch, lactic acid is then obtained by fermentation of glucose by lactobacillus. Lactic acid has two stereoisomers: L- and D-lactic acid. Therefore, there are three kinds of PLA, poly-L-lactide (PLLA), poly-D-lactide (PDLA), and poly-DL-lactide (PDLLA). The PDLLA is amorphous and can be obtained by polymerization of a racemic mixture of L- and D-lactide, where L- and D-lactide are usually equimolar [50,51].

PLA is one of the most common biodegradable polyesters and is approved by the US Food and Drug Administration (FDA) as a biomedical material. Due to its unique properties, such as high modulus, high tensile strength, favorable processability, and excellent biocompatibility, PLA has aroused numerous research interests and has been widely used in the biomedicine field (e.g., tissue engineering scaffolds, sutures, and drug delivery systems) [45,52–54]. It takes more than 2 years for PLA implants to be fully absorbed, and the degradation rate can be accelerated by copolymerizing PLA with other units to prepare PLA copolymer implants (e.g., PLA-TMC-GA) [32,42,49,146]. The primary mechanism of PLA degradation in vivo is the hydrolysis of the backbone ester bond. The degradation occurs not only on the surface of PLA but also inside the PLA implant. The degradation products are lactide monomers and lactide oligomers [55]. Lactide degradation products can enter the normal tricarboxylic acid cycle of the human body and be discharged from the body [52].

There are a variety of novel biodegradable occluders using PLA or its copolymers as the frame material, such as Lifetech Absnow PLLA occluder (Lifetech Scientific, Shenzhen, China) and SHSMA totally biodegradable PLA occluder (Shanghai Shape Memory Alloy Co., Ltd., now affiliated to Lepu medical, Beijing, China). Besides, the frame of the Carag bioresorbable septal occluder (CARAG AG, Switzerland) is composed of eight absorbable poly (L-co-glycolide) (PLGA) monofilaments. PLGA is obtained by copolymerizing PLA with poly (glycolide) (PGA). PGA is the simplest linear aliphatic polyester with good hydrophilicity and far faster degradation rate than PLA. It has been used in medical sutures since the 1960s [56]. Xing et.al. synthesized lactide-glycolide-1,3-trimethylene carbonate (LA-GA-TMC) terpolymer as raw material for 3D printed occluder by two-step synthesis method, in which 1,3-trimethylene carbonate (TMC) is a ductile biodegradable polyester [32,50]. Additionally, PLA was mixed with iron oxide magnetic nanoparticles to prepare a magnetic-responsive occluder, and the occlusion process was controllable [45].

In summary, we conclude that pure PLA can be directly used as occluder frame material (skeleton/filaments), and its feasibility has

Table 3
Representative non-degradable VSD occlusion devices.

Device	Institution	Frame	Membrane	Sheath [F]	Approval Status	Features
Amplatzer muscular VSD occluder	Abbott, Abbott Park, IL, USA	Nitinol	Polyester		FDA	(1) Developed for high-risk patients with the standard surgical repair; (2) Can be delivered through femoral or arterial route
Amplatzer PI muscular VSD occluder	Abbott, Abbott Park, IL, USA	Nitinol	Polyester			(1) Suitable for damaged muscular tissue of septum in patients with myocardial infarction; (2) Can be delivered through femoral or arterial route
Amplatzer membranous VSD occluder	Abbott, Abbott Park, IL, USA	Nitinol	Polyester		No longer clinically available	Can avoid interference with aortic or AV valve during implantation due to the non-concentric configuration
Occlutech mVSD occluder	Occlutech International AB, Helsingborg, Sweden	Titanium oxide-coated Nitinol	PET	6–11	CE mark	(1) No distal hub, fewer metal materials; (2) Unique braiding technology gives the device a soft tip in the sheath; (3) Short disc rims reduce the pressure on cardiac tissue
Occlutech pmVSD occluder	Occlutech International AB, Helsingborg, Sweden	Titanium oxide-coated Nitinol	PET	6, 7	CE mark	(1) No distal hub, fewer metal materials; (2) Wide shank ensures stable anchoring; (3) Unique braiding technology gives the device a soft tip in the sheath
Nit-Occlud Lê VSD occluder [125,126]	PFM Medical, Cologne, Germany	Nitinol	Polyester	6, 7	CE mark	(1) Can be used to close both pmVSD and mVSD; (2) Low risk of AV block
Heart^{R} mVSD/pmVSD occluder	Lifetech Scientific, Shenzhen, China	Nitinol	PTFE	5–12	CE mark; CFDA	Fatigue-resistance
KONAR-MF VSD occluder [127]	Lifetech Scientific, Shenzhen, China	Nitinol	PTFE/Membrane-free	4-7	CE mark	(1) Reduced risk of AV block; (2) Suitable for both pmVSD and mVSD
Cera mVSD/pmVSD occluder [128]	Lifetech Scientific, Shenzhen, China	TiN-coated Nitinol	PTFE	5–12	CE mark; CFDA	TiN-coated Nitinol frame improves biocompatibility
Cocoon VSD occluder [129]	Vascular Innovations Co., Nonthaburi, Thailand	Platinum-coated Nitinol	PP	6, 7		(1) The platinum coating improves biocompatibility and provides radio opacity for positioning; (2) Economical

Details of each occlusion device are provided in the **Supplementary Information**.

been extensively verified [33,36,44,57]. In addition, the mixing of PLA and magnetic nanoparticles can realize remote magnetic control [45]. Some of the developed occluders also use PLA copolymers as the frame materials, which have improved ductility and hydrophilicity, as well as faster degradation rate [32,42].

2.1.2. PDO

PDO is a semi-crystalline polymer with multiple repeating ether-ester units that can be obtained via ring-opening polymerization of dioxanone [58]. The T_g and T_m of PDO are approximately -10°C and 110°C, respectively. The ether oxygen group in the backbone and the extra -CH_2- group in the polymer chain endow its flexibility and elasticity. PDO is degraded by hydrolysis, and its chain breakage is more likely to occur in amorphous regions than in crystalline regions. PDO implants can be completely absorbed in about 6 months. The degradation products are mainly discharged through urine, and the rest are discharged by digestion or as carbon dioxide [59]. PDO was approved by the FDA in 1981 as a biodegradable suture for clinical application. In addition, PDO demonstrates potential applications in gastrointestinal stents, intragastric stents, and gene/drug delivery systems [47,58–64]. When applied to occluders, PDO filaments are usually used to weave the occluder. For example, Qin et.al. developed ASD and VSD occluders woven by PDO monofilaments with a diameter of 0.298 mm. Animal experiments showed that the occluders exhibited good biocompatibility and biodegradability [37,65].

2.1.3. PCL

PCL is a biodegradable polyester, which can be prepared by polycondensation of 6-hydroxyhexanoic acid and ring-opening polymerization of ε-caprolactone. The T_g and T_m of PCL are approximately -60°C and 60°C, respectively [66]. The degradation of PCL can be carried out by chemical (acid and base-catalyzed ester hydrolysis) or enzymatic reactions. Compared with PLA, PCL is more stable and has a longer degradation time, because each monomer of PCL has fewer ester bonds than PLA. Generally, it takes 2–3 years for PCL implants to be fully degraded in a biological environment [67,68]. Due to biodegradability, adjustable mechanical properties, and miscibility with many other polymers, PCL has become an important biomedical material. Its applications include various scaffolds, long-term drug delivery systems, occlusion devices, etc. [31,34,41,68–70]. Researchers from Nanyang University of technology developed the double-umbrella occluder, PCL-PLC PDA occluder, and Chinese lantern occluder [31,34]. The three occluders are made of PCL, polylactic acid-co-E-caprolactone (PLC), and PCL/PLC blends. PLC, as a copolymer of PCL, is more flexible than PCL. In addition, researchers at Chang Gung University designed a biodegradable ASD occluder consisting of eight PCL spokes [41].

Other materials used as frames for the next-generation occluders include fully biodegradable poly-4-hydroxybutyrate (P4HB) and non-degradable silicone composites, which are used in BioTrek occluder and 3D printed patient-customized inflatable LAA occluder, respectively [26,71].

2.1.4. Membrane materials

The role of the membrane is to improve occlusion capability and promote endothelialization. Since the concept of the biodegradable device was first introduced into occluder (BioSTAR occluder, NMT Medical, Boston, USA) and porcine intestinal collagen was used as the membrane, biodegradable membranes have been gradually used [35]. PLA and its copolymers are the most

Table 4
Representative non-degradable LAA occlusion devices.

Device	Institution	Frame	Membrane	Sheath [F]	Approval Status	Features
PLAATO device [25,130]	Appriva Medical, CA, USA	Nitinol	ePTFE	14	Discontinued	First transcatheter LAA occlusion device
Watchman device [131]	Boston Scientific, Marlborough, MA, USA	Nitinol	PET	14	FDA; CE mark	(1) One row of 10 "straight" fixation anchors; (2) Intra-LAA design avoids interference with surrounding tissues; (3) The reduced surface area facing the left atrium decreases the risk of thrombosis
Watchman FLX device [132]	Boston Scientific, Marlborough, MA, USA	Nitinol	PET	12,14	CE mark	(1) Two rows of 18 "J"-shaped fixation anchors increase device stability; (2) Reduced metal exposure (more polyester membrane coverage area); (3) Closed distal end with PT-IR markers; (4) Length is shortened compared with Watchman device
Amplatzer Cardiac Plug [30,133]	Abbott, Abbott Park, IL, USA	Nitinol	Polyester	9–13	CE mark	Seals LAA at the orifice
Amplatzer Amulet device (ACP 2) [134,135]	Abbott, Abbott Park, IL, USA	Nitinol	Polyester	12,14	CE mark	(1) Provides broadest size range; (2) Full cross-sectional orifice coverage; (3) The proximal of the device determines the proper placement position (independent of the distal anatomy)
LAmbre device [136]	Lifetech Scientific, Shenzhen, China	Nitinol	PET	8–10	CE mark; CFDA	(1) Easy to use; (2) Suitable for various LAA anatomies; (3) Fully recapturable and repositionable; (4) Patented anchor design increases device stability
Occlutech LAA occluder [137]	Occlutech International AB, Helsingborg, Sweden	Nitinol	Poly (carbonate) urethane	12–14	CE mark; withdrawn	(1) Inverted loops at the distal rim maintain the position of the occluder; (2) Eight pairs of anchors in the middle of the device; (3) ball-forceps connection; (4) Nonpermeable membrane with improved nanostructure
LACbes device [138]	Shanghai Push Medical, Shanghai, China	Nitinol	Polyester	9–14	CFDA	The anchor cylinder and sealing disc are connected by a thin waist
WaveCrest LAA occluder [28,48]	Coherex Medical Inc. (acquired by Biosense Webster)	Nitinol	ePTFE	15	CE mark	(1) Single-lobe Nitinol frame; (2) Has more anchors (20 points) than any other devices; (3) Allows injection of contrast agent at the distal end to assess LAA closure
Ultrasept LAA device [139]	Cardia Inc., Eagan, MN, USA	Nitinol	PVA	10–12		(1) Patented "dual articulating joint"; (2) Unique bulb-and-sail design
Lariat suture delivery system [140]	SentreHEART, Redwood City, CA, USA	Teflon-coated, braided polyester suture (non-absorbable)	Membrane-free	13	FDA; CE mark	(1) Compatible with a variety of anatomical shapes and sizes; (2) Suture closure. No foreign bodies in contact with blood are left; (3) Hybrid closure route involving both endocardial and epicardial approaches
Sierra ligation system [141]	Aegis Medical Innovations, Vancouver, Canada	Ligator	Membrane-free		Research device and has not been approved for commercial use	(1) Seals LAA by percutaneous epicardial approach; (2) Compared with the Lariat suture delivery system, there is no need for additional septal puncture

Details of each occlusion device are provided in the **Supplementary Information**.

widely used biodegradable membranes [33,44,57,65], and other materials including P4HB, porcine small intestine submucosa, PLC, and heparin-coated porcine intestinal type I collagen are also used in occlusion devices [37,41,72,73]. The membrane materials used in each next-generation device are listed in Table 5.

2.2. Partially/completely biodegradable occlusion devices

2.2.1. BioSTAR and BioTrek occluders

The BioSTAR occluder (Fig. 3a; NMT Medical, Boston, USA) is an improvement of the STARFlex occluder (NMT Medical, Boston, USA). The MP35N metal frame of the STARFlex occluder is preserved, and the biodegradable heparin-coated porcine intestinal type I collagen membrane is used as a replacement for the non-degradable polyester membrane [35]. Since 90to 95% of the device is biodegradable, the septum can be passed through to access the left side of the heart, facilitating future treatments [35,74]. Additionally, the BioSTAR occluder is retrievable and repositionable providing the device is not completely disconnected from the delivery system.

BioSTAR occluder is particularly suitable for small-to-moderate septal defects and has shown favorable early outcomes [73,75]. Compared with the STARFlex occluder with the nonabsorbable polyester membrane in the control group, the BioSTAR occluder exhibited a faster healing response, and the heparin coating on its surface reduced thrombus formation, thus enhancing the biocompatibility. The collagen membrane began to remodel into the heart tissue at 1 month after implantation, then degraded significantly at 6 months, and was completely replaced by the autogenous tissue at 24 months. The clinical trial of the BioSTAR Evalua-

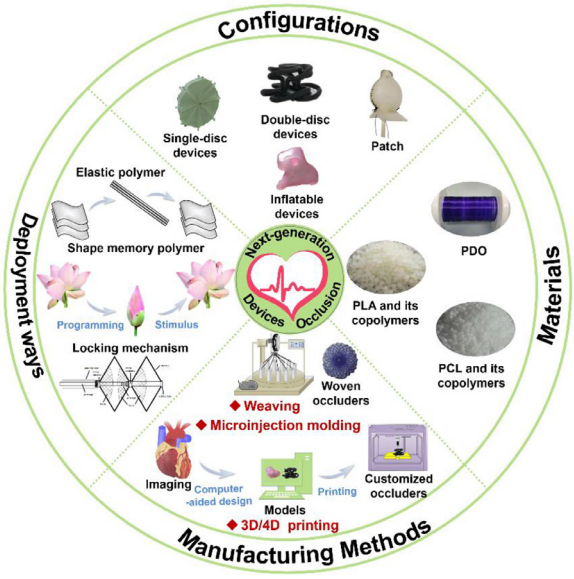

Fig. 2. Overview of materials, configurations, deployment strategies, and manufacturing methods for next-generation occlusion devices. (1) Materials. The frame materials primarily include biodegradable PLA, PDO, PCL, and their copolymers. (2) Configurations. The configurations of next-generation occlusion devices include double-disc devices, single-disc devices, patches, and inflatable devices. (3) Deployment strategies. High-elastic polymer and SMP are able to self-deploy, while most conventional polymers cannot automatically deploy. In this case, the design of the locking mechanism is an ideal choice to ensure the smooth deployment of the conventional polymer-based occluders. (4) Manufacturing methods. Weaving is the most common manufacturing method for occluders, and very few occluders are manufactured by microinjection molding. 3D/4D printing is an efficient and emerging technology for the rapid manufacturing of customized occluders [26,33,37,41,45–47].

tion Study (BEST) was carried out in 58 patients with ASD or PFO, and the procedure was successfully implemented in 57 patients. At 1 month and 6 months follow-up, 92 and 96% of the defects were closed, respectively. Transient atrial arrhythmias occurred in 8.6% of patients and no other major adverse events occurred [76]. The emergence of the BioSTAR occluder represents a key step from non-degradable to biodegradable occlusion devices, which stimulates the development of biodegradable occluders.

Developed after the BioSTAR occluder, the BioTrek occluder (Fig. 3b; NMT Medical, Boston, USA) is fully biodegradable. It is made of P4HB and its degradation products are carbon dioxide and water. It has the advantages of light inflammation response and favorable biocompatibility. In 2010, it was reported that the device was under pre-clinical evaluation, but there were no further reports due to the collapse of NMT Medical [71,77].

2.2.2. Carag bioresorbable septal occluder

The Carag bioresorbable septal occluder (CBSO; Fig. 3c; CARAG AG, Switzerland) is composed of two nonabsorbable PP double-disc fabrics, which are fixed to a frame of eight absorbable PLGA monofilaments through nonabsorbable sutures and PT-IR markers. CBSO also includes a non-degradable polyetheretherketone (PEEK) holder and a Phynox nut (composed of cobalt chromium nickel, radiopaque) for frame fixing and X-ray visualization. The delivery system consists of two coaxial control sheaths, which enable the left and right discs of the occluder to be independently expanded and locked [42].

CBSO was implanted into 24 pigs with ASD and followed up for 15 months. 1 month later, there was 1 death unrelated to device implantation. After 15 months, all CBSOs were in place, and no residual shunt occurred. In addition, CBSOs were rapidly and fully endothelialized in animal models, with only a few inflammatory responses remaining stable over time. Degradation of the device and replacement of the device by the autologous tissue demonstrated favorable biocompatibility [42]. The clinical trial involved 8 ASD patients and 6 PFO patients. The follow-up of 6 months revealed 4 cases of PFO and 6 cases of ASD were completely closed, and 1 case developed a 2 mm residual shunt. Follow-up for 24 months (2 cases) and 12 months (8 cases) showed no major adverse events related to surgery or occluder were found, and there was no thrombosis and ASD recanalization. The development of CBSO lays a good foundation for a fully biodegradable occluder due to its fully absorbable frame.

2.2.3. Double BioDisk

The Double BioDisk (DBD; Cook Medical, Bloomington, IN, USA) is a self-expandable and self-centering occlusion device for ASD closure, jointly developed by Cook Medical and Dotter Institute. As displayed in Fig. 3d, it includes two elastic Nitinol rings covered with platinum coils and the submucosa of the porcine small intestine as a blood flow barrier. DBD is also repositionable if needed.

The feasibility study was conducted by implanting the DBD device into 10 sheep with ASD. The device was in a satisfactory position after deployment without a residual shunt, spontaneous embolism, or arrhythmia. Follow-up showed that the ASD was completely closed in 8 sheep. The histological examination revealed the healing process, in which the discs gradually incorporated with the adjacent myocardium and the gap between the discs progressively decreased. The neointima extended from the periphery to the center of the disc to cover both discs. The follow-up of 6 and 12 months revealed that the porcine small intestine submucosa was completely remodeled into cardiac connective tissue and the device was completely endothelialized [43]. DBD is the third generation cardiac septal occlusion device designed by the team. The first generation is Monodisk, consisting of a rigid stainless steel frame covered with nylon membrane [78]. The second generation is BioDisk, which uses the same frame and membrane materials as DBD to close PFO [79].

2.2.4. Transcatheter Patch and Prolipsis Patch

The Transcatheter Patch (TP, Fig. 3e; Custom Medical Devices, Athens, Greece) is a soft, compliant, and inflatable device composed of a bioabsorbable polyurethane foam that surrounds the support balloon. TP has been shown to be applicable for closing various defects, including PDA, PFO, ASD, and VSD. It is particularly suitable for LAA closure due to the matching geometry. The support balloon is inflatable, thus allowing a single device to conform to most LAA sizes (15–25 mm). TP is fixed in the LAA by surgical adhesive to reduce the possibility of LAA perforation. The surgical adhesive is bioabsorbable and can be cleared from the body within a month. A nylon loop is sewn to the bottom of TP and connected with nylon thread to enable the device to be retrievable [46]. Additionally, Fig. 3f illustrates the latest version of TP, Prolipsis Patch [48]. The clinical experience of TP combined with surgical adhesive demonstrated that 85% (17/20) of LAAs were completely occluded, and 3 other TPs were retracted because they were not attached to the LAA wall. No recurrent stroke occurred during the 1-year follow-up.

More importantly, the wireless TP enables rapid endothelialization without the need for anticoagulation therapy, while metal LAA devices require anticoagulation therapy a few days after implantation. Hence, TP combined with surgical adhesive provides an alternative to metal LAA occlusion devices [80].

2.2.5. PCL ASD occluder

The PCL ASD biodegradable occluder consists of eight PCL spokes fabricated by microinjection molding and PLGA/collagen nanofibrous membranes prepared by electrospinning (Fig. 3g). The

membranes and PCL spokes are integrated by hot-spot welding. The biodegradable occluder is cable-controlled and has a self-locking mechanism. The compression resistance of the occluder is comparable with that of the Amplatzer occluder, and the mechanical properties of the occluder are not significantly reduced after 12 weeks of in vitro degradation. In addition, the biomimetic PLGA/collagen membrane can significantly promote cell proliferation [41].

2.2.6. Double umbrella occluder

The Double umbrella (DU) occluder is a double-disc device composed of eight symmetrically spokes covered with PLC membranes. The double discs are made of PCL, and the spokes in the right atrium disc are made of PLC. As shown in Fig. 4a and b, the double discs are connected by a retractable stem and deployed in a typical umbrella-shaped structure [77]. ASD/PFO defect was created in 2 swine models and 2 DU occluders were implanted. There were no major adverse events during the follow-up of 1 month. X-ray fluoroscopy and echocardiography showed that both DU occluders were stably in place without a residual shunt. After 1 month of implantation, DU occluders remained intact and were surrounded by fibrous granulation tissue and connective tissue (Fig. 4c, d). The study also had some limitations. For example, the height between two discs was not adjustable; for septum thickness $<$ 1mm, thrombus may form in the gap between the disc and the septum; for septum thickness $>$ 15 mm may cause residual shunts. In addition, the device cannot be completely repositioned [34].

2.2.7. PCL-PLC PDA occluder

The PCL-PLC PDA occluder is a self-expanding and fully biodegradable device (Fig. 4e) [72,82]. Similar to the structure of the DU occluder, the left disc is composed of four anchoring spokes, and the right disc consists of three spokes and a membrane. The left and right discs are connected by a stem. Mechanical properties, such as modulus of elasticity and strain recovery rate, can be adjusted by changing the composition of the two components (PCL and PLC). Due to different responsibilities, different parts of the device are prepared with PCL-PLC blends of different compositions. Pure PLC is chosen as the membrane material because of its favorable elasticity and recovery performance; PCL/B blend with the highest modulus is selected as the stem material because the stem needs to bear the maximum stress; PCL/PLC30 blend is chosen as the spoke material because the spoke as the supporting structure needs to provide both mechanical strength and recovery force. In addition, $BaSO_4$ is added to both the stem and left atrium spoke for positioning.

As shown in Fig. 4e–g, in vitro degradation tests indicated that the right disc began to break at 4 months and the entire device disintegrated at 6 months. This degradation time was sufficient to complete endothelialization. A PDA model was created in a pig and closed with a PCL-PLC PDA occluder. The closure of PDA was completed within 2–3 min after the occluder was pulled out, which indicated that it was feasible to close the human PDA with the occluder [72,82].

2.2.8. Chinese lantern occluder

The Chinese lantern (CL) occluder is made of completely absorbable PLC and PCL [31]. As shown in Fig. 4h and i, the device consists of seven parts, including head films, waist, tail films, head tube, tail tube, loop wire, and lock tube. The waist length of the CL occluder is tunable according to the actual septum thickness, ensuring better sealing performance. The deployment process of CL occluder depends on the pull-fold working mechanism (Fig. 4j), and the specific process is as follows: first, the head films and the tail films are pushed out of the sheath in turn; then, the ASD is closed by pulling the guide wire twice to fold the two films into flat shape in the left and right atria respectively. However, the residence time of the head and tail films made of the elastomeric copolymer PLC in the sheath should not be too long, otherwise, it will affect the recovery of films to a flat shape. CL occluder can be retrieved and repositioned, which is superior to the DU occluder designed by the same group. It is noteworthy that CL occluder provides a valuable demonstration of the locking mechanism of biodegradable occluders. A preclinical study was carried out by establishing ASD and PFO models in swine, and the device showed good radiopacity and integrity. 1 month after the procedure, no residual shunt was observed, and the endothelialization of the device films was observed [31].

2.2.9. Biodegradable PDO ASD occluder

The Biodegradable PDO ASD occluder (Fig. 5a; Changhai Hospital, Second Military Medical University, Shanghai, China) is a self-expanding occlusion device prepared by weaving and thermoforming technology using PDO monofilaments with a diameter of 0.298 mm [37]. The diameters of the left and right discs, as well as the waist length, are 15 mm, 10 mm, and 3 mm, respectively. Woven PLA films are filled into the double discs to prevent blood flow from the right atrium to the left atrium. Two tantalum particles are fixed at symmetrical positions on both sides of the disc for X-ray positioning and monitoring.

Acute ASD models were successfully established in 18 dogs, and successful occluder implantation was achieved in 16 dogs. Dogs were euthanized at different time intervals after surgery. Overall, the occluder was able to complete endothelialization within 12 weeks with fewer complications and better biocompatibility. In addition, all occluders were in place stably and there was no thrombosis on the surface of the device. The degradation performance of the occluder after implantation was studied by gross observation and histological examination. At 8 weeks after the operation, the surface of the occluder was covered with a reddish-white membrane, and the PDO monofilaments maintained their shape. At week 12, the surface of the occluder showed continuous endothelial cells, and the PDO monofilaments at the edge of the disc began to disintegrate. At 24 weeks, most of the disintegrated PDO monofilaments were replaced by dense proliferative fibrous connective tissue, which was beneficial to prevent the loss of tantalum particles and ASD recanalization. Besides, PLA films were also degraded.

However, due to the large diameter of the PDO monofilament (0.298 mm, Nitinol monofilament ~0.1mm) used for woven occluder, the transportation of occluders for large-sized defects will be challenging. Therefore, more efforts are needed to develop biodegradable monofilament materials with a smaller diameter and satisfactory mechanical properties.

2.2.10. Biodegradable PDO VSD occluder

The Biodegradable PDO VSD occluder (Fig. 5b; Changhai Hospital, Second Military Medical University, Shanghai, China) is developed by the same team as the Biodegradable PDO ASD occluder. It is a double-disc device connected by a thin waist of different lengths. Each disc is 13 mm in diameter and is woven from PDO monofilaments with a diameter of 0.298 mm and a molecular mass of 183 kDa. PLLA non-woven fabrics (20 g m^{-2}) are used to fill two discs, and four tantalum particles are symmetrically sewn on the edges of the double discs for fluoroscopy tracking. Transcatheter closure of VSD was performed in 16 dogs and PDO VSD occluder was successfully implanted in 15 dogs. The degradation rate of the occluder was well matched to the self-recovery rate of the organism. During 6 months of follow-up, the occluder remained in place and no VSD recanalization was observed [65].

Table 5
Next-generation occlusion devices.

Device	Institution	Applicable defect (s)	Biodegradable/ Non-degradable	Frame/Skeleton	Membrane	Sheath [F]	Status	Features
BioSTAR occluder [35]	NMT Medical, Boston, MA, USA	ASD/PFO	Partially biodegradable	MP35N	Heparin-coated porcine intestinal type I collagen	10	CE mark; discontinued	(1) Accelerated healing response; (2) Enhanced biocompatibility; (3) 5–10% of the metal frame will be left after degradation
BioTrek occluder [71,77]	NMT Medical, Boston, MA, USA	ASD/PFO	Biodegradable	P4HB	P4HB		Pre-clinical evaluation; discontinued	(1) An improvement of BioSTAR occluder; (2) Fully biodegradable
Carag bioresorbable septal occluder [42]	CARAG AG, Switzerland	ASD/PFO	Partially biodegradable	PLGA	PP	12	CE mark	Frame is biodegradable
Double BioDisk [43]	Cook Medical, Bloomington, USA	ASD/PFO	Partially biodegradable	Nitinol covered with platinum coils	Porcine small intestine submucosa	10	Animal experiments	(1) Nitinol rings covered with platinum coils; (2) The submucosa of the porcine small intestine is used as a blood flow barrier
Transcatheter Patch [46,142]	Custom Medical Devices, Athens, Greece	ASD, VSD, PDA, PFO, especially suitable for LAA	Biodegradable	Frameless	Latex support balloon and PU foam patch	12–13	CE mark	(1) Suitable for the closure of various cardiac defects, including ASD, VSD, PDA, PFO, and LAA; (2) Support balloon is inflatable, thus allowing a single device to conform to most LAA sizes (15 mm-25 mm); (3) TP fixed in LAA by surgical adhesive; (4) Facilitates rapid endothelialization without the need for anticoagulation therapy
PCL ASD occluder [37]	Chang Gung University, Taiwan, China	ASD	Biodegradable	PCL	PLGA/collagen	Not loaded in a sheath	In vitro tests	(1) Its compression resistance is comparable to that of Amplatzer occluder; (2) PLGA/collagen membrane promotes cell proliferation
Double umbrella occluder [34]	Nanyang Technological University, Singapore	ASD/PFO	Biodegradable	PCL (discs); PLC (spokes in right atrium disc)	PLC	9–11	Animal experiments	(1) Made of fully biodegradable polymers; (2) Two discs are made of PCL for better anchoring; (3) Spokes of the right atrium disc are made of PLC (more flexible than PCL) to facilitate rapid deployment; (4) Films are made of PLC to facilitate catheter delivery; (5) Non-relocatable
PCL-PLC PDA occluder [72,82]	Nanyang Technological University, Singapore	PDA	Biodegradable	PCL/B; PCL/PLC30	PLC	9	Animal experiments	PCL-PLC blends with different compositions are selected according to the requirements of mechanical properties and recoverability of each part of the device
Chinese Lantern occluder [31]	Nanyang Technological University, Singapore	ASD/PFO	Biodegradable	PCL, except waist (PLC)	PLC	9	Animal experiments	(1) Pull-fold working mechanism; (2) Retrievable and repositionable; (3) Waist length is tunable according to the actual septum thickness; (4) Provides a valuable demonstration for the locking mechanism of biodegradable occluders
Biodegradable PDO ASD occluder [37]	Changhai Hospital, Second Military Medical University, Shanghai, China	ASD	Biodegradable	PDO	PLA	14	Animal experiments	(1) Woven from biodegradable PDO monofilaments; (2) Can be deployed automatically; (3) The delivery of large-sized occluders is challenging; (4) Appropriate degradation rate

(*continued on next page*)

Table 5 (*continued*)

Device	Institution	Applicable defect (s)	Biodegradable/ Non-degradable	Frame/Skeleton	Membrane	Sheath [F]	Status	Features
Biodegradable PDO VSD occluder [65]		VSD	Biodegradable	PDO	PLLA	12	Animal experiments	(1) Woven from biodegradable PDO monofilaments; (2) Can be deployed automatically; (3) Appropriate degradation rate
Lifetech Absnow PLLA occluder [36]	Lifetech Scientific, Shenzhen, China	ASD	Biodegradable	PLLA	PLLA	10–12	Clinical trials	(1) The first absorbable PLLA occluder implanted in humans for ASD closure; (2) Featured delivery system with a locking mechanism enables the occluder to smoothly deploy and retract
SHSMA totally biodegradable PLA occluder [33]	Fuwai Hospital, Beijing, China; Shanghai Shape Memory Alloy Co., Ltd (Lepu Medical, Beijing, China)	ASD/PFO	Biodegradable	PLLA	PDLLA	12–14	Animal experiments	(1) The locking mechanism can maintain the different states of the occluder; (2) Two discs of the device are connected by the PLLA frame, replacing the conventional waist; (3) The occlusion process can be performed under the guidance of echocardiography, without the need for metal X-ray markers
Nitinol-SMP foam PDA cage [144]	Texas A&M University, TX, USA	PDA	Non-degradable	Nitinol	SMP PU foam	4	In vitro experiments	(1) SMP PU foam is used to occlude PDA; (2) SMP PU foam can rapidly expand (~ 2 min) in 37 °C water; (3) Low cost and low profile
3D printed PLLA-TMC-GA occluder [32]	The Affiliated Women and Children's Hospital of Qingdao, China University, Qingdao, China	Septal defect	Biodegradable	PLLA-TMC-GA	PLLA-TMC-GA	Not loaded in a sheath	In vitro experiments	(1) Favorable cytocompatibility, hemocompatibility, and histocompatibility; (2) Novel printable terpolymer LA-GA-TMC is used as the material for 3D printing; 3) 3D printing is used as the fabrication method;
3D printed patient-customized inflatable LAA occluder [26]	New York-Presbyterian Hospital and Weill Cornell Medicine and Cornell University, New York, USA.	LAA	Non-degradable	Silicone composite of Dragon Skin 20, Sylgard 184, and ChronoFlex AR; biocompatible epoxy		18	Animal experiments	(1) Patient-customized inflatable LAA occluder; (2) Device geometry matches the anatomy of the patient's LAA, which can maximize the stable anchoring and complete occlusion of LAA; (3) Maximized anchoring surface area facilitates the reduction of local stress; (4) Can reduce the risk of damage to surrounding tissues
4D printed bioinspired LAA occluder [145]	Harbin Institute of Technology, Harbin, China	LAA	Biodegradable	Shape memory PLA-Fe_3O_4 composite	Shape memory PLA	13	In vitro experiments	(1) Patient-specific; (2) Bioinspired configuration helps reduce the risk of tissue wear; (3) Tailored mechanical properties
4D printed shape memory polymer ASD occluder [45]	Harbin Institute of Technology, Harbin, China	ASD	Biodegradable	Shape memory PLA-Fe_3O_4 composite	Shape memory PLA	14	In vitro experiments	(1) Magnetic-responsive. The deployment can be controlled remotely; (2) Unique structure and shape memory effect; (3) 4D printed personalized device

2.2.11. Lifetech Absnow PLLA occluder

The Lifetech Absnow PLLA occluder (Fig. 5c; Lifetech Scientific, Shenzhen, China) is a self-expandable, biodegradable double-disc ASD occlusion device woven by 36 PLLA monofilaments with a diameter of 0.15 mm [44]. The PLLA membranes are filled in two discs and the waist. Seven PT-IR X-ray markers are designed at different sites of the device to ensure fluoroscopy visibility. As shown in Fig. 5d and e, the delivery system includes a handle, a delivery cable, a hemostatic valve, a loader, and an assistant loader. The control part of the handle is composed of a back cover, a button, and a locking wheel. The handle is able to switch the "locked" and "unlocked" states of the preloaded device through the lock wheel, and the device can be repositioned and recaptured with the button. The specific process is as follows: The left disc is expanded by moving the button to the middle of the handle, and the right disc is expanded by moving the button further distally. The retraction of the occluder can be achieved by moving the button in the opposite direction. This featured delivery system with a locking

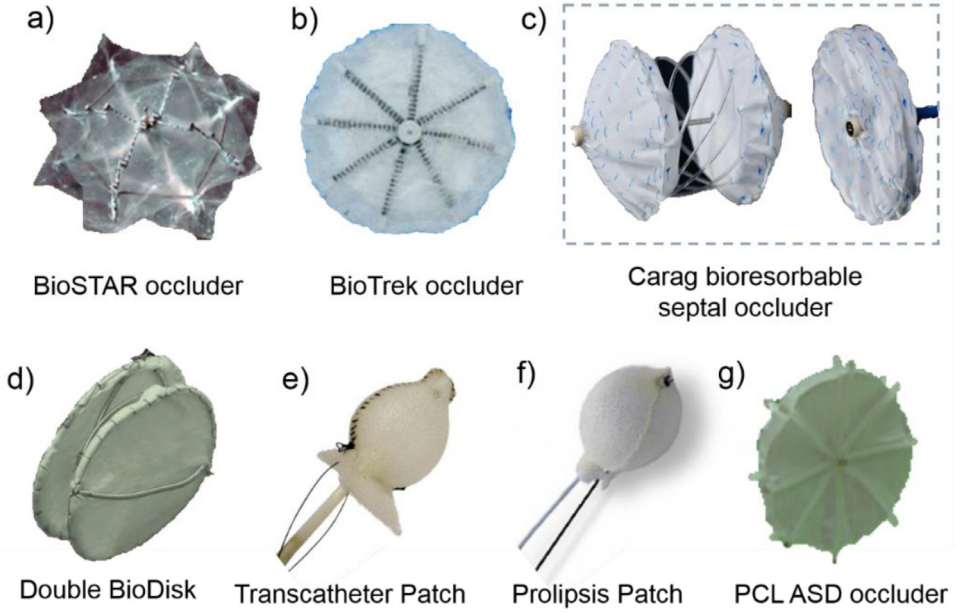

Fig. 3. (a) BioSTAR occluder [73]. (b) BioTrek occluder [81]. (c) Carag bioresorbable septal occluder [42]. (d) Double BioDisk [79]. (e) Transcatheter Patch [46]. (f) Prolipsis Patch [48]. (g) PCL ASD occluder [41].

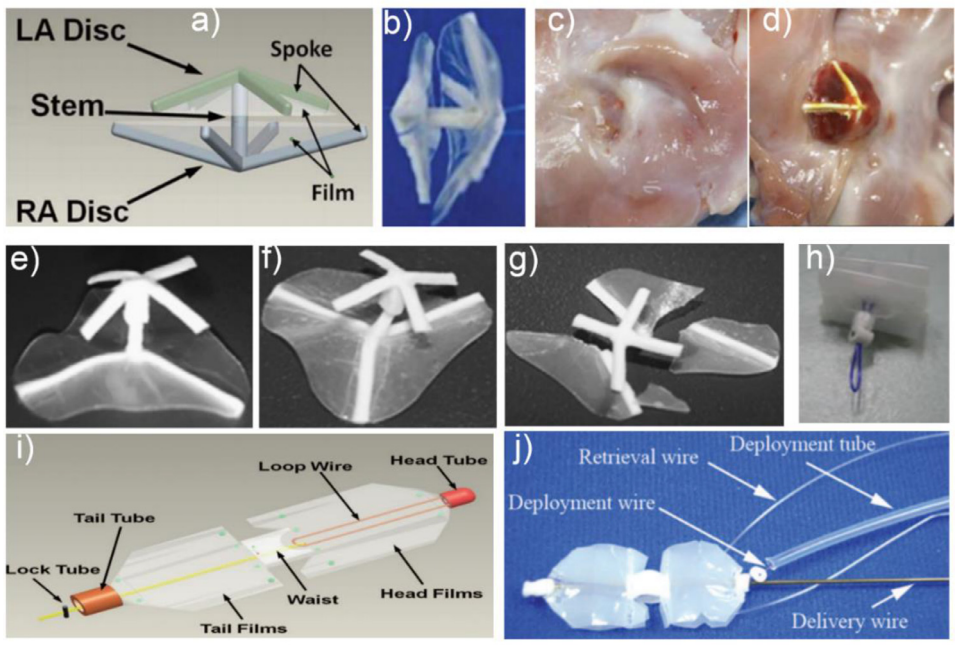

Fig. 4. Double umbrella occluder. (a) Design schematic; (b) device prototype; (c) right atrium disc and (d) left atrium disc of the explanted Double umbrella device after 1-month implantation [34]. PCL-PLA PDA occluder degraded in vitro for (e) 0 months, (f) 4 months, and (g) 6 months [72]. (h) Deployed Chinese Lantern occluder, (i) detailed schematic of Chinese Lantern occluder, and (j) Chinese Lantern occluder and its delivery system [31].

mechanism enables the occluder to smoothly deploy and retract. In addition, the occluder reserves the potential of trans-septal interventions.

The preclinical study of Absnow PLLA occluder in swine models showed well endothelialization, degradability, and long-term biocompatibility. At 36 months after implantation, PLLA was almost completely degraded with very few inflammatory reactions [33,36,44]. The first-in-human experience of the Absnow PLLA occluder enrolled 5 pediatric patients. All devices were successfully implanted without complications associated with the procedure. During the 6 months of follow-up, 1 patient experienced residual shunt and no other major adverse events such as device displacement or thromboembolism occurred [36].

As the first breakthrough study of implanting PLLA occluder into the human body for ASD closure, it has been proved that Absnow PLLA occluder is feasible for the closure of small to medium-sized ASDs without significant residual shunts or severe adverse events [36].

2.2.12. SHSMA totally biodegradable PLA occluder

The SHSMA totally biodegradable PLA occluder is jointly designed by Fuwai Hospital and SHSMA. The occluder is composed

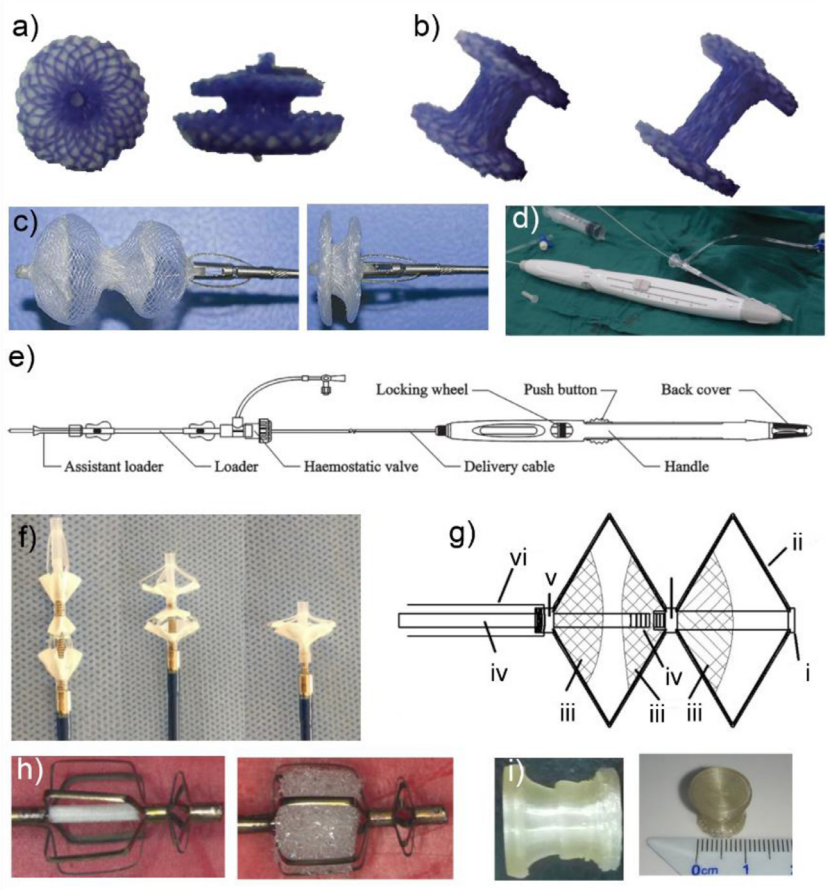

Fig. 5. (a) Biodegradable PDO ASD occluder [37]. (b) Biodegradable PDO VSD occluders with different waist lengths (left: 7mm, right: 10mm) [83]. (c) Lifetech Absnow PLLA occluder [57]; (d) photo of the delivery system of Lifetech Absnow PLLA occluder; (e) delivery system details of Lifetech Absnow PLLA occluder [36]. (f) SHSMA totally biodegradable PLA occluder in different states (from left to right: delivery state, original state, and deployment/lock state); (g) details of SHSMA totally biodegradable PLA occluder (i) Locking tube; (ii) skeleton; (iii) fabric; (iv) wire rope; (v) lock installation; (vi) pushing tube) [33]. h) Nitinol-SMP foam PDA cage with compressed (left) and expanded (right) foam [144]. (i) 3D printed PLLA-TMC-GA occluder [32].

of PLLA pentagonal skeletons, PDLLA fabrics, and a locking tube welded to skeletons. Fig. 5f shows the different states of the SHSMA totally biodegradable PLA occluder. The delivery system consists of an external push tube and an internal push wire rope (Fig. 5g). Through the cooperation of the push tube and the wire rope, the folding and unfolding states of the occluder can be smoothly switched to serve the delivery and occlusion. The locking mechanism of the device can maintain the different states of the occluder. Innovatively, the two discs of the device are connected by the PLLA frame, replacing the conventional waist. This design is not conducive to the closure of large-sized ASDs, and is more suitable for ASDs with narrow pathways but requiring large-area closure, such as multifenestrated ASD and PFO [33]. In addition, the occlusion process was performed under the guidance of echocardiography. Therefore, X-ray markers for fluoroscopy guidance are not required, which contributes to the complete absorption of the device. However, it is worth noting that echocardiographic-guided percutaneous ASD closure includes transthoracic echocardiography (TTE)-guided percutaneous ASD closure and transesophageal echocardiography (TEE)-guided percutaneous ASD closure, where TEE-guided percutaneous ASD occlusion has the disadvantages of general anesthesia and insertion of an esophageal ultrasound probe.

The device was successfully implanted into 18 sheep with ASD of approximately 12 mm in diameter, and the procedure success rate was 100%. During the 24-month follow-up, the occluder was in the correct position without thrombosis, residual shunt, AV valve dysfunction, or other complications. After 12 months of implantation, the occluder was completely endothelialized. At 24 months, the degradation of the PLLA frame continued and its molecular weight decreased to 9% of the original molecular weight. As the first demonstration of a totally biodegradable occluder without even metal markers, the feasibility and effectiveness of the device for ASD occlusion has been preliminarily proved [33].

2.3. SMP and 3D/4D printed occlusion devices

Although commercially available occlusion devices can provide effective closure, the limited specification of devices and the obstacles of traditional manufacturing techniques to fabricate devices with complex structures still lead to an increased risk of complications such as residual shunt, erosion, dislodgement, and even embolization [84–87]. For example, Occlutech LAA occluders were recalled in 2016 due to the high incidence of dislodgement.

The emergence of three-dimensional (3D) printing technology provides new opportunities for patient-customized occlusion devices, which can effectively improve the success rate of closure and reduce the risk of complications [45,88–90]. 3D printing allows rapid prototyping of structures with arbitrary geometries and heterogeneous materials [91]. There have been a few attempts on 3D printing occlusion devices, which are currently in the experimental stage [26,32,92].

SMP, a unique class of deformable material, has been widely used in biomedicine, especially in minimally invasive surgery, be-

cause of its exciting properties that can be programmed to convert between arbitrary temporary configuration and initial permanent configuration [93–98]. A typical shape memory process is comprised of two steps, programming, and recovery. As illustrated in the "Deployment strategies" part in Fig. 2, the blooming flower is the initial permanent configuration. By applying external stimulus (such as heat, magnetic field, etc.) to raise the temperature of the flower above its transition temperature (T_{trans}), the flower can be programmed into any temporary configuration. The flower bud configuration is taken as an example of a temporary configuration and the bud configuration can be fixed by lowering the temperature below T_{trans}. Finally, when the bud is reheated above T_{trans}, the bud automatically recovers to its initial blooming flower configuration [88,94]. When SMP is introduced into the occlusion device, its temporary low-profile configuration can be used for delivery and its permanent configuration can be used for closure (Fig. 8a). More importantly, its deployment is adaptive and controllable [45,88].

Four-dimensional (4D) printing is the integration of 3D printing and intelligent materials (e.g., SMP), which adds an additional dimension of space or time transformation for 3D printing. It can realize the switch of 3D printed components between various configurations through environmental stimuli [93]. In particular, the magnetic field is considered to be a safe and non-contact actuation method that allows autonomous deployment of SMP in inaccessible places [53,54]. In short, the 4D printed occlusion device can not only be patient-customized but also be automatically deployed in the body in a controlled manner.

2.3.1. Nitinol-SMP Foam PDA cage

The Nitinol-SMP foam PDA cage (NFC, Fig. 5h) consists of a Nitinol self-expanding frame and an SMP PU foam. PU foam can rapidly expand (~ 2 min) in 37 °C water to quickly occlude PDA. The integration of the frame and SMP PU foam is achieved by threading compressed foam through the central wire of the frame. Additionally, NFC is characterized by low cost and low profile and can be transported via a 4 F catheter. NFC was used to occlude simplified PDA models in vitro, and the results showed that NFC was stable in position under physiological pressure or slightly higher pressure [144]. Compared with other metal occluders, the amount of Nitinol used in NFC is significantly reduced, which can decrease the possibility of early and long-term complications caused by Nitinol to some extent.

2.3.2. 3D printed PLLA-TMC-GA occluder

The 3D printed PLLA-TMC-GA occluder is a personalized septal defect occlusion device manufactured by 3D printing technology (Fig. 5i). LA-GA-TMC terpolymer was synthesized as printing material, in which the ratio of lactide: glycolide: trimethylene carbonate was 6: 1: 1.7. Compared with PLLA, the degradation rate of PLLA-TMC-GA terpolymer will be accelerated as TMC and GA units will reduce the regularity and crystallinity of the chain. According to ISO-10993 (Biological and clinical evaluation of medical devices), the cytocompatibility, hemocompatibility, and histocompatibility of LA-GA-TMC were systematically evaluated. The relative cell proliferation rate of different concentrations of LA-GA-TMC extract was more than 70%, indicating well cytocompatibility. In addition, the hemolysis rate was lower than 5% and no strong coagulation reaction was induced, demonstrating the favorable blood compatibility [32,99]. At the same time, the implantation of three occluder materials (PLLA-TMC-GA, Nitinol, and PLLA) in New Zealand white rabbits showed that PLLA-TMC-GA possessed the best histocompatibility. This work validated the printability of the novel terpolymer LA-GA-TMC and preliminarily demonstrated the potential feasibility of its clinical application [32].

2.3.3. 3D printed patient-customized inflatable LAA occluder

The current LAA occlusion devices suffer from the following deficiencies: (1) Most devices have a standard circular geometry, and the closure of the LAA with irregular anatomy may cause leakage around the device; (2) To achieve complete closure, oversized (10–20%) device is usually selected, which increases unnecessary pressure on the LAA tissue. To address these limitations, a patient-customized inflatable LAA occluder has been developed based on non-invasive CT imaging [26]. The specific advantages are as follows: (a) The inflatable balloon-type device made of elastomer materials can fit the complex anatomy of LAA, which is conducive to complete closure; (b) The device with customized geometry can maximize the anchoring surface area after implantation and inflation, thus reducing the local stresses caused by the oversized device or surface barbs used for fixation; (c) The soft elastomer material can reduce the risk of damage to surrounding tissues and increase compliance with LAA anatomy.

The manufacturing process of the patient-customized inflatable LAA occluder was mainly divided into three steps: Firstly, the LAA mold was fabricated by a 3D printer according to the model scanned by CT imaging; secondly, the thin-walled LAA occluder was prepared using a commercial elastomeric silicone composite (Dragon Skin 20, Sylgard 184 and ChronoFlex AR) by conventional molding technology; finally, polycarbonate urethane was coated on the surface of the molded occluder to increase blood compatibility. In addition, a multifunctional valve was designed at the proximal end of the device for anchoring, delivery, filling, and recovery. As shown in Fig. 6a, three typical LAA anatomies were fabricated, including cauliflower, chicken wing, and cactus. Fig. 6b exhibits the delivery, deployment, and occlusion process of the inflatable LAA occluder. After implantation, biocompatible epoxy was injected into the lumen of the device to expand the device and conform to the LAA anatomy. An 18 French (F) sheath was used to deliver the occluder into the LAA of a canine, and the advantages of the customized device as well as the anchoring stability of the device were verified (Fig. 6c, d) [26].

Later, similar patient-customized inflatable occluders were manufactured by the same research group using the method described above, and the mechanical properties of the devices were further studied. The anchoring stability of the customized occluder was verified by measuring the tensile force. The wall shear stress caused by non-patient-customized spherical occluder and customized occluder on the heart model was calculated by computational fluid dynamics simulation. The results showed that the spherical occluder may cause more clots due to the presence of low shear regions, while the customized occluder did not show similar regions [92]. More recently, inspired by frog toe pads, this group designed a biologically inspired patient-specific LAA occluder, with the expectation that surface micropatterns would enhance the device stability and avoid the use of external valves. Pull-out force (the force required to pull the occluder out of the LAA) tests showed that the patient-specific occluder could increase the pull-out force by 15% compared to the spherical occluder, and the introduction of surface micropatterns could increase the pull-out force by an additional 50% [143].

2.3.4. 4D printed bioinspired LAA occluder

The 4D printed bioinspired LAA occluder (Fig. 7) was designed based on the optimal bioinspired network, which was explored by iterative optimization to mimic the "J-shaped stress-strain curve of LAA tissue. The similarity of stress-strain behaviors is conducive to the co-deformation of LAA occluder and LAA tissue, thus reducing the risk of wear and perforation. The occluder was manufactured by 4D printing, which endowed it with a patient-specific and transformable configuration, which can ensure a perfect fit with LAA and facilitate interventional treatment. The heat-induced 4D

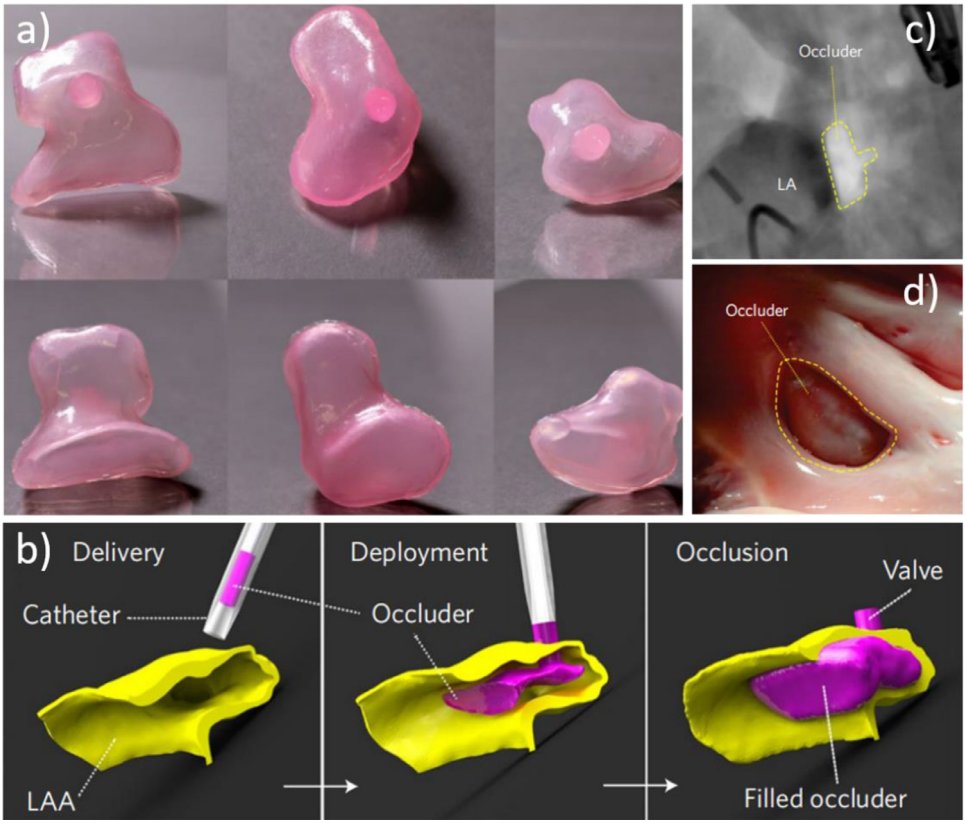

Fig. 6. (a) Images of 3D printed inflatable LAA occluders with different anatomies (from right to left: cauliflower, chicken wing, and cactus). (b) The delivery, deployment, and occlusion process of inflatable LAA occluder. (c) Perioperative fluoroscopy image of the LAA occluder after inflation. (d) Photograph of the occluder at the 24-h post-operative autopsy (to examine anchoring stability) [26].

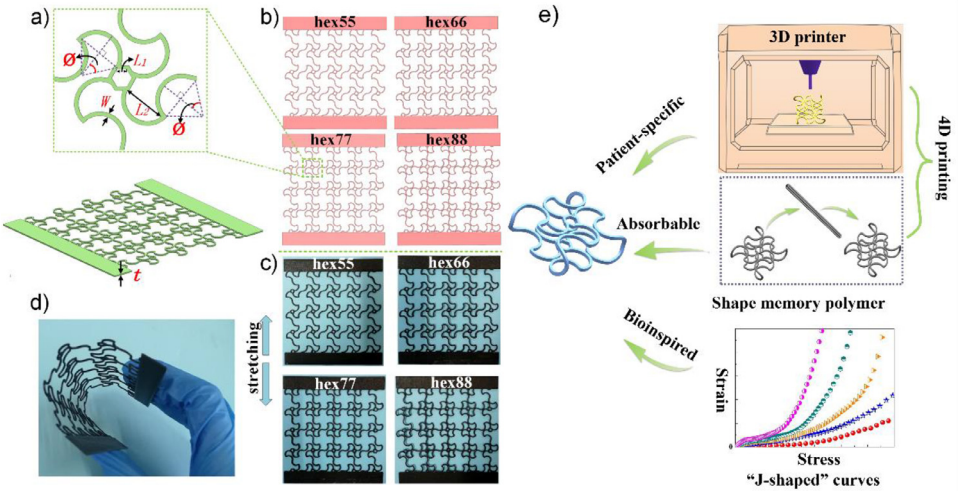

Fig. 7. (a–d) Four candidate bioinspired networks. (a) Geometric parameters. (b) 3D models of bioinspired networks. (c) 4D printed bioinspired networks. (d) Flexibility demonstration of the bioinspired network. (e) The configuration and features of 4D printed bioinspired LAA occluder. The features are patient-specific, absorbable, and bioinspired [145].

transformation of the occluder demonstrated outstanding shape recovery performance, and the magnetism-induced shape recovery process verified that the dynamic and remote-controlled 4D transformation of the occluder was accessible. In addition, the deployment of the catheter-delivered LAAO in isolated swine heart preliminary showed that the occluder was feasible for LAA occlusion. Besides, the bioinspired design concept was not only applicable to LAA occluders, but also to other occlusion devices or implants [145].

2.3.5. 4D printed shape memory polymer ASD occluder

The 4D printed shape memory polymer ASD occluder consists of an integrated support frame and membranes. The frame made of shape memory PLA-based magnetic nanocomposite is manufactured by 4D printing technology, and the membrane made of shape memory PLA is prepared by electrospinning technology. By mixing the Fe_3O_4 magnetic nanoparticles with PLA, the occluder is magnetic-responsive, thus its deployment is remotely controllable [45]. The combination of unique structure and shape memory ef-

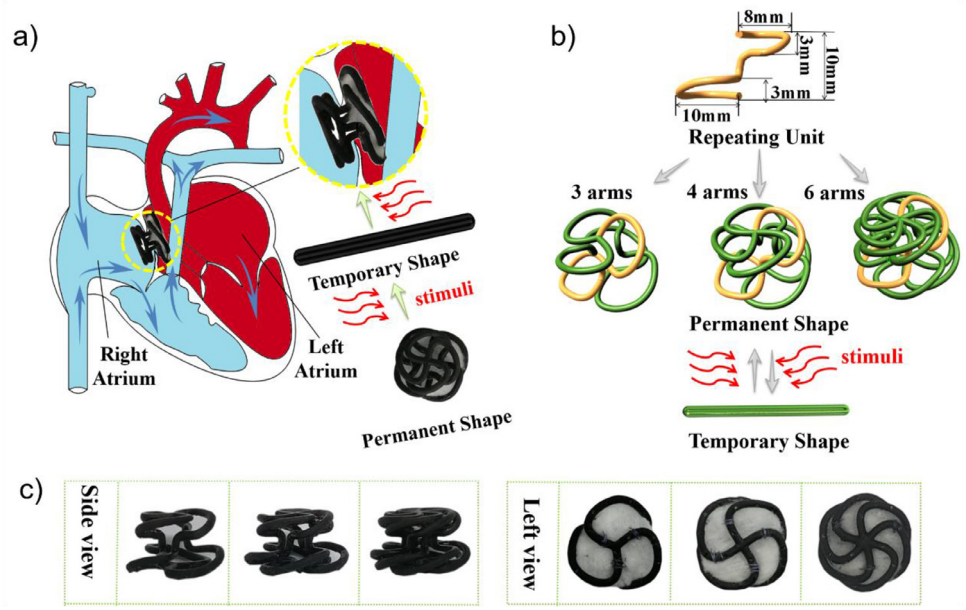

Fig. 8. (a) The programming process of 4D printing shape memory occluder. (b) Design details of occluder frames with various numbers of arms. (c) Optical images of 4D-printed occluders [45].

fect enables the occluder to have a high rate of change in cross-sectional area from a permanent geometry to an arbitrary temporary configuration. The delivery and deployment process is as follows (Fig. 8a): firstly, the shape memory occluder is deformed from the original double-disc configuration to a temporary linear configuration by heating. The linear configuration has a reduced cross-sectional area, which facilitates the transportation of the occluder in the sheath; then, after reaching the target position, the occluder automatically recovers to the double-disc configuration under the stimulus, thus achieving the occlusion of the defect.

The results of cell culture and subcutaneous implantation in Sprague-Dawley rats showed that the occluder contributed to cell proliferation and autologous tissue coverage. In vitro degradation experiments showed that the occluder can maintain adequate mechanical strength to seal the defect after 16 weeks. Additionally, in vitro feasibility test demonstrated the occluder was able to occlude ASD completely and rapidly. This work takes the ASD occlusion device as an example and other types of occlusion devices are capable of being modeled and manufactured using similar methods. Besides, the personalized device is expected to ensure ideal matching and stable fixation, thus reducing complications and increasing the success rate of closure [45].

3. Conclusion and outlook

In summary, we provide a current review of next-generation occlusion devices for ASD, PFO, PDA, VSD, and LAA, with particular emphasis on materials, configurations, manufacturing methods, deployment strategies, and experimental/clinical outcomes. In addition, the representative features of various occlusion devices are summarized. Biodegradable occluders are considered as a promising alternative to metal occluders and are far superior to metal occluders in terms of biocompatibility, degradability, and long-term device-associated complications. However, the development of biodegradable occluders remains challenging and more efforts can be focused on the following aspects in the future.

(1) Appropriate strength and flexibility. Sufficient strength is needed for the occluder to provide support for the defect until complete endothelialization. Flexibility is also required as the occluder should be loaded into the sheath for interventional delivery.
(2) Small diameter delivery sheath. Compared with metal occluders, biodegradable polymer occluders require a larger delivery sheath, thus it is necessary to develop biodegradable materials with excellent mechanical properties at small diameters (no more than 0.1mm if possible).
(3) Autonomous deployment. Unlike Nitinol, most of the conventional biodegradable polymers are not capable of self-unfolding after being pulled out. To solve this problem, the locking mechanism can be designed to enable smooth deployment. In addition, the development of SMP-based occlusion devices is also a solution.
(4) Proper degradation rate. Ideally, the degradation rate of the biodegradable occluder matches the endothelialization rate. However, some current biodegradable occluders (e.g., PLA and PCL occluders) take 2–3 years or more to fully degrade, while endothelialization can be completed in approximately 6 months. Therefore, the development of biomaterials with a controllable degradation rate merits further efforts.
(5) Fully retrievable and repositionable multiple times. Repositioning is a crucial feature in case of inaccurate deployment positions.

In addition, the evaluation of long-term efficacy and safety of biodegradable occluders is lacking. Only several biodegradable occluders have been tested clinically, thus more patients and longer follow-up time are needed to further assess the outcomes.

As an emerging manufacturing technology, although 3D printing is still in its infancy in the field of medical devices, it may become an indispensable method for rapid fabricating customized implants and bring revolutionary technological updates. Additionally, 4D printing endows 3D printed devices with the ability of dynamic transformation. In the future, it is expected that 4D printed occlusion devices can not only be deployed automatically and adaptively but also accommodate physiological growth, which is particularly important for infant CHD patients. But they still face many challenges, such as the precise control of the deployment process by external stimuli.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.actbio.2021.04.050.

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