Chapter

Transcatheter Treatment of Aortic Stenosis and Regurgitation

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Abstract

Since the successful application of transcatheter aortic valve implantation (TAVI) in 2002, the interventional treatment of valvular heart disease has developed rapidly. The interventional treatment of aortic valve stenosis or insufficiency has been more mature, and many new-generation TAVI valves have been developed. The recommended level of TAVI technology in the European and American heart valve disease guidelines has increased year by year. In 2019, the multi-center randomized controlled study on patients with low-risk aortic stenosis and conventional aortic valve replacement also showed the advantages of interventional treatment technology, such as small trauma, fast recovery and less complications, and better hemodynamics, which greatly promoted the development of TAVI technology.

Keywords: transcatheter aortic valve implantation, aortic valve stenosis, aortic valve regurgitation, heart team, heart valve disease

1. Introduction

Aortic valve disease is common in the elderly people. In clinical practice, many elderly patients, as well as patients with other organ dysfunctions, cannot tolerate the valve replacement surgery of open chest with cardiopulmonary bypass. Transcatheter aortic valve implantation (TAVI) technology can complete valve replacement without thoracotomy, cardiac arrest, and cardiopulmonary bypass. Its advantages are obvious. This chapter will review the research and development history of TAVIi technology and different design features of TAVI valve, especially the application effect of China-designed TAVI valves in China. What's more, TAVI technology brings not only technological innovation, but also a new team cooperation mode for disease treatment, which can better provide heart valve disease patients with higher quality and safer tsreatment. Finally, in addition to the aortic stenosis, earliest indications of TAVI, it can also be used for the treatment of aortic valve regurgitation. The new generation of TAVI valve has a unique design helpful in leaflets fixation and clamping, which can complete the interventional treatment easily.

2. The development history of TAVI techniques

Aortic valve stenosis is a common cardiovascular disease. In western countries, the incidence is about 2.0% in people aged ≥65 and 4.0% in people aged ≥85, which

is second only to hypertension and coronary heart disease [1–3]. As early as the 1960s, researchers imitated vascular stents to treat aortic insufficiency by placing metal stents, but these designs stopped after animal trials because of many problems in hemodynamics, postoperative anticoagulation, and so on. Among the non-operative interventional techniques for early aortic stenosis, only balloon dilatation (balloon aortic valvuloplasty, BAV) can be approved for clinical use. The technique, pioneered by Alain Cribier in 1985, is mainly used in patients with severe aortic stenosis who cannot be operated by routine open heart surgery. Many patients can improve short- and medium-term results, but the 1-year recurrence rate can be as high as 80% [4, 5]. However, due to the urgent need for high-risk patients undergoing thoracotomy, more than 1500 patients with severe aortic stenosis have received this treatment.

In the course of development since then, the stent interventional therapy of coronary artery disease has given a lot of revelation to the interventional therapy of valvular disease. In February 1989, at a medical conference in Phoenix City, USA, after listening to an academic report on coronary intervention stents, Sweden doctor Henning R. Andersen had a whim: if calcified coronary artery stenosis can be solved with metal stents, can aortic valve stenosis be done in a similar way? The first metal stent material that Andersen tried was the most commonly used sternal fixation wire in cardiac surgery, which was molded into a U-shaped structure in order to achieve a telescopic purpose. In May 1989, the prototype conceptual system of TAVI surgery emerged. From idea to feasibility verification, it took Andersen only two and a half months to revolutionize the diagnosis and treatment of aortic valve disease in the twenty-first century. The technology of transcatheter aortic valve implantation was born. Finally, in 1995, the famous patent for Andersen interventional valve was approved in the United States [6].

In the early stage after the feasibility verification of TAVI technology, it went through a long and difficult road of not being recognized. Andersen submitted the completed paper to the *Journal of the American College of Cardiology* (in 1990, when the influence factor of JACC was 5.9), but the reply was that "there is no advantage of this study to be published in JACC magazine." (It has too low priority for publication in JACC). Subsequently, the improved article in 1991 was submitted to Circulation (then impact factor 9.0), and the reply was still rejected. In 1992, at the European Heart annual meeting and the American Heart Association (AHA) annual meeting, the TAVI technology research report submitted by Andersen was arranged to be presented in a poster, and no one paid attention to it.

After that, the first TAVI animal experimental operation was successful, which confirmed the feasibility of the design concept. The article on animal experiments was published in European Heart Journal in 1992 [6]. TAVI technology has finally begun to attract attention, and other similar stent valve designs with animal studies have also begun to emerge. Alain Cribier's team also conducted in-depth research on this technology in 1993 and 1994, including the research and development of balloon-dilated valve stents, selection of stent materials, length and shape design considerations, and so on. However, throughout the 1990s, there was still no breakthrough in TAVI technology due to the high failure rate in animal experiments and the engineering and technical bottleneck in the manufacture of stent valves.

In 2000, Philipp Bonhoeffer and others first tried to use bovine jugular vein to make valve into platinum metal stent and then loaded it on the balloon delivery system to carry out sheep pulmonary valve replacement. The valve also successfully completed the first human pulmonary valve implantation in the same year [7]. However, there are great defects in the follow-up funding and design, which leads to the gradual cessation of the technology research.

Alain Cribier's team continued the study of balloon dilatation of the stent valve, testing the stainless steel stent in 12 aortic valve stenosis specimens obtained from human surgery, confirming that the stent could open the natural valve repeatedly, regardless of the valve's calcification. And they concluded the ideal height of the stent may be 14–16 mm, which can avoid blocking the coronary opening and interventricular septum or affecting the anterior leaflet of the mitral valve. Then Percutaneous Valve Technologies, a PVT company led by Alain Cribier, was founded in 1999 with the help of investors and medical valve companies. The engineer R&D team of the Israeli subsidiary officially began the design and development of the interventional valve. After a great deal of laboratory work, the first TAVI valve model (balloon dilatation) was born soon [8]. On April 16, 2002, Alain Cribier successfully completed the world's first TAVI operation with Cribier-Edwards interventional valve in Lyon, France, which opened the prelude to the development of TAVI technology. Since then, 40 operations have been completed [9]. Edwards acquired PVT for $150 million after an initial investment in 2003.

Alain Cribier used the transfemoral vein method to enter the aortic valve for TAVI. John Webb of Canada collaborated with Edwards to develop retrograde arterial implantation. The technique has a deflectable sheath that can easily pass through the aortic arch and the narrowed valve orifice [10]. John Webb and his colleagues also performed the first transapical valve implantation [11]. Walther et al. promoted the number of cases of TAVI via Edwards' apical approach as an easier way to implant the valve [12].

After Jacques Seguin founded CoreValve in the United States in 2001, Eberhard Grube carried out the first clinical implantation of CoreValve valve in 2005 after previous animal experiments [13]. The results proved the feasibility of using self-expanding valve for TAVI. At the ACC meeting in 2006, Grube reported the first group of 14 patients who underwent TAVI with self-expanding CoreValve valves. At that time, only nine of these patients had no adverse cardiac events in the first 2 weeks. The device can be implanted via femoral artery approach. The CoreValve valve has been continuously improved since then, and the company was acquired by Medtronic in February 2009. Since then, the CoreValve valve has been replaced by a series of Evolut valves. In 2007, the Edwards SAPIEN valve and CoreValve valve first entered the European market and obtained CE approval. Since 2012, they have been approved by the FDA in the United States for surgical high-risk patients with aortic valve stenosis. Since then, the technology has developed by leaps and bounds, and research centers in Europe and the United States have successfully carried out more than 20 clinical multicenter randomized controlled trials, proving the safety and effectiveness of TAVI technology.

This is an epoch-making minimally invasive surgical technique that does not require thoracotomy and extracorporeal circulation or cardiac arrest. A large number of expert consensus and guidelines have been issued, and the recommendation level of TAVI has been gradually improved. Andersen successfully performed TAVI surgery on his father in 2011, and he defined this time as the end of a perfect cycle of his research.

In the European 2012 guidelines, TAVI candidates are limited to surgical high-risk patients and require the presence of surgeons and the heart team (heart team) to make decisions [14]. Through the safety and effectiveness of TAVI technology with the rapid development of the new generation of valve and technical experience, many clinical research results continue to get good results, and the recommendation level of TAVI in European and American valvular disease guidelines is getting higher and higher. In 2010, the PARTNER 1B study pointed out that although TAVI has incidence of massive hemorrhage and vascular complications in patients with inoperable aortic valve stenosis, the incidence of all-cause mortality,

readmission and cardiac symptoms is significantly lower than that of standard treatment [15]. The results of 5-year follow-up of PARTNER IB (inoperable) were released at the 2014 Annual Meeting of Transcatheter Cardiovascular Therapeautics (TCT), suggesting that compared with standard treatment, TAVI had significant benefits in terms of all-cause death rate (71.8%: 93.6%), cardiovascular death (57.3%: 85.9%), readmission rate (47.6%: 87.3%), and improvement of cardiac function (III: IV = 14.3%: 40%). In 2016, the PARTNER 2 study turned to the medium-risk population, confirming that the mortality, disability, and stroke incidence of TAVI and surgical surgery was similar [16]. The PARTNER III study and the EVOLUTE study published similar results in 2019. In these randomized controlled study of patients with low-risk aortic valve stenosis, whether it is balloon-expandable valve or self-expanding valve, the mortality and complication rate of TAVI group is better than that of conventional thoracotomy group. As a result, the United States and European Drug Regulatory agencies have extended the use of TAVI to patients with low-risk aortic stenosis since 2019 [17, 18].

In 2015, about 40,000 patients in Europe received TAVI treatment, and that number will rise to 60,000 in 2020. The number of patients with TAVI indications in Europe is expected to exceed 114,000/year, and if extended to low-risk patients, it can increase to 177,000/year. In France, 1600 and 8000 patients were treated with TAVI in 2010 and 2015, respectively, and the figure is expected to reach 10,000 in 2016. Germany receives TAVI treatment for every 1 million residents, which has the highest TAVI implementation rate in Europe. There were more than 15,000 cases in Germany in 2016, three times as many as in 2011. The number of valve replacement cases in routine surgery remained relatively stable, with no less than 10,000 cases per year. In developed countries such as Germany (2013) and the United States (2019), the number of TAVI surgeries has exceeded that of conventional thoracotomy aortic valve replacement, and the gap is still widening. A total of more than 400,000 TAVI operations have been completed worldwide.

In 2018, Durko et al. used Monte Carlo mathematical model combined with 37 clinical studies of 26,402 cases of severe aortic valve stenosis to predict the number of patients with TAVI indications each year in Europe and the United States. In patients over 65 years old, the incidence of severe aortic stenosis was 4.4‰ per year. 68.3% patients with severe aortic stenosis had related symptoms. Despite severe symptoms of aortic stenosis, 41.6% did not undergo surgical aortic valve replacement. Of the nonsurgical patients, 61.7% received TAVI treatment. This model predicts 114,757 European and 58,556 North American TAVI candidates each year. The conclusion is that there are currently about 180,000 patients a year in the European Union and North America who can be considered potential candidates for TAVI. If the indications for TAVI are extended to low-risk patients, this number may increase to 270,000. These findings have a significant impact on healthcare resource planning in 29 countries [19].

The European Valve observation registration study (EURObservational Research Programme VHD II) conducted a survey at 22 centers in 28 countries to show changes in the structure of heart valve patients and their impact on clinical treatment. 7247 patients with VHD (including 4483 inpatients and 2764 outpatients) were enrolled in the study. Compared with a similar survey conducted in 2005, the latest survey in 2019 showed that the actual treatment strategies of patients with aortic valve disease were more in-line with the guidelines and the proportion of transcatheter therapy was gradually increasing (39% of aortic stenosis and 17% of mitral regurgitation) [20].

The SAPIEN 3 valve is the third generation in the SAPIEN series of valves developed by Edwards. The valve stent contains an outward reflexed skirt, which can prevent perivalvular leakage. The delivery system as a whole becomes smaller,

shrinking to 14F (16F for 29 mm valves). At the same time, the conveying system has good controllability, so that the near-center section of the conveying system can be bent and maintain better coaxiality. The SAPIEN 3 Ultra is an improved and upgraded version of the SAPIEN 3 valve system, and a 14F sheath can be used for all sizes of valves [21]. Centera is a self-expanding valve developed by Edwards Corporation. This valve is quite different from Medtronic's self-expanding valve. Its nickel-titanium stent is short, similar to a balloon-expandable valve, using a bovine pericardial valve. There is a metal wire at the waist of the stent, which can be tightened to retract the valve so that it can be retrieved. The conveying system is 14F, which can be bent to ensure the release with good coaxiality. The electric release handle makes the release easier, and the valve can be released by a single operator. Centera valve design combines the characteristics of self-expandable stents (recyclable stents with good deformability) and ball-expanded stents (short stents and low incidence of pacemakers) [22].

The Evolut R valve is an upgraded version of the Medtronic CoreValve valve. The valve enhances the radial force at the annulus level, and the lower end of the skirt extends downward to prevent perivalvular leakage. The valve stent is shorter, so that the coaxial line of the stent is better after release. The shape of the stent is more straight and cylindrical. More importantly, a nickel-titanium casing is arranged at the near end of the delivery system, and before the valve stent is completely released, the valve can be pulled back to the nickel-titanium casing to achieve retrieved; thus the position of the valve can be readjusted. On the basis of Evolut R, Evolut pro wrapped a pericardial patch around the lower segment of the stent to reduce the incidence of perivalvular leakage and pacemaker implantation [23–25].

The Lotus Edge valve is a product developed by Boston Science Co., Ltd., which is an upgraded version of the Lotus valve. The Lotus valve stent is made of Ni-Ti alloy. The diameter of the short axis of the stent can be shortened after lengthening longitudinally, so as to achieve the purpose of recycling. The lower part of the device has an adaptive sealing ring, which can reduce the incidence of perivalvular regurgitation. Lotus Edge retains the advantages of full retrieved valve of Lotus, prevention of perivalvular leakage, early valvular work, and so on. At the same time, the delivery system is improved to make it softer and more curved. More important is the implantation depth protection technology to prevent the valve from entering the outflow tract too deep, thus reducing the incidence of conduction block. In previous clinical trials, the implantation rate of Lotus pacemakers was as high as 35.5% and was later withdrawn from the market. Lotus Edge is expected to reduce the pacemaker implantation rate compared with Lotus. In April 2019, the Lotus Edge valve was approved for sale by the FDA in the United States [26].

ACCURATE neo is a self-expanding valve implanted via artery, and it is also a design of Ni-Ti alloy stent and supra-annular valve. Its unique design lies in that it contains an anchoring device and can be positioned automatically. The release of the valve is different from that of other self-expanding valves. Generally, the self-expanding valve first releases the proximal end and then releases the distal end. During the ACCURATE neo release procedure, the distal end is first released, the anchoring device exposed, and the valve stent is leaded down to the autologous aortic annulus level and then the proximal part is released. It also contains the outer edge of the skirt to prevent the valve from leaking. The distal stent grid has a large aperture and does not interfere with percutaneous coronary intervention after valve implantation. The lower part of the stent is covered by the inner layer and the outer layer of the pericardium to prevent perivalvular leakage. Its delivery system is equivalent to 15F. In the latest large randomized controlled study, 739 patients (mean age 82.8 years, STS score 3.5%) were randomly divided into two groups: ACCURATE neo valve 367 cases and SAPIEN 3 valve 364 cases. The main end point

of ACCURATE neo 30 days and SAPIEN 3 did not achieve non-inferiority (24% vs. 16% personality 0.42). Although there was no difference in 30-day mortality (2 vs. 1%) and stroke (2 vs. 3%) between the two groups, the incidence of acute renal injury (3% vs. 1%) and moderate perivalvular leakage (9 vs. 3%) was higher in the ACCURATE neo group [27].

The JenaValve valve is specially designed [28, 29]. The stent valve with three fixed keys is implanted through the apical approach. TF-JenaValve is the new version of JenaValve via the femoral artery. The JenaValve is a short stent with a large mesh hole at the upper end, which is beneficial to the introduction of the coronary artery. The outer edge of the stent contains three anchoring parts, which can prevent the stent from being fixed to the bottom of the three aortic sinuses. The artificial valve is designed for supra-annular valve. The JenaValve deployment first releases the proximal anchoring device, then pushes it to the autologous aortic valve annulus, automatically locates and gets stuck, then releases the proximal stent, and finally releases the distal connecting device. The delivery system of TF-JenaValve is 18F, which has a bending function to ensure the coaxiality of the release valve and the aortic valve annulus. The design of the JenaValve with a fixed key makes it possible to treat aortic regurgitation and patients with low coronary artery openings. This is similar to the Chinese domestic J-Valve.

The design of the Engager valve produced by Medtronic is similar to that of the JenaValve valve. It is also a valve implanted through the apical approach. By placing the control arm with anatomical positioning function at the root of the aortic sinus, the valve stent can be positioned accurately, and the complications can be reduced [30, 31].

3. The development of TAVI technology in China

According to incomplete statistics, China has a total population of 1.4 billion, including 44.8 million elderly people over the age of 75 (3.4%), and about 1.5 million patients (3.4%) with severe aortic valve stenosis, including about 0.2 million high-risk patients and 0.3 million moderate-risk patients. A single-center survey led by Gao Runlin showed that among the 139,496 patients examined by echocardiography from January 2010 to December 2015, the detection rate of severe mitral regurgitation was the highest (0.68%). This was followed by mitral stenosis (0.38%), aortic stenosis (0.28%), and aortic regurgitation (0.27%) [32]. From January 2009 to December 2013, Liu et al. investigated 19,428 patients with abnormal valvular structure or function in Guangdong People's Hospital, of which 13,549 (69.7%) were relatively certain to be valvular heart disease through clinical data, patient characteristics, and echocardiography. Among these patients, rheumatic heart disease accounted for 37.0%, and congenital valvular disease accounted for 13.9%. Degenerative valvular disease accounted for 11.5%, ischemic valvular disease accounted for 12.7%, infectious valvular disease accounted for 3.1%, and autoimmune-mediated valvular disease accounted for 0.7%. In 5 years, rheumatic heart disease decreased from 42.8% in 2009 to 32.8% in 2013 ($P < 0.001$), while degenerative valvular heart disease increased from 8.8% to 14.5% ($P < 0.001$), ischemic valvular disease increased from 9.2% to 11.3% ($P = 0.003$), and congenital valvular disease increased from 9.0% to 12.3% ($P < 0.001$). The prevalence of degenerative valvular disease is dominant in patients over 65 years old much more than rheumatic valvular disease [33]. The level of medical treatment level in different regions of China is uneven, and the evaluation of surgical risks and taboos is different from that of foreign countries. A 20-year review of data from Changhai Hospital affiliated to the Second Military Medical University in Shanghai showed

that among the 6300 patients who underwent valve replacement of the left heart system, only 2.0% were over 70 years old, and the maximum age was 79 years old [34]. Another study included 521 consecutive valve surgery patients, of whom 53 (10%) were assessed to be at the highest risk before operation, with an average STS score of only 3.25 [35].

In 2002, the world's first TAVI operation was completed; in 2010, the first China TAVI operation was completed (GE Junbo, Zhongshan Hospital) [36].

In 2012, China's first independent intellectual property valve product Venus A began clinical trials; 7 cases were completed nationwide.

In 2015, GE Junbo, Wang Jianan, and other organizations have reached the consensus of Chinese experts on transcatheter aortic valve replacement [37].

In 2017, the Venus A valve via the femoral artery and the J-Valve valve via the apical approach were officially approved and put on the market, marking a new era of interventional therapy for valvular heart disease in China. In 2017, the United States issued the consensus of experts on the clinical decision-making path of transcatheter aortic valve replacement for adult aortic valve stenosis [38].

In 2018, more than 1000 TAVI operations were completed nationwide in China. GE Junbo and Wang Jianan [39] published the Chinese expert consensus on transcatheter aortic valve replacement team construction and operation standard. Wu Yongjian and others issued the clinical pathway of transcatheter aortic valve implantation in China [40]. Zhang Yun and others organized the China expert consensus on perioperative echocardiographic examination of transcatheter aortic valve implantation [41]. Cheng Weiping and Li Lihuan organized the Chinese anesthesia expert consensus on TAVR surgery clinical Ppathway Mmanagement [42]. Wang Chunsheng and others published the Chinese transcatheter aortic valve implantation (TAVI) multidisciplinary expert consensus [43]. Xu Zhiyun and Lu Fanglin started the interventional tricuspid valve clinical trials with LUX valve. Hu Shengshou and Meng Xu led the mitral stitch technique of trans-apical artificial chordae tendineae implantation to begin clinical trials. GE Junbo and Zhou Daxin led the trans-apical mitral valve double-hole valve clamp technique to begin clinical trials.

In 2019, the VitaFlow valve (via the femoral artery) was approved to be put on the Chinese market. 2000 TAVI operations were performed by cardiologists and surgeons all over the country. Xu et al. led the establishment of the Academic Committee on Interventional Therapy of Cardiac Valvular Disease and published the expert consensus on the responsibilities and requirements of cardiac surgeons in cardiac team Building [44]. Haibo and others developed innovation with J-Valve valve in valve techniques for mitral and tricuspid tissue valve deterioration [45]. Both Edwards SAPIEN valve and domestic Taurus valve have completed clinical trials and are expected to be on the market within 2 years. Runlin et al. released good 5-year follow-up results of Venus A valve and J-Valve valve, which showed that their safety and effectiveness had been verified in the medium and long term.

At present, a total of 150 centers in China have the ability to carry out TAVI surgery, of which there are about 10 units; the cumulative number of TAVI cases is more than 100 cases. Different from Europe and the United States, Chinese patients with bicuspid aortic valve are in the majority, with more severe calcification, more weakness in elderly patients, and more complications when they see a doctor later. And at present, there are obvious differences in TAVI experience and team construction among different centers in China, most of which are in the initial stage of the learning curve, with both opportunities and challenges. With the introduction of a new generation of valves into clinical practice, the success rate of TAVI in various centers in China will continue to improve, and more clinical experience needs to be accumulated. In the aspect of image evaluation, combined with the individual characteristics of the Chinese

population, the multiplane valvular three dimentional measurement technique proposed by Wu Yongjian of Fuwai Hospital, the small balloon measurement method put forward by the Zhongshan Hospital affiliated to Fudan University, and the sequential balloon measurement strategy put forward by Wang Jianan of the Second Affiliated Hospital of Zhejiang University Medical College. The optimized measurement technology of optimal reshaping put forward by Chen Mao of West China Hospital of Sichuan University and the concept of effective annular diameter and effective valve area of TAVI surgery put forward by Meng Xu and Zhang Haibo of Beijing Anzhen Hospital have made substantial contributions to the development of TAVI technology in China. The new generation of interventional valve represented by SAPIEN 3, Evolut R, and Centera has mainly improved the defects of early interventional valve, which is characterized by lower incidence of perivalvular leakage, retrievable, small delivery system, and automatic localization. At present, it is considered that the new interventional valve with the above two characteristics can be classified as the second-generation valve. In the research and development of the second-generation valve, China has gradually caught up with the pace of the world, and new-generation valves such as J-Valve developed by Suzhou Jiecheng Company, VitaFlow II valve developed by Shanghai Minimally Invasive Medical Devices Co., Ltd., and Venus A plus valve developed by Hangzhou Qiming Company have been implanted in the first patient one after another.

Venus A valve is the first TAVI valve on the market in China, which was implanted through the femoral artery. Up to October 2019, a total of more than 2000 Venus A TAVI operations have been performed in 142 centers in China. Among them, there were 19 centers with more than 20 TAVI cases, 16 centers with 10 cases, and 16 centers with less than 10 cases. The prospective multicenter observational study, which began in 2012 to evaluate the safety and efficacy of Venus A valve in the treatment of severe aortic valve stenosis, followed up patients with TAVI for 5 years. The results showed that the 5-year all-cause mortality rate was 20.8% and the cardiovascular mortality rate was 15.8%. The risk ratio of age > 85 years old was 1.47 [95%CI (1.12 ~ 2.00), P = 0.007], and the risk ratio of STS > 8 was 1.56 [95%CI (1.21–2.01), 0.033]. On March 29, 2019, at the China Interventional Cardiology Conference (CIT2019) in Beijing, Gao Runlin reported the results of a 5-year follow-up study with severe Venus A valve stenosis or severe regurgitation of 0 and moderate velocity increase or moderate regurgitation of less than 10%. The second generation interventional aortic valve system developed by Venus A plus has a retrievable function. Structurally, the valve release recyclable function is realized through innovative sheath design. The conveying system uses a 19F guide sheath. On the basis of the retrievable function, the Venus A pilot adds an adjustable bending function to ensure the coaxiality of the valve release. Qiming Venibri Valve is the world's first preinstalled TAVI valve, so that the valve can be used in the catheterization room, saving valuable time for critically ill patients to save lives [46].

VitaFlow II is a second-generation interventional aortic valve system developed by Shanghai Minimally Invasive Medical Devices Co., Ltd., which has the function of retrievable and anti-perivalvular leakage and belongs to the second-generation interventional aortic valve. VitaFlow II valve stent is the same generation of VitaFlow. Structurally, the valve release retrievable function is realized through innovative sheath design, that is, repositioning and rerelease. The design of the inner and outer tubes of the transportation system has an enhanced structure, which not only ensures the stability and accuracy of the release but also realizes the multidirectional bending function, so as to reduce the damage to blood vessels and reduce the probability of vascular complications. According to the characteristics of thinner femoral artery in Chinese elderly patients, the internal catheter sheath was

set up to realize the integrated puncture function and reduce the vascular damage caused by the transportation system (equivalent to 16–18F sheath).

J-Valve is a self-expanding Ni-Ti stent, and there are three flexible fixed bond steel rings around the stent. Different from JenaValve in which fixed bond and Ni-Ti stent are welded, the J-Valve fixed bond and Ni-Ti stent are connected by string, which is beneficial for the movement of the fixed bond at the bottom of the sinus during release and better fit to the aortic sinus bottom. The conveying system is 18–22Fr with adjustable bending function. The valve release procedure is similar to that of JenaValve [47]. TF-J-Valve is the femoral artery version of J-Valve, and the valve design is basically the same as J-Valve. TF-J-Valve exploratory clinical trials are mainly conducted in Canada and have confirmed the technical feasibility [48].

4. Indications of TAVI in low-risk patients

Multiple death reasons analysis maintained by the National Center for Statistics from 2008 to 2017 [49] showed that the mortality rate due to aortic stenosis in the elderly in the United States has declined since 2013, while the number of TAVI hands has increased from 4627 in 2012 to nearly 35,000 in 2016. It is speculated that the observed death rate trend may be related to TAVI.

On March 17, 2019, in the American College of Cardiology (ACC) annual meeting, the low-risk patients TAVI studies PARTNER III and EVOLUT results were released, marking the comprehensive arrival of the TAVI era of severe aortic valve stenosis. Martin Leon of Columbia University Medical Center in New York officially released the results of PARTNER III study at the conference [17]. For low-risk patients with severe aortic stenosis, the incidence of 1-year death, infarction, and rehospitalization in patients with Edwards balloon-expandable TAVI valve implantation was significantly lower than that in patients undergoing open heart surgery. The study included 1000 patients from 71 centers, with an average age of 73 years and an average STS score of 1.9%. The main end point of the study was the compound end points, including 1-year death, infarction, and rehospitalization event rate. The results showed that the event rate of the main end point in the TAVI group was significantly lower than that in the surgical operation group (8.5% vs. 15.1%). The 30-day infarction rate (0.6 vs. 2.4%), infarction or death event rate (1.0% vs. 3.3%), and new atrial fibrillation rate (5.0% vs. 39.5%) in the TAVI group were significantly lower than those in the operation group. In addition, patients in the TAVI group had a shorter average hospital stay (3 days vs. 7 days) and a lower risk of a 30-day poor prognosis (death or low KCCQ score) (3.9% vs. 30.6%). There was no difference in the incidence of major vascular complications, permanent pacemaker implantation, and moderate or severe perivalvular leakage between the two groups.

The Evolut study included 1468 patients who underwent Medtronic self-expanding TAVI valves, of which 1403 underwent TAVI or surgery [18]. The average age of these patients was 74 years, and the main end point of the study was a 24-month complex event of death or crippling infarction. The incidence of major end point events at 24 months in the TAVI group was 5.3%, while that in the surgical group was 6.7%. The incidences of 30-day disabled infarction (0.5 vs. 1.7%), bleeding complications (2.4% vs. 7.5%), acute renal injury (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) in the TAVI group were significantly lower than those in the surgical group. However, moderate or severe perivalvular leakage (3.5 vs. 0.5%) and permanent pacemaker implantation rate (17.4% vs. 6.1%) were higher than those in the surgical group. At 1 year, the mortality rate in the TAVI group was 0.4%, while that in the surgical group was 1.2% (no significant).

The TAVI group had lower all-cause mortality and incidence of disabled infarction (but not statistically significant) (2.9% vs. 4.6%), significantly reduced crippling infarction (0.8% vs. 2.4%), and significantly reduced hospitalization for heart failure (3.2%vs. 6.5%). In addition, in the TAVI group, the transvalvular pressure difference was lower (8.6 mmHg vs. 11.2 mmHg), and the effective valve orifice area was larger (2.3 cm^2 vs. 2.0 cm^2) at 12 months. Despite the high proportion of perivalvular regurgitation after TAVI, only 22% of the patients received the third-generation valve. The new valve increases the edge of the skirt to reduce perivalvular leakage, so it is expected that the regurgitation rate will decrease as the new device utilization rate increases.

At present, there are about 60,000 TAVI operations in the United States every year. This may increase to 75,000 if patients at moderate risk received TAVI and to 100,000 or more if extended to low risk. The ultimate goal of TAVI surgery is that TAVI can be performed in all comers. It means no matter what the risk, no matter what the anatomy, and even what age; as long as it is the need for intervention of aortic valve disease, TAVI always can be done.

The two studies of PARTNER III and EVOLUT in 2019 are an eye-catching new research progress of TAVI technology. On this basis, the FDA and the European Drug Regulatory Agency have approved the extension of TAVI surgical indications from surgical high-risk patients with severe aortic stenosis to surgical low-risk patients, which indicates that TAVI technology will continue to develop rapidly towards the goal of the whole population in the future. It is believed that more research evidence will be published one after another, the guidelines for the diagnosis and treatment of cardiac valvular disease will change greatly, and interventional valvular technology will play a more and more important role.

5. The concept of heart team in TAVI procedure

Because of the old age of patients and high-risk factors, TAVI procedure is still relatively risky and difficult, so it is necessary to make a variety of emergency plans during the operation, including the most dangerous emergency such as heart rupture and arrest. Compared with coronary stent intervention, the probability of conversion to emergency surgery is similar, but the harm of TAVI is much higher. The risk of emergency during coronary stent was 0.2%, and the mortality rate was 1%. However, the data of 27,760 TAVI patients enrolled in 79 European centers in 2017 showed that the probability of emergency surgery was 0.76% [50]. The 3-day, perioperative, and 1-year mortality rates were 34.6%, 46%, and 78%, respectively. The average age of patients who needed emergency heart surgery was 82.4 years old, and 67.5% of the patients were female with Logistic EuroSCORE score of 17.1% and STS score of 5.8%. The analysis showed that the incidence of emergency heart surgery during TAVI decreased from 1.07% in 2013 to 0.70% in 2014 and has remained stable since then. It implies the clinical experience play important role in the procedure.

The most common causes of emergency cardiac surgery during TAVI are left ventricular perforation (28.3%) and annular rupture (21.2%) caused by guide wire. The mortality rate of patients in this situation was as high as 34.6% within 72 hours after operation. The total in-hospital mortality rate of these patients was 46.0%, and the mortality rate of patients with valvular annulus rupture was the highest (62%). The analysis also showed that the independent predictors of in-hospital death after emergency cardiac surgery were age > 85 years (OR = 1.87, P = 0.044), valvular annulus rupture (OR = 1.96, P = 0.060), and immediate emergency cardiac surgery (OR = 3.12, P = 0.037). Of these patients undergoing emergency

cardiac surgery, 114 survived during hospitalization, with a 1-year survival rate of only 40.4%.

It should be emphasized that complications of TAVI are usually more critical, faster, and more difficult to predict. In particular, TAVI indication will soon be extended to low-risk patients, to ensure the safety of these patients is more important at this time. The cooperation of multiple heart teams can better ensure the safety of patients.

Perhaps the greatest contribution of TAVI technology to medical treatment is not the techniques itself or clinical effect, but a unique medical cultural phenomenon. For the first time, barriers between medical disciplines have been replaced by multidisciplinary collaboration to deal with a state of disease. As Cribier pointed out in his review of the 20th anniversary of TAVI procedure [8], the development of TAVI technology has for the first time created a model of collaboration among cardiac doctors. It is difficult for cardiologists or surgeons alone to complete all the links involved in TAVI surgery, but the two can complement each other and provide safer and effective treatment for these high-risk and elderly patients. Therefore, in many countries and regions in Europe and the United States, only TAVI cases that have been signed by the heart team can be reimbursed by the medical insurance. According to the 2012 European Society of Cardiology/European Society of Cardio-Thoracic Surgery (ESC/EACTS) guidelines for the management of cardiac valvular disease, TAVI can be considered for high-risk patients with symptomatic severe aortic valve stenosis, but requires a "heart team" comprehensive analysis and evaluation (II/B) [51]. The newly released American Heart Association/American College of Cardiology (AHA/ACC) guidelines on valvular heart disease in 2017 also give the highest level of recommendation on the importance of heart teams during TAVI procedure [52].

The American Society of Thoracic Surgeons (AATS), in conjunction with the American College of Cardiology, the Society of Cardiovascular Angiography and Intervention, and the College of Thoracic Surgeons (STS), released the latest edition of 2018 AATS/ACC/SCAI/STS Expert Consensus Systems of Care Document: Operator and Institutional Recommendations and Requirements for Transcatheter Aortic Valve Replacement [53]. The new consensus points out that in order to ensure the safety and effectiveness, TAVI procedures should be performed in centers that meet the following criteria. At least 50 TAVI cases (or 100 in 2 years) and at least 30 surgical aortic valve replacements (or 60 in 2 years) are performed in the hospital each year. The standards also include various medical quality requirements for morbidity, mortality, and quality of life within a limited time, as well as conducting quality assessment/improvement plans. The consensus also points out that TAVI operators, as members of a multidisciplinary team, should have participated in at least 100 cases of transfemoral TAVI in their career, of which at least 50 were primary operations. Surgeons on the TAVI team should have performed at least 100 surgical aortic valve replacements in their careers or at least 20 (or 50 in 2 years) in the year before the start of the TAVI program. In Chinese experts consensus about the heart team construction [44], it implies that the surgeon in TAVI team should have valve surgery experience more than 15 years and perform aortic valve surgery at least 25 cases a year. In addition, surgeons should actively participate in the TAVI procedure like wire and valve manipulation and not only just stand by.

Carl Tommaso, one of the co-chairs of the expert consensus committee, commented that the TAVI procedure safety evaluation will be used to define centers whether this operation can be performed safely or not. In the past 6 years, more and more centers have performed TAVI, and the indications are being extended to surgical low-risk elderly patients, so it is time to redefine TAVI recommendations.

Some studies have shown that there are fewer postoperative adverse events in hospitals that perform more TAVI operations, and the accumulated TAVI experience is related to the improvement of postoperative outcomes. In 2018, the *Journal of the American Medical Association Cardiology* (JAMA Cardiol) published an observational cohort study [54] that included 60,538 TAVI operations performed in 438 hospitals from 2011 to 2016, with an average age of 82.3 years. Hospitals with a high amount of surgical valve replacement (annual average ≥ 97 / year) are more likely to start TAVI in the early stage, and the amount of TAVI increases faster with time. The average TAVI cases of hospitals with high surgical valve replacement volume to those with low volume was 32 vs. 19 in the first year, 48 vs. 28 in the second year, 82 vs. 38 in the third year, and 118 vs. 54 in the fourth year ($P < 0.001$). Combined with the analysis of hospital TAVI and surgical valve replacement volume, the 30-day mortality rate in high TAVI volume hospital was lower. When the hospital also has a high volume of surgical valve replacement, the effect is more obvious. Patients with high surgical valve replacement volume and high TAVI volume had the lowest 30-day mortality (for hospitals with low surgical valve replacement volume and TAVI volume: OR = 0.77; 95%CI, 0.66–0.89). Hospitals with both high volume of surgical valve replacement and TAVI cases may have the best outcome, which confirms the importance of hospital clinic experience.

6. TAVI treatment of pure aortic valve regurgitation

The analysis of echocardiography data from Shanghai Zhongshan Hospital (including 0.3 million patients) indicates [55] that the incidence of aortic valve stenosis in China may be significantly lower than that in western countries, while aortic regurgitation (AR) is more common than aortic stenosis [56]. A retrospective data analysis from Shanghai Changhai Hospital in the past 20 years showed that the proportion of AR in patients undergoing surgical aortic valve replacement was significantly higher than that in patients with AS [57, 58]. The latest China-DVD multicenter study in 2019 showed that among the 8638 patients with valvular heart disease in China, there were 894 cases of aortic regurgitation, 430 cases of aortic stenosis, 286 cases of mitral stenosis, and 2248 cases of mitral regurgitation [59]. Patients with simple AR are still mainly treated by surgery. However, the influence of aortic regurgitation on the left ventricle and the induced symptoms of heart failure are very different from those of aortic stenosis. In patients with aortic regurgitation, the left ventricle enlarged more obviously, and the ejection fraction decreased more. But due to the late appearance of pulmonary congestion comparing with aortic stenosis, the clinical symptoms often appeared late, many patients went to see doctor very late when combined serious heart dysfunction. At this time, the patient's heart disease is not only aortic regurgitation but also left ventricular enlargement and heart failure. Even if aortic valve surgery solves valvular regurgitation, it will take longer time for heart function to recover. On the contrary, the cardiac function of many patients with aortic valve stenosis can recover in a short time after operation. Studies [60, 61] showed that about 10% AR patients are unable to undergo surgery because of old age and severe multiple organ dysfunction. Only 20% AR patients with a left ventricular ejection fraction ranging from 30% to 50% have received surgery. When the left ventricular ejection fraction is less than 30%, the proportion of patients undergoing surgery is as low as 3%. According to statistics, the annual mortality rate of patients treated with conservative medicines is as high as 10–20%, and the 10-year complication rate and mortality rate are not optimistic.

Because of the long stent structure design, the Medtronic CoreValve valve may be anchored at multiple points which may be helpful in the TAVI treatment of pure AR. In 2010, Ducrocq et al. reported that CoreValve was used to treat a high-risk AR patient with good results [62]. This is a self-expanding valve and can be implanted through the femoral artery. Its advantage lies in the long stent over 50 mm and the special three-stage fixation mechanism, in which the lower part squeezes the primary lobe through higher radial expansion, the middle part is compressed to avoid coronary artery blockage, and the upper part expands to fix to the ascending aorta and provides longitudinal coaxial stability. Therefore, even in the absence of valve calcification, the valve can theoretically be anchored in other positions. However, there are also some difficulties in the use of this valve [28, 63]. (1) Inadequate anchoring can easily lead to valve displacement, resulting in a higher incidence of secondary valve implantation and postoperative moderate and severe perivalvular leakage. Roy et al. [64] studied 43 AR patients with TAVI from 14 centers. The results showed that the rates of second valve implantation and the postoperative moderate perivalvular leakage were 19% and 21%, respectively. (2) Since the CoreValve is mainly fixed at the annulus with strong radial force, it is usually necessary to make the artificial valve diameter slightly larger than that of the autologous annulus in order to obtain sufficient radial support to make the anchoring more stable, which also leads to a higher risk of annulus tear.

Since then, the second- generation TAVI valve has higher implantation rate due to the anchoring clip design which may help to locate and fix the valve. In 2013, Seiffert et al. [65] summarized the treatment effect of JenaValve in 5five patients with pure AR without calcification. The operation was performed through apical approach, and the success rate of valve implantation was 100%. There was no obvious residual regurgitation of aortic valve, and the cardiac function of the patients recovered satisfactorily after follow-up. In 2014, a Chinese team comprised of Da et al. [66] reported the excellent results of J-Valve, the China- designed second-generation TAVI valve, in the treatment of a high-risk AR case. J-Valve is designed to be implanted through the apical approach with three U-shaped positioning keys, which can be easily self-adjusted to enter the bottom of the aortic valve sinus. After the stent valve is released, the valve can be fixed and clamped together with the positioning key to assist the radial support to anchor the valve. Since 2017 J-Valve was officially put on the market for commercial use in China. In 2019, about 800 J-Valve TAVI procedures were performed in China, in which more than half was pure AR, and the clinical effect was very satisfied. At present, the transfemoral J-Valve system has begun clinical trials in Canada and the United States with promising results [48].

In 2016 one meta-analysis [67] summarized 13 TAVI studies with 237 pure AR patients who could not tolerate surgical valve replacement. Among them, the utilization rate of self-expanding valve accounted for 79%, the implantation success rate was 77–100%, the 30-day all-cause mortality rate was 7%, and the incidence of postoperative moderate and severe valvular regurgitation was 9% (0% in JenaValve subgroup). It can be seen that although the study included JenaValve, a second-generation TAVI valve, the incidence of moderate and severe regurgitation and valve displacement after AR TAVI procedure was significantly higher than that of aortic stenosis.

In 2017 Yoon et al. [68] concluded that the new generation of TAVI valve with positioning-assisted anchoring system for the treatment of pure AR has higher implant success rate than the first-generation valve (81.1% vs. 61.3%), greatly reducing postoperative residual valvular regurgitation and perivalvular leakage (4.2% vs. 18.8%), and the probability of reimplantation of a second valve is greatly

reduced (12.7% vs. 24.4%). Totally 331 AR patients underwent TAVI, with an average STS score of 6.7%. 119 cases (36%) used early valves, and 212 cases (64%) used a new generation of valvular systems. The STS score of patients with new-generation valve implantation system was lower (6.2 ± 6.7 vs. 7.6 ± 6.7), but there was no statistical difference. The new generation of valves is more likely to get through the femoral artery access (87.4% vs. 60.8%). There was no significant difference in 30-day mortality between the two groups. The 1-year all-cause mortality rates of the two groups were 24.1% and 15.6%, respectively. The 1-year all-cause mortality was related to the degree of postoperative aortic regurgitation. The mortality rate of cases with moderate and severe regurgitation was 46.1%, while mild regurgitation decreased to 21.8%. Multivariate analysis showed that more than moderate post-operative regurgitation was an independent predictor of 1-year all-cause mortality (increased by 2.85 times). And this data is not included in China's J-Valve system reports.

In 2018, De Backer et al. [69] reported 254 high-risk AR patients in 46 centers, with an average age of 74 ± 12 years, a STS score of 6.6 ± 6.2%, with first-generation valve of 43%, and second-generation valve of 57%. The success rate of new generation valve implantation was significantly higher (82% vs. 47%), valve displacement decreased (9% vs. 33%), and aortic valve regurgitation decreased (4% vs. 31%). Both small or large valve size will easily lead to valve displacement. In 2019, Takagi et al. [70] summarized the TAVI efficacy of 11 studies with 911 pure AR patients. The overall valve implantation success rate was 80.4%, of which the early valve and the new-generation valve were 67.2% and 90.2%, respectively. Moderate and severe perivalvular leakage was 7.4% (early and new-generation valves were 17.3% and 3.4%, respectively). The 30-day all-cause mortality rate was 9.5% (early and new-generation valves were 14.7% and 6.1%, respectively). During the follow-up from 4 months to 1 year, the all-cause mortality rate was 18.8% (early and new-generation valves were 32.2% and 11.8%, respectively). Vascular complications accounted for 3.9% (rates of early and new-generation valves were 6.2% and 3.0%, respectively). Life-threatening major bleeding was 5.7% (early and new-generation valves were 12.4% and 3.5%, respectively). In summary, the new generation of TAVI valve has a good therapeutic effect.

In China, there are also surgical high-risk cases in which the ascending aorta is not wide or the left ventricular outflow tract is small; some tried to use high stent self-expanding Venus A valve to treat pure AR patients. The results show that the valve displacement rate and the chance of reimplantation of the second valve are still very high (up to more than 50%). And there is also valve displacement into the ascending aorta or slipping in the left ventricle which may affect mitral valve function. These may result in doing open-chest surgery to remove the valve immediately. Therefore, this method is only suggested to be performed for high-risk patients and when other second-generation TAVI valves like J-Valve are not available.

The J-Valve valve with independent intellectual property rights in China is designed with three U-shaped positioning keys suitable for the anatomical structure of the aortic valve and sinus. The valve is released in two parts and then combined to play a role, which can more accurately locate the bottom of the aortic sinus and clamp the leaflet. J-Valve can effectively play a role in both aortic stenosis and regurgitation. A multicenter clinical study of trans-apical J-Valve in the treatment of high-risk noncalcified pure AR patients concluded data from 2014 to 2018 [71] in China. A total of 82 patients, aged 73.86.3 years, were included. The score of European cardiac surgery risk assessment system was 17.5 ± 8.1%. During the TAVI operation, four patients were converted to thoracotomy due to valve transposition, and the success rate of valve implantation was 95% (78/82). During hospitalization,

one case died of moderate perivalvular leakage complicated with multiple organ failure, and one case died of pulmonary infection. There was no residual aortic regurgitation in 82.1% (64/78) patients, mild perivalvular leakage in 16.7% (13/78) patients, and permanent pacemaker placement in 7.6% (6/78) patients due to III °atrioventricular block. The left ventricular end-diastolic volume decreased from (197.7 ± 66.8) ml to (147.2 ± 53.3) ml at 1 month after TAVI. The average transvalvular gradient was (9.5 ± 4.1) mmHg, which showed good hemodynamic performance.

For the common problems of lack of calcification anchoring and aorta dilatation in AR patients, the former has been solved to a certain extent by the continuous improvement of the second-generation TAVI valve with newly designed anchoring system, while the latter is still a difficult problem that cannot be solved at present. Therefore, many patients can only choose thoracotomy or even conservative medicine treatment. In addition, compared with patients with severe AS, patients with AR are often accompanied by more serious clinical symptoms, such as pulmonary hypertension, cardiac insufficiency, and so on. At the same time, late left ventricular hypertrophy, myocardial fibrosis, and cardiac insufficiency caused by AR may not be reversed even after TAVI, so these patients tend to have a poor prognosis and need longer time of medication treatment for the heart function recovery [29]. All these problems may take physicians more efforts in clinic to get good results for those AR patients with heart dysfunction besides of the TAVI procedure.

7. Conclusion

With the continuous development of interventional valve treatment technology, the interventional treatment of aortic stenosis and aortic insufficiency is more mature; many new generations of TAVI valves are emerging, which can be more convenient for clinicians to use, which can achieve more satisfactory treatment results. As for the development of TAVI technology and the extension of follow-up time, the indications of TAVI technology are also expanding. It is reasonable to believe that TAVI technology will be the main treatment technology in the future.

Acknowledgements

I would like to thank our heart valve center of cardiac surgery department of Beijing Anzhen Hospital, Capital Medical University. Their joint efforts made our center the first unit in China to successfully carry out interventional therapy technology for all four major heart valve diseases. Thanks to president Wei Yongxiang and vice president Zhou Yujie for their consistent strong support and trust in the development of new technology in our team. Thanks to professor Meng Xu, discipline director, for his planning and design, our center began to track the latest preface technology of TAVI technology as early as 2006 and kept close academic contact with the international advanced center. Thanks for the selfless dedication and support of our center's TAVI team, including cardiac surgery, cardiology, anesthesiology, imaging, hybrid operation room, intensive care unit, ultrasound department, interventional department, etc. At the same time, I also thank TAVI teams of other heart centers in China for their support and help.

Conflict of interest

I confirm that there are no conflicts of interest.

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