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Review

Polymeric heart valves for surgical implantation, catheter-based technologies and heart assist devices

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ABSTRACT

Efficient function and long-term durability without the need for anticoagulation, coupled with the ability to be accommodated in many different types of patient, are the principal requirements of replacement heart valves. Although the clinical use of valves appeared to have remained steady for several decades, the evolving demands for the elderly and frail patients typically encountered in the developed world, and the needs of much younger and poorer rheumatic heart disease patients in the developing world have now necessitated new paradigms for heart valve technologies and associated materials. This includes further consideration of durable elastomeric materials. The use of polymers to produce flexible leaflet valves that have the benefits of current commercial bioprosthetic and mechanical valves without any of their deficiencies has been held desirable since the mid 1950s. Much attention has been focused on thermoplastic polyurethanes in view of their generally good physico-chemical properties and versatility in processing, coupled with the improving biocompatibility and stability of recent formulations. Accelerated in vitro durability of between 600 and 1000 million cycles has been achieved using polycarbonate urethanes, and good resistance to degradation, calcification and thrombosis *in vivo* has been shown with some polysiloxane-based polyurethanes. Nevertheless, polymeric valves have remained relegated to use in temporary ventricular assist devices for bridging heart failure patients to transplantation. Some recent studies suggest that there is a greater degree of instability in thermoplastic materials than hitherto believed so that significant challenges remain in the search for the combination of durability and biocompatibility that would allow polymeric valves to become a clinical reality for surgical implantation. Perhaps more importantly, they could become candidates for use in situations where minimally invasive transcatheter procedures are used to replace diseased valves. Being amenable to relatively inexpensive mass production techniques, the attainment of this goal could benefit very large numbers of patients in developing and emerging countries who currently have no access to treatment for rheumatic heart disease that is so prevalent in these areas. This review discusses the evolution and current status of polymeric valves in wide-ranging circumstances.

1. Introduction

1.1. Background to heart valve disease and devices

While many factors determine the healthy functioning of the heart, most of them being electromechanical in nature, the ability of the valves of the heart to control, in an energetically favourable capacity, the flow of blood in and out of the heart and its chambers is of crucial significance. The failure of valves to carry out this function in certain disease states, especially as a consequence of the general ageing process, has been known for a long time, and the use of medical devices to effect greater control over blood flow represents one of the most important contributions that biomaterials

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[1] All three authors declare a potential conflict of interest, being Directors of the company Strait Access Technologies, Cape Town, South Africa, that is developing technologies to treat rheumatic heart disease.

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and implantable devices have made to health care. Traditionally the patient population perceived to be at most risk have been the elderly individuals in the developed countries of North America, Europe and parts of Asia/Australasia, who suffer from the degenerative changes of either stenosis or incompetence. The age of patients in this group at first heart valve surgery has typically been in excess of 70 years, and a median freedom from valve-related complications of 15 years, has been considered to be a very satisfactory resolution to the problem. For several decades, the market for prosthetic heart valves, dominated by the needs of this patient cohort, has been considered to be mature and static.

However, the whole area of heart valve disease, and indeed heart failure itself, has been undergoing rapid change since the beginning of the twenty-first century, and there is now a perceived need for new types of devices. The circumstances relate to different ends of the age spectrum. At the elderly end of this spectrum, more and more individuals require valve replacement or repair, but, because of age or co-morbidities, are unsuitable for the open-heart surgery that is required for attention to the valves; this has caused an immense interest in minimally-invasive techniques and catheter delivered valves, whose structure and design has to be quite different to the normal surgically implanted prosthesis. Also, the ageing population has brought an increase in patients with serious heart failure conditions. For some time now, the technology has been available, albeit at very high cost, to allow artificial hearts or heart-assist devices to be used. There are many types of design, which has lead to some innovations of valve concepts, although not all of these devices actually utilize valves.

Secondly, and of far greater significance numerically, there is still an increasing number of young adults in the developing world who acquire rheumatic heart disease. Very many individuals in sub-Saharan Africa, and also in parts of Asia and South America suffer from this condition and they die when relatively young because of the damage that their heart valves sustain as a result of this disease. The availability of open-heart surgery, and of expensive prostheses, is extremely limited, such that new concepts and new devices for the treatment of these individuals has become an imperative. This situation is exacerbated by the fact that the changes to valve structure that occur in rheumatic heart disease, arising from inflammation, are different to the usual degeneration-induced changes in old age, so that procedures and devices may have to be different.

There is, therefore, a newly recognized need for larger numbers and different types of heart valve treatment. This may be seen from an estimate that the total number of patients requiring heart valves would triple, from 290,000 in 2003 to over 850,000 by 2050 based on population growth and ageing alone [1] and indeed, due to the previously under-estimated incidence of rheumatic heart disease in developing nations, this number is likely to be very much higher [2,3].

During the half-century of the clinical use of heart valve prostheses, several different types of material have been used in their construction, but for much of that time only a small number of generic constructs have been common, principally the metal-carbon combinations for mechanical valves and some treated animal tissues for the so-called bioprosthetic valves. Synthetic polymers rarely featured. They do, however, have some very attractive features and are likely to form the basis of new types of device. This review focuses on the development of such polymers and their prospects for the future. In doing so, these materials and devices have to be placed into the context of conventional and alternative materials.

1.2. Commercial heart valve prostheses

As with some surgical treatments of other parts of the cardiovascular system, it is possible to consider the use of transplanted tissue, in this case transplanted human valves. Such procedures, for example the Ross procedure that utilizes transplanted homograft pulmonary vales [4] represent an important place in the history of valve disease. Whether they are homograft or allograft, however, they constitute only a small percentage of procedures today due to limited availability and demanding surgical techniques.

There are two main types of commercially available prosthetic valves, the mechanical and bioprosthetic valves, and these account for the overwhelming majority of surgically implanted valves. While almost half of the implanted valves were mechanical in the late 1990s [5], more than 80% prostheses implanted in the industrialised world today are tissue valves [6,7]. Current tilting disc valves typically comprise annular rings containing mostly two pyrolytic carbon occluders; they have high durability but relatively un-physiological haemodynamics in terms of turbulence and shear stresses and consequently require lifelong anticoagulation due to the associated thrombogenicity [3,8]. Bioprosthetic valves consist of leaflets made from chemically treated animal valves or leaflets, or from animal derived pericardium; these valves may be stented or un-stented. Compared to mechanical valves they have better haemodynamics in view of their similarity to natural flexible leaflet valves, and do not require lifelong anticoagulation, but they do have limited durability due to calcification and degeneration processes [3,9]. As we note later, degeneration of valves is particularly aggressive and rapid in younger patients, including those with rheumatic heart disease. The bioprosthetic valves also have a smaller effective orifice area than current mechanical valves [10]. Although both types of valve do have their deficiencies, these are largely manageable, and cardiac surgeons do have a reasonable selection of devices for the vast majority of their eligible, aged patients; indeed there are widely used algorithms that advise on the choice of device on the basis of patient age and risk factors [11].

The one obvious drawback to surgically implanted valves is the self-evident need for open-heart surgery. This is expensive and not everyone with heart valve disease is well enough to be exposed to the procedure. For these reasons, transcatheter valves that can be delivered through minimally invasive techniques, through a vein or an artery or through the apex of the heart have recently been developed [12]. The aortic valve has been the usual target, with the procedures referred to as Transcatheter Aortic Valve Replacement (TAVR) or Implantation (TAVI). They were initially limited, by regulatory agencies, to the patients who were most at risk with open-heart surgery or young people in whom it was considered best to limit multiple open procedures [13,14], but these indications are now expanding [15]. Clinically employed transcatheter valves usually consist of collapsible/expandable metal stents containing soft leaflets similar to those used in surgically implantable bioprosthetic valves.

1.3. Availability and costs

Although we do not discuss the detailed economic aspects of heart valves here, these factors clearly play a role in the strategies for the technology development. Surgically implantable bioprosthetic and mechanical valves are expensive because of the R&D, clinical trial, regulatory, manufacturing and insurance costs. Bioprosthetic valves have the additional burden of the labour-intensive fabrication that requires hand sewing of tissues to frames. While these costs, when transferred to the prices of the finished product, may be bearable by many patients in many developed countries, that may not be so in poorer countries, even taking into account adjustment of costs to local economies.

There has been some success in the development and manufacture of valves within the developing countries themselves, exemplified by the Chitra valve made in India [16]. The occluders of

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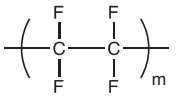
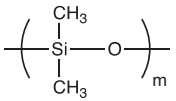
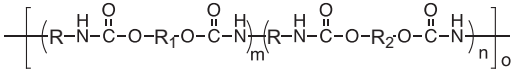
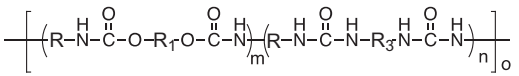
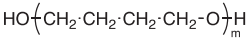
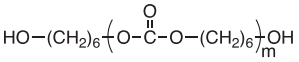
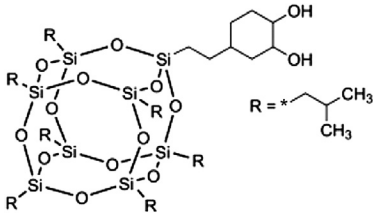
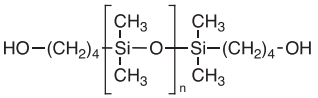
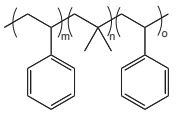
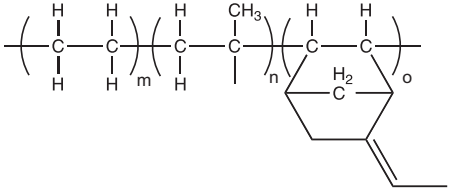
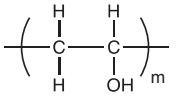
Table 1
Polymeric materials used in synthetic heart valves.

#	Designation	Basic structure	Properties and comments	Ref
1	Polytetrafluorothylene (PTFE) and expanded PTFE		Very stable, hydrophobic, crystalline polymer. ePTFE: consists of stretched material to form node/fibril microstructure. Biocompatible and biostable.	[28]
2	Polysiloxanes (Silicone) (e.g. PDMS)		Chemically stable polymers with suboptimal mechanical properties for thin leaflet manufacture	[27,28]
3	Thermoplastic Polyurethane (TPU)		Polymer with segmented hard and soft segments: R = diisocyanate; R_1 = soft segment R_2 = diol extender	[153]
4	Thermoplastic Polyurethane urea (TPUU)		Similar to TPU but with diamine extender(R_3). Improved segregation and hydrogen bonding may lead to improved chemical and physical properties.	[153]
3/4a	Polyether urethane (urea): PEU or PEUU		TPU or TPUU with R_1 = polyether glycol, e.g. polytetramethyleneglycol (left). Susceptible to oxidative degradation.	[153]
3/4b1	Polycarbonate urethane (urea) PCU or PCUU		TPU or TPUU with R_1 = polycarbonate, e.g. polyhexamethylene carbonate glycol (left). Susceptible to hydrolytic degradation but less so than ester soft segments (not shown)	[153]
3/4b2	POSS-PCUU		Nanocomposite polycarbonate urethane ureas containing trans-cyclohexanediolisobutyl-silsequioxane (left)	[42]
3/4c	Polysiloxane urethane (urea) PSU		TPU or TPUU with R_1 = polysiloxane, e.g. hydroxybutyl terminated poly-(dimethylsiloxane) (left). Recent data suggest may be susceptible to hydrolysis.	[69]
5	Styrene-isobutylene-styrene (SIBS)		Synthetic A-B-A block copolymer elastomer. Susceptible to creep when used as leaflet material. Crosslinked variants (xSIBS) also developed to reduce/eliminate creep.	[79,80]
6	Ethylene-propylene-dimer-monomer rubbers (EPR)		Extrudable and solvent processable polymer that is cross-linked using e.g. peroxides to render very stable elastomeric materials.	[87]
7	Polyvinyl alcohol		Water soluble polymer rendered into insoluble gel by freezing, heat or chemical cross-linking	[88]

these mechanical valves are made from ultra high molecular weight polyethylene rather than the pyrolytic carbon used in most devices. These valves may be available at one-third of the cost of an imported valve, and indeed they are now exported from India to other developing countries.

With transcatheter valves – particularly if the insertion procedure can be simplified and thus make implantation independent from open-heart surgery - the theoretical need is greatest in developing economies [3] but the affordability gap is so large as to make widespread implementation inconceivable. Valves may cost in the region of $30,000 and, although open-heart surgery is not required it is still necessary to utilize high-technology facilities so that, in most countries the total cost will be significantly more.

Lower cost TAVI procedures for developing countries are therefore a major priority. Although there are obviously other considerations, the ability to mass-produce valves from inexpensive polymers is an immensely important factor.

1.4. Experimental valves

It is also necessary to place polymeric valves, and especially flexible leaflet valves on which we concentrate in this review, into the context of other potentially disruptive technologies. This includes hard polymeric components of valves, as with the Chitra valve mentioned above and some valves that have used materials such as Delrin [17]. More importantly here we should mention the developments in regenerative medicine and the so-called tissue-engineered valves. From a biomaterials perspective, the emphasis here has been on synthetic degradable polymers and decellularised tissues [9,18,19]. There are still many technical challenges [20] but they may well eventually compete with flexible polymer leaflet valves, especially in paediatric cardiology, where classical valves have the drawback of not growing with the patient. It is conceivable that tissue-engineered valves may be able to do this, obviating the need for multiple surgical interventions.

1.5. Structure of the review

The classification of polymeric valves could be made according to a variety of criteria; they will be discussed here according to the specific polymers employed, the geometries used in leaflet designs and production techniques for their fabrication. We discuss first the materials (Table 1) used in the modalities of surgical implantation, heart assist devise and transcatheter systems. These sections are followed by discussions of valve design and fabrication routes, including surface modifications.

2. Surgically implantable valves

Flexible leaflet polymeric valves date back to the pioneering work in the late 1950s by Akutsu [21], Roe [22] and Braunwald [23], leading to the first human implants in the mitral [23,24] and aortic [25,26] positions in the 1960s. Despite this fact that polymer valves were first implanted in humans over fifty years ago, they have not yet gained clinical acceptance in this mode, and clinical use has remained limited, as we shall see, to total artificial hearts and ventricular assist devices.

2.1. Polysiloxanes

Polysiloxanes, more commonly referred to as silicones, are polymers with alternating silicon and oxygen atoms in the molecule backbone and with the possibility of a variety of pendant groups attached to the silicon, resulting in the repeat structure $-[SiR_2-O-]-$. In the most common form, R is CH_3, giving polydimethylsiloxane. Condensation or addition reactions, with cross-linking through radicals, leads to a range of highly elastic materials; these have been used in many medical devices in view of their generally excellent biostability, biocompatibility and fatigue resistance [27,28]. It is not surprising that this type of elastomer featured prominently in the early history of flexible leaflet valves (Table 2).

One of the first flexible trileaflet valves made from a silicone (Silastic 50, Ellay Rubber Company) was developed in the late 1950s [22,29]. The 380 μm thick leaflets were initially housed in a silicone cylinder; valves evaluated in a dog ascending aorta model showed satisfactory function in early stages [29] but long-term survival could not be achieved in a subsequent subcoronary model [30]. Later versions were made from a different silicone (General Electric SE-555) and slightly thicker leaflets (430–500 μm), using a composite steel band – silicone sponge- Dacron sewing ring [26]. Although some valves were shown to remain intact for 786 million cycles in accelerated in vitro tests conducted at a frequency of 58 Hz, giving the equivalent of 18 years at 80 beats per minute, the program was discontinued because of a high mortality rate in clinical trials with 18 patients, between 1960 and 1962 [25,26]. Most of these deaths occurred because of clinical complications and not failure of the leaflet mechanism although some emboli were noted in three of the patients. We should note in passing that the frequency of 58 Hz used in the pre-clinical tests is not conducive to proper opening and closing of the valve, possibly giving unrealistic expectations, and most studies since then have used substantially lower frequencies.

Mohri et al. revisited the trileaflet silicone valves in the 1970s and tested various Dow Corning formulations, with leaflet thicknesses ranging from 225 to 510 μm [31]. Some early combinations exhibited poor durability, with tearing at 3.9 years, but valves at the preferred thickness of 330 μm were able to withstand 17.7 to 23.8 equivalent years in accelerated tests, with an average of 900 million cycles at 17 or 33 Hz, using triangular leaflets of Dow Corning Silastic MDX4-4059. Gerring et al., in Oxford, worked with Dow Corning Silastic 5505 –coated polyester fabric with a film thickness of 120 μm, giving good survival, up to 30 months in a young calf model (pulmonary position), with just 2 out of 7 animals dying from thromboembolic events [32]. Chetta and Lloyd used a room temperature vulcanizing silicone, RTV-615 of General Electric, and achieved between 65 and 280 million cycles at 21 Hz [33].

Silicones do not appear to have been used, even experimentally since the 1980s and we are unlikely to see a reversal of this position. It did become obvious during these early studies that not only were the conditions of accelerated testing extremely important but also that durability was critically dependent on batch-to-batch variations and the precise design and surface conditions.

2.2. PTFE and ePTFE

Polytetrafluoroethylene, PTFE, commonly known by the trade name Teflon®, is a highly crystalline fluorinated homochain polymer, has a reputation for inertness and low surface energy, both arising from the strengths of the C–C and C–F bonds. This inertness usually leads to good biocompatibility [28] and applications within medical device technology.

Braunwald and Morrow reported on clinical trials using flexible tricuspid Teflon fabric valves and a number of variations on the composition and form, largely based on the Muller-Littlefield valve [34], and implanted valves in 23 patients [35] (Table 2). These valves tended to become stiff, and regurgitation was noted through holes in some of the leaflets, with examples of tears and complete shredding being reported. There were some calcific deposits but not extensive calcification.

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Table 2
Silicone, (e)PTFE, SIBS and PVA and PE surgical valves.

Author Year	Method/stent/housing Leaflet material	In vitro tests	In vivo evaluation	Ref
Roe et al. 1958	Compression moulding and curing Cylindrical Silicone tube Silastic 50 (Ellay) silicone (380 μm)	5-10 mmHg resistance to systolic flow. Resist static backpressures of >500 mmHg.	Ascending aortic implants in dogs showed satisfactory early function but no long-term survival in subcoronary implants (7/51 survived 3–12 months). Some clot formation around valves.	[26,29]
Braunwald and Morrow 1965	PTFE fabric with and without PTFE coating	N/A	Implanted in 23 patients, 13 of who required reoperation. Valve failure due to stiffening, tearing, and some calcification.	[35]
Roe et al. 1966	Casting thermocompression in moulds Steel/Silicone/Dacron sewing ring GE SE-555 silicone (430–500 μm)	Up to 786 mc (18yrs eq.) in accelerated tests at 18Hz. *PD: 10 mmHg opening pressure with dP = 12–40 mmHg depending on size.	18 clinical implants between 1960 and 1962. High mortality rate due to clinical complications not valve failure. 8 from fibrillation/bleeding; 6 postoperatively. 4 survived 33–61 months	[25,26]
Mohri et al. 1973	Thermocompression in 3-piece mould Stainless steel or Lexan stent Dow Corning Silastic MDX4 (330 μm)	18 to 25.5 years equivalent durability at 17–34 Hz. Tears usually from free edge of coaptation area	N/A	[31]
Gerring et al. 1974 “Oxford valve”	Planar sandwich press cast and glued to polyester velour sewing ring Dow 5505 silastic coated textile (120 μm)	N/A	Series of implants with up to 30-month survival in 40–70 kg calf pulmonary valve model.	[32]
Imamura et al. 1977	Multilayers of bonded 1 μm porosity ePTFE reinforced and sewn to support stents (8–31 μm total thickness)	N/A	Implanted in tricuspid position in 28 dogs. Good function in 12 animals up to 15 months. Remainder dysfunction due to stiffening.	[136,154]
Chetta and Lloyd 1980	Moulding and RT curing General Electric RTV-615 silicone (356 μm)	1.5 to 7 equivalent years durability at 21 Hz. 20 mmHg transvalvular pressure drop	N/A	[33]
Kolff et al. 1989	Silicone leaflets and stents moulded in one	Highly accelerated air testing at 1000Hz: breakage at same location as in real-time tests.	N/A	[96]
Nistal et al. 1990	Goretex® ePTFE valves	N/A	Sheep tricuspid position for up to nearly 5 months. Stiffening and calcification of leaflets	[36]
Jiang et al. 2004	Cavity moulded polyvinyl alcohol cryogenic leaflets, stent and sewing ring	N/A	N/A	[88]
Ando and Takahashi 2009	PTFE membranes folded and hand-stitched into Dacron grafts	N/A	Implanted in 139 patients in pulmonary position after Ross procedure with good durability up to 10 years.	[37]
Mohammadi et al. 2009-2011	PVA-Bacterial cellulose composite valves; one-piece cavity moulding by freeze-thaw process	Anisotropic materials with valves characterized by finite element modelling.	N/A	[89,90,155]
Wang et al. 2010	Composite SIBS/polyester fabric leaflets on SIBS stent with Dacron sewing ring. Some *DMPC coated	N/A	4 SIBS aortic valve replacement in sheep. 3 premature mortalities at 6–10 wks due to material failure or myocardial infarction; 1 full term (20 wks).	[82]
Claiborne et al. 2013	Compression moulded Dacron fabric impregnated with SIBS, and unreinforced xSIBS	*FEA optimization of geometry for minimized stress and *DTE for reduced thrombogenicity.	N/A	[85,86]
Prawel et al. 2014	Hyaluronan–swollen Polyethylene leaflets clipped into surgical frame	Large *EOA and low regurgitation, and reduced whole blood clotting time and cell adhesion	N/A	[92]

*PD: Pulse duplicator; DMPC: Dimyristoyl phosphatidylcholine; FEA: Finite element analysis; DTE: Device thrombogenicity emulation, EOA: Effective orifice area.

The microporous form of PTFE, known as expanded or ePTFE and mostly recognized as Gore-Tex® products from WL Gore & Associates, is widely used in vascular grafts. Valves of this material were investigated in a sheep model in the tricuspid position for up to 34 weeks [36]. Half the valves had one or more stiffened leaflets in explantation and macroscopic calcification was seen in the commissural areas, that is the junctions between adjacent leaflets. Ando and Takahashi reported on the use of hand-made valves consisting of Gore-Tex leaflets suspended in Dacron conduits in the treatment of 139 paediatric patients undergoing pulmonary reconstruction due to Ross procedures and congenital heart disease [37]. These were quite successful, with good durability for up to 10 years, although these conduits do not experience the same demanding conditions of normal heart valve replacement.

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Apart from the last mentioned application and the use of ePTFE in the construction of artificial chordae tendineae in mitral valve repair [38–40], PTFE based materials had not gained traction in surgical valve manufacture, mainly because of the tendency to calcify and stiffen. Phosporylcholine coated ePTFE has, however, received renewed interest for the manufacture of transcatheter pulmonary valves, as described in section 4.

2.3. Polyurethanes

Polyurethanes constitute a wide variety of polymeric materials with broad-ranging properties. They may be thermoset materials or thermoplastic, including thermoplastic elastomers, which can have virtual crosslinks formed by microphase separation. Many forms are heat and solvent processable, allowing them to be easily formed into complex shapes. The diverse structures represented by this class of material have led to many applications in medical devices [28].

The segmented thermoplastic polyurethanes (TPUs) and polyurethane ureas (TPUUs) are composed of hard and soft segments and these have formed the basis of developments of flexible leaflet heart valves (Table 3). One fundamental concern has always been the resistance to degradation since the polymers usually contain degradation-susceptible bonds, where the degradation may be hydrolytic or oxidative, with influences of metal ions, enzymes and mechanical stress [41]. Susceptible forms included the popular polyether urethanes (PEU) and polyether urethane ureas (PEUU). Nevertheless there have been profound changes to this family of polymers over the years, with much improvement over the early hydrolytically unstable polyester soft segment based materials. Included in these later formulations are polycarbonate urethane ureas (PCUUs), polycarbonate based materials that contain polyhedral oligomeric silsequioxane nanoparticles (POSS) [42] and those that contain polysiloxane soft segments (PSUs) (Table 1).

Braunwald performed the first successful polyurethane mitral valve replacement on a patient who survived for several months [43]. Also in the late 1950s the first three-cusp polyurethane valves, using Estane, a PEU of BF Goodrich, of 130–180 μm thickness, resembling native semilunar valves, were implanted in mitral, tricuspid and aortic positions in dogs [21]; there was high mortality, with fibrin deposition leading to stenosis and emboli. A polyurethane version of the Oxford valve discussed in Section 2.1 was made, using Biomer, a segmented PEUU from Ethicon, with leaflet thicknesses of 70–80 μm, but without the reinforcing fabric. Calves receiving these valves in the pulmonary position survived for more than 18 months [32]. Growth of the animals and increased right ventricular systolic pressure limited these experiments. In the 1980s two further types of trileaflet polyurethane valve, one made of Biomer, the other of a DuPont Lycra Spandex type material were developed [44–46]. The Lycra valves showed low regurgitation in vitro, and lasted for a year or more in large animal models, calcification and thrombosis became evident in mitral and tricuspid positions in growing calves [46]. Calcification was also seen with 280 μm Biomer valves in juvenile sheep [45].

Work on polyurethane valves over the next two decades was dominated by two groups, one based in Aachen, Germany and the other in Glasgow, Scotland. Early work by the group of Reul in Aachen included interesting monoleaflet mitral valves with textile and metal reinforcement (Fig. 1) targeted at mitral and tricuspid positions [47–49], and more conventional trileaflet designs shown in Fig. 2 for aortic replacement [50]. Much of the work was carried out at the University of Aachen, the Helmholtz Institute Aachen and the two companies ADIAM and Mecora. Their work involved attempts to optimize the design of Avcothane-51 valves, this being a polyether/silicone based polyurethane [51]; the design aimed to produce smooth washout, minimum leaflet stress and maximum durability [52].

An aliphatic PCU (ENKA 1025/1 or ENKA/AKZO) was subsequently used by Jansen and Reul, in which the leaflets were formed on a stretched stent in the half-open position, minimizing stresses during both opening and closing [53,54]. These valves had very low energy losses, and lifetimes of between 400 and 650 million cycles were achieved in accelerated testing. Mitral implants in young calves showed extensive thrombotic deposits associated with surface roughness on the cusps, with extrinsic calcification seen in the most extensive deposits. ADIAM then developed bi- and trileaflet valves from a PCU for mitral and aortic positions respectively [55–58], as shown in Fig. 3 [3]. In vitro durability of the mitral valves ranged from 600 to 1000 cycles (16–26 year equivalents) [57,58] while the aortic trileaflet showed, over a sustained period of development, improvements from 300 to 600 million [56,58].

In vivo comparisons of these bileaflet valves with two different bioprosthetic valves in the growing calf mitral model for 20 weeks showed little regurgitation, mild leaflet thickening and calcification and no degeneration with the PCU valves, while calves receiving the bioprostheses experienced early congestive heart failure due to severe calcification, degeneration and thrombosis [57]. When the trileaflet valves were compared to the same bioprostheses in the aortic position, the synthetic valves had a variable degree of calcification, degeneration was mild and there was little thrombus [56].

Wheatley, in Glasgow, worked with a variety of polyurethanes (Fig. 4) [3,59]. Early studies concentrated on a PEU (Estane) and a PEUU (Lycra). Durability of more than 300 million cycles at 12 Hz was achieved with ellipto-hyperbolic Estane valves [60], while this was extended to 800 million with a diamine-extended PEUU at optimal 150 μm thickness. *In vitro* dynamic testing showed some calcification in the leaflets of these valves, with tears at the free edge or commissures, and at degradation sites [60,61]. Static in vitro and *in vivo* calcification assessment highlighted the effect of low molecular mass components in the polymers, as methanol and chloroform extracted polymers showed differential degrees of calcification. Hydrodynamic function tests in a simulated mitral position of a pulse duplicator demonstrated that the valves had similar mean pressure drops to bioprostheses, with less reverse flow and energy loss than both bioprosthetic and mechanical valves [62]. In a 6-month sheep mitral model the polyurethane valves performed as well as a mechanical valve in terms of haemodynamics, while a porcine valve became compromised with time. Calcification of the polyurethane valve was evident, usually associated with surface thrombus and degraded areas on the leaflets [63].

The Glasgow group, working with the Universities of Leeds and Liverpool proposed a new valve design with a conical attachment area and spherical upper/free edge area, referred to as a conico-spherical valve. The first valves were made from Tecothane, a PEU, with leaflets between 73 and 111 μm. These gave at least 360 million cycles, with symmetrical opening and closing and superior effective orifice area, lower regurgitation and lower energy losses than either control tilting disc mechanical and porcine bioprosthetic valves [64]. Kinematic tests of similar valves with 150 μm leaflets showed that most performance parameters, including bending strains and leaflet movement, were dependent on the cycle rate [65].

The group subsequently made similar valves out of the polysiloxane soft segment based polyurethane Elast-Eon 3, with leaflets in the range 48–238 μm. Haemodynamic performance was dependent on thickness but not on the material elastic modulus [66]. These Elast-Eon valves were implanted in the mitral position of young sheep for 6 months, after which the leaflets had a fine proteinaceous surface layer but no evidence of thrombus formation, fibrin deposition or calcification [67,68]. Although there was

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Table 3
Polyurethane surgical heart valves.

Author, Company, Location, year	Method Stent/housing Leaflet material	Design	In vitro evaluation	In vivo evaluation	Ref
Akutsu et al., 1958	Dipcoated from solution in THF solution onto open moulds and glued into ring.	Trileaflet patterned on dog leaflets 5–7/1000 inch	N/A	Mitral, aortic and tricuspid implants in dogs. High mortality, often caused by clotting on leaflet surfaces.	[21]
McGoon 1960	200 denier PTFE cloth + impregnated PU	Bi- and trileaflet	N/A	98 devices implanted before being abandoned 2 years later	[50]
Braunwald NIH March 1960	Fabric + liquid PU between male and female moulds. Dacron + open cell liquid PU	Bileaflet valve with Teflon cordage	N/A	27 dogs mitral position successful placement 2 human implants: 60 h and 4 m survival 1st PU valve human; 1st successful *MVR in human	[23,24]
Ghista et al. 1977	Avcothane PSU dipcoated onto moulds	Trileaflet	10–19 mmHg pressure gradient. 1 million cycles then on-going.	N/A	[52]
Reul et al. Aachen 1978/9	Monoleaflet valves reinforced with textile and metal strips and knitted or woven fabric sewing rings	Monoleaflet elliptical/cylindrical	Similar peak opening pressures and mean diastolic pressure difference in pulse duplication tests to natural mitral valves. Vortex filling of ventricle.	N/A	[47–49]
Wisman Penn state 1982	Multiple dip coating; Lubricated knife cutting PP or polyacetal SPU	Trileaflet with (hemicylindrical)	Good triangular opening; full coaptation	Tricuspid up to 3.5 y Calves: calcification and thrombo after 1 y despite aspirin/dipyridamole Sheep/goats: longer survival	[46]
Kolff et al. 1989	Pellethane valves	Trileaflet	Highly accelerated air testing at 1000 Hz: breakage at same location as in real-time tests	5 valves implanted in juvenile sheep; one death at 15 months due to calcification.	[96]
Jansen et al. Aachen 1991–1992	Leaflets formed on expanded J3 stent and dipcoated in essentially flat state	Trileaflet	Low systolic pressure drop (<3 mmHg) and low regurgitation (4–10%). 400–648 mc durability	7 mitral implants in calves for 5 months with 6 bioprosthetic controls. Superior in function and mortality to BP valves. Some calcification associated with surface roughness.	[53,54]
Fisher et al. Leeds 1994–1996	Eurothane leaflets (150–210 μm) flat cast and solvent bonded to PU coated frame	Trileaflet (alpharabola)	100 mc durability shown. Alpharabola design has lower steady flow opening flow and pressure than spherical design; similar in pulsatile flow. Improvement to 160 mc when dip-cast onto frame.	N/A	[73,74]
Wheatley et al. Glasgow 1995–2000	Initially Estane and Lycra dipcoated onto PU frames; later PEEK frames. Shift to Elasteon™ PSU for effect of modulus and leaflet thickness	Trileaflet (ellipto-hyperbolic)	300 mc durability (12 Hz): holes in base or tearing near commissures. Dynamic calcification lower than similar BP valves. Extended to 800 mc with visible calcification at 590 mc. No correlation found between leaflet thickness and durability for PEU, but correlated with PEUU (150 μm optimum). Elasteon valves: Thickness correlated with pressure and energy losses; modulus only significantly affects parameters at high outputs.	Rat subcutaneous 3months: 0.2 mg/g calcification. Cf. *BP = 2 mg/g. Calcification often associated with thrombi. Subsequent valves using PEEK frames implanted in 6 m sheep mitral model. PU superior to mechanical and BP controls: constant haemodynamics, low fibrin adsorption and no pannus overgrowth.	[60–63,68,156]
	Tecothane (PEU) dipcoated onto 23 mm PEEK frame	Trileaflet (Conico-spherical)	Significantly lower pressure gradients and larger EOA than BP and mechanical control	N/A	[64,65]

(*continued on next page*)

Table 3 (*continued*)

Author, Company, Location, year	Method Stent/housing Leaflet material	Design	In vitro evaluation	In vivo evaluation	Ref
Fisher et al. Leeds 2001–2003			valves. 360 mc durability achieved. Maximum bending strains at commissures		
Debits et al. Aachen/Munich 2003–2006	100–300 μm PCU mitral and 80–200 μm aortic leaflets by dropping technique. polyurethane stent and fleece-like PU sewing rings	Mitral: Bileaflet Aortic: Trileaflet	Mitral: 600–1000mc durability Aortic: 300–600 mc durability;	MVR: 20wks in calves: outperformed bioprostheses (BP); mild calcification and mild leaflet thickening and regurgitation. AVR: 20wks in calves: 5/7 excellent clinical long-term course; 2/7 died at 27 and 77d due to pannus overgrowth.	[55–58]
Yoganathan et al. 2005–2006	Aortech valves: 120–180 μm Elasteon leaflets on PEEK frames	Trileaflet Prototypes A, B and C	Full flow field and shear analyses consistent with location of thrombus formation in preliminary animal experiments.	Thrombus formation along stent inflow region in A, and additionally in high central region in prototype B.	[59,71]
Seifalian et al. UCL, London 2009–2012	Semi-stented POSS-PCUU leaflets (1200-200 m) dipcoated onto Nitinol scallops	Trileaflet design based on FEA for minimised energy absorption	Less transvalvular pressure and larger EOA than commercial porcine control. Lower energy loss especially at high output.	N/A	[42,76]

NIH: National Institute of Health; MVR: Mitral valve replacement; AVR: Aortic valve replacement; EOA: Effective orifice area. PEEK: Polyether ether ketone.

some surface enrichment of the siloxane groups, the explanted leaflets showed very little difference to the pre-implant valves; they were structurally intact, retained their mechanical properties and showed no signs of degradation. There is some evidence of degradation of these PDMS soft segment polyurethanes after extended exposure to water at elevated temperatures [69,70]; the relevance of accelerated hydrolysis testing at elevated temperatures is not clear.

Yoganathan also studied three types of Elast-Eon valves, that had either a closed commissure, semi-open or open design [59,71]. High shear and velocity, with increased thrombogenic potential were noted at the leakage jet during diastole, at the trailing edge during peak forward flow and at the centre orifice jet downstream of the valve. Fisher, in Leeds, developed an alpharabola design, in which the radius of curvature increased from the centre of the leaflet at the free edge towards the base of the valve and perimeter of the leaflets. Finite element modelling of this design showed a reduction in principal tensile stress to 60% of that of spherical leaflet geometry. Valves of this design were made from a thermoformed low modulus Eurothane with leaflet thickness between 150 and 200 μm and from a similar modulus dip-casting polyurethane [72–74]. The dip-cast valves had greater durability (160 vs. 100 million cycles) and both had better opening and closing characteristics than spherical leaflets.

Finally in connection with polyurethanes, the nanocomposite POSS-PCUU materials developed by Seifalian in London have shown good mechanical properties and surface characteristics [42]. A prototype heart valve made from this material on a Nylon stent is shown in Fig. 5a [75]. Semi-stented aortic valves (SSAV) (Fig. 5b) [76] with leaflets of either 100, 150 or 200 μm were assessed in pulse duplicator tests, and also subjected to finite element modelling, giving favourable characteristics compared to bioprosthetic valves [76–78].

2.4. Other polymers

Although several other elastomeric polymers have occasionally been evaluated, few are worthy of further consideration here. The one main exception is poly(styrene-b-isobutylene-b-styrene), known as SIBS, produced by Innovia. It has mechanical properties intermediate between silicones and polyurethanes and is highly degradation resistant [79,80]. It may be used with or without fibre reinforcement. SIBS impregnated Dacron meshes of 240 μm thickness showed no significant difference in thrombogenicity in a ventricular assist device compared to mechanical or bioprosthetic valves [81]. Early attempts at surgically implantable valves suffered some problems in a 20-week sheep aortic model, with stent deformation and creep, leading to exposure of the reinforcing mesh and attendant calcification and thrombogenic effects [82]. Further designs have shown some biocompatibility improvements [83]. Innovia has also developed a cross-linked version, xSIBS, intended to improve creep performance and avoid the need for fibre reinforcement [84]. There are recent reports of improved haemodynamics and reduced thrombogenicity with valves made of such polymers [85,86].

Mention must also be made of the work of Baaijens concerning another olefinic material, cross-linked ethylene-propylene-diene-monomer (EPR) rubbers (K520 from DSM). Valves were constructed from multiple layers of the elastomer reinforced by fibers [87], although further data appears not to be available. Devices have also been made of polyvinyl alcohol (PVA) rendered insoluble by one-piece cavity moulding – freeze thawing procedures [88] and PVA – bacterial cellulose composites, designed to mimic the anisotropic mechanical performance of natural valves [89–91]. Hyaluronan-swollen polyethylene films were very recently used in

Fig. 1. Monoleaflet polyurethane valves developed by Reul and colleagues. (a) metal reinforced, and (b and c) textile reinforced valves in the closed and open position respectively.

clip-on surgical frames to produce prototype valves with high effective orifice areas, low regurgitation percentages, and reduced blood clotting [92].

3. Heart assist devices

Refractory end-stage heart failure is a major cause of morbidity and mortality. Along with medication, cardiac resynchronization, implantable defibrillators and transplantation, therapy for patients with such a condition has increasingly relied on some form of mechanical circulatory support [93]. Several major considerations determine the engineering design of these systems, including the need for valves. The concern whether the device is intracorporeal or extracorporeal, whether it addresses right, left or both ventricles (right ventricular assist, left ventricular assist, total artificial heart respectively), whether it is intended as a bridge to recovery, bridge to transplantation or destination therapy, and whether it has a pulsatile, continuous axial or continuous centrifugal mechanism. The latter point is the most relevant here since pulsatile systems require valves and the continuous systems do not. Although the search for an effective total artificial heart has been conducted for almost half a century, very few devices have actually had regulatory and clinical success, including the SynCardia (SynCardia Systems) and Abiocor (Abiomed) systems [94,95]. Early pulsatile left ventricular assist devices (LVAD) included the Heartmate XVE of Thoratec and the Excor of Berlin Heart. Flexible leaflet valves were of major interest for these short-term options since there were reduced durability and anticoagulation requirements and because of their lower cost [96].

Three LVADs with polyurethane valves were commercially produced (Table 4), with a range of sizes and correspondingly scaled valves, and used in both adult and paediatric cases. The Berlin Heart Excor mentioned above was shown to have a durability in vitro of over 5 years, and clinical performance was achieved for over a year in some cases [97,98]. The Medos VAD was developed in Aachen [99] and has been used clinically in paediatric cases [100]. These two systems were based on different design philosophies, the first using a non-bulbous root to improve washout, the latter using a bulbous sinus-like housing to facilitate leaflet function. The third company involved with these types of systems, Abiomed, developed two products a VAD [101,102] and a total artificial heart [103,104]. Zimmerman et al. showed no difference in the clinical efficacies of the devices from these companies and concluded that selection should be based on practical issues on a patient basis. Arabia et al. also published a comparison of these three VAD systems [105].

There have been several other experimental heart assist devices under development, most of which have used polyurethane or silicone valves. Imachi et al. in Tokyo used Cardiothane, a polyurethane – silicone copolymer using the jellyfish design discussed earlier [106,107]. There were some issues with durability in early examples but better designs produced better results [108]. The Luo-Ye VAD developed recently in China also utilizes polyurethane valves [109]. A Mexican-Canadian group has used injection-moulded silicone valves [110], which initially showed small transvalvular gradients but then limited hydrodynamic performance because of stenotic characteristics [111]. The occasional non-polyurethane/silicone valve has been produced, for example the Hexsyn material (poly 1-hexene cross-linked with methylhexadiene) [112] but long-term results have not been published. Some examples of heart assist devices are shown in Fig. 6 [102,103].

Obviously the high cost and limited life expectancy in the patients restricts the use of these heart assist devices. Future uses and developments would seem to be primarily based on flexible polyurethane valves in pulsatile systems or valve-less continuous systems.

4. Catheter-based valves

The history of catheter-mounted valves actually dates back to 1965, when Davies used a cone shaped parachute valve made by the US Catheter Company for temporary relief of aortic insufficiency. Although the material was not specified, it appears to be synthetic origin (Fig. 7) [113,114]. The design was subsequently improved in 1986 with an umbrella-shaped device placed in the aortic annulus of dogs.

There are several reported designs of catheter-based heart valves that use polyurethane materials for leaflets and occluders (Table 5). The first was a trileaflet valve in a stainless steel stent developed by Percutaneous Valve Technologies, with good results in a sheep model [115]. However, the company changed the material to pericardium, this valve, acquired by Edwards Lifesciences, becoming the widely used Sapien valve. Three other designs are based on the trileaflet geometry. The first, from Mecora in Aachen, is based on a traditional trileaflet form mounted on a Nitinol stent. It had 100–150 μm thick dipcoated leaflets, fitting into a very low profile, 14F, catheter delivery system (Fig. 8a) [116]. Good haemodynamic results in sheep models have been published [117]. The second was developed by Bluestein and colleagues using the SIBS/Dacron composite materials discussed previously and tested in a left heart simulator (Fig. 8b) [118]. Seifalian's group at UCL are developing the third example, namely a self-expanding polymeric TAVI valve made from Nitinol and POSS/PCUU. The valves can be crimped to 18F and are under pre-clinical evaluation. (Fig. 8c) [119,120].

Two designs deviated from the usual leaflet geometry but did have polyurethane occluders. Sochman et al. used a self-expanding Z-stent containing a collapsible polyurethane covered tilting disc [121], with a mechanism that allowed the disc to be snapped into place after deployment with a 10F catheter. Acute canine implantation experiments in a supra-coronary aortic model showed successful delivery and disc movement. Hashimoto used repositionable stent design with three Nitinol coils and locking wires with a conical or umbrella-shaped valve [122]. Acute implantation trials were performed via the common carotid artery, with successful placement and good function, although with some regurgitation and thrombus formation. A recently described

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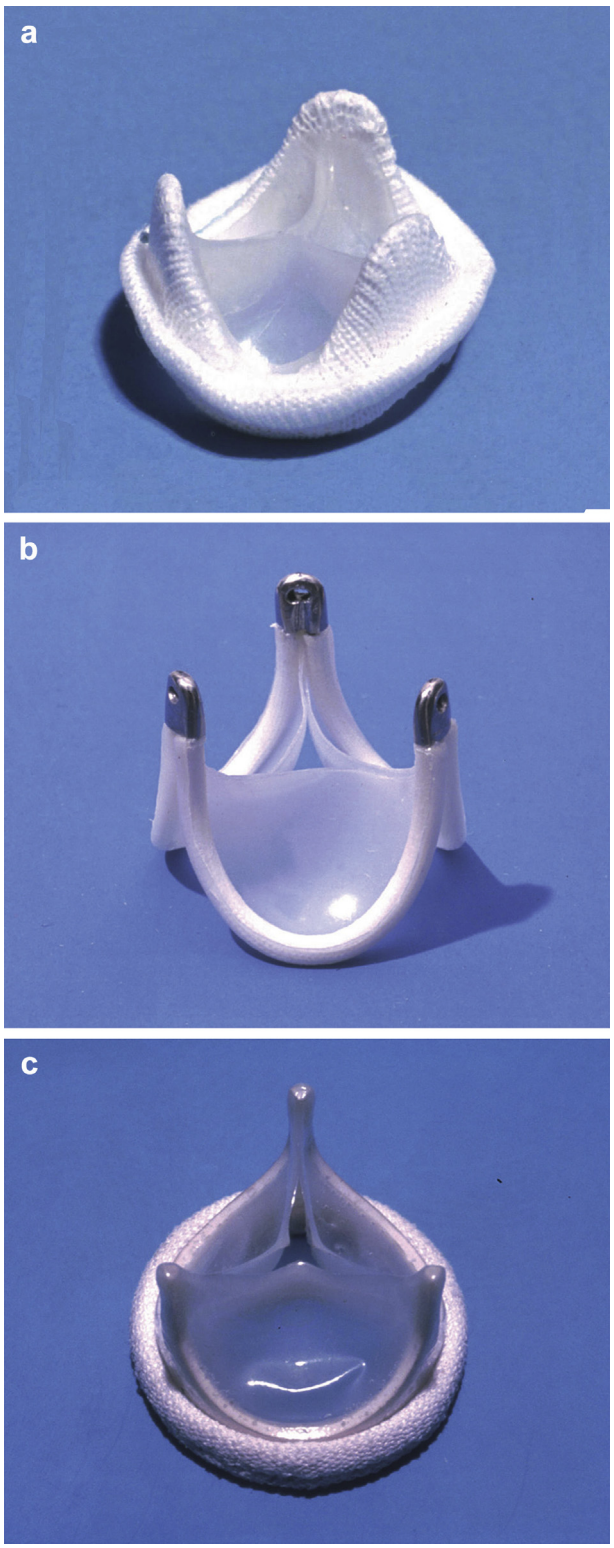

Fig. 2. Trileaflet polyurethane valves developed by the Aachen group. (a) the Reul-Ghista trileaflet valve, (b) the Reul-Häussinger valve and (c) the Helmholtz Institute valve.

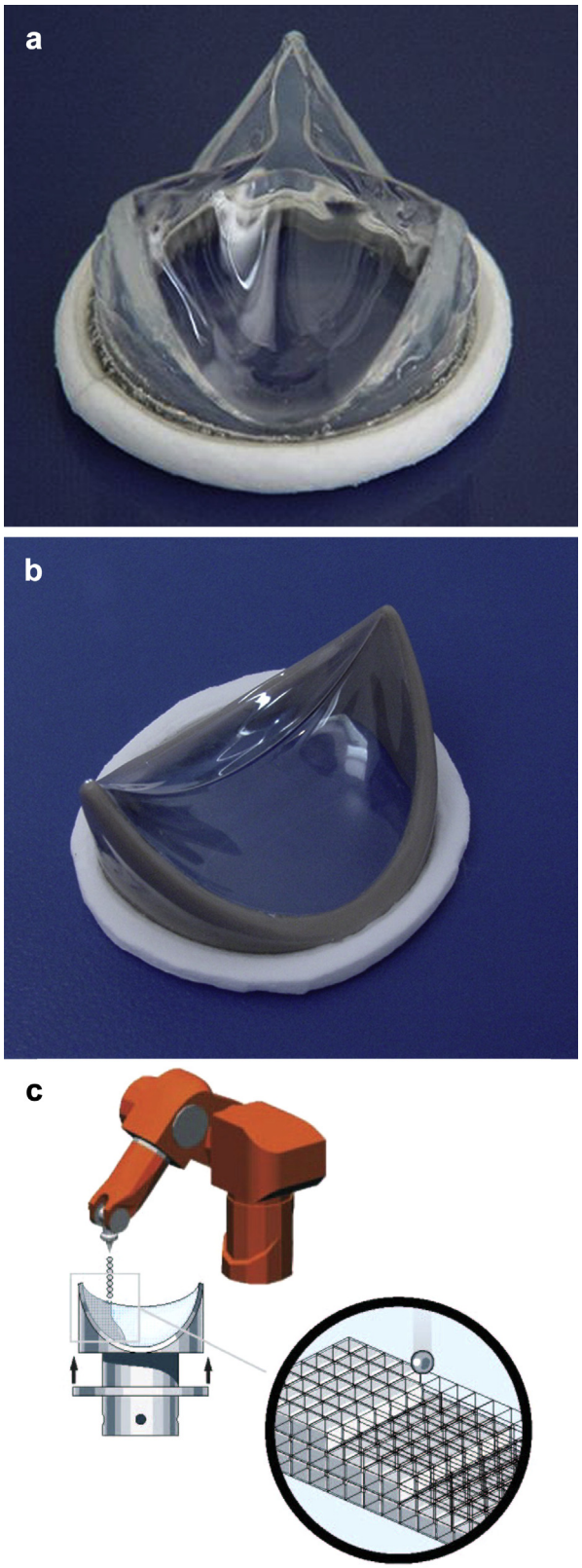

Fig. 3. (a) Aortic Trileaflet and (b) mitral bileaflet polycarbonate urethane valves developed by ADIAM life sciences, Erkelenz, Germany, produced by a robotic droplet deposition technique schematically depicted in (c).

catheter based pulmonary valve is of the more traditional trileaflet design. It is manufactured from ePTFE that has been precoated with PC and sewn to a balloon expandable Co–Cr stent (Fig 8d) [123]. Ten valves were transapically implanted into the sheep pulmonary position and early stage results show good function and positioning

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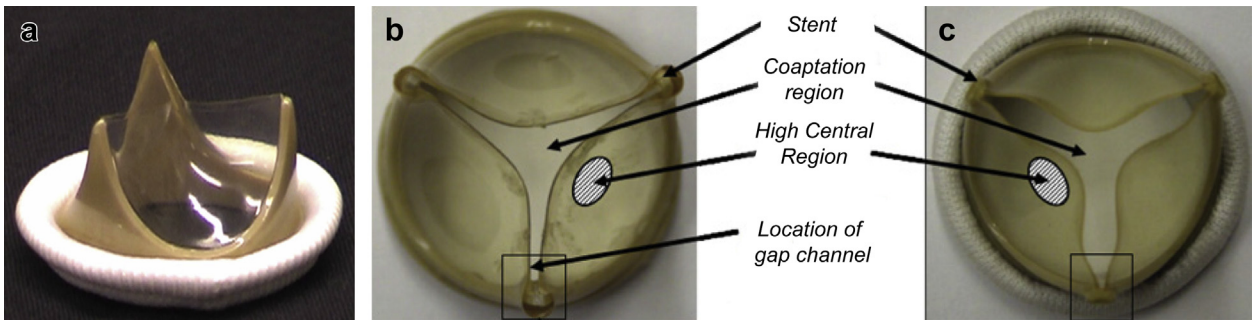

Fig. 4. (a) Polyurethane heart valves developed by the Glasgow group: Ellipto-hyperbolic Estane® dipcoated on a PEEK frame and (b) two designs of Elast-Eon® leaflets (closed and open commissures, respectively).

with no sign of dislocation, and a single explant at this timepoint showed no calcification.

In general, at this stage, although the trend in transcatheter valves has moved towards pericardial material and away from synthetic polymers, there are two clear advantages of the latter, these being the lower cost of manufacture and the ability to crimp to smaller diameters and deliver in 10–14F catheters compared to the 18–20F with pericardial designs.

5. Valve geometry

Pericardial valves are prepared from essentially flat pieces of tissue. There are no restrictions on the form of valves prepared from synthetic polymers, which should be a significant advantage. The obvious starting point for the design of these valves is the geometry of the natural valves; since polymers and natural tissues have different mechanical characteristics, it is not necessarily a prerequisite for synthetic valves to replicate exactly the natural form, but it is sensible to consider that form in valve design.

In reality, heart valves have varying forms, some being supported by chordae and others being unsupported. All those that are unsupported are of trileaflet structure; this form has been shown to be superior in stress distribution than bi- or quarto-leaflet analogues [124]. The central flow of the trileaflet design also has better mechanical efficiency, hydraulic characteristics and flow patterns that cause much less blood trauma than mechanical devices [41]. In trileaflet structures with a planar free edge design, the total free edge of a closed leaflet is very close to the length of the cord that suspends the leaflet, allowing a greater opening area

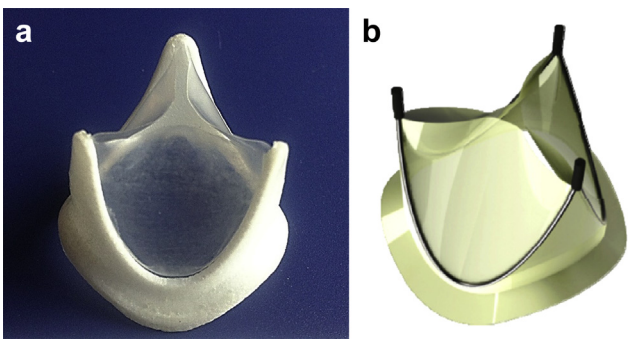

Fig. 5. POSS-PCUU heart valve prototype (a) developed by UCL (surgical valve on a Nylon stent) and schematic representation (b) of the semi stented aortic aimed at facilitating surgical implantation and improved haemodynamics, under development by the same group.

than in a bileaflet design [26]. Notwithstanding this, bi- and quarto-leaflet designs of artificial valves can be successful, as with the bileaflet polyurethane valves [57,58] and a quarto-leaflet bioprosthesis [8].

The elliptical natural aortic sinuses [125] cause recirculating flow and provide rapid closure of leaflets with negligible backflow [33]. Aortic leaflets themselves have traditionally been considered to be portions of spherical surfaces; Thubrikar has discussed the historical evolution of valve anatomy knowledge, various terms such as semilunar, sigmoid, adjacent hemispheres and interlocking circles being used in descriptions over several centuries [125] (Table 6). More recently Mercer et al. approximated the leaflet shapes as paraboloids of revolution with foci at the base of the leaflets [126], while Hamid described the geometry as an elliptical paraboloid [127].

Chong et al., in 1978, measured an excised human aortic valve and described the geometry in terms of principal radii of curvature and subtended angles [128]. Others have considered the valve to be cylindrical to slightly conical [125,129]. Geometrical parameters include the radii at the base and commissures, valve height, surface and free edge angles, radius of the outermost wall sinus and coaptation height. Support for the cylindrical leaflet model comes from the description of homograft leaflet shape [130] and the successful clinical use of pericardial valves that use this geometry [131]. Table 7 gives may be consulted for chronological information on the introduction different types of heart valves in the context of material development and milestones in cardiac surgery.

Peskin and McQueen introduced an alternative way of describing the aortic leaflet geometry using fractal analysis [132]. Their analysis determined structure on the basis of function, that is the need to support a uniform pressure in the closed position, and involved the computation of the fractal structure of the reinforcing fibers.

Many prosthetic valves have been designed with attempts to mimic the natural valves by approximating leaflet shapes using swept conical sections, spheres and variable curvatures in addition to cylindrical sections, while others have been adapted to reduce stresses and improve function and durability. In the majority of cases, the designs are of necessity described qualitatively rather than quantitatively.

With respect to trileaflet geometry, as noted earlier, Roe et al. determined that cone-shaped cusps were more resistant to collapse than dome-shaped cusps, and indeed were better than a myriad of previously discussed flat, nozzle and windsock shapes [26,29]. Perhaps the best description of valve geometry was provided by the Glasgow group [62]. Their design had three polyurethane leaflets suspended from a cylindrical support frame. The leaflet shape in the closed position was defined in terms of conic sections that were elliptical in the radial direction and a

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Table 4
Flexible leaflet polymeric valves used in ventricular assist devices and total artificial hearts.

Researcher/Product/Company	Valve material/description	Comments	Ref.
Commercial devices			
Berlin Heart Excor *VAD Fehling Medical AG Syscore GmbH	Polyurethane trileaflet with cylindrical profile in non-bulbous housing/Dipcoated Carmeda heparin coating	*FDA approved Adult and paediatric use LVAD also available with Sorin mechanical valves	[97,98,157]
MEDOS VAD-III Medos Medizinetechnic Mecora Medizinetechnic	Polyurethane trileaflet in bulbous PU housing/Dipcoated	Modelled on human Aortic and Pulmonary valves. Adult and paediatric use.	[99,105,157,158]
Abiomed AB5000 VAD Abiomed Inc.	Polyurethane trileaflet Angioflex® PEU	FDA approved Adult and paediatric use	[101,102,159]
Abiocor *TAH	Polyurethane trileaflet Angioflex® PEU	First totally implantable TAH FDA *HDE approved	[103,104]
Experimental devices			
Kiraly et al. (1982)	Hexsyn rubber trileaflet Compression moulded	Short term trials; in vitro and *in vivo*.	[112]
Imachi et al. (1988)	Cardiothane (PU/Silicone copolymer/blend) Solvent cast	Jellyfish design. Successful 125-day implants.	[106–108,160,161]
Kolff (1989)	Pellethane PEU trileaflet Vacuum and solution cast Silastic HP-100 trileaflets	Flexible silastic stents for redundancy at closure.	[96]
Yin/Claiborne et al. (2005/11)	Polyester mesh impregnated with SIBS (Quatromer™)	Thromogenic potential similar to mechanical and bioprosthetic valves in platelet activation tests	[81,83]
Sacristan et al. (2010)	Silicone One piece injection-moulded	Small transvalvular pressures, but poor haemodynamics; stenotic	[110,111,162]

*VAD: Ventricular Assist Device; FDA: Food and Drug Administration; TAH: Total Artificial Heart; HDE: Humanitarian Device Exemption.

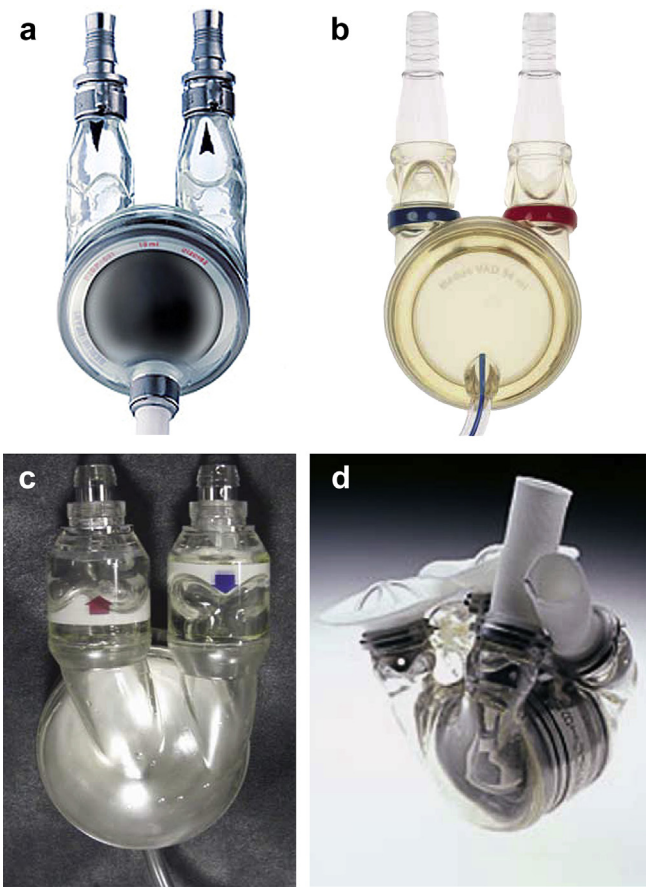

Fig. 6. Heart assist devices that use polyurethane flexible trileaflet valves: (a) Berlin Heart Excor VAD, (b) Medos VAD III, (c) Abiomed AB5000 VAD and (d) Abiomed Abiocor TAH.

continuous series of hyperbolae circumferentially. The major axis length of the hyperbolae was set by the mid-leaflet ellipse and increased continuously from the free edge to the leaflet base. The design of Fisher's group in Leeds at first sight seems different, being described as having a variable curvature of 'alpharabola' shape [72]. The precise shape within this continuum is defined by the shape parameter 'alpha' which has a value between 0 and 1. When alpha is 1, the radius of curvature of the leaflets is constant, giving a spherical leaflet. In reality, these designs are not much different, the latter may be characterized by 'spherico-hyperbolic' instead of 'elliptico-hyperbolic conicoid'. These are also similar to the 'hyperboloid of revolution' described by Jiang et al. with their PVA valve [88].

The leaflet geometry used in the POSS-PCUU valves [76] has been defined as a ruled surface between the intersection of the cylindrical stent with an inclined plane and an arc, normal to the axis, joining the commissures [77]. The lateral portions of the leaflets are subsequently reflected through the inclined plane and the leaflet edge trimmed along a plane normal to the valve axis. The SIBS percutaneous polymeric valve [118] used geometry based on the formula and constants proposed by Thubrikar [125], while the surgically implantable valve initially had leaflets that were

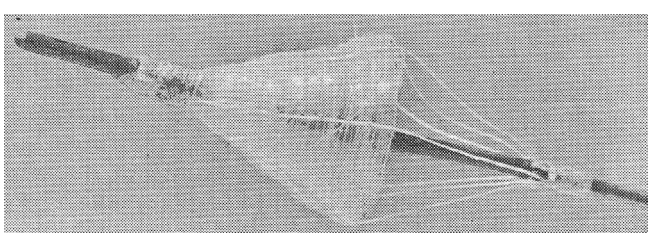

Fig. 7. Cone-shaped transcatheter-based valve made for the temporary relief of aortic insufficiency as originally described by Davies in 1965.

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Table 5
Catheter based polymeric heart valves.

Author/Location Year	Stent	Valve	Implant procedure	Results	Ref
Davies 1965, 1986	N/A	Synthetic	Aortic annulus of dogs after avulsing leaflet	Impressive improvement in diastolic pressure	[113,114]
Sochman et al. Prague/Oregon 2000	Gianturco Z-stent (3 cm long× 20–25 mm diameter self expanding stainless steel (0.2" wire)	100 μm PU membrane covered collapsible tilting disk; rubber annulus and stainless steel strip	Aortic implant in 4 dogs via carotid using 10F and 12F catheters	Good function observed for 3 h with some migration that could be obviated by use of barbs.	[121]
Attmann et al. Kiel/Aachen Mecora 2006	Diamond pattern Nitinol self expanding	100–150 μm dipcoated PU trileaflet made by Mecora GmbH	Transfemoral into Pulmonary position of 2 sheep using 14F catheter	1-month competency with low gradients.	[116]
Metzner et al. Kiel/Aachen/ Mecora 2006, 2010	Diamond pattern Nitinol self expanding. 22 mm diameter; 28 mm length.	100–150 μm dipcoated PU trileaflet made by Mecora GmbH	Transfemoral into Pulmonary position of 7 sheep using 14F catheter no anticoagulation.	1-month competency with no para-valvular leaks. No macroscopic calcification.	[117]
Hashimoto et al. Tatorri, Japan 2008	Repositionable Spiral Nitinol with guide/control wires	Umbrella shaped PU (Desmorac 4125)	Acute aortic valve implants via carotid using 10F introducer in 5 pigs	1-h observation with no to slight regurgitation.	[122]
Claiborne et al. Stony Brook 2009	Nitinol self expanding	SIBS/Dacron trileaflet	N/A. In vitro simulations on left heart simulator	N/A. In vitro gradients of <15 mmHg and <5% regurgitation	[118]
Seifalian et al. UCL, London 2012	Nitinol self expanding	POSS/PCUU trileaflet 23, 26 and 29 mm	Acute implants into sheep via brachiocephalic route	No coronary interference, good function, no significant regurgitation	[119,120]
Zhang et al. Shanghai, China 2014	Cobalt–Chromium balloon expandable	Phosphorylcholine coated ePTFE stitched to stent.	Transapical pulmonary implantation in 10 Sheep. 1 animal sacrificed at 4 wks for explant.	Good positioning and function. No dislocation, deformation, thrombus or calcification at 4wks.	[123]

spherical, later changed to cylindrical, with either low or medium profile [83,85,86].

It is interesting to note that both the first and one of the most successful polymeric valves was of bileaflet design, and intended for the mitral position. The first comprised the PU-covered Dacron leaflets with attached Teflon cordae [23]. Arguably the most successful flexible leaflet polymeric valve, at least in terms of *in vitro* durability, is the ADIAM bileaflet valve, the only design known to have reached one billion cycles. It has a kidney-shaped stent with two asymmetrical struts supporting a large anterior and smaller posterior leaflet, effectively mimicking the natural mitral valve. This design creates natural flow patterns and vortices into the ventricle and prevents prolapse; opening of the valve is facilitated by the suspension bridge design [58]. A Japanese valve intended for pulsatile pumps had a circular flexible disc attached to a frame along the diameter, producing two flaps. Leaflets were made thick, up to 150 μm, to minimize regurgitation, but the valves had limited durability [133]. The same group in Japan produced a variation of this theme, known as the jellyfish valve which, although being a flexible valve, is neither bi- nor tricuspid. The original prototype comprised a brass disc with eight circular perforations, on top of which a 200 μm membrane of cast polyurethane was screwed at its centre [106]. The disc was later changed to a 12-spoke structure cast from polyurethane [134].

6. Manufacturing techniques

Several techniques have been used to process polymers into the complex 3D leaflet shapes. The first determinant of desirable techniques is the nature of the polymer itself. Thermoplastic materials may be processed using heat or, if the polymer is sufficiently soluble, solvent processing, whereas moulding techniques are required if the materials are thermosets.

Dip casting is technologically one of the simplest methods as it involves dipping a mould into a solution of the polymer, removing the mould and then evaporating the solvent. In practice, repeatability in terms of the desired thicknesses and quality is not trivial. Solvent volatility, polymer concentration/viscosity, dipping number (single vs. multiple), technique and speed, drying position (upright, upside down, rotating), atmospheric conditions (temperature, pressure, the use of gasses), mould shape and surface properties all affect the distribution of material (leaflet thickness) and quality (surface morphology, uniformity, bubble formation, imperfections, durability) and function.

6.1. Polyurethane valves

The J-3 polyurethane valve is interesting as it is manufactured in a half-open configuration. The top of the metal mould was flared so that the arms of the stent could be expanded between the minimal area leaflet surfaces. Dip coating of leaflets and stent integration occurred in one step, using cleanroom conditions within a dry glove box, and the valve was tumbled in a controlled motion during drying to ensure even leaflet thickness [53,54]. This method also avoided shape-memory effects, which can occur when leaflets are made in a pre-curved closed position.

ADIAM later improved the manufacturing technique by employing a combination of dip coating and dropping methods with polymers of different hardnesses, with soft outer layers and medium hardness cores. The polymer was applied in a controlled dropwise fashion to achieve accurate control over leaflet thickness, which varied between 80 and 200 μm depending on position. The use of flexible stent posts ensures good closing and a precision laser ensured leaflet separation [55,56,58]. They also produced a scalloped bileaflet valve for the mitral position with large (300 μm) anterior and small (100 μm) posterior leaflets and sewing rings made from fleece-like sprayed polyurethane [57].

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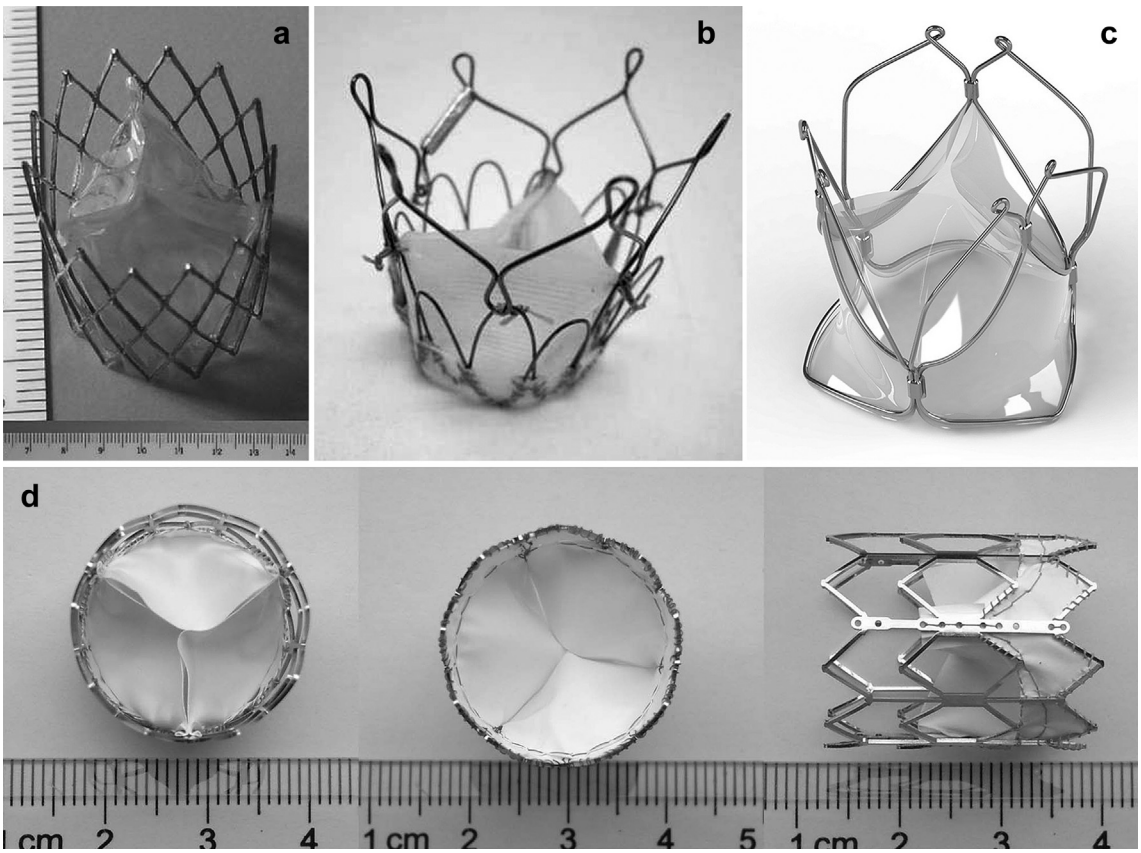

Fig. 8. Catheter deliverable polymeric heart valves: (a) Mecora PU/Nitinol trileaflet design, (b) Claiborne SIBS/Dacron/Nitinol trileaflet valve, (c) UCL POSS/PCUU/Nitinol Triskele valve and (d) Trileaflet ePTFE valve in a balloon expandable Co–Cr stent developed by Zhang et al. in Shanghai.

Dip coating onto injection-moulded polyurethane or machined PEEK frames fitted onto metal forming mandrels (Estane of Lycra in dimethylacetamide) was used by Wheatley to produce their elliptohyperbolic valves. The solvent was evaporated under slight positive pressure at 70–80°C, vented into a water trap to ensure complete evacuation [62]. When using the Elast-Eon material, the method was varied to involve dipping and drying under inert atmosphere, using single or multiple coatings on pre-warmed steel formers containing the PEEK frame [66,67].

The alpharabola and spherical designs of the Leeds group were made by a combination of techniques. Included here was solvent bonding, in 8% polymer in dimethylformamide (DMF), of leaflets cut from solvent cast polyurethane films to PEEK frames dipcoated with 250 μm polyurethane. In a different system, stented mandrels were successively dipped in 25, 25 and 12% polyurethane solutions in DMF, followed by drying. Removal from the moulds was facilitated by extended immersion in water, and leaflets cut with a sharp blade. The POSS-PCUU valves of Seifalian have been made by variations of dip coating, although attempts were made to use electrospraying.

6.2. Silicone valves

Early silicone valves were formed in one-piece using compression moulding, heating the mould to 180 °C under high pressure and curing at 200 °C for 4 h. A similar process was followed 15 years later using highly polished three-piece metal moulds into which the silicone was injected, but latter versions used a three-posted metal stent to yield an integrated scalloped design [31]. With room temperature curing materials, the process can be simpler, as hand-made moulds from plaster or silicone can be used to form the desired shape by using centrifugation and/or evacuation to fill the cavity [33]. Injection moulding has also been used to produce one-piece VAD valves. This method has resulted in variability in leaflet thickness, although apparently without deleterious effect on haemodynamic performance [135].

6.3. ePTFE valves

Due to its high melt viscosity, PTFE requires different processing techniques than those used for the majority of thermoplastics, and methods more appropriate for metals are often used. In medical devices it is usually the microporous ePTFE that is employed, for example in vascular grafts. ePTFE valves have been made by bonding multiple layers anisotropically and sewn to support stents [136]. Nistal et al. have reported valves with solid PTFE but without a clear indication of manufacturing methods [36]. The Japanese PTFE valves were hand made by folding sheets and sewing them together [37].

6.4. SIBS valves

SIBS percutaneous valves were made by impregnating Dacron fabric with the polymer, dissolved in toluene, followed by air-drying, forming a cylinder by stitching the fabric, stitching this to a Nitinol stent and then annealing the leaflets into shape. Surgically implantable valves using this material were produced by filling machined aluminium alloy moulds with raw 23% styrene xSIBS and cross-linking under high pressure and temperature [86]. Several other methods have been used with SIBS valves, including compression moulding, solvent casting and thermoforming.

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Table 6
Trileaflet polymeric heart valve geometries.

Investigator/Year	Leaflet geometry	Comment/Equation	Reference
Natural leaflets			
Philistion ca 400BC Erasistratus ca 300BC da Vinci 1452-1519 Mercer 1973 Hamid et al., 1986 Thubrikar et al., 1990	Semilunar Sigmoid Hemispherical Paraboloid of revolution Elliptical paraboloid Cylindrical/Conical	Description of the shape of natural aortic leaflets dates back to antiquity. It has been described by Leonardo da Vinci, more recently by Thubrikar, and remains subject to investigation and used by many as a basis upon which to design polymeric valve geometry.	[126] [73,126] [127] [46,125,129]
Synthetic leaflets			
Roe et al. <1958	Flat, nozzle and windsock	These designs were originally investigated by Roe and then discarded.	[29]
Roe et al. 1966	Dome shaped, conical and cone shaped	Cone-shaped trileaflet cusps were found more resistant to collapse than “dome-shaped” cusps	[26]
Mohri et al. 1973	Semi-domed Triangular	Changed from semi-domed to triangular, first with a sinus and then without as preferred geometry	[31]
Reul et al. 1977	Analytically optimized shapes	1. For smooth washout 2. For minimum stress	[52]
Wisman et al. 1982	Hemicylindrical	10 mm diameter hemicylindrical polyurethane leaflets	[46]
Lockie et al. 1993	Cylindrical	Dilation of aortic root has marked effect on leaflet function and geometry (triangular orifice)	[129]
Fisher et al. 1994	Alpharabola	$y^2 + z^2 = 2R_L(x-g) + \alpha(x-g)^2$	[72,73]
Mackay et al. 1996	Ellipto-hyperbolic	$[(x-E_0)/E_{major}]^2 + [z/E_{minor}]^2 = 1$ $[(x-H_0)/H_{major}]^2 - [y/H_{minor}]^2 = 1$	[62]
Butterfield et al. 2001	Conical/spherical	Conical lower surface adjacent to frame with spherical upper surface extending to free edge	[64]
Jiang et al. 2004	Hyperboloid of revolution	$\frac{x}{a^2} + \frac{y^2}{a^2} + \frac{(z-z_0)^2}{b^2} = -1$	[88]
Mohammadi et al. 2009	Bezier curves	Bezier curves based on elliptical paraboloid and the de Casteljau algorithm	[90,91]
Claiborne et al. 2009	Conical/cylindrical	Based on Thubrikar's description, with surgically implantable valve leaflets originally of spherical and later cylindrical geometry	[118,125]
Rahmani et al. 2012	Parametric	Defined as a ruled surface between the intersection of the cylindrical stent with an inclined plane and an arc (normal to the axis) joining the commissures	[76,77]

7. Polymer treatments

A variety of surface and bulk treatment has been proposed for the reduction of thrombogenicity and calcification of polymeric valve leaflets, and for the maximization of durability. The main challenges here are the limited surface area and volume of the leaflets and the sustained stability and activity of the treatments. This is especially demanding considering that about 6000 L of blood wash over the leaflets daily, so that active agents are readily depleted or overwhelmed, even if they act in a catalytic manner.

Early attempts at augmentation of the anticlotting properties of flexible leaflet valves involved the surface bonding of graphite-benzalkonium chloride-heparin layers, but the contribution of the coating was unclear as valves failed due to a variety of factors [137]. Bernacca and Wheatley looked at a number of surface treatments for polyurethanes, including polyethylene oxide (PEO) surface layers [138]. PEO did not affect either film thickness or hydrodynamic properties but was detrimental to calcification and durability. Heparin, taurine and aminosilane modifications did increase fatigue life, moderately with PEUU and significantly with PEU valves. In contract to PEO, sulfonated PEO coated onto both polyurethane valves and vascular grafts has been shown to improve blood compatibility and biostability and decrease calcification [139,140].

Calcification is, of course, not only related to the surface of the leaflet but also to the polymer composition. The mechanism of calcification of polyurethanes is not clear, but various processes have been proposed, including cation complexation by the polyether soft segment [60,141] and chelation [142], or deposition of thrombi and cellular debris [143]; it should be noted, however, that calcification can be seen in the absence of thrombi [144,145]. Calcification has often been associated with surface cracks or abrasion marks, although it is not clear which is cause and which is effect [144], while others have implicated leaflet strain during repeated flexing [146,147].

Extraction of low molecular mass components from polyurethanes has been shown to reduce calcification [60,61]. Leaflets made of the relatively biostable Elast-Eon appear to have reduced calcification, suggesting a mechanistic correlation [63,66]. Bisphosphonates are well known for their effect on mineralization, and localized slow release of phosphonates has been shown to inhibit calcification [148]; also phosphonated polyurethanes have reduced tendency to calcify in animal models [145,149,150]. Cholesterol modification of polyurethanes has also appeared to be a promising approach as endothelial cell attachment and retention has been shown both in vitro and *in vivo* when pulmonary vales leaflets were seeded with autologous endothelial cells [151,152].

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Table 7
Synthetic, bioprosthetic and mechanical heart valve development highlights in the context of material development and milestones in cardiac surgery.

Year	Event, pioneers and location
1920s	First attempt at repair of mitral stenosis by Elliot Cutler in Boston and Sir Henry Soutar in London [163]
1937	Otto Bayer synthesizes the first polyurethanes at I.G. Farben in Leverkusen, Germany. [164]
1938	Accidental discovery of PTFE (Teflon™) by Roy Plunkett at Kinetic Chemicals in New Jersey [165]
1941	First polyester fibre (Terylene) produced by British scientists J.R. Whinfield based on early work by Wallace Carothers [165]
1943	Dow Corning formed to produce a new class of polysiloxane materials, generally known as silicones [166]
1950	Mitral valvotomy established by Bailey in the United States and Lord Brock and O.S. Tubbs in the United Kingdom [163]
1950s	CS Schollenberg et al. discover TPUs at the research laboratories of BF Goodrich [165]
1952	Charles A. Hufnagel implants caged-ball heart valves, the first long-term success in prosthetic heart valves at Georgetown University Medical School [167,168]
1957	Surgical correction of mitral regurgitation by annuloplasty under direct vision in Minnesota by C Walton Lillehei, father of open-heart surgery [169]
1958/9	Tetsuzo Akutsu (Cleveland Clinic), Nina Braunwald (NIH) and Benson Roe (UCSF) perform pioneering research into polymeric heart valves [21–23]
1960	First mitral heart valve replacement designed, fabricated and implanted by Nina Braunwald at the National Heart Institute (NHI) at the NIH using polyurethane valves [43]
1960	First aortic valve replacement by Benson Roe at the University of California School of Medicine, San Francisco, California using silicone valves [25]
1960	Dwight McGoon performs repair of mitral insufficiency due to ruptured chordae tendineae at the Mayo Clinic. [163]
1960	Starr-Edwards Silastic Ball Valve becomes first commercially available valve [167]
1961	Robert Frater experimented using autogenous pericardium for free-hand valves or parts of valves [170]
1962	Homograft valves introduced by Donald Ross and Brian Barratt-Boyes [163]
1965	First description of a polymeric catheter-mounted valve used by Davies [114]
1966	Roe achieves in vitro durability of 786 million cycles with silicone surgical valve [25,26]
1967	First heart transplant by Christiaan Barnard at Groote Schuur Hospital, Cape Town, South Africa
1969	Introduction of the first tilting disk heart valve, the Bjork-Shiley. [171]
1972	The Hancock (Medtronic) porcine valve was the first commercially available biologic heart valve. [172]
1977	Introduction of carbon bileaflet mechanical heart valves by St Jude Medical [171]
1978	Monoleaflet polyurethane mitral valves developed and described by Reul at al [47–49]
1985	Alain Cribier performs the first balloon aortic valvuloplasty in 1985 [13].
1992	Andersen describes first transluminal heart valve replacement using tissue valve mounted in balloon expandable stent. [173]
1992	The Berlin Heart, the first commercially available pulsatile assist device for small children employs trileaflet polyurethane valves as an option [97]
1995/7	Wheatley et al. reach 800 million cycle in vitro durability using PEUU leaflets on PEEK frames [60,61]
2000	First human percutaneous pulmonary valve replacement performed by Bonhoeffer et al. using a bovine jugular valve mounted in a self-expanding stent. [174]
2002	First human percutaneous aortic valve replacement performed by Cribier et al. [13]
2003/4	The Aachen/Munich group reach 600-1000 million cycle durability in vitro with the ADIAM polyurethane tri- and bileaflet valves for aortic and mitral applications respectively [59–61]
2006	First in man study of Corevalve™ self expanding percutaneous heart valve [175]
2006	Attmann et al. develop a catheter based valve composed of polyurethane leaflets suspended in a Nitinol stent [116]
2009	Claiborne et al. at Stoney Brook describe SIBS and xSIBS surgical and catheter based valves. [118]
2010	Alex Seifalian's group at UCL, London, develop and evaluate the “Triskele” POSS-PCUU valve in a Nitinol stent [119,120]
2011	The FDA approves the first catheter based heart valve, the Edwards Sapien™. [176]
2014	Catheter-based ePTFE/Nitinol valve for pulmonary position described by Zhang et al. in Shanghai [123]
2014	First human totally endoscopic aortic valve replacement [177]

8. Conclusions from fifty years of development

This review has introduced the different types of replacement heart valves currently available, and has identified a need for alternative valves that could provide good long-term function and durability without the need for anticoagulation. Additionally, the unsolved need for inexpensive valves and replacement procedures for sufferers of rheumatic heart valve disease has been highlighted. The use of stable polymeric materials to fabricate the leaflets of heart valves has been discussed in terms of applications as

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surgically implantable valves, valves used in ventricular assist devices, and those that can be inserted via minimally invasive procedures.

Clearly it has not been a trivial task integrating the two aspects of polymer chemistry and valve design into safe and effective devices; the very fact that work has proceeded for over half a century without significant and substantial clinical success confirms this position. The reality is that for the routine replacement of valves in the typical patient population with age-related valve disease, the now-conventional mechanical and bioprosthetic valves perform well, and their attendant deficiencies, of clotting and calcification, are largely manageable. It would be foolish for polymer technologists to deny this. The one clinically relevant area of polymer valve use today, that of heart assist devices, rely on the anticipated short period of use as the main justification for their choice, along with minor considerations of reduced cost. These devices will never be used in large numbers.

As usual with medical devices, the need to look again at material selection comes with the introduction of some disruptive technology. With heart valve disease, an immense change to the clinical landscape arose with the introduction of minimally invasive implantation techniques and the transcatheter valves, initially with those that use the transfemoral route. The need to collapse valves and crimp them onto a stent within the lumen of a catheter essentially rules out the use of rigid metals and carbons, i.e. the traditional mechanical valve is no longer an option.

Most TAVI valves are currently made of pericardium. This is largely pragmatic in view of the lack of success with polymers but pericardium is not without disadvantages. Processing is labour-intensive. It would also be preferable to use materials that could be crimped into smaller diameter delivery systems. In the treatment of rheumatic heart disease, the usual young age of the patients means that calcification of pericardium is likely to be more dramatic than with older patients. There is still, therefore, a major requirement for polymeric valves.

Which polymer(s) offer the best potential here is still largely a matter of conjecture. The details given in this review suggest that, on the basis of current biomaterials technology, the number of possibilities that can provide the required combination of mechanical functionality and durability, biocompatibility and processability is rather small.

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