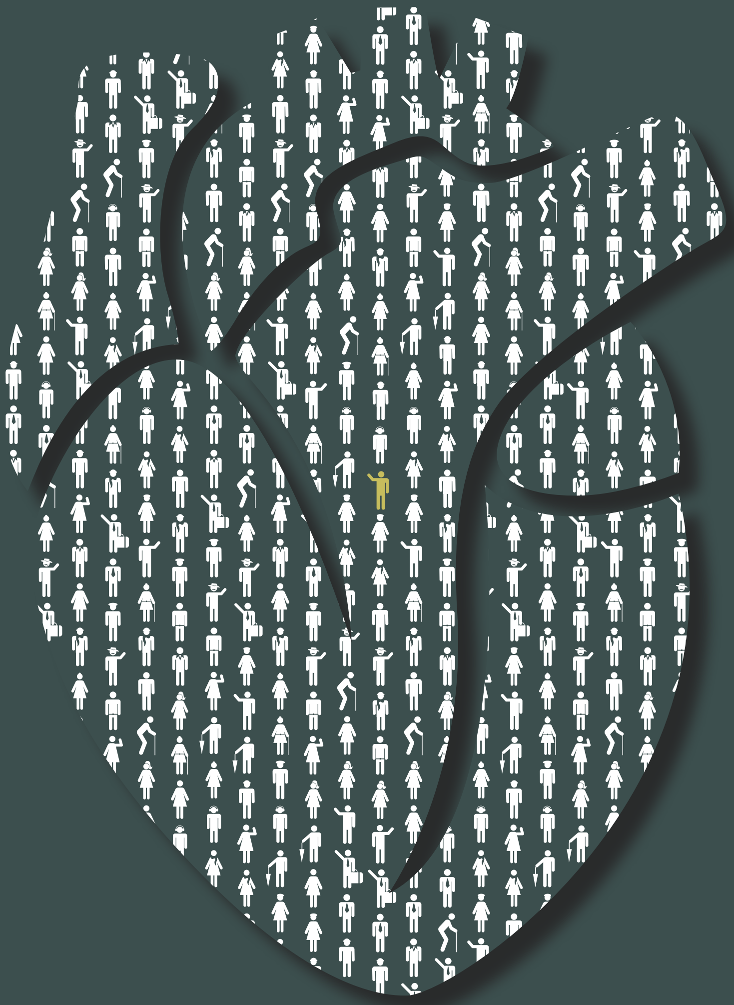
PERSONALIZED TREATMENT
IN MITRAL VALVE SURGERY



JULES R. OLSTHOORN

Personalized Treatment in Mitral Valve Surgery

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Personalized Treatment in Mitral Valve Surgery

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General introduction

INTRODUCTION

Historical Interpretation of Mitral Valve Function

The heart has played an important role in understanding the body since antiquity. In the fourth century before Christ, the Greek philosopher Aristotle identified the heart as the most important organ of the body. [1] The Renaissance revival of anatomy made it possible for physicians to clarify the basic structures of the heart by dissections of human bodies, in which Leonardo da Vinci played a crucial role. [2] By this point, they commonly agreed the heart was divided into four parts with two ventricles and two auricles. By the middle of the sixteenth century, a handful of physicians begun to wonder about several key hypotheses of the heart. Yet it was until the English physician William Harvey wrote his On the Circulation of the Blood in 1628, that a viable alternative to Galenic physiology (the liver as the central organ) became widely accepted and is still used today. [3]

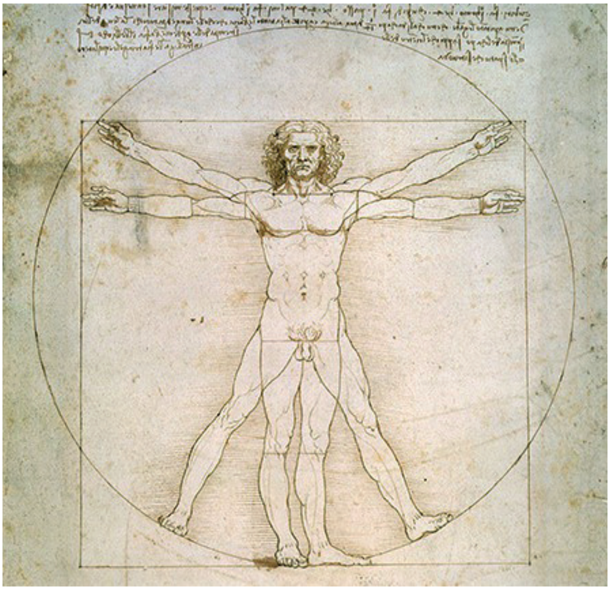


Figure 1. Leonardo's Vitruvian man. (Reproduced with permission from Francis C Wells.., Copyright Elsevier).

Leonardo Da Vinci

Leonardo da Vinci, born in 1452 in Tuscany, is seen as one of the first who described the cardiovascular system as we know it today.[4] As an artist, sculptor, and inventor, da Vinci wanted to know, not only how the body was constructed, but also explore the function of the essential organs. He discovered that the heart, not the liver, was at the core of the blood system. He noted that both atria contract when the ventricles dilate, explaining the movement of blood from the atria to the ventricles. [5] He also noted that both the right atrium and ventricle are larger than the left atrium and ventricle. Leonardo da Vinci had a particular fascination for the cardiac heart valves and concluded that all valves should open and close completely, otherwise the heart will not function adequately, with regurgitation of blood in the atria from the ventricles. "The upper are separated by certain little doors from the lower ventricles. Furthermore, if it is one and the same, there is no need for the membranous doors which separate one from the other. The cusps of the greater valves of the heart [*mitral and tricuspid*] are closed by the percussion of the blood which escapes from the lower ventricles of the heart to the upper ventricle outside the heart [*atrium*]. They are reopened by the reflux of the blood pushed from the upper ventricles into the lower. And the vacuum which would be generated by the opening of the lower ventricles when they reopen is the cause of pulling back into themselves the blood of the upper ventricles when they are emptied."[5]

In his manuscripts, Leonardo described the heart valves in detail, accompanied by magnificent, detailed drawings of the mitral valve (MV), which are currently in the possession of Her Majesty Queen Elizabeth II. In his manuscripts he wrote, "In front the gates are found to be membranous and they are held from behind, that is, protected from within, by threads which prevent their reversal." [5] As an engineer he was the first to understand and describe the function of the MV with the subvalvular apparatus. He described the nature of this complex interplay, by making a comparison with pulleys, weights, and ropes. Leonardo thought that in the contraction phase of ventricular action, the pull on the lateral wall tensioned the leaflets and drew them into apposition. In diastole the pull of the papillary muscle contraction caused the leaflets to open. Leonardo realized that this was how the valve closed, and he drew this vitally important relationship multiple times.

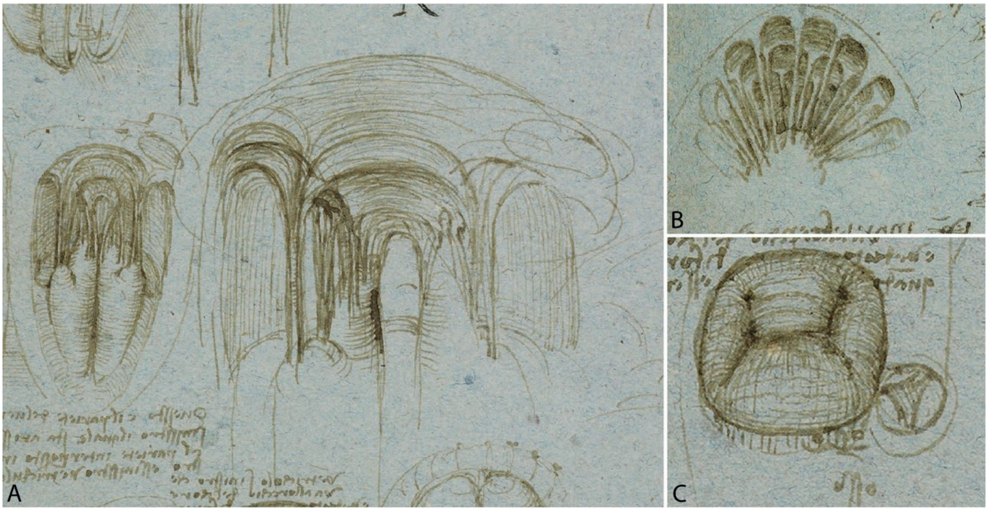


Figure 2. Detailed drawings of the mitral valve by Leonardo Da Vinci. (A) The subvalvular apparatus (B) The Chordae Tendinae (C) The coaptation surface. (Reproduced with permission from Francis C Wells., Copyright Elsevier).

Leonardo perceived the valve leaflets consisted of two separate layers. Where the cords spread out on the underside of the leaflets, they diminish in thickness. The atrial side of the leaflet has a smooth covering of uniform thickness. This distinction of layers in the leaflets was extremely accurate for that time and is still used today. Da Vinci was the first to describe a coaptation surface between the anterior and posterior leaflet, which is crucial in reconstructive MV surgery. The coaptation surface has the effect of load distribution, somewhat in the same way as the keystone in an archway does. Remove the keystone and the arch falls. However, it was Andreas Vesalius who suggested the term "mitral" to describe the left atrioventricular valve owing to its resemblance to a view of the bishop's mitre. [6]

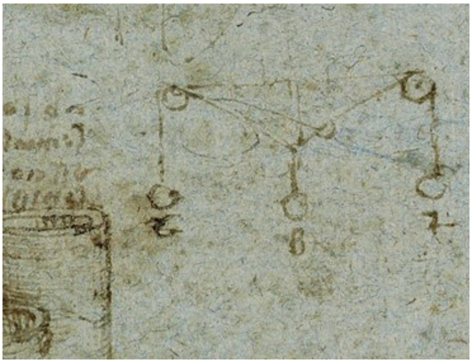


Figure 3. A comparison with pulleys, weights, and ropes. (Reproduced with permission from Francis C Wells.., Copyright Elsevier).

Mitral Valve Physiology

The function of the MV apparatus is dependent on a complex interplay between the annulus, the anterior- and posterior leaflet, the primary, secondary and tertiary chordae tendineae, the papillary muscles and the left ventricle.[7-9] The valve is obliquely situated in the heart and has a close relation to the aortic valve (AV) through the fibrous aortic-mitral curtain. The MV and AV angulate on two separate planes with an angle of approximately 120 degrees. The MV opens during diastole to allow blood flow to the left atrium to fill the decompressed left ventricle (LV). During systole the increase pressure in the LV causes the valve to close, preventing blood from leaking into the left atrium and assuring that the stroke volume is ejected through the AV. The MV annulus is saddle-shaped and has a greater intercommissural diameter compared to the anterior-posterior diameter.[10] The leaflets are divided in an anterior leaflet (AML) and posterior leaflet (PML), which are in turn divided into three scallops (number 1 to 3) from lateral to medial. The MV leaflets are attached to LV and papillary muscle through the chordae tendineae. There are three types of chordae based on their insertion level: the primary chordae insert on the free margin of the leaflets, the secondary chordae insert on the rugged surface of the leaflets, and the tertiary chordae insert only on the basal part of the posterior leaflet. [11] The chordae insert in the two dominant papillary muscles, an anterolateral and posteromedial head.

Mitral valve annulus

The MV annulus constitutes the anatomical demarcation between the left atrium and the LV. According to the insertion of the valve leaflets, the annulus is divided in an anterior and posterior segment. The anterior annulus is generally more developed compared to the posterior segment of the annulus. The anterior annulus at the anterior leaflet, together with the fibrous trigone, is more resistant to pathologic dilatation compared to the posterior part of the annulus and less frequently affected by annular calcification. The right fibrous trigone is a dense junctional area between the mitral, tricuspid, non-coronary cusp of the aortic annuli and the membranous septum. The atrioventricular conduction bundle passes through the right fibrous trigone. The left fibrous trigone is situated at the junction of both left fibrous borders of the aortic and the mitral valve.

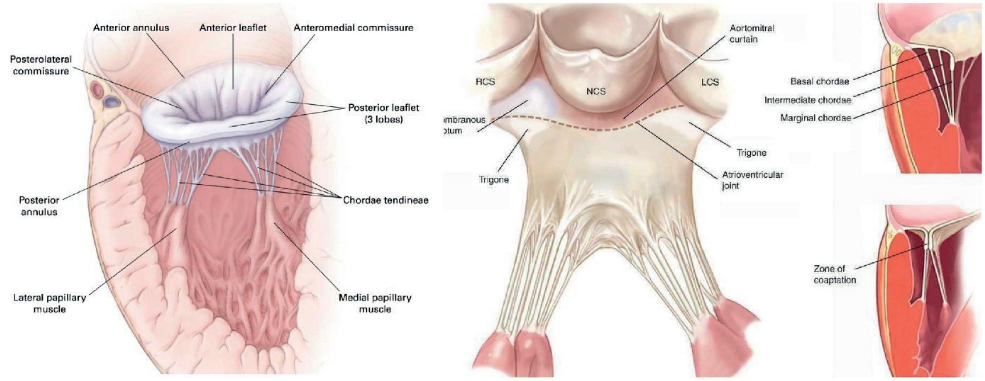


Figure 4. Detailed anatomy of the mitral valve. (Reproduced with permission from Otto et al., Copyright Massachusetts Medical Society and Castilloa et al., Copyright Revista Española de Cardiología)

The leaflets

The AML is in fibrous continuity with two of the three AV leaflets (the non-coronary and left coronary cusp), therefore its alternatively called the aortic leaflet. The opposite leaflet, PML, is also named the mural leaflet. The surface area of both leaflets taken together is 2.5 times the area of the valvular orifice. [7] The AML has a rounded free edge and occupies a third of the annular circumference and is usually continuous, without indentations. Whereas the PML is long and narrow, has a quadrangular shape, lining the remainder of the circumference. The PML typically has two well defined indentations, which divides the leaflet into three segments (i.e., P1, P2 and P3). The scallops of the leaflets are not equal in size, the middle scallops tend to be larger in most adult hearts. [12] The commissures define a distinct area of the leaflet where the AML and PML come together at their insertion into the annulus. Indentations between leaflets at the commissures do not reach the annulus, but the leaflets fuse 5mm before reaching the annulus. When both leaflets coaptate the valve resembles a smile (or Bishop’s Mitre).

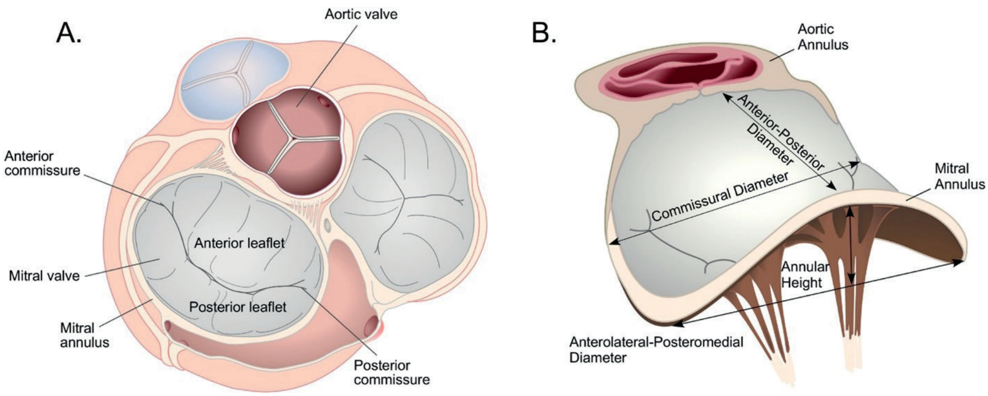


Figure 5. (A) Cardiac plane showing the orientation of the mitral valve to the other heart valve. (B) Three-dimensional structure of the mitral valve annulus. (Reproduced with permission from Jolley et al. Copyright Elsevier).

Chordae tendinae

The chordae tendinae are the chord like structures connecting the leaflets to the papillary muscle. The chordae tendinae are primarily responsible for the end-systolic position of the AML and PML. Marginal chordae (primary chordae) are inserted on the free margin of the leaflets and function to prevent prolapse of the free edge of the leaflet. Intermediate chordae (secondary chordae) insert on the ventricular surface of the leaflets and relieve valvular tissue of excess tension.[11] They may also be important in preserving ventricular shape and function. Basal chordae (tertiary chordae) are limited to the posterior leaflet and connect the leaflet base and mitral annulus to the papillary muscle.

Papillary muscles

The chordae tendinae are connected to the ventricle via the papillary muscles. The complex interplay of the MV is integrally related to the function and dimensions of the LV. However, there is also a reverse interplay, where the chordae tendinae and papillary muscle retain the shape of the left ventricle. [13, 14] Two papillary muscles arise from the apical and middle parts of the left ventricular wall. From an anatomical standpoint, the anterolateral papillary muscle usually has a single head, while the posteromedial papillary muscle commonly has double or multiple heads.[15] The posteromedial papillary muscle has a single blood supply usually from the posterior descending artery, while the anterolateral papillary muscle is usually supplied by both the left anterior descending artery and left circumflex artery. [16]

Mitral Valve Pathology

Valvular heart disease (VHD) is a major contributor to loss of physical function, quality of life and longevity. In industrialized countries, the prevalence of valvular heart disease (VHD) is estimated at 2.5% [17] Rheumatic heart disease (RHD) remains by far the most common manifestation of VHD worldwide and affects approximately 41 million people. By contrast, the prevalence of calcific aortic stenosis and degenerative mitral valve disease is 9 and 24 million people, respectively. [18] Mitral regurgitation is a more heterogeneous condition than either aortic stenosis or RHD. The heterogeneousness of mitral valve disease makes treatment challenging. Furthermore, as the spectrum of mitral valve disease is broad, the comparison of outcomes between disease entities, treatments and centers warrants caution.

Mitral Valve Stenosis

Mitral valve stenosis represents 12% of patients with VHD referred to the hospital. [19] The main etiology contributing to the prevalence of MS are degenerative calcifying MV disease and rheumatic disease, of which the last is the most common cause of VHD worldwide. Rheumatic heart disease is thought to be related to an exaggerated immune response initiated by cross-reactivity between a streptococcal antigen and the valve tissue[20] Asymptomatic MV stenosis has a good prognosis, with 20-year survival exceeding 80%. Ten-year survival rates range from 30 to 60% after symptom onset. [21] Patients with MS are more frequently treated with mitral valve replacement (MVR). However, in experienced centers around the world, durable mitral valve repair is achieved (MVr). [22, 23]

Mitral Valve Regurgitation

Mitral regurgitation (MR) is the second most frequent indication for valve surgery in Europe. Causes of MR can be divided into primary and secondary etiologies. Primary MR, sometimes called degenerative mitral valve regurgitation (DMR) or organic, is due to an intrinsic lesion of the MV apparatus. [24] The most frequent cause of primary MR in industrialized countries is MV prolapse, which is due to chordae tendinae rupture, in most cases. [25] Mitral valve prolapse is a common disorder, afflicting 2% to 3% of the general population. [26, 27] If left untreated, MR can lead to depleting symptoms including cardiac arrhythmia, congestive heart failure and irreversible heart damage.

Carpentier’s functional classification

In order to allow intercollegial communication, Carpentier developed a classification system based on a pathophysiologic triad, which describes the inter-relationship between etiology, lesions and leaflet motion dysfunction. [28, 29] Carpentier’s classification of dysfunction is based on the opening and closing motions of the MV leaflets in relation to the annulus. Carpentier stated that there are only two functional anomalies: the opening and closing motions of each leaflet are either increased as with leaflet prolapse or diminished as with restricted leaflet motion. Leaflet prolapse is present when the free edge of the leaflet overrides the plane of the orifice/annulus during systole. Restricted leaflet motion defines a condition in which a leaflet does not open normally during diastole.

Patients with type I MV dysfunction present with normal leaflet motion. Mitral regurgitation in these patients is due to annular dilation or leaflet perforation. Type II describes an increased leaflet motion, with the free edge of the leaflet overriding the annular plane during systole. A leaflet prolapse may result from chordal rupture or elongation or from papillary muscle rupture or elongation. Patients with type IIIa MV dysfunction have a restricted leaflet motion during both systole as diastole. Restricted leaflet motion may result from commissural fusion, leaflet thickening, chordal fusion, and/or chordal thickening. In type IIIb there is restricted leaflet motion during systole, which is in most cases caused by apical papillary muscle displacement due to left ventricular enlargement.

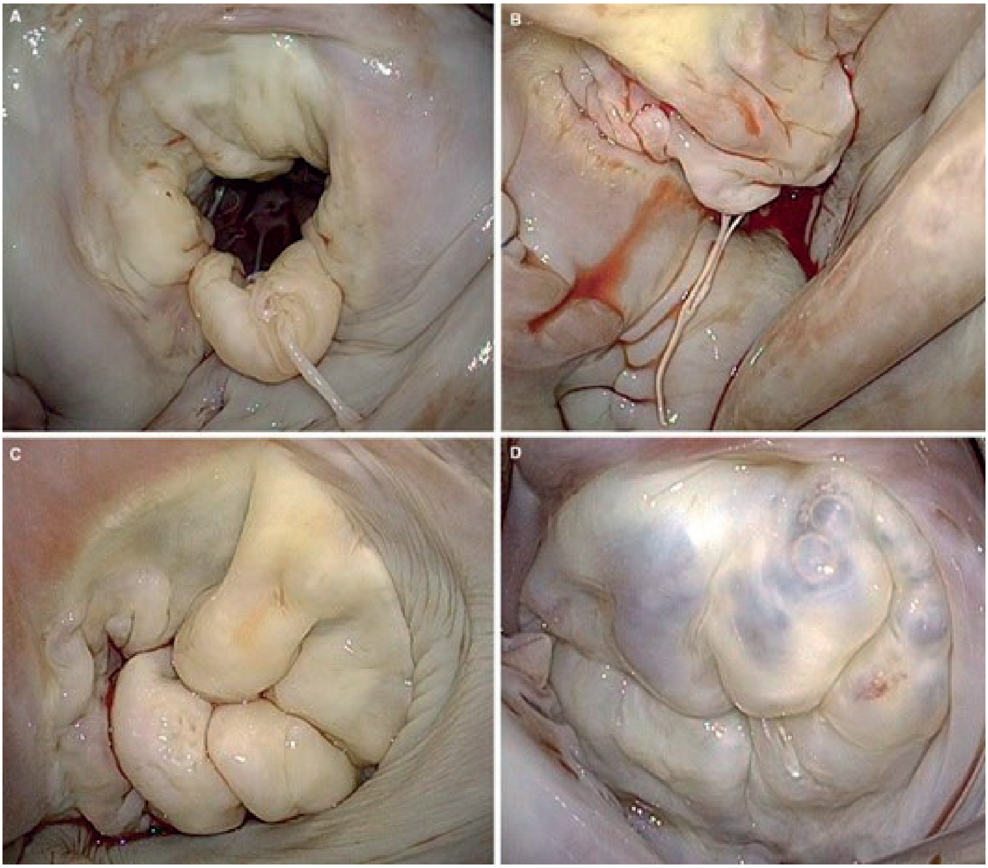


Figure 6 Surgical images of the lesions most frequently associated with degenerative disease of the mitral valve. (A) posterior prolapse due to chordae tendineae rupture. (B) anterior prolapse due to elongation, thinning and rupture of chordae tendineae. (C) anterior and posterior prolapse secondary to elongation of the chordae tendineae and myxomatous degeneration of several segments; note the pathologic clefts in the posterior leaflet.(D) Barlow's disease with myxomatous degeneration of both leaflets. (Reproduced with permission from Castilloa et al., Copyright Revista Española de Cardiología)

The most common diseases that cause degenerative mitral valve disease are Barlow's disease and fibroelastic deficiency. Fibro-elastic deficiency is mostly seen in patients 60 years and older, who present with a short history of valve incompetence. Mitral valve regurgitation in these patients is mostly caused by rupture of a single chord which result in prolapse of a single segment. Prolapse of the P2 segment is the most seen pathology in these patients. [30]

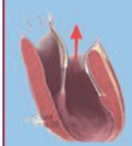
Dysfunction	View Atrial	Lesions	Etiology
Type I Normal motion 		Annular dilatation Annular deformation Perforation of leaflets Clefts in leaflets	Ischemic heart disease Dilated cardiomyopathy Endocarditis Congenital pathology
Type II Excess motion 		Myxamotous degeneration Elongation of chordae Rupture of chordae Elongation of papillary muscle Rupture of papillary muscle	Degenerative disease Fibroelastic deficiency Marfan syndrome *Forme fruste* Barlow's disease Endocarditis Rheumatic disease* Trauma Ischemic heart disease Ehler-Danlos disease
Type IIIA Restricted motion (Retraction) 		Thickening of leaflets Retraction of leaflets Thickening of chordae Retraction of chordae Fusion of chordae Calcification Fusion of commissures Ventricular fibrosis	Rheumatic disease Carcinoid syndrome Radiotherapy Systemic lupus erythematosus Ergotamine consumption Hypereosinophilic syndrome Mucopolysaccharidosis
Type IIIB Restricted motion (Apical displacement) 		Tethering of leaflets Papillary displacement Ventricular dilatation Ventricular aneurysm Ventricular fibrosis	Ischemic heart disease Dilated cardiomyopathy

Figure 7. Pathophysiologic triad of mitral regurgitation. *Finding leaflet prolapse in the context of rheumatic disease only occurs if a type III dysfunction exists or pseudo-prolapse is identified. (Reproduced with permission from Castilloa et al., Copyright Revista Española de Cardiología)

In 1887 the syndrome of a midsystolic click and systolic murmur, currently known as Barlow's disease, was first described by Cuffer and Barbillon[31]. However, it was until the 1960s that these findings were recognized to be due to MV prolapse. [32] Barlow's disease is characterized by several features, of which the main features are excess leaflet tissue, with billowing or prolapse of both the AML and PML, annular dilatation and annular disjunction. Chordal elongation is the most common cause of prolapse with multiple segments involved. It generally occurs in patient 60 years and younger, who have a long history of a heart murmur. Barlow's disease is seen as one of the most complex forms of DMR and is the most challenging pathology to repair.

Type I is a less common form of DMR and is most seen in patient with significant atrial dilatation. In most cases atrial dilatation is caused by atrial fibrillation or may occur in patients with connective tissue disorders. Type IIIa MV dysfunction is mostly seen in patients with rheumatic disease, whereas Type IIIb is mostly seen in patients after myocardial infarction.

Characteristics	FD	Advanced FD	Forme fruste	Barlow's disease
Age at diagnosis	>60 years	>60 years	Variable	<60 years
History of MR	<5 years	<5 years	Variable	>10 year
Leaflet tissue	Normal/Translucent	++	++/+++	+++
Anterior leaflet tissue	+	+	++	+++
Posterior leaflet tissue	++	++	++/+++	+++
Segments affected	Single segment (P2)	Single segment (P2)	Multisegment	Multisegment
Chordae tendineae	Thin and ruptured	Thin and ruptured	Variable	Thickened and elongated
Annular dilatation	Ninguna (≤32 mm)	↑ (≤32 mm)	↑↑ (32-36 mm)	↑↑↑ (≥ 36 mm)
Calcification	None	+	+/++	+++

Figure 8. The spectrum of mitral valve disease from fibroelastic deficiency (FD) to Barlow's disease. (Reproduced with permission from Castilloa et al., Copyright Revista Española de Cardiología)

The History Of Mitral Valve Surgery

At the beginning of the last century, MS due to rheumatic heart disease was a public health problem resulting from poor sanitation, an absence of antibiotics and incomplete understanding of the mode of transmission resulting in rheumatic fever. [33] Rheumatic fever, which in turn causes rheumatic heart disease, affects the MV by causing fusion of both the anteromedial as posterolateral commissures of the valve resulting in MS. [34] Mitral valve stenosis causes obstruction of blood flow, which result in pulmonary congestion, pulmonary hypertension and eventually right ventricle heart failure. [35]

In the 1900's many young individuals were affected by rheumatic fever and in turn MS, which, at that time had no (surgical) treatment options. However, the historical pathway illustrates the many small steps taken by cardiac surgeons in the past century to treat MS, expanding the techniques learned to other disease entities involving the MV, and form the basis to eventually perform surgery on the mitral valve through a minimally invasive approach (MIMVS).

The first written communication referring to the surgical treatment of MS, was written by Thomas Lauder Brunton, working at the London Hospital in 1902.[36] He was the first who postulated that mechanical or surgical opening of the heart valve, could improve the output of the heart. He recognized that MS, in the end stage of the disease, was refractory to all medical treatment modalities. In the following period, between 1907 – 1914, several physicians [37-39] studied and developed animal models for creating and treatment of MS. Simultaneously, Cutler was working on an instrument which could be used to cleave the MV, to open up the valve and improve the atrioventricular blood flow. [40] The device was named the cardiac valvulotome. [41]

In 1923, the first patient was successfully treated for MV disease by a surgical operation. An 11-year-old patient was brought to Elliot Cutler and his colleague Samuel Levine, in an almost comatose state due to low output cardiac failure. Through a median sternotomy, a transapical, bilateral mitral commissurotomy was performed with the use of a neurosurgical tenotomy knife. The patient recovered well and was discharged after two weeks.[42] After the initially seemingly successful procedure and completing of the mitral valvulotome, the understanding of the severe MR the device would cause, was limited. In the period following, several patients were operated with this new invented device. Unfortunately, all patients died due to acute cardiac decompensation caused by the MR. In 1929, at the American Surgical Association meeting, Cutler announced that he was declaring a moratorium on this operation due to its high mortality.[43]

In 1925, following the first successful case by Dr. Elliot Cutler, Henry Souttar performed the first closed chest MV valvulotomy. Through a left thoracotomy and the left atrial appendage, he inserted his finger and dilated the MV and relieved the stenosis, nowadays known as the finger fracture valvuloplasty. [44] This procedure became the standard surgical procedure during the following years and can be considered the first minimally invasive mitral valve surgical procedure. After the second world war and the dead of Dr. Elliot Cutler, his work was continued by Dwight Emery Harken. The results were published in 1948, which were the first to show that the surgical treatment of MS, could be performed safely and reproducibly without sternotomy.[45] During this time period he worked closely with Dr. Laurence B. Ellis, a cardiologist and exemplifies the concept that MV disease are best treated by a team involving cardiac surgeons and cardiologists. [46]

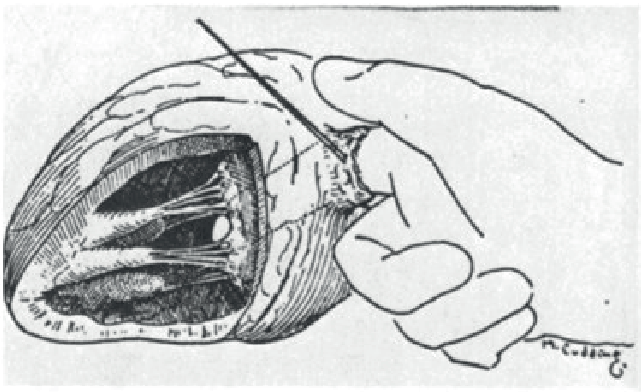


Figure 8. The first closed chest MV valvulotomy. (Reproduced with permission from Dwight Emary Harken, Copyright Elsevier)

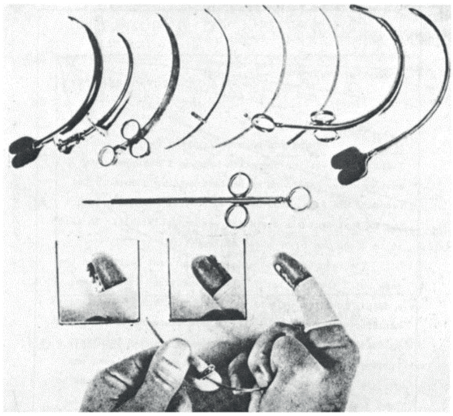


Figure 9. Cardiac Valvulotomes (Reproduced with permission from Dwight Emary Harken, Copyright Elsevier))

In 1953, the groundbreaking invention and the first successful application of cardiopulmonary bypass was performed by Gibbon, which started a new era in the field of cardiothoracic surgery. [47] In the years following, several new procedures were developed and performed, not limited to the field of MV disease. Although MVr for mitral insufficiency was already performed by Dr. C. Walton Lillehei at the university of Minnesota in 1957[48], most surgeons believed MR required valve replacement.

In 1960, the first artificial MV prothesis was implanted by Dr. Nina Starr Braunwald at the National Institutes of Health.[49] Mitral valve surgery was subsequently revolutionized by Dr. Albert Starr and his colleague M. Lowell Edwards at the University of Oregon, who developed the first commercially artificial (*or mechanical)* MV in the early 1960s. [50] In the beginning of MVR, the subvalvular apparatus, including the papillary muscles and chordae were excised. The initial good short-term results, with the mitral Starr-Edwards ball valve were followed by a return of congestive heart failure due to severe cardiomyopathy. This shortcoming was overcome in 1975, by Walton Lillehei, by preserving the papillary muscles and chordae tendinea. [51] Moreover, in addition to the improvements in surgical valve implantation techniques, Dr Alain Carpentier developed a *biological* porcine MV prothesis. [52] Despite the improved implantation techniques and development of artificial MV prothesis, patients were subjected to the devastating complications with a prosthesis in a low-flow position. Therefore, there was an increasing interest for the development of reconstructive MV surgery for the surgical treatment of MR.

After that first successful MV repair by Walton Lillehei, many more followed in a later era. Dr. Dwight C. McGoon of the Mayo Clinic published several techniques, which are still in use today, for MR in 1960. [53] He was the first to publish the technique of restoration of a ruptured chorda. [53] Several decades later, in 1983, Carpentier published the most influential paper in the history of MV surgery entitled "The French Correction".[28, 54] The manuscript outlined the classification of MV lesions based on the MV's functional principles. Nowadays, these principles still form the basis for MVr in MR, particularly in degenerative myxomatous MV disease. The results presented by Carpentier inspired many surgeons throughout the world.

The classic operation designed by Carpentier involved cutting out the ruptured cord segment of the PML and creating advancement flaps of the whole PML of the MV. [29] Initially, MVr was performed without the use of annuloplasty rings. However, the recurrence rates between MVr with and without annuloplasty ring showed dramatic differences.[55] The importance of MVr with the use of an annuloplasty ring was first introduced by Carpentier. [56] These techniques have proven their use, and nowadays the techniques proposed by Alain Carpentier are classified as the *resect* technique. [57]

Indeed, two different strategies, that can also complement each other, can be considered; *resect or respect*. The latter technique, during which the diseased MV leaflet is not resected but restored with artificial neochordae, has been advocated by many, mimicking and respecting nature. [58] The goal of the "respect rather than resect" approach is to correct the prolapse without leaflet resection and to transform the posterior leaflet into a smooth and vertical buttress, ensuring an optimal coaptation surface. [59]

Important evolutions in perfusion technologies, with smaller cannulas and the possibility of vacuum-assisted venous drainage allowed maximal intrathoracic space, which allowed smaller incisions. These inventions opened the door towards minimally invasive mitral valve surgery. In 1996 and onwards, several cardiothoracic surgeons (Carpentier,[60] Navia[61], Chitwood[62], Cosgrove[63], Perier and Mohr[64]) started with video-assisted mitral valve surgery, paving the way for these minimally invasive techniques, as we still use it nowadays.

Relevance Of Mitral Valve Disease and Current Guidelines

Mitral regurgitation is the second-most frequent VHD in Europe. [65, 66] Degenerative MV disease is mostly seen in well-developed high-income countries, as in low-income countries, rheumatic etiology is still the most frequent cause of MR.[67] Approximately 24 million people worldwide are affected (with a higher prevalence in older age groups). No reliable data on the global prevalence of secondary MR are currently available. The absolute prevalence of DMR has increased significantly over the past 20 years (by 70% between 1990 and 2017), with little change in the age-standardized prevalence and a fall in age-standardized mortality (by 32% from 1990 to 2019). [68]Extreme variations in the resources available to treat VHD persist, with very limited access to surgical or transcatheter procedures in many parts of the world owing to the combination of high device costs and available workforce capacity and expertise.

Community Prevalence

Echocardiography is the first-choice imaging modality to grade MV disease. In the OxVALVE study[69], the community prevalence of moderate or greater MR was seen in 2.4%. The prevalence is strongly age-dependent, with rise to 7.7% in patients ≥75 years. Most patients were asymptomatic with NYHA class I (65.3%). However, still a small proportion of patients had mild symptoms, NYHA class II was seen in 32.7% of patients and NYHA class III in 2.0% of patients. In primary MR the most observed mechanism was Carpentier type I in 39.4% of patients. Carpentier type II was seen in 17.7% of patients. In patients with secondary MR, Carpentier type IIIb was the most frequently observed mechanism.

Guidelines

The current ESC/EACTS Guidelines for the management of VHD formulated recommendations for primary and secondary MR separately. Furthermore, current evidence justifies a distinction between symptomatic and asymptomatic patients.[70] Surgery is indicated in symptomatic patients with severe primary MR, when the surgical risk is acceptable. In patients without symptoms, surgical treatment should be guided by the presence of secondary triggers. A decreased LV ejection fraction (≤60%), increased LV end systolic diameters (≥40mm), increased indexed left atrial volume (≥ 60 mL/m^2) or an increased diameter (≥ 55mm), the presence of pulmonary hypertension (>50 mmHg) and onset of atrial fibrillation are all associated with a worse outcome.[71-77] Urgent surgery is only indicated in patients with acute symptomatic severe MR (i.e., papillary muscle rupture, endocarditis) Asymptomatic patients with severe MR and LVEF >60% should be followed clinically and by echocardiography every 6 months and patients with moderate MR can be followed on a yearly basis.

The current guidelines recommend MVr as the surgical intervention of choice in primary MV disease when durable results are expected, with a class I (level B evidence) recommendation. Mitral valve repair is associated with better long-term survival compared to MVR. [78, 79] Furthermore, a lower operative mortality and fewer valve-related complications are observed for MVr compared with

MVR. When repair is not feasible, MVR with preservation of the subvalvular apparatus is favored. [80] In this light, the adage is: an optimal repair trumps a good replacement, but a good replacement trumps a suboptimal repair.

Patients with secondary MR represent a different disease entity. In these patients' valve intervention is only recommended in patients with severe MR who remain symptomatic despite guideline-directed medical therapy. However, when patients require other surgery for coronary artery disease or other valve disease, the MV should be addressed during the same procedure.

Repair techniques

Mitral valve repair can be achieved with a plethora of different repair techniques. The chosen technique is mostly at the preference and experience of the surgeon. Repair techniques for PML prolapse includes (resect): quadrangular resection, quadrangular resection with sliding plasty, triangular resection, folding technique, and butterfly techniques or the respect approach, with correction of the prolapse by using polytetrafluoroethylene. Isolated PML prolapse can be repaired equally effectively by leaflet resection or by creation of artificial chordae. [81] For PML prolapse, the choice of repair technique is dictated primarily by the predicted risk of postoperative systolic anterior motion (SAM). In case with low risk of SAM, simple resection can be performed. However, when there is a high risk of SAM, a sliding repair can be performed to position the coaptation point more posteriorly. Artificial chordae can be used in either situation, as the position of the coaptation point can be adjusted by the length of the chordae.

Anterior leaflet prolapse is most effectively treated by creation of artificial chordae, chordal transfer or papillary muscle transposition. [82, 83] The primary challenge with artificial chordae is the judgment of chordal length. In general, chordae to the PML will be shorter than those to the anterior leaflet. Once initial chordal length has been determined, the LV is insufflated with saline and the point of coaptation is determined. All repair strategies for DMR should be accompanied by insertion of a prosthetic annuloplasty ring. However, the method of MVr is highly operator dependent.

When utilizing a systematic approach, a successful and durable repair can be achieved in most DMR cases. However, surgeons should (almost) never accept a repair that ends with MR that is greater than mild (1+). Even mild MR at the completion of the repair is associated with an increased risk of late repair failure. [84]

Outcomes Of Current Surgical Treatment

Once a patient develops symptoms, MV surgery with repair or replacement, in patients with severe primary MR, will uniformly result in improvement or resolution of symptoms. However, the former strategy to only intervene surgically if symptoms occur is currently slowly abandoned, as once left ventricle dysfunction occur, MV disease has already transitioned to irreversible LV damage, and prognosis is worse. [85] Mitral valve repair is associated with a lower operative mortality, greater long-term survival and quality of life, and lower incidence endocarditis and bleeding from anticoagulation compared with mitral valve replacement. [86] Currently, an increase in surgically treated patients is observed. [87]

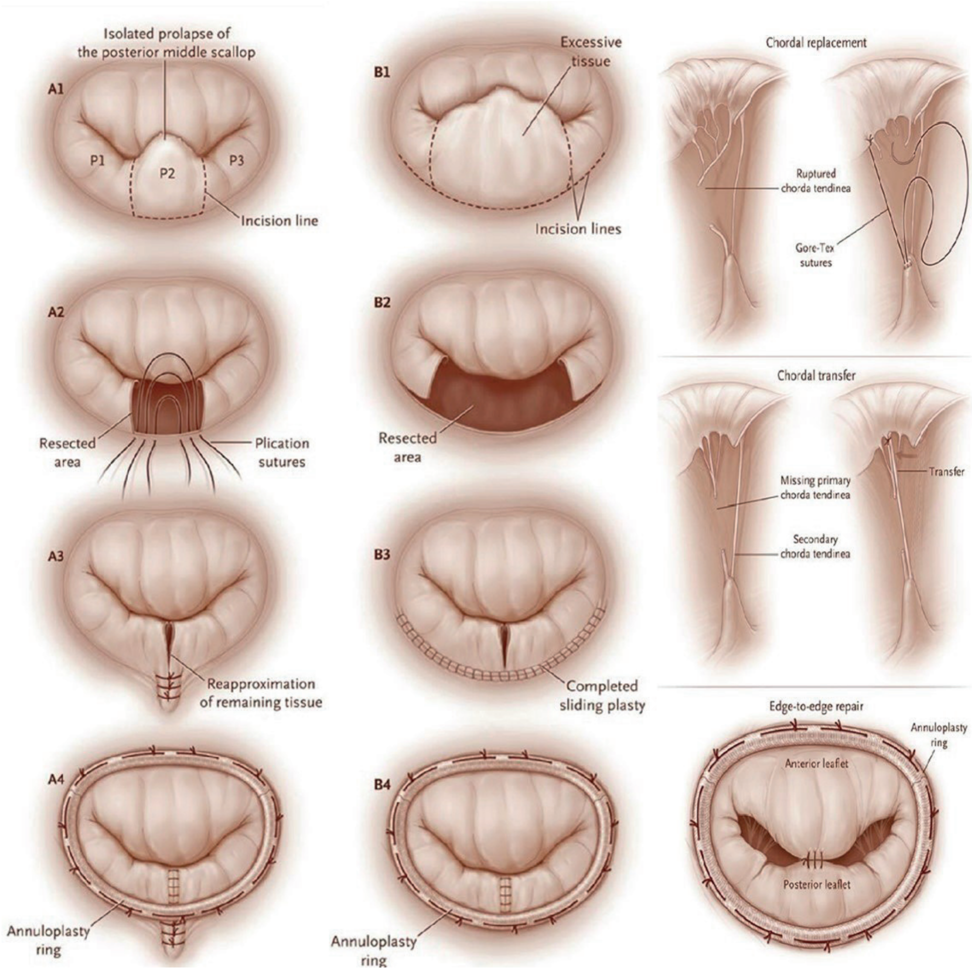


Figure 10. (Left side) Isolate prolapse of P2 segment with a quadrangular resection. (middle) excessive tissue with a sliding plasty of P2 (right) Chordal replacement, chordal transfer and edge-to-edge repair. (Adapted and reproduced with permission from Coutunho et al., Copyright BMJ)

Recent reports show very high rates of MVr, with a low peri-operative mortality in all types of lesions and valve complexity. [88, 89] At high volume centers, the repair rate for posterior leaflet prolapse is >98%, and 90-95% for anterior and bileaflet prolapse respectively. [88, 90] Also excellent 20-year durability in posterior leaflet repair with acceptable durability in anterior and bileaflet repair are reported. The reoperation rate per year after any subset of leaflet prolapse, whether it is posterior

(0.5%), anterior (1.6%), or bileaflet (0.9%), are similar to MV replacement (0.74%). [88] In experienced centers, MVr can be done with an operative mortality of less than 1%. However, if we compare these outcomes of single high-volume centers to the current known registry data, the repair rate of mitral valve disease is lower. In The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database, the overall MV repair rate was 65.6% for patients undergoing isolated MV operations.[87] In the most recent analysis, the overall operative 30-day mortality was 2.0. Interestingly, among all patients with isolated MV operations, 5.6% had an attempted repair followed by a replacement (during the same operation). For DMR 4.8% of all operations resulted in a replacement after an unsuccessful repair. Surgical procedures and their outcomes are dependent on skills of individual surgeons and anatomy of the individual patients. A plethora of studies show an association between surgical volume and outcome across all the surgical subspecialties, whereby surgical volume is in fact a surrogate marker of surgical skills and cumulated experience to address the variability in individual anatomy of patients subjected to the same surgical procedure.

The Current American Heart Association/American College of Cardiology guidelines of special interest,[91] as these guidelines state that mitral valve repair for asymptomatic patients with preserved left ventricular function is reasonable, when the likelihood of a successful and durable repair is greater than 95%, with an expected mortality rate of less than 1%. Therefore, they encourage referral to a Heart Valve Center of Excellence.

Minimally Invasive Mitral Valve Surgery

The mitral valve has been traditionally approached through a median sternotomy. However, significant advances in surgical optics, instrumentation, tissue telemanipulation, and perfusion technology have allowed for MV surgery to be minimally invasive. For MIMVS to become accepted widely, at least equivalent, if not better, short- and long-term outcomes must be demonstrated compared with sternotomy. Current literature shows no difference in mortality between MIMVS and sternotomy. [92] Regarding the safety of MIMVS, no difference in perioperative stroke were found and MIMVS is associated with a significant reduction in reoperation for bleeding, a trend towards shorter hospital stay (LOHS), less pain and faster return to preoperative function levels than conventional surgery. In most studies, even in series from high-expert centers, longer cardiopulmonary bypass and aortic cross-clamp times are observed. Minimally invasive techniques such as minimally invasive mitral valve repair require between 75 and 125 operations to overcome the associated steep learning curve. Therefore, MIMVS is still not widely adopted world-wide due to steep-learning curves. In the STS database, majority of patients (74.1%) underwent mitral valve surgery through conventional sternotomy, whereas (23%) underwent less invasive surgical approaches. Robotic-assisted technology was reported in 8% of all procedures.

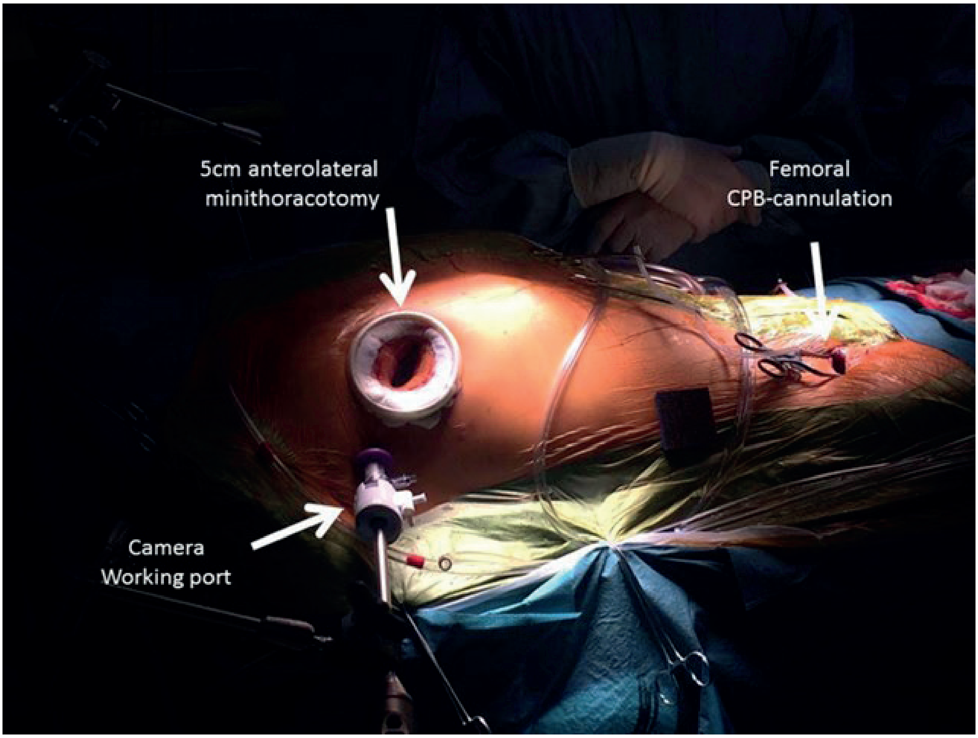


Figure 11. Our institution's operational set-up for minimally invasive mitral valve surgery

Personalized Medicine

Mitral valve (MV) disease is the most common, but also the most heterogeneous valvular pathological condition in the general population. In mitral valve surgery the individual anatomical variations, the lack of standardization, the steep learning curves (for a minimally invasive approach), the variety of repair techniques makes the quality of care extremely operator dependent. The field of MV surgery has changed tremendously over the last decades. Surgeons are in a transition from a standard open approach (sternotomy) towards minimal access approaches and eventually even minimally invasive techniques. Furthermore, the technological advancements have resulted in an increasing spectrum of treatment modalities. It will become increasingly important to match every individual patient to the best available treatment modality. As we strive to improve the quality of care for patients, we tailor our medical therapies to the appropriate and specific patient populations. In this paradigm-shift in medicine we are moving from pathology-based treatment to personalized medicine in mitral valve disease. Personalized medicine is an emerging concept involving managing the health of patients based on their individual characteristics. In MV disease, the concept of personalized medicine can be divided in three separate phases: the pretreatment phase, a personalized treatment phase, and a post treatment phase.

In this concept surgeons should not exclusively focus on the operation itself but concentrate on the whole process of treatment from the pre-treatment phase to the post-treatment phase. Embedded in personal medicine is the strive to work with dedicated teams throughout the treatment. Additionally, in the pretreatment phase, all patients considered for mitral valve intervention should undergo a standardized preoperative diagnostic pathway evaluated by a dedicated MV heart team after which they are allocated to their designated treatment. In this philosophy, precise patient selection and extensive pre-operative planning with the newest technologies including 3D imaging reconstruction, 3D printing, and simulation is imperative. The concept of personalized medicine is to enhance the quality of care by enhancing the patient's safety and improve the efficacy and reproducibility of our treatments. We should strive to extrapolate individual results to a successful formula adaptable by others to provide excellence to our patients worldwide. The concept of personalized medicine for MV surgery could make complex MV procedures more reproducible, more effective, and safer in the hands of many more surgeons.

SCOPE AND AIM OF THIS THESIS

The aim of the thesis is to improve the overall outcomes of patients referred with mitral valve disease. This thesis focuses on providing evidence for the concept of personalized medicine in mitral valve surgery, investigation the individual phases of patient selection and preoperative planning as well as perioperative care, with emphasis on minimally invasive mitral valve surgery.

OUTLINE

Chapter 2 describes the current standardized diagnostic pathway for mitral valve patients, with insight into our strategy of clinical decision-making for allocation of an individualized treatment and demonstrate the clinical outcome of all patients referred to the dedicated mitral valve heart team, surgically, interventionally and conservatively treated, in a tertiary referral center.

In **Chapter 3,** the effect of a dedicated mitral valve heart team on survival, compared to a general heart team, is presented.

Chapter 4 describes the concept of preoperative planning for minimally invasive mitral valve surgery. An overview of current literature on this topic together with our institutions experience in this field as a guidance for surgeons starting this program is presented.

In **Chapter 5,** the process of three-dimensional mitral valve modeling, printing and simulations and its clinical implications for mitral valve surgery is described.

Chapter 6 describes the surgical set-up and techniques for minimally invasive mitral valve surgery.

In **Chapter 7,** the incidence of a phenomenon, the so-called unexpected anterior leaflet prolapse during saline testing for isolated posterior leaflet repair, is investigated with predisposing factors underlying its occurrence and the consequences for surgical repair.

Chapter 8 describes the comparison of two different antithrombotic therapies after mitral valve repair, with important implications for current practice and peri-operative care.

Chapter 9 describes the effect of primary minimally invasive mitral valve surgery compared to sternotomy on short- and long-term outcomes in the Netherlands.

In **Chapter 10,** the outcomes of a minimally invasive approach compared to resternotomy for reoperative mitral valve surgery in the Netherlands are described.

Chapter 11 investigated the risk of adding tricuspid valve surgery to a minimally invasive mitral valve procedure.

In **Chapter 12,** the quality of life after minimally invasive mitral valve surgery compared to sternotomy is presented, based on data from the Netherlands Heart Registration

In **Chapter 13,** a systematic review and meta-analysis of observational studies is presented comparing right mini thoracotomy to sternotomy for reoperative mitral valve surgery.

In **Chapter 14,** a systematic review and meta-analysis of observational studies is presented comparing right anterolateral thoracotomy versus sternotomy for resection of benign atrial masses.

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PART I

PATIENT SELECTION,
PREOPERATIVE PLANNING
AND INTRAOPERATIVE GUIDANCE.

Chapter 2

Multidisciplinary decision-making in mitral valve disease: the mitral valve heart team

Samuel Heuts, **Jules R Olsthoorn**, Sem M M Hermans, Sebastiaan A F Streukens, Jindrich Vainer, Emiel C Cheriex, Patrique Segers , Jos G Maessen and Peyman Sardari Nia.

Netherlands Heart Journal, 27(4), 176-184

ABSTRACT

Background

Although decision-making using the heart team approach is apparently intuitive and has a class I recommendation in most recent guidelines, supportive data is still lacking. The current study aims to demonstrate the individualized clinical pathway for mitral valve disease patients and to evaluate outcome of all patients subjected to the dedicated mitral valve heart team.

Methods

All patients who were evaluated for mitral valve pathology with or without concomitant cardiac disease between January 1st 2016 and December 31st 2016 were prospectively followed and included. Patients were evaluated and treatment strategy was determined in the dedicated mitral valve heart team.

Results

One hundred-and-fifty-eight patients were included, 67 patients were treated surgically (isolated and concomitant surgery), 20 by trans-catheter interventions and 71 conservatively. Surgically treated patients had a higher 30-day mortality rate (4.4%), which decreased when specified to a dedicated surgeon (1.7%) and to primary, elective cases (0%). This was also observed for major adverse events within 30 days. Residual Mitral Regurgitation > grade 2 was more present in the catheter-based intervention group (23.5%) compared to the surgical group (4.8%).

Conclusion

In conclusion, the multidisciplinary heart team for mitral valve disease is a valuable venue to select patients for different treatment modalities. Our research group will focus on a future comparative study using historical cohorts to prove potential superiority of the dedicated multidisciplinary heart-team approach.

BACKGROUND

The concept of a multidisciplinary decision making team has been well established in various disciplines within the medical field,[1, 2] and has been associated with improved survival.[3, 4] Recently, the multidisciplinary heart team has been introduced within the area of cardiology and cardiac surgery, specified to decision-making for coronary revascularization and trans-catheter aortic valve replacement.[5-7] Although decision making in the heart team is apparently intuitive and has a Class I recommendation in most recent guidelines,[8-10] supporting comparative data is still lacking.[11-13] For mitral valve disease, only few studies reported their first experience in multidisciplinary decision-making, limited to trans-catheter mitral valve therapies.[14, 15] The variety in mitral valve treatment options is increasing with trans-catheter and off-pump surgical interventions.[16-18] Furthermore, surgical mitral valve repair has proven to be associated with a steep learning curve and outcome is significantly procedural volume related.[19, 20] Therefore, a dedicated mitral valve care team seems even more warranted for treatment of mitral valve disease. Recently, we introduced the concept of a dedicated mitral valve heart team in our centre. This multidisciplinary approach focuses on a balanced treatment strategy for individual patients based on their specific mitral valve pathology, anatomical eligibility, comorbidities, background and wishes. Aim of the current study is to demonstrate standardized diagnostic pathways in mitral valve patients, give insight into our strategy of clinical decision making for allocation of an individualized treatment pathway and to demonstrate the clinical outcome of all patients subjected to the dedicated mitral valve heart team.

METHODS

All consecutive patients who were discussed for mitral valve pathology between January 1st 2016 and December 31st 2016 in the dedicated mitral valve heart team were prospectively included in the current study. Patients were referred from 4 regional hospitals or our own centre. Data was collected prospectively.

Mitral valve heart team

The traditional heart-team consists of one cardiac surgeon and one interventional cardiologist with random subspecialties and rotates frequently. Furthermore, patients are being discussed by different heart-teams during their work-up lacking continuity.

However, the mitral valve heart team consists of a dedicated mitral valve surgeon, one interventional cardiologist with experience in catheter-based mitral valve therapies and two imaging cardiologists with expertise in advanced echocardiography (one senior imaging cardiologist; >30 years' experience, 100-150 procedures annually, one fellow imaging cardiologist; 2 years' experience, 200 procedures annually, EACVI certified). The mitral valve heart team meetings convened once a week and only proceeded when all members were present. All referred patients underwent transthoracic echocardiography at the site of referral, but all echocardiographies were evaluated for severity and mechanism of MR in the heart team. When a patient was allocated to surgical treatment, valve reparability was assessed. Patient characteristics, valvular pathology and patient anatomy were considered and discussed comprehensively for treatment allocation. All degenerative valves were deemed eligible for repair. Isolated valve repairs/replacements were evaluated for an endoscopic approach.

In addition to diagnosis and determination of treatment strategy, the complete mitral valve heart team is also involved in the treatment phase, where interventions are being evaluated by the dedicated imaging cardiologists in the operating room, and patients are being evaluated and treated postoperatively by members of the team. Finally, in case of late complications or recurrence of MR, patients are reintroduced in the mitral valve heart team for evaluation and indication for potential additional therapies.

Mitral Interventions

At the heart and vascular institute of our centre, a variety of mitral valve therapies is provided. Mitral valve therapies are divided in three groups: surgical, catheter-based interventions or conservative (pharmacological) treatment.

Surgical mitral valve repair or replacement is performed through sternotomy or fully endoscopically. In selected patients, mitral valve repair can be performed on beating heart through a trans-apical approach (NeoChord, NeoChord Inc., Minneapolis, MN, USA).[16, 21] Percutaneous treatments performed by the interventional cardiologist include edge-to-edge repair (MitraClip, Evalve Inc, Menlo Park, CA, USA)[18] and percutaneous annuloplasty (Carillon, Cardiac Dimension, Kirkland, WA, USA).[17].

Diagnostic Modalities

All patients underwent transthoracic echocardiography (TTE) at the site of referral.

Additionally, all patients eligible for surgical or trans-catheter mitral valve repair underwent 3D transesophageal echocardiography (TEE) and all patients with isolated mitral valve pathology eligible for surgical intervention, underwent CT for three-dimensional (3D) anatomical reconstruction of the aorta and peripheral vessels to assess eligibility for an endoscopic approach.[22] Coronary angiography (CAG) was performed for evaluation of potential concomitant coronary artery disease.

Outcomes

Baseline risk assessment and clinical symptom severity was graded by the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and New York Heart Association classification for dyspnoea respectively. Echocardiographic characteristics were assessed and quantified using an integrative approach.[23]

Safety outcomes were defined as mortality and Major Adverse Cardiac and Cerebrovascular Events (MACCE) within 30 days (mortality within 30 days, myocardial infarction, reoperation for failure of surgical repair, stroke, renal failure, deep wound infection, sepsis) and overall survival.

Statistical Analysis

The distribution of continuous variables was assessed for normality using the Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation or median and range in the presence of skewness. Categorical variables were presented as frequencies and percentages. Survival was estimated by the Kaplan-Meier method. Data analysis was performed using commercially available software (SPSS version 24, IBM, Armonk, New York, USA).

RESULTS

A total of 158 consecutive patients were discussed in the mitral valve heart team. Patients were allocated to their designated treatment modality. Sixty-seven patients were treated surgically, 20 with catheter-based interventions and 71 conservatively (Figure 1).

Repair rate of MR based on degenerative disease was 100%. Within the surgically treated group, 46 patients underwent on-pump surgical mitral valve repair, 8 beating heart mitral valve repairs were performed and thirteen patients underwent biological or mechanical mitral valve replacement for rheumatic or ischemic disease or Systolic Anterior Motion (SAM).

In the catheter-based intervention group, 15 patients (75%) underwent a percutaneous edge-to-edge repair and 5 patients (25%) percutaneous annuloplasty. Reasons for conservative treatment were: MR not severe enough for intervention (30 cases, 42%), patient's wish (17 cases, 24%), deteriorated clinical state (16 cases, 23%) and non-mitral surgical/interventional treatment (8 cases, 11%). Baseline characteristics are depicted in Table 1.

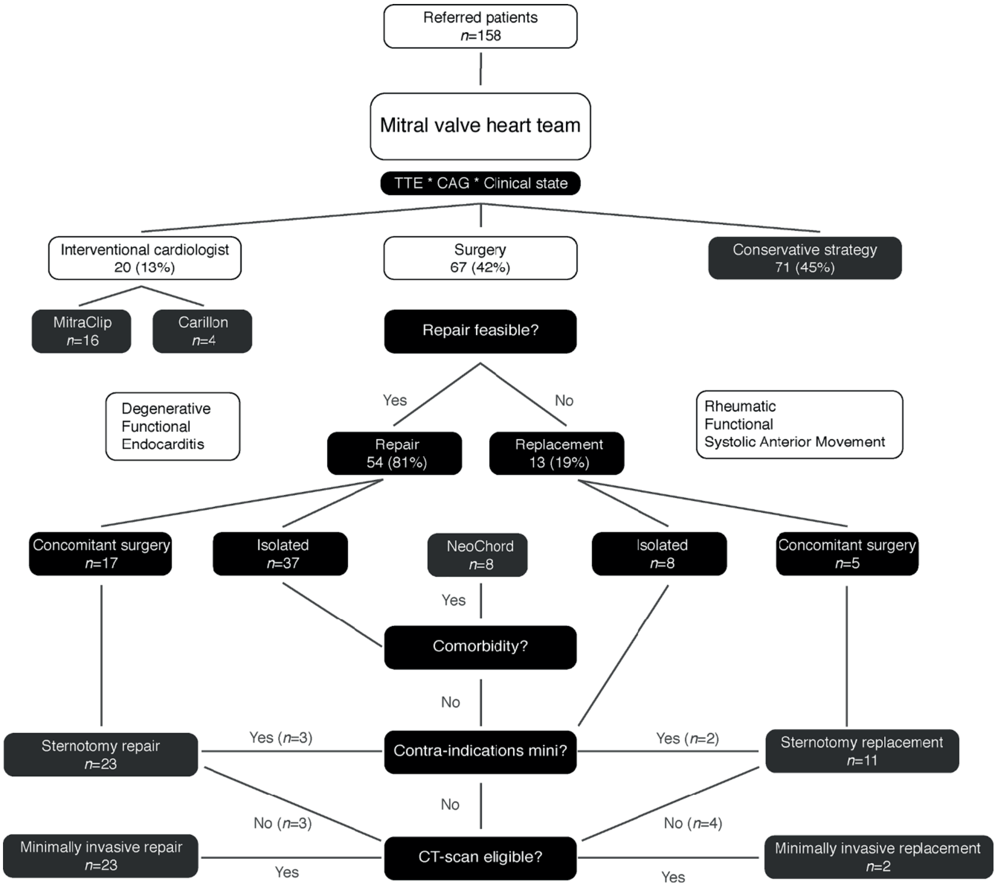

Figure 1. Flowchart of decision making in the mitral valve heart team.

TTE: Transthoracic Echocardiography, CAG: Coronary Angiography, CT: Computed Tomography

Table 1. Baseline and surgical characteristics

	Surgery n= 67	Catheter-based interventions n= 20	Conservative n= 71
Age (years)	63 (15)	69 (11)	73 (11)
Gender (male)	43 (64%)	16 (80%)	35 (49%)
BMI (kg/m2)	26.5 [23.3–29.0]	24.3 [22.3–27.6]	25.1 [23.1–28.2]
Diabetes	8 (11%)	1 (5%)	10 (14%)
PHT	30 (45%)	11 (55%)	34 (48%)
Reoperation	3 (5%)	5 (25%)	16 (23%)
EuroSCORE log	4.38 [2.21–7.83]	4.57 [2.78–7.59]	6.51 [3.22–10.30]
EuroSCORE II	1.51 [0.88–3.19]	2.03 [1.53–3.04]	2.33 [1.35–4.13]
NYHA classification			
No dyspnoea	12 (17%)	2 (10%)	12 (17%)
I	2 (3%)	1 (5%)	2 (3%)
II	26 (39%)	11 (55%)	32 (45%)
III	22 (33%)	6 (30%)	23 (32%)
IV	5 (8%)	0	2 (3%)
Surgery type			
Isolated MVS	45 (67%)		
Concomitant surgery	22 (33%)		
Surgical approach			
Endoscopic (% isolated valves)	25 (68%)		
Sternotomy (% isolated valves)	12 (32%)		

BMI body mass index, PHT pulmonary hypertension, EuroSCORE European system for cardiac operative risk evaluation, NYHA New York Heart Association classification for dyspnoea, MVS mitral valve surgery

Surgically treated patients tended to be younger of age with fewer comorbidities and a lower surgical risk based on the EuroSCORE. Twenty-two patients (33%) underwent concomitant surgery. An endoscopic approach was used in 23 of 35 patients with isolated valve disease, whereas sternotomy was performed in 12 patients. Reoperations, endocarditis and non-elective cases were included in the analyses as well. Baseline echocardiographic parameters are presented in Table 2.

Table 2. Baseline echocardiographic parameters

	Surgery n= 67	Catheter-based interventions n= 20	Conservative n=71
LVEF (%)	60 [54–63]	29 [16–44]	51 [19–75]
LVEDD (mm)	56 (8)	64 (12)	59 (9)
MR severity			
Grade I	0	0	8 (11%)
Grade II	2 (3%)	0	26 (37%)
Grade III	4 (6%)	3 (15%)	12 (17%)
Grade IV	61 (91%)	17 (85%)	18 (25%)
MS	0	0	7 (10%)
MR cause			
Degenerative	43 (64%)	4 (20%)	20 (31%)
Functional	14 (21%)	16 (80%)	35 (55%)
Rheumatic	6 (9%)	0	5 (8%)
Endocarditis	2 (3%)	0	0
SAM	2 (3%)	0	2 (3%)
Other	0	0	2 (3%)
Leaflet prolapse (% surgical degenerative)			
PML	30 (70%)		
AML	4 (9%)		
Bileaflet	9 (21%)		

LVEF left ventricular ejection fraction, LVEDD left ventricular end diastolic diameter, MR mitral regurgitation, MS mitral stenosis, SAM systolic anterior motion, PML posterior mitral leaflet, AML anterior mitral leaflet.

Thirty-day mortality was assessed for all groups. There was no mortality within 30 days for the catheter-based intervention group, whereas 3 patients died within 30 days of decision in the conservative group (4.2%). For surgically treated patients, a distinction was made between (i) the overall group, (ii) the group treated by a dedicated mitral valve surgeon, and (iii) elective, primary cases operated on by a dedicated mitral valve surgeon. For the overall group (n=67, treated by 3 surgeons) 30-day mortality was 4.4% (3 cases, Figure 2A). For the group treated by the dedicated surgeon (n=60) 30-day mortality was 1.7% (1 case, a reoperation, Figure 2B) and for primary, elective group (n=57) there was no 30-day mortality observed (Figure 2C).

A similar decrease in occurrence of MACCE within 30 days was found. In the catheter-based intervention group, one patient had to undergo Left Ventricular Assist Device implant after edge-to-edge repair (5%). Sixteen percent had complications in the overall surgically treated group

(Figure 2D), 11.7% in the dedicated group (Figure 2E) and 7.7% in the primary, elective group (Figure 2F).

Postoperative echocardiography performed at 3 months after discharge revealed 23.5% of patients treated with a catheter-based intervention to have residual MR > grade 2, compared to 4.5% in the surgically treated group (3 patients, Figure 3).

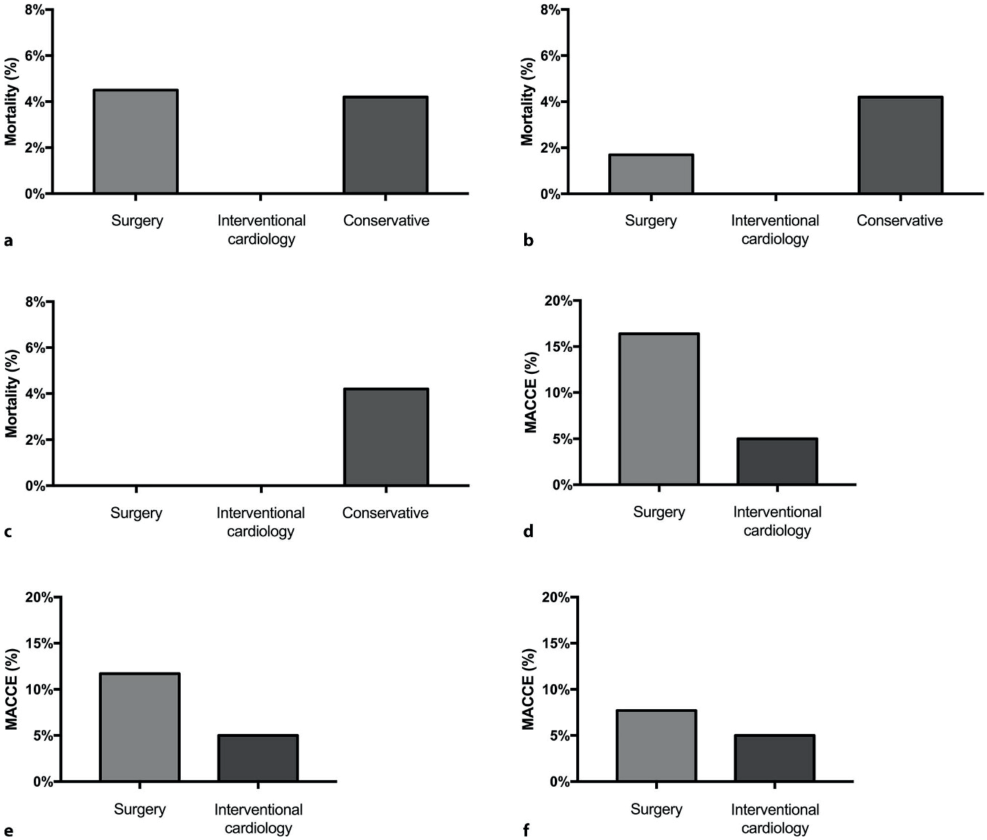

Figure 2.

Thirty-day mortality (A-C) rate and Major Adverse Cardio- and Cerebrovascular Events (D-F) for the surgical (orange), catheter-based intervention (blue) and conservative group (green). *2A+D: overall surgical group (orange), 2B+E: surgical group treated by a dedicated mitral valve surgeon (orange), 2C+F: primary, elective group treated by a dedicated mitral valve surgeon (orange)*

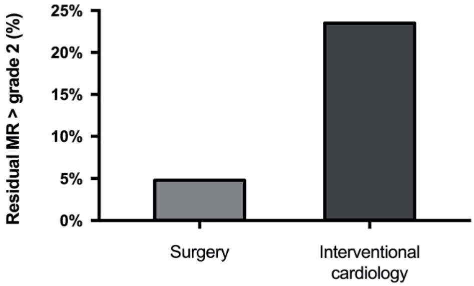

Figure 3.

Residual MR > grade 2 for the surgical (orange) and catheter-based intervention group (blue). *MR: Mitral Regurgitation*

Survival was estimated using the Kaplan-Meier method at a median follow-up of 450 days (range 138-673 days) and is depicted in Figure 4 for the various groups, demonstrating beneficial long-term survival for surgically treated patients. Additionally to the stratification for surgically treated groups, figure 4D provides information on survival of the patient group with severe MR, revealing a poor short-term prognosis for the conservatively treated group.

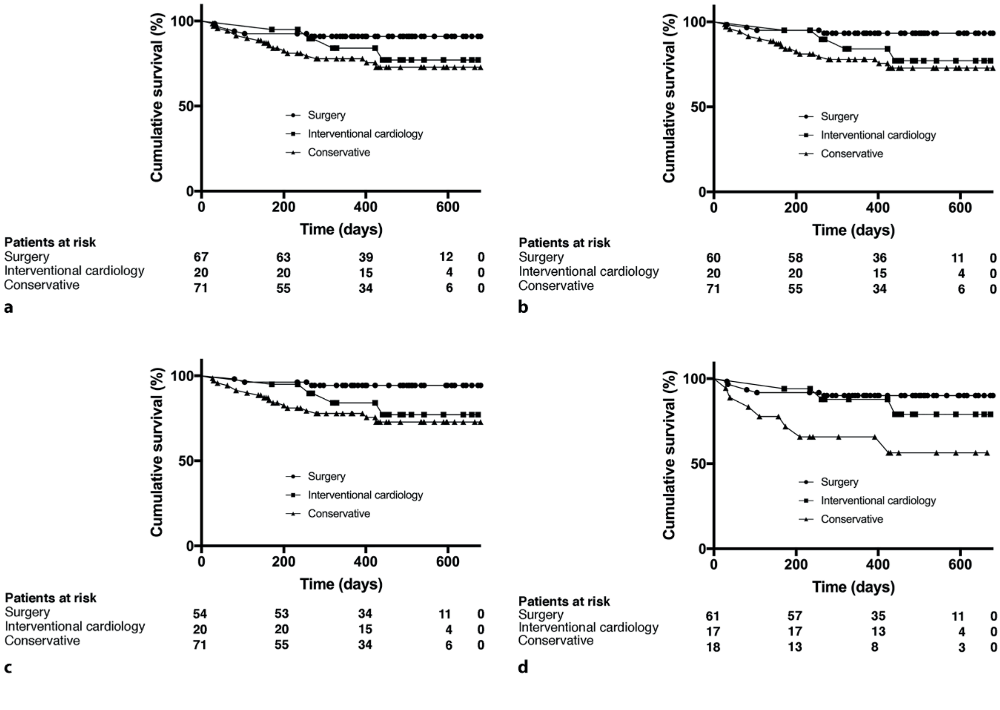

Figure 4. Survival analysis using Kaplan-Meier curves for the various treatments with a median follow-up of 450 days (range 138 - 673 days).

4A: overall surgical group (orange), 4B: surgical group treated by a dedicated mitral valve surgeon (orange), 4C: primary, elective group treated by a dedicated mitral valve surgeon (orange), 4D: stratified for patients with severe MR. Patients at risk at a given time are depicted below each graph.

Additional Observations

All patients with isolated valve disease and without contraindications underwent contrast-enhanced CT angiography with 3D reconstruction to assess anatomical eligibility for endoscopic surgery (n=44). Seven patients were excluded for an endoscopic approach based on CT due to suboptimal accessibility of the peripheral vessels for Cardiopulmonary Bypass (CPB) cannulation or aberrant aortic diameters.

Furthermore, out of these 44 scans, 12 incidentalomas were found, of which 4 were actual carcinomas requiring further follow-up and/or treatment (2 non-small cell lung carcinomas, 1 cholangiocarcinoma, 1 thyroid carcinoma (Table 3).

Table 2. Incidentalomas

CT scans during work-up (n= 44)	Incidentalomas (n= 12, 27%)
Abdominal mass/tumour	4
Thoracic mass/tumour	7
Abdominal aortic aneurysm	1
Actual carcinomas	4

DISCUSSION

Although intuitive, there is no supportive data of the use of the heart team in decision making for cardiovascular disease.[11]

In this first study on a dedicated mitral valve heart team, we present the implementation of a recently introduced dedicated mitral valve heart team at our centre. The current study included all patients referred for mitral valve disease to our centre within one year (2016, n=158). Almost half of patients (45%) were treated conservatively. This can be explained by the (1) high-risk population of patients with mitral stenosis and end-stage heart-failure, (2) advanced age (>80 years) and high-rate of severe pulmonary hypertension and (3) the fact the mitral valve team is well established and known by referring centres and patients are referred in an early stage of mitral valve disease. The latter is illustrated by the number of patients who were treated conservatively due to insufficient grade of MR for intervention (42%). These patients will be followed-up annually for disease progress. Twelve percent of patients were treated with a catheter-based intervention, using either the percutaneous edge-to-edge repair (75%) or percutaneous annuloplasty (25%). These patients were older, with a higher surgical risk, but more importantly had a predominantly reduced LVF. Therefore, a trans-catheter intervention was indicated.

Sixty-seven (43%) were treated surgically. Mitral valve reparability was assessed in the heart team pre-operatively and a repair rate of 100% was achieved for degenerative valves. Of all mitral pathologies, 84% was repaired, 16% was replaced. Of note, isolated and concomitant mitral surgery were both included in the analysis. In selected cases, trans-apical beating heart valve repair (NeoChord) was performed when eligible. These older patients, with an overall elevated surgical risk and comorbidities, were eligible for repair but were expected to have a complicated postoperative course. Furthermore, with the emergence of several multimodality imaging techniques, the current study provides an algorithm for the use of the modalities (CT, 3D anatomical reconstructions, TTE, TEE, CAG) in various stages of the standardized diagnostic pathway. This algorithm, provided in figure 1, could prevent unnecessary diagnostics and reduce associated costs, patient-burden and exposure to radiation.

Routine CT-thorax scan was performed in patients being evaluated for endoscopic mitral valve surgery. We were able to exclude 7 patients in the pre-operative course because of inaccessibility or unsuitability of the vessels for this approach. Eventually 25 patients underwent endoscopic surgery, in which no conversions occurred.

Catheter-based interventions proved to be safe (no 30-day mortality, 5% MACCE), but had a relatively high probability of residual MR > grade 2 (23.5%) compared to the surgical group (4.5%), in line with prior studies.[24] Furthermore, after an initial uneventful course, these patients had shorter overall survival, presumably based on their age, poorer clinical state and diminished cardiac function.

A trend towards lower 30-day mortality with fewer major complications for patients treated by a dedicated surgeon was observed, confirming previous studies.[25] These studies demonstrated better outcomes and survival in mitral valve surgery when performed by a dedicated surgeon on a weekly basis after completion of the learning curve,[19, 20, 26] indicating surgical volume to be a determinant of repair rate, freedom of reoperation and survival.

Survival was estimated with a median follow-up of 450 days. A relatively high cumulative mortality was observed in the conservatively treated group (25.4%). Most deaths occurred in the subgroup which was treated conservatively because of a deteriorated clinical state. This finding was also observed in a comparable revascularization study.[27] Additionally, conservatively treated patients with severe MR had a poor short-term prognosis, potentially explained by a combination of a myriad of factors contributing to a higher surgical risk, such as advanced age, severe mitral stenosis with subsequent end-stage heart-failure and a high rate of severe pulmonary hypertension.

As an additional observation, we found a relatively high rate of incidentalomas on pre-operative CT-scans performed in the planning of endoscopic surgery. Out of 44 patients, 12 incidentalomas (27%) were found, of which 4 (9%) were actual carcinomas requiring further follow-up and/or treatment. Several other CT screening studies describe lower prevalence of tumours on screening.[28] However, little is known yet about the complex interplay between cardiovascular disease and cancer, which could both be a different manifestation of common underlying risk factors,[29] explaining this finding in a patient group with extensive cardiovascular disease.

Limitations

The current study cohort consists of a relatively small heterogeneous group (n=158). The study comprehends a single-arm study in which superiority of the multidisciplinary heart team approach cannot be proven. However, this was beyond our scope, as we aimed to demonstrate the prospective results of implementation of a dedicated mitral valve heart team in a centre performing a broad range of mitral valve therapies. Furthermore, the study is subjected to selection bias for the described treatment modalities and is therefore not able to detect potential differences between these therapies. However, the current study is the first to describe and give insight into clinical decision-making in a mitral valve disease patient group as a whole and will function as a scientific basis for future studies on a multidisciplinary approach, in order to eventually potentially prove superiority.

As it seems unethical to study the heart-team in a randomized fashion, our research group is focussing on a future study, using a historical cohort, in order to provide potential evidence for superiority of the dedicated heart team approach.

CONCLUSION

The current study demonstrated the implementation of a multidisciplinary mitral valve heart team, gave insight into our strategy for clinical decision-making, treatment allocation and demonstrated short-term clinical outcomes of patients with mitral valve disease. Our research group will focus on a comparative study with historical cohorts, potentially providing a scientific basis for the current recommendations in guidelines aswe believe a multidisciplinary approach will improve efficiency and patient outcome.

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Chapter 3

Multidisciplinary decision-making in mitral valve disease: the mitral valve heart team

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ABSTRACT

Objectives

Although in both the US and European guidelines the 'heart team approach' is a class I recommendation, supporting evidence is still lacking. Therefore, we sought to provide comparative survival data of patients with mitral valve disease referred to the general and the dedicated heart team.

Methods

In this retrospective cohort, patients evaluated for mitral valve disease by a general heart team (2009–2014) and a dedicated mitral valve heart team (2014–2018) were included. Decision-making was recorded prospectively in heart team electronic forms. The end point was overall survival from decision of the heart team.

Results

In total, 1145 patients were included of whom 641 (56%) were discussed by dedicated heart team and 504 (44%) by general heart team. At 5 years, survival probability was 0.74 [95% confidence interval (CI) 0.68–0.79] for the dedicated heart team group compared to 0.70 (95% CI 0.66–0.74, P = 0.040) for the general heart team. Relative risk of mortality adjusted for EuroSCORE II, treatment groups (surgical, transcatheter and non-intervention), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics for patients in the dedicated heart team was 29% lower [hazard ratio (HR) 0.71, 95% CI 0.54–0.95; P = 0.019] than for the general heart team. The adjusted relative risk of mortality was 61% lower for patients following the advice of the heart team (HR 0.39, 95% CI 0.25–0.62; P < 0.001) and 43% lower for patients following the advice of the general heart team (HR 0.57, 95% CI 0.37–0.87; P = 0.010) compared to those who did not follow the advice of the heart team.

Conclusions

In this retrospective cohort, patients treated for mitral valve disease based on a dedicated heart team decision have significantly higher survival independent of the allocated treatment, mitral valve pathology and baseline characteristics.

INTRODUCTION

Multidisciplinary decision-making has been well established for various fields of medicine and is associated with improved survival[1–4]. Although the heart team approach to cardiovascular disease is apparently intuitive and has a class I indication in recent guidelines[5,6], supporting evidence on its composition and its effect based on comparative data is still lacking[7,8]. Mitral valve disease is one of the most complex and heterogeneous pathologies in cardiovascular medicine. Further, with the development of new devices and approaches for managing mitral valve pathology, the plethora of scientific information on novel strategies, and the complexity of patient groups with advanced age and comorbidity, the multidisciplinary dedicated mitral valve heart team decision-making approach to manage mitral valve pathology is even more warranted[9]. The current report aims to provide comparative survival data of patients with mitral valve disease referred to the general and the dedicated heart team.

PATIENTS AND METHODS

Study design

Since July 2009, heart team discussions and evaluations have been prospectively recorded in real time (during the heart team discussions) on electronic custom-made forms. The forms include relevant medical history, current medical problems, medications, New York Heart Association classification for dyspnoea, all relevant diagnostic investigations, all variables required for determination of the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), Team members, discussions, treatment proposals and the final treatment allocation (Video 1, Supplementary Material, Appendix). For the current study, we examined the prospectively registered data of all patients with mitral valve disease from July 2009 through December 2018 who were discussed by the general (up until 2014) or the dedicated mitral valve (from 2014 onwards) heart teams. This is a retrospective, comparative, nonrandomized interventional cohort study based on prospectively registered data. Our local ethical committee waived the need for the informed consent due to the observational and retrospective nature of the study (METC 15-4-065).

General heart team

From 2009 until 2014, the general heart team consisted of 2 members: a cardiothoracic surgeon and an interventional cardiologist. The heart team convened daily at the same time and discussed all patients with cardiovascular pathologies (even single vessel coronary disease). The composition of the general heart team altered daily and was random. Additionally, as further investigations were sometimes required to make a final decision, patients might have been discussed on multiple occasions.

Dedicated mitral valve heart team

In 2014, we established a dedicated mitral valve heart team in which only patients with any isolated or concomitant mitral valve pathology were discussed[10]. The dedicated heart team consisted of dedicated mitral valve surgeons (defined as >25 mitral valve procedures/year), interventional cardiologists responsible for catheter-based mitral valve interventions and imaging cardiologists with expertise in advanced echocardiography and mitral valve pathology (>100 transoesophageal echocardiography's annually, European Association of Cardiovascular Imaging certified). The team convened once a week at the same time, and the meeting took place only if all members were present. For patients needing urgent treatment, the team would convene between the official schedules. All referred patients underwent transthoracic echocardiography at the site of referral, but the dedicated heart team evaluated all echocardiograms. To make a final decision on treatment algorithm, if needed, the dedicated heart team would invite patients to the mitral valve outpatient clinic for further evaluation, or additional investigations.

Study population and data collection

From July 2009 to December 2018, a total of 24 955 patients were evaluated for different cardiovascular pathologies in the heart team. Data from patients with any isolated or concomitant mitral valve pathology were retrieved (Figure 1: Flow chart). All clinically relevant variables were collected based on prospective recorded heart team forms, medical records and prospectively collected data. In total, 1332 patients were discussed for mitral valve disease. From this patient cohort, 187 patients were excluded because of active endocarditis, emergency operations and inoperable status at presentation. These patients were excluded, as decision-making was not consistently made by the general or dedicated heart teams; in these cases, decisions were made by an endocarditis team or by a dedicated multidisciplinary team for very complex cases, whereby the presence of experts from other disciplines was required. Follow-up was completed for all patients on 13 March 2020. The data were validated by 2 independent observers, and further validated by a local dedicated data quality surveillance team (Business Information Management team).

<u>Mitral valve treatment decisions</u>

Surgical treatment

Surgical mitral valve repair or replacement was performed via sternotomy or using a minimally invasive (endoscopic port-access) approach.

Transcatheter intervention

In selected patients, mitral valve repair was performed on the beating heart using a transapical approach (NeoChord, NeoChord Inc., Minneapolis, MN, USA)[11]. Percutaneous treatments were performed with edge-to-edge repair (MitraClip, Evalve Inc, Menlo Park, CA, USA) or percutaneous annuloplasty (Carillon, Cardiac Dimension, Kirkland, WA, USA) [12, 13].

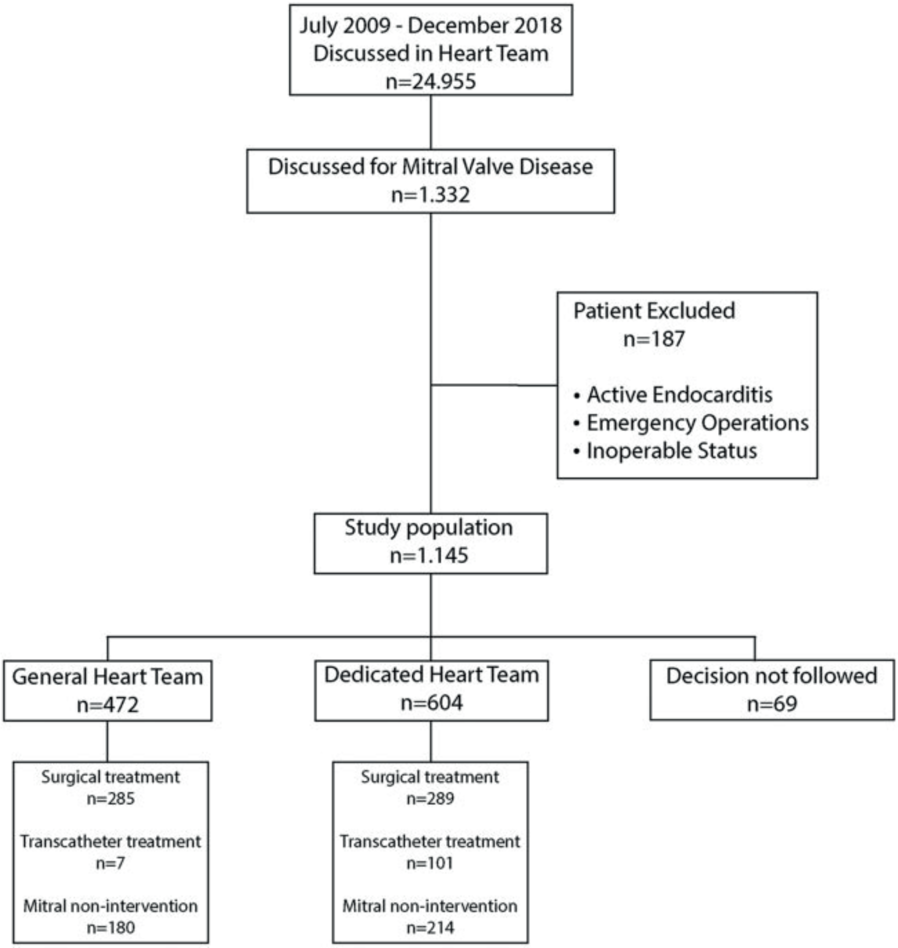

Figure 1. Patient flowchart.

Mitral non-intervention group

Patients who did not have an indication for a mitral valve intervention based on the available guidelines[5, 6] were treated conservatively and followed up. Patients with non-optimal medical therapy received guideline-directed medical therapy. Patients undergoing any other cardiac interventions (e.g., coronary artery bypass grafting) with concomitant mitral valve disease who were not deemed eligible for concomitant mitral valve surgery were allocated to the non-intervention group. All patients who did not follow the advice of the heart team for an intervention and wished to be treated conservatively, or patients who were given the advice of conservative treatment and were subsequently operated on in another centre (only 1 patient), were allocated to this non-intervention group.

Outcomes

Baseline risk assessment and clinical symptom severity were graded by the EuroSCORE II and New York Heart Association classification, respectively. Echocardiographic characteristics and mitral valve regurgitation severity were assessed and quantified using an integrative approach based on most recent guidelines[14]. The primary end point was defined as overall survival and was calculated from the date of final decision of the heart team. As 2 consecutive periods with and without the dedicated heart team were considered, the overall survival analyses were limited to 5 years (i.e., all patients were censored after a maximum of 5 years) to prevent considerable imbalance in median follow-up time between the 2 groups

Statistical analysis

Baseline characteristics for all included patients are stratified by type of heart team in terms of mean and standard deviation or median and interquartile range for continuous variables, and count and percentage for categorical variables. Normality of the continuous variables was tested by visual inspection of the histograms and the Shapiro–Wilk test. Continuous data were compared using Student's t-test or Mann–Whitney U-test. Categorical data are expressed as frequencies and percentages and were compared using the v2 test. Median follow-up time was presented including the 25th and 75th percentiles. The Kaplan–Meier method was used to plot survival probability over the 5-year follow-up. Kaplan–Meier tables were used to estimate survival probability at 1 and 5 years. Crude differences in survival were tested using the log-rank test. Cox proportional hazards regression was used to quantify the relative difference in survival over time using hazard ratios (HRs) including 95% confidence interval (CI). The groups were adjusted for initial mortality risk for mitral valve pathology, baseline characteristics, EuroSCORE II and treatment modality in a multivariable model. The survival analyses were performed in 2 fashions: intention-to-treat analyses (patients stratified into general and dedicated heart team, regardless of whether or not they followed the advice of the heart teams) and per-protocol analyses (patients stratified into general heart team, dedicated heart team, and those who did not follow the decision of the heart team). Data were analysed using R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

In total, 1145 patients were included in this study of whom 641 (56%) were discussed by the dedicated heart team and 504 (44%) by the general heart team. The median follow-up time was 41.1 months (25th percentile 22.8, 75th percentile 60.0 months). The survival was completed in all patients and no patient was lost to follow-up. In addition to this, there were no missing data in the reported analyses and all the analyses were performed with complete data of 1145 patients. At baseline, there were significant differences in New York Heart Association class, renal function, prevalence of atrial fibrillation, urgency of the procedure and the EuroSCORE II (Table 1).

Table 1. Baseline characteristics of 1145 patients discussed by the general heart team or dedicated mitral valve heart team for isolated or concomitant mitral valve pathology

	General heart team (n = 504)	Dedicated heart team (n = 641)	P-value[a]
Age[b]	70 (62–76)	71 (64–77)	0.160
Sex (female), n (%)	228 (45.2)	286 (44.6)	0.83
Previous cardiac surgery, n (%)	53 (10.5)	82 (12.8)	0.33
Left ventricular ejection function, n (%)			0.051
>50%	279 (55.4)	398 (62.1)	
31–50%	154 (30.6)	180 (28.1)	
21–30%	54 (10.7)	44 (6.9)	
<21%	17 (3.4)	19 (3.0)	
NYHA classification, n (%)			0.033
I	127 (25.2)	184 (28.7)	
II	189 (37.5)	261 (40.7)	
III	165 (32.7)	182 (28.4)	
IV	23 (4.6)	14 (2.2)	
Chronic lung disease, n (%)	57 (11.3)	53 (8.3)	0.083
Pulmonary hypertension[c], n (%)	22 (4.4)	27 (4.2)	0.70
Extracardiac arteriopathy, n (%)	49 (9.7)	51 (8.0)	0.39
Renal impairment, n (%)			**<0.001**
GFR >80	355 (70.4)	343 (53.4)	
GFR 50–80	98 (19.4)	215 (33.6)	
GFR <50	50 (9.9)	82 (12.8)	
Dialysis[d]	1 (0.2)	1 (0.2)	
Previous myocardial infarction, n (%)	11 (2.2)	12 (1.9)	0.71
Diabetes mellitus on insulin, n (%)	18 (3.6)	20 (3.1)	0.74
Atrial fibrillation, n (%)	143 (28.4)	248 (38.7)	0.001
Cerebrovascular accident, n (%)	55 (10.9)	78 (12.2)	0.50
Urgency, n (%)			**0.001**
Elective	467 (92.7)	622 (97.0)	
Urgent	37 (7.3)	19 (3.0)	
EuroSCORE II overall[b]	3.03 (1.26–5.04)	1.90 (1.03–3.93)	0.001
EuroSCORE surgery	2.38 (1.20–4.34)	2.45 (0.99–3.74)	0.004
EuroSCORE transcatheter	1.97 (1.07–4.62)	2.18 (1.42–3.68)	0.60
EuroSCORE mitral non-intervention	2.35 (1.38–3.75)	1.84 (1.10–3.53)	0.019

(a) Statistical testing performed between general and dedicated heart team. (b) Presented as median (25th–75th percentile). (c) Defined as pulmonary artery pressure >55 mmHg. (d) Fisher's exact if expected cell count <5.*GFR: glomerular filtration rate; NYHA: New York Heart Association.*

Mitral valve pathology and treatment allocation

The majority of patients presented with mitral regurgitation (Table 2). Of all patients evaluated by the heart teams, 574 (50.1%) were treated surgically, 108 (9.4%) with transcatheter techniques and 463 (40.4%) did not undergo any mitral intervention (mitral non-intervention). More interventions (surgical plus transcatheter) were performed on patients in the dedicated heart team group; this was because there were a greater number of transcatheter mitral valve interventions in this group (15.8% in the dedicated heart team group vs 1.4% in the general heart team group). More patients were treated surgically in the general heart team than in the dedicated heart team group (56% vs 45.1%, respectively). Of patients who were treated surgically, significantly more patients who had been discussed by the dedicated heart team underwent isolated mitral valve surgery than patients who had been discussed by the general heart team (76.1% vs 57.9%, respectively); conversely, more patients discussed by the general heart team underwent concomitant mitral valve surgery (23.9% in the dedicated heart team group vs 42.1% in the general heart team group) (Table 2). Across both groups of patients, 463 (40.4%) were allocated to mitral non-intervention group. About 62% (287) of these patients did not have an indication for any intervention (surgical or transcatheter) based on the available guidelines, and 23% (107) had been receiving sub-optimal medical therapy, so their therapy was optimized. Sixty-nine patients (15%) did not follow the treatment decision of the heart team (patient preference) and were thus allocated to this non-intervention group. Of those 69 patients, 32 (46.4%) had been discussed by the general and 37 (53.6%) by the dedicated heart team; 60 (87%) had been advised to undergo surgical treatment, 8 (11.6%) had been given the option for transcatheter treatment and 1 (1.4%) had been recommended a conservative option (and was subsequently operated on at another centre). Baseline characteristics of these patients compared with patients who did follow the advice the heart team are shown in Supplementary Material, Tables S1 and S2.

Mortality analyses

During maximal follow-up, 330 (28.8%) patients died. Overall, 30-day mortality was 26 (5.2%) and 19 (3.0%) P = 0.06 for the general heart team and dedicated heart team, respectively. The overall 1-year mortality in general heart team was significantly higher in comparison with the dedicated heart team, 74 (14.7%) vs 57 (8.9%), respectively, P = 0.002. Furthermore, the 1-year mortality in surgical group was significantly higher in general heart team compared to Dedicated heart team (41 (14.4%) vs 20 (6.9%), P = 0.004). The mortality rates for other subgroups are displayed in Table 3.

Table 2. Evaluation and treatment decision of 1145 patients discussed by the general heart team or dedicated mitral valve heart team for isolated or concomitant mitral valve pathology

	General heart team (n = 504), n (%)	Dedicated heart team (n = 641), n (%)
Indication		
Regurgitation	451 (89.5)	578 (90.2)
Stenosis	40 (7.9)	36 (5.6)
MR/MS	13 (2.6)	27 (4.2)
MR severity[a]		
Grade I	25 (5.4)	23 (3.8)
Grade II	130 (28.0)	138 (22.8)
Grade III	140 (30.2)	83 (13.7)
Grade IV	169 (36.4)	361 (59.7)
MR aetiology[b]		
Degenerative	166 (35.8)	317 (52.4)
Functional	258 (55.6)	237 (39.2)
Rheumatic	18 (3.9)	31 (5.1)
Other	22 (4.7)	20 (3.3)
Surgical treatment	285 (56.5)	289 (45.1)
Isolated mitral surgery[c]	165 (57.9)	220 (76.1)
Concomitant surgery	120 (42.1)	69 (23.9)
Minimally invasive[d]	20 (7.0)	150 (68.2)
Mitral repair	222 (77.9)	229 (79.2)
Mitral replacement	63 (22.1)	60 (20.8)
Transcatheter intervention	7 (1.4)	101 (15.8)
MitraClip	7 (100)	72 (71.3)
Carillon		6 (5.9)
NeoChord		23 (22.8)
Mitral non-intervention	212 (42.1)	251 (39.2)

(a) MR severity presented for all patients with isolated MR or combined MR/ MS. (b) MR aetiology presented for all patients with isolated MR or combined MR/MS. (c) Including tricuspid and rhythm surgery. (d) Within isolated surgery (including tricuspid and rhythm). MR: mitral regurgitation; MS: mitral stenosis.

Table 3. Thirty-day and 1-year mortality allocated by treatment strategy

	General heart team (n = 504), n (%)	Dedicated heart team (n = 641), n (%)	P-value
30-day mortality			
Overall	26 (5.2)	19 (3.0)	0.058
Surgical	21 (7.4)	11 (3.8)	0.063
Isolateda MV surgery	8 (4.8)	4 (1.8)	0.14
Elective isolateda MV surgery	7 (4.4)	3 (1.4)	0.10
Transcatheter	0	3 (3.0)	1.00
Mitral non-intervention	5 (2.4)	5 (2.0)	1.00
1-year mortality			
Overall	74 (14.7)	57 (8.9)	0.002
Surgical	41 (14.4)	20 (6.9)	0.004
Isolated[a] MV surgery	15 (9.1)	9 (4.1)	0.046
Elective isolated[a] MV surgery	13 (8.2)	8 (3.7)	0.064
Transcatheter	2 (28.6)	11 (10.9)	0.20
Mitral non-intervention	31 (14.6)	26 (10.4)	0.16

(a) Including tricuspid and rhythm surgery. MV: mitral valve.

SURVIVAL ANALYSES

Intention-to-treat analyses

The Kaplan–Meier analysis stratified by 2 groups is shown in Fig. 2A, with the table of patients at risk in each group for each 6-month interval. The log-rank test showed a crude difference in survival probability between groups (P = 0.040). The 12-month survival probability was 0.91 (95% CI 0.89–0.93) in the dedicated heart team group and 0.86 (95% CI 0.83–0.89) in the general heart team group. At 5 years, the survival probability was 0.74 (95% CI 0.68–0.79) for the dedicated heart team group and 0.70 (95% CI 0.66–0.74) for the general heart team group. Kaplan–Meier analyses for the surgical and non-intervention groups are shown in Fig. 2B and C. At 5 years, the survival probability for patients who underwent a surgical treatment was 0.84 (95% CI 0.77–0.89) in the dedicated heart team group compared with 0.77 (95% CI 0.72–0.82) in the general heart team (Fig. 2B). The log-rank test showed a crude difference in survival probability between groups (P = 0.013). The survival probability for patients in mitral non-intervention group was 0.76 (95% CI 0.69–0.82) in the dedicated heart team group compared with 0.61 (95% CI 0.54–0.67) in the general heart team group (Fig. 2C). The log-rank test showed a crude difference in survival probability between groups (P = 0.031). The unadjusted HR for the dedicated heart team group compared with the general heart team group was 0.78 (95% CI 0.60–0.99; P = 0.044). The HR for the dedicated heart team group compared with the general heart team group, adjusted for EuroSCORE II, treatment group (surgical, transcatheter and non-intervention), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics, was 0.71 (95% CI 0.54–0.95; P = 0.019; Model I). These 13 other baseline characteristics were: age, sex, atrial fibrillation, insulindependent diabetes, extracardiac arteriopathy, renal impairment, chronic lung disease, pulmonary hypertension, left ventricle function, previous cardiac surgery, recent myocardial infarction, New York Heart Association and urgency of the treatment. The HR did not change significantly in a model when adjustment was made only for EuroSCORE II, treatment group (surgical, transcatheter and non-intervention) and mitral valve pathology (degenerative, functional, rheumatic and others) (HR 0.72, 95% CI 0.55–0.94; P = 0.017; Model II) or in a model when adjustment was made for treatment group (surgical, transcatheter and non-intervention), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics (HR 0.69, 95% CI 0.52–0.91; P = 0.009; Model III). HRs for all analysed factors in different models are presented in Table 4

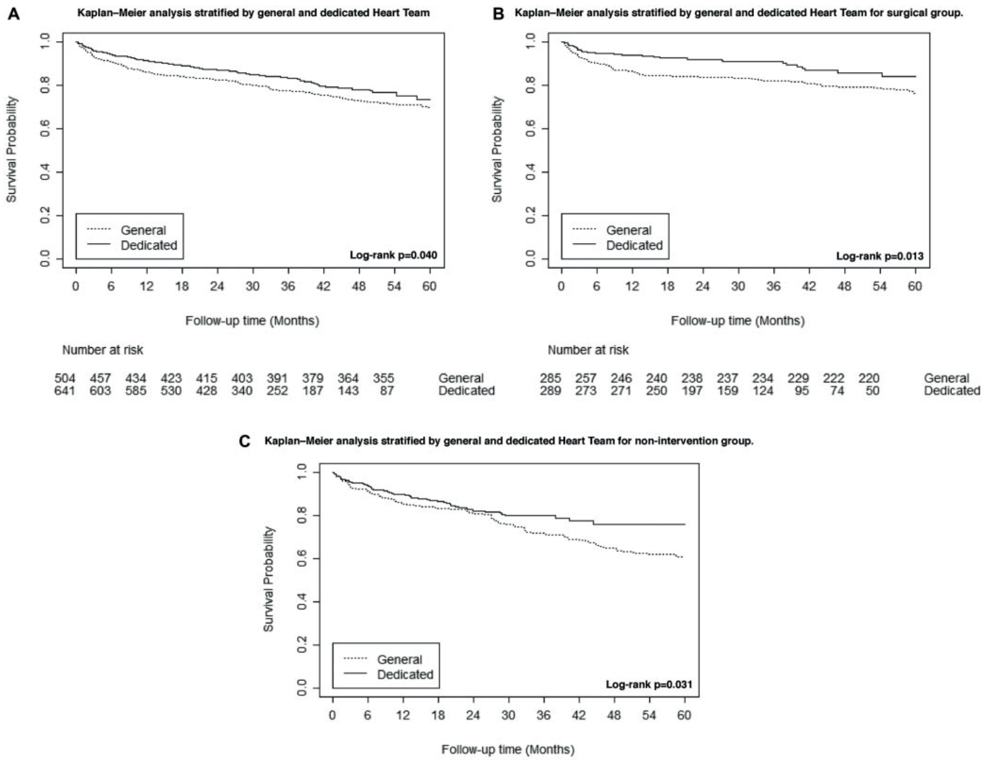

Figure 2.

(A) The Kaplan–Meier analysis stratified by general and dedicated heart team. The log-rank test showed a crude difference in survival probability between groups (P = 0.040). (B) The Kaplan–Meier analysis stratified by general and dedicated heart team for surgical group. The log-rank test showed a crude difference in survival probability between groups (P = 0.013). (C) The Kaplan–Meier analysis stratified by general and dedicated heart team for non-intervention group. The log-rank test showed a crude difference in survival probability between groups (P = 0.031).

Per-protocol analysis

The Kaplan–Meier analysis stratified by 3 groups based on whether they followed the advice is shown in Fig. 3, including the table of patients at risk in each group for each 6-month interval. At 5 years, the survival probability was 0.75 (95% CI 0.69–0.80) in the dedicated heart team group compared with 0.72 (95% CI 0.68–0.76) and 0.46 (95% CI 0.32–0.58) in the general heart team group, and in the group who did not follow the heart team advice, respectively. The log-rank test showed significant differences in survival probabilities ($P < 0.001$). The unadjusted HR for the dedicated heart team group compared with the group that did not follow the advice was 0.47 (95% CI 0.32–0.68; $P < 0.001$). The unadjusted HR for the general heart team group compared with the group that did not follow the advice was 0.36 (95% CI 0.24–0.53; $P < 0.001$). The HR adjusted for EuroSCORE II, treatment group (surgical, transcatheter and non-intervention), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics for the general heart team group compared with the group that did not follow the advice of the heart team was 0.57 (95% CI 0.37–0.87; $P = 0.010$; Model I). The HR comparing survival in the dedicated heart team group with the group that did not follow the advice of the heart team was 0.39 (95% 0.25–0.62; $P < 0.001$; Model I).

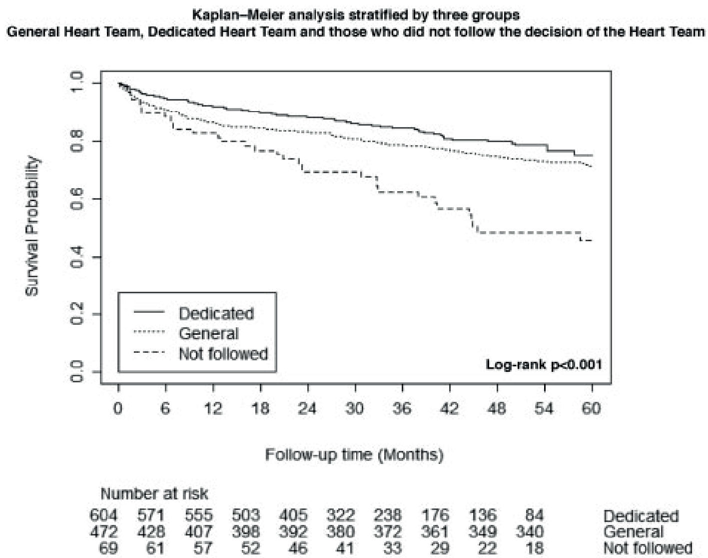

Figure 3. The Kaplan–Meier analysis stratified by 3 groups (general heart team, dedicated heart team and those who did not follow the decision of the heart team) is shown in Fig. 2. The log-rank test showed significant differences in survival probabilities ($P < 0.001$).

The HRs did not change significantly in a model when adjustment was made only for EuroSCORE II, treatment groups (surgical, transcatheter and non-intervention) and mitral valve pathology (degenerative, functional, rheumatic and others): HR of the general heart team group vs the group that did not follow the advice of the heart team was 0.55 (95% CI 0.36–0.84; $P = 0.005$; Model II); HR for the dedicated heart team group vs the group that did not follow the advice of the heart team was 0.38 (95% 0.25–0.60; $P < 0.001$; Model II).

Table 4. Multivariable-adjusted relative risk of mortality by Cox proportional regression analysis for heart team groups in 3 intention-to-treat analysis models

Variables	Model I			Model II			Model III		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Heart team									
General	1			1			1		
Dedicated	0.71	0.54–0.95	0.019	0.72	0.55–0.94	0.017	0.69	0.52–0.91	0.009
Treatment			0.006			<0.001			0.007
Surgical	1			1			1		
Transcatheter	1.94	1.21–3.11	0.006	2.82	1.86–4.27	<0.001	1.81	1.13–2.89	0.014
Mitral non-intervention	1.63	1.16–2.29	0.005	1.82	1.39–2.44	<0.001	1.67	1.19–2.34	0.003
Mitral valve pathology			0.240			0.149			0.366
Degenerative	1			1			1		
Functional	1.00	0.71–1.40	0.994	1.21	0.84–1.51	0.447	1.05	0.75–1.46	0.782
Rheumatic	0.75	0.40–1.43	0.388	0.61	0.32–1.16	0.131	0.82	0.44–1.55	0.544
Others	1.46	0.92–2.34	0.109	1.35	0.86–2.13	0.194	1.43	0.90–2.28	0.133
EuroSCORE II	1.06	1.01–1.11	0.011	1.12	1.09–1.15	<0.001			
Age	1.04	1.03–1.06	<0.001				1.05	1.03–1.06	<0.001
Sex									
Man	1						1		
Female	0.88	0.68–1.14	0.347				0.87	0.69–1.16	0.401
Atrial fibrillation									
No	1						1		
Yes	1.04	0.79–1.34	0.846				1.04	0.80–1.35	0.792
Insulin-dependent diabetes									
No	1						1		
Yes	1.18	0.69–2.02	0.554				1.30	0.76–2.22	0.331

Table 4. Continued

Variables	Model I			Model II			Model III		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Extracardiac arteriopathy									
No	1						1		
Yes	1.44	0.99–2.10	0.058				1.72	1.22–2.43	0.002
Renal impairment									
Normal	1						1		
Moderate/severe/dialysis	1.07	0.77–1.50	0.687				1.26	0.92–1.71	0.148
Chronic lung disease									
No	1						1		
Yes	1.26	0.88–1.81	0.213				1.28	0.89–1.84	0.181
Pulmonary hypertension									
No	1						1		
Moderate/severe	0.93	0.64–1.33	0.674				1.00	0.70–1.43	0.982
Left ventricular function									
Good	1						1		
Moderate/poor/very poor	1.22	0.94–1.68	0.129				1.36	1.02–1.80	0.035
Previous cardiac surgery									
No	1						1		
Yes	1.03	0.68–1.56	0.902				1.40	1.00–1.94	0.045
Recent myocardial infarction									
No	1						1		
Yes	1.60	0.79–3.25	0.194				1.74	0.86–3.51	0.123
NYHA									
I–II	1						1		
III–IV	1.51	1.18–1.94	0.001				1.63	1.28–2.09	<0.001

Urgency									
Elective	1						1		
Urgent	1.24	0.70–2.19	0.462				1.38	0.79–2.41	0.254

Intention-to-treat analysis: patients stratified into general and dedicated heart team regardless of whether they followed the advice of the heart teams.
Model I: heart team (general, dedicated), EuroSCORE II, treatment group (surgical, interventional and conservative), mitral valve pathology (degenerative, func-tional, rheumatic and others) and 13 other baseline characteristics.
Model II: heart team (general, dedicated), EuroSCORE II, treatment group (surgical, interventional and conservative) and mitral valve pathology (degenerative, functional, rheumatic and others).
Model III: heart team (general, dedicated), treatment groups (surgical, interventional and conservative), mitral valve pathology (degenerative, functional, rheumat-ic and others) and 13 other baseline characteristics.
95% CI: 95% confidence interval; HR: hazard ratio; NYHA: New York Heart Association.

Intention-to-treat analysis: patients stratified into general and dedicated heart team regardless of whether they followed the advice of the heart teams. Model I: heart team (general, dedicated), EuroSCORE II, treatment group (surgical, interventional and conservative), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics. Model II: heart team (general, dedicated), EuroSCORE II, treatment group (surgical, interventional and conservative) and mitral valve pathology (degenerative, functional, rheumatic and others). Model III: heart team (general, dedicated), treatment groups (surgical, interventional and conservative), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics. 95% CI: 95% confidence interval; HR: hazard ratio; NYHA: New York Heart Association.

It was also not significantly changed in a model when adjustment was made for the treatment group (surgical, transcatheter and non-intervention), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics: HR for the general heart team group vs the group that did not follow the advice of the heart team was 0.54 (95% CI 0.35–0.84; $P = 0.006$; Model III); HR for the dedicated heart team group vs the group that did not follow the advice of the heart team was 0.36 (95% 0.23–0.57); $P < 0.001$; Model III. HRs of all analysed factors in different models are presented in Table 5.

Per-protocol analysis: patients stratified into general and dedicated heart team regardless of whether they followed the advice of the heart teams. Model I: heart team (general, dedicated, decision not followed), EuroSCORE II, treatment group (surgical, interventional and conservative), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics. Model II: heart team (general, dedicated, decision not followed), EuroSCORE II, treatment group (surgical, interventional and conservative) and mitral valve pathology (degenerative, functional, rheumatic and others).

Model III: heart team (general, dedicated, decision not followed), treatment groups (surgical, interventional and conservative), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics.
95% CI: 95% confidence interval; HR: hazard ratio; NYHA: New York Heart Association.

Table 5. Multivariable-adjusted relative risk of mortality by Cox proportional regression analysis for heart team groups in 3 per protocol analysis models

Variables	Model I			Model II			Model III		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Heart team			<0.001			<0.001			<0.001
Decision not followed	1			1			1		
General	0.57	0.37–0.87	0.010	0.55	0.36–0.84	0.005	0.54	0.35–0.84	<0.001
Dedicated	0.39	0.25–0.62	<0.001	0.38	0.25–0.60	<0.001	0.36	0.23–0.57	0.006
Treatment			0.014			<0.001			0.021
Surgical	1			1			1		
Transcatheter	2.00	1.24–3.21	0.004	2.81	1.84–4.28	<0.001	1.91	1.19–3.06	0.007
Mitral non-intervention	1.41	0.99–2.00	0.057	1.53	1.13–2.08	0.006	1.42	1.00–2.03	0.050
Mitral valve pathology			0.135			0.063			0.162
Degenerative	1			1			1		
Functional	1.12	0.80–1.57	0.516	1.24	0.92–1.67	0.153	1.17	0.84–1.63	0.353
Rheumatic	0.73	0.38–1.39	0.336	0.62	0.33–1.17	0.142	0.77	0.40–1.45	0.417
Others	1.57	0.98–2.51	0.058	1.40	0.89–2.21	0.142	1.55	0.97–2.48	0.066
EuroSCORE II	1.05	1.00–1.09	0.052	1.11	1.08–1.14	<0.001			
Age	1.04	1.02–1.06	<0.001				1.04	1.03–1.06	<0.001
Sex									
Man	1						1		
Female	0.91	0.70–1.17	0.449				0.91	0.71–1.18	0.480
Atrial fibrillation									
No	1						1		
Yes	1.01	0.78–1.31	0.947				1.03	0.79–1.33	0.855
Insulin-dependent diabetes									
No	1						1		
Yes	1.22	0.71–2.09	0.554				1.31	0.77–2.22	0.328

Table 5. Continued

Variables	Model I			Model II			Model III		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Extracardiac arteriopathy									
No	1						1		
Yes	1.46	0.99–2.14	0.054				1.70	1.20–2.40	0.003
Renal impairment									
Normal	1						1		
Moderate/severe/dialysis	1.13	0.80–1.59	0.480				1.29	0.95–1.76	0.102
Chronic lung disease									
No	1						1		
Yes	1.31	0.91–1.87	0.151				1.32	0.92–1.90	0.135
Pulmonary hypertension									
No	1						1		
Moderate/severe	0.97	0.67–1.39	0.847				1.02	0.71–1.46	0.918
Left ventricular function									
Good	1						1		
Moderate/poor/very poor	1.28	0.95–1.72	0.101				1.37	1.03–1.82	0.032
Previous cardiac surgery									
No	1						1		
Yes	1.08	0.71–1.65	0.718				1.38	0.99–1.92	0.055
Recent myocardial infarction									
No	1						1		
Yes	1.62	0.80–3.28	0.185				1.73	0.85–3.49	0.128
NYHA									
I–II	1						1		
III–IV	1.50	1.17–1.93	0.002				1.59	1.25–2.03	<0.001
Urgency									
Elective	1						1		
Urgent	1.22	0.69–2.16	0.487				1.32	0.75–2.30	0.333

Per-protocol analysis: patients stratified into general and dedicated heart team regardless of whether they followed the advice of the heart teams.
Model I: heart team (general, dedicated, decision not followed), EuroSCORE II, treatment group (surgical, interventional and conservative), mitral valve pathology (degenerative, functional, rheumatic and others) and 13 other baseline characteristics.
Model II: heart team (general, dedicated, decision not followed), EuroSCORE II, treatment group (surgical, interventional and conservative) and mitral valve path-ology (degenerative, functional, rheumatic and others).
Model III: heart team (general, dedicated, decision not followed), treatment groups (surgical, interventional and conservative), mitral valve pathology (degenera-tive, functional, rheumatic and others) and 13 other baseline characteristics.
95% CI: 95% confidence interval; HR: hazard ratio; NYHA: New York Heart Association.

DISCUSSION

At Maastricht University Medical Centre, we have, as the single cardiothoracic centre in the province of Limburg, institutionalized the heart team approach to all patients undergoing any cardiac intervention (even single coronary disease). As there is no private practice and limited supra-regional referrals in the Netherlands, the patient population presented in the current study is less bound to selection bias. The rationale for a dedicated mitral valve heart team was based on indirect evidence from studies in which dedication for and experience in mitral valve surgery were associated with outcomes [17–20]. In addition to this is evidence that the dedication for mitral valve pathology is just as important for imaging and interventional cardiology[21, 22]. With the advent of new transcatheter technologies, and the complexity and variability of mitral valve pathology, the establishment of dedicated mitral heart teams seems warranted. A general heart team would not necessarily bring together the required expertise for the treatment of patients with mitral valve disease. Additionally, the progressive nature of mitral valve pathology, the integrative approach to its assessment, the importance of timing of interventions, the variability in treatment options and the operator dependence of its outcome make the decision-making crucial in the care of patients with mitral valve pathologies. We also postulate that the decision-making process and expertise of the decision-makers have significant bearing on the survival difference observed in this study. The current study demonstrates that multidisciplinary decision-making is important for the prognosis of patients with mitral valve disease: we observed that patients who did not follow the advice of the heart team had the worst prognosis at 5 years. This is important in light of some reports that show a substantial proportion of patients with severe mitral valve regurgitation are not referred for any intervention and presumably treated conservatively or too late[23, 24]. The strengths of current study are that the heart team decision-making process was collected prospectively in real time, there were no missing data, the follow-up was completed in all patients, the inclusion of all-comers for mitral valve disease, the large sample size and the use of multivariable analysis to adjust for confounding factors. In addition to the above, we analysed in different multivariable models the effect of the dedicated heart team on survival.

Limitations

The principal limitation of our study is that it does not have the strength of a randomized controlled trial. However, a randomized controlled trial was not possible because of the prolific introduction of the heart team approach, its codification as class I indication in the guidelines and its mandatory character in the light of evolving options in new therapeutics. Additional limitation is that we compared patients from 2 different time periods, and that it is perceived that surgical mortality also decreases over time [25]. It remains unclear whether this is a consequence of centralization and increasing centre and individual experience, or the tendency to operate earlier on patients[26], based on recent guidelines[27]. Adjusted analyses cannot control for all confounding factors. Furthermore, there were less transcatheter treatment options being used in the first period. Although we adjusted for this difference in multivariable analysis and transcatheter treatment options were associated with poorer outcome (benefiting the general heart team group), we acknowledge that patients might have been allocated differently in the contemporary times. Although we acknowledge these differences, we also argue that some differences between the heart teams and time periods are the inherent consequences of the implementation of a dedicated mitral heart team programme.

CONCLUSION

In conclusion, patients treated by the dedicated mitral valve heart team had significantly higher survival rates in this comparative cohort study. The results presented provide the first supporting evidence for the implementation of the dedicated mitral valve heart team to improve patient outcomes.

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SUPPLEMENTARY MATERIALS

Table S1. Baseline characteristics of 1,145 patients treated based on the decision of the general Heart Team, dedicated mitral valve Heart Team or those who did not follow the decision for isolated or concomitant mitral valve pathology.

	Decision not followed (n=69)	General Heart Team (n=472)	Dedicated Heart Team (n=604)	p-value***
Age*	77 [69, 83]	70 [62, 76]	70 [64, 77]	0.112
Sex (female)	35 (50.7%)	206 (43.6%)	274 (45.4%)	0.573
Previous cardiac surgery	7 (10.1%)	49 (10.4%)	79 (13.1%)	0.175
Left ventricular ejection fraction				**0.023**
>50%	48 (69.6%)	258 (54.7%)	371 (61.4%)	
31-50%	11 (15.9%)	147 (31.1%)	176 (29.1%)	
21-30%	8 (11.6%)	52 (11.0%)	38 (6.3%)	
<21%	2 (2.9%)	15 (3.2%)	19 (3.1%)	
NYHA classification				**0.029**
I	20 (29.0%)	119 (25.2%)	172 (28.5%)	
II	25 (36.2%)	176 (37.3%)	249 (41.2%)	
III	24 (34.8%)	154 (32.6%)	169 (28.0%)	
IV	0	23 (4.9%)	14 (2.3%)	
Chronic lung disease	3 (4.3%)	55 (11.7%)	52 (8.6%)	0.098
Pulmonary hypertension**	1 (1.4%)	22 (4.7%)	26 (4.3%)	0.779
Extracardiac arteriopathy	5 (7.2%)	47 (10.0%)	49 (8.1%)	0.292
Renal impairment				**0.000**
GFR >80	61 (88.4%)	325 (68.9%)	311 (51.5%)	
GFR 50-80	6 (8.7%)	97 (20.6%)	210 (34.8%)	
GFR <50	2 (2.9%)	49 (10.4%)	82 (13.6%)	
Dialysis	0	1 (0.2%)	1 (0.2%)	
Previous myocardial infarction	0	11 (2.3%)	12 (2.0%)	0.435
Diabetes Mellitus on insulin	3 (4.3%)	15 (3.2%)	20 (3.3%)	1.000****
Atrial fibrillation	24 (34.8%)	134 (28.4%)	233 (38.6%)	0.001
Cerebrovascular accident	11 (15.9%)	51 (10.8%)	71 (11.8%)	0.630
Urgency				**0.001**
Elective	69 (100%)	435 (92.2%)	585 (96.9%)	
Urgent	0	37 (7.8%)	19 (3.1%)	

EuroSCORE II overall*	1.74 [0.99, 3.50]	2.37 [1.30, 4.09]	1.88 [1.14, 3.69]	0.003
EuroSCORE surgery		2.38 [1.20, 4.34]	1.81 [0.99, 3.74]	0.004
EuroSCORE transcatheter		1.97 [1.07, 4.62]	2.18 [1.42, 3.68]	0.600
EuroSCORE mitral non-intervention	1.74 [0.99, 3.50]	2.35 [1.45, 3.70]	1.94 [1.14, 3.78]	0.058

NYHA: New York Heart Association.
* presented as median [25th, 75th percentile]
** defined as pulmonary artery pressure >55 mmHg
*** statistical testing performed between general and dedicated heart-team
**** Fisher's exact if expected cell count <5

Table S2. Evaluation and treatment of 1,145 patients based on the decision of the general Heart Team, dedicated mitral valve Heart Team or those who did not follow the decision, for isolated or concomitant mitral valve pathology

	Decision not followed (n=69)	General heart-team (n=472)	Dedicated heart-team (n=604)
Indication			
Regurgitation	58 (84.1%)	424 (89.8%)	547 (90.6%)
Stenosis	10 (14.5%)	35 (7.4%)	31 (5.1%)
MR/MS	1 (1.4%)	13 (2.8%)	26 (4.3%)
MR severity*			
Grade I	1 (1.7%)	24 (5.5%)	23 (4.0%)
Grade II	7 (11.9%)	125 (28.6%)	136 (23.7%)
Grade III	17 (28.8%)	129 (29.5%)	77 (13.4%)
Grade IV	34 (57.6%)	159 (36.4%)	337 (58.8%)
MR etiology**			
Degenerative	30 (50.8%)	158 (36.2%)	295 (51.5%)
Functional	25 (42.4%)	242 (55.4%)	228 (39.8%)
Rheumatic	1 (1.7%)	18 (4.1)	30 (5.2%)
Other	3 (5.1%)	19 (4.3%)	20 (3.5%)
Surgical treatment		285 (60.4%)	289 (47.8%)
Isolated mitral surgery***		165 (57.9%)	220 (76.1%)
Concomitant surgery		120 (42.1%)	69 (23.9%)
Minimally invasive****		20 (7.0%))	150 (68.2%)
Mitral repair		222 (77.9%)	229 (79.2%)
Mitral replacement		63 (22.1%)	60 (20.8%)
Transcatheter intervention		7 (1.5%)	101 (16.7%)
MitraClip		7 (100%)	72 (71.3%)
Carillon			6 (5.9%)
NeoChord			23 (22.8%)
Mitral non-intervention		180 (38.1%)	214 (35.4%)

MR: mitral regurgitation; MS: mitral stenosis
* MR severity presented for all patients with isolated MR or combined MR/MS
** MR etiology presented for all patients with isolated MR or combined MR/MS
*** including tricuspid and rhythm surgery
**** within isolated surgery (including tricuspid and rhythm)

Chapter 4

Planning minimally invasive mitral valve surgery

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ABSTRACT

Minimally Invasive Mitral Valve Surgery (MIMVS) has still not been widely adopted as standard approach for surgical treatment of mitral valve disease due to a lack of consistent supporting evidence. Several studies have demonstrated MIMVS to be associated with shorter hospitalization stay, less bleeding and less wound infections, in spite of increased risk of stroke and longer operating times. In our philosophy, these complications can be reduced by use of precise patient selection and extensive pre-operative planning. The current review aims to present an overview of current literature on this topic together with our institutions experience in this field. Advanced application of echocardiography and Computed Tomography (CT) with three-dimensional anatomical reconstruction could lead to an exclusion of high-risk patients for MIMVS, resulting in a reduction of complications and leading to potential superiority of this procedure compared to conventional surgery. With emergence of trans-catheter and surgical off-pump mitral valve procedures, echocardiography will play an increasingly important role, as these operations require echo-guidance. Due to technological advancements in the field of CT, we foresee this imaging modality to become more widely accepted and available, facilitating a more precise assessment of cardiac function and valvular pathology.

INTRODUCTION

Although Minimally Invasive Mitral Valve Surgery (MIMVS) was already described in the late 1990's [1, 2], adoption rate of this technique remains rather low >20 years later (15% of all mitral procedures in the United States) and MIMVS is not mentioned in most recent valvular heart disease guidelines [3-6]. This can partly be explained by the accompanying increased technical difficulties in MIMVS with a steep learning curve [7], potentially holding interested surgeons back in starting or continuing such a comprehensive program [8]. Additionally, there is still a lack of convincing data favoring this technique, with only a few inconclusive randomized controlled trials and limited meta-analyses of retrospective studies dealing with this subject [9-11]. In general, most of these comparative studies demonstrate less bleeding, less wound infections, more rapid detubation and shorter intensive care unit and hospital stay in spite of longer cardiopulmonary bypass (CPB) and clamping times with an increased risk of stroke. Echocardiopgrahic follow-up of these patients revealed no difference in residual mitral regurgitation (MR).

However, access [12] (different locations and sizes of incisions), vision [13] (direct, video-assisted or totally endoscopic) and CPB cannulation strategies [14] (antegrade vs. retrograde) vary between centers and make these results even more difficult to compare and interpret.

In our philosophy, precise patient selection and extensive pre-operative planning is imperative for this procedure and could lead to a reduction in complications following MIMVS, potentially resulting in superiority of MIMVS over conventional surgery through a median sternotomy. Therefore, in our institution, all patients considered for MIMVS undergo a standard pre-operative diagnostic pathway evaluated by a dedicated mitral valve heart team after which they are allocated to their designated treatment (Figure 1). In this philosophy of *Personalized Medicine*, we select the patients that benefit most of our standardized technique, rather than adapting the surgical technique to the specific patient [15].

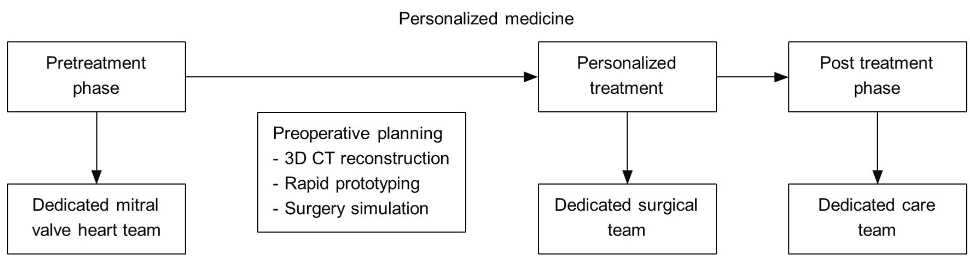

Figure 1. Concept of personalized medicine.
3D: three-dimensional; CT: computed tomography.

The current review aims to present an overview of current literature on this topic together with our institutions experience in this field as a guidance for surgeons starting this program, in order avoid potential preventable complications.

STANDARDIZED DIAGNOSTIC PATHWAY

All patients referred for surgical correction of mitral valve disease are discussed in our weekly convening dedicated mitral valve heart team. If a patient is considered eligible for a minimally invasive approach (i.e., no need for concomitant coronary artery bypass grafting, aortic valve replacement etc.), the patients undergoes a standardizes pre-operative diagnostic pathway consisting of the following modalities.

Electrocardiography

All current and past electrocardiographic examinations are reviewed for occurrences of atrial fibrillation (AF) and ventricular dyssynchrony. In case of a reported episode of AF, the patient is discussed in our dedicated rhythm heart team (consisting of rhythm surgeons and electrophysiologists). According to most recent guidelines, patients with paroxysmal, persistent and long-standing persistent AF have a Class I indication for concomitant surgical ablation and are planned for a concomitant procedure [16].

Chest X-ray

Standard performed chest X-rays are assessed for deviant thoracic anatomy and height of the right hemi diaphragm. Additionally, acute and chronic pulmonary pathology can be identified using this simple imaging modality, potentially influencing the pre-operative planning pathway.

Echocardiography

Before referral to our institution, patients undergo standard transthoracic echocardiography (TTE) at their own hospital, which is assessed by imaging specialists of our mitral valve heart team. As most important limitation, this technique is highly operator- and interpreter-dependent, warranting assessment by imaging cardiologists with (echocardiographic) expertise in valvular heart disease. As an advantage, TTE is widely available, cost-effective and has excellent results for functional assessment [17].

For evaluation of severity of mitral valve disease, TTE remains the gold standard. Using TTE, MR severity is evaluated by valve morphology, colour flow jet, vena contracta width, pulmonary vein flow, time-velocity integral of mitral inflow, effective orifice regurgitant orifice area and regurgitant volume [18]. However, regarding colour flow jet, one should be careful to base assessment of severity solely on the extent of the jet. Although a large jet reaching the pulmonary veins is usually considered severe, small jets reaching just above the mitral valve can be misleadingly interpreted as non-severe but can potentially be influenced by increased left atrial pressure [19]. Additionally, young patients with extensive myxomatous valve disease (Barlow's) can exhibit all signs of severe MR, but due to mitral annular disjunction, the valve itself can be fully displaced into the atrium without a large colour flow jet [20]. Therefore, severity assessment should be determined using an integrative approach including all (if available) aforementioned qualitative, semi-quantitative and quantitative parameters. In addition to severity of MR, TTE gives a general overview of cardiac function and other valvular pathologies. In relation to the mitral valve, it is imperative to evaluate pulmonary artery pressure, right ventricular function and potential concomitant tricuspid regurgitation (TR). Although right ventricular function is not evaluated by most risk scores, right ventricular dysfunction has proven to be an under-recognized predictor of mortality after cardiac surgery [21]. Furthermore, thresholds for concomitant tricuspid repair in mitral valve surgery have lowered over the past years and concomitant repair has been associated with improved outcomes [22]. According to recent guidelines, additional tricuspid repair should be considered in case of tricuspid annular dilatation >40mm, even regardless of severity of TR.

In case of degenerative MR with prolapsing segment(s), repair is likely, warranted and associated with lower morbidity, mortality and improved survival compared to mitral valve replacement [23-25]. For functional MR, echocardiographic parameters can help to determine probability of a successful repair. The following unfavorable echocardiographic parameters have been described; annular dilatation >50mm, involvement of >3 leaflet scallops including the anterior mitral valve leaflet and severe mitral annular calcification [26]. Furthermore, Carpentier functional type IIIa (rheumatic) valves and ischemic valves (Carpentier type IIIb) with severe ventricular dilatation have a low repair probability (the latter due to postoperative ventricular remodeling).

If repair is likely, as in degenerative disease, patients in our institution undergo subsequent transesophageal echocardiography (TEE), as it is superior to TTE for localization of mitral prolapse [27], to determine the exact mechanism of regurgitation (i.e., specific prolapsing segments) in order to predict procedural repair strategy. Using TEE, precise measurement of the anterior mitral leaflet length and intercommissural distance can aid to predict the required ring size for mitral repair [28].

In complex degenerative pathology, three-dimensional (3D) reconstruction of the diseased valve can be created using dedicated software [29], allowing the operator to assess the valve from all angles (**Figure 2**). Additionally, these computer aided designs are superior in ring size prediction [28]. For specific cases, these reconstructions can even be used to 3D print (rapid prototyping) the patient specific pathological valve, which is discussed in another chapter of this issue.

Figure 2. Three-dimensional mitral valve reconstruction based on TEE images. The model can be stopped at any moment during the cardiac cycle for optimal assessment of valvular pathology.

3D: three-dimensional; TEE: transesophageal echocardiography

Coronary Angiography

As for all non-coronary cardiac procedures, coronary angiography (CAG) is paramount for evaluation of potential subclinical coronary artery disease (CAD) requiring concomitant coronary artery bypass grafting. In addition to evaluation of CAD, CAG can also be used for planning of mitral valve surgery. First, mitral annular calcification can be assessed in location and extent, potentially influencing procedural strategy. Furthermore, and most importantly, the trajectory of the circumflex artery (RCx) can be determined in relation to the mitral valve. A less well-known, uncommon, but disastrous complication in mitral valve surgery is accidental (partial) occlusion of the RCx [30, 31]. It is even thought to be an under-recognized and under-reported complication, as many patients present with ischemia-like features and reduced ventricular function directly after mitral valve surgery [32]. This complication can be the result of either (i) complete obliteration of the RCx lumen by annular sutures or (ii) by kinking of the RCx towards the mitral valve due to traction of annular sutures (Figure 3, 4). Retrospectively, this complication was observed most in patients with a left dominant coronary system [33]. This can be explained by the course of the RCx, which runs closer to the mitral valve in hearts with left dominance [34]. Coronary angiography should be used as a guidance in procedural strategy in patients with left dominance, as left dominance is not a contraindication for MIMVS or conventional mitral valve surgery, rather a warning. Care should be taken in placement of annular sutures around the anterolateral commissure, as post-mortem studies revealed this to be the area with the shortest distance to the RCx, corresponding to the proximal one-third of the coronary artery [33].

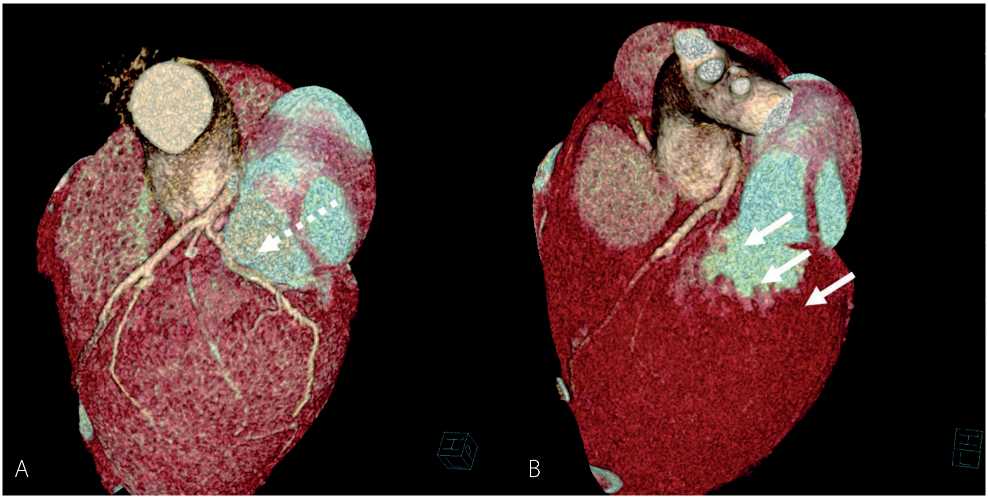

Figure 3. Pre- and postoperative contrast enhanced cardiac CT in a patient with postoperative iatrogenic occlusion of the RCx after mitral valve repair.

(A) pre-operative CT revealing an intact RCx (dotted arrow) and (B) postoperative CT 3 months after mitral valve repair showing a fully obliterated RCx (arrows) due to annular sutures.
CT: Computed Tomography, RCx: circumflex artery.

Figure 4. Direct postoperative invasive coronary angiography after mitral valve repair revealing an iatrogenic total occlusion of the proximal RCx

Computed Tomography and anatomical reconstructions

Indication for surgical approach (i.e., minithoracotomy or sternotomy) is based on anatomical features and comorbidities. In order to assess anatomical eligibility, standard contrast-enhanced Computed Tomography (CT) scans are performed at our institution in all patients in work-up prior to mitral valve interventions. Computed Tomography is a relatively low-cost non-invasive diagnostic imaging modality which produces computer-processed combinations of a predefined number of X-rays. An important downside of this modality is the use of radiation and its subsequent attributable cancer risk [35]. With recent technological advancements, such as automated tube voltage selection, tube current modulation and ultra-fast scan acquisition, radiation dose can be reduced markedly [36, 37]. Combined with a reduction of contrast media volume used, decreasing prevalence of contrast induced nephropathy, CT has become more widely available and accepted [38]. As described previously, these CT images can then be used to acquire a 3D reconstruction of the patients' anatomy (Vesalius 3D, PS-Medtech, Amsterdam, the Netherlands) [39].

The first step in realising these high-quality, reliable and reproducible reconstructions of patients' anatomy prior to surgery is the initial image acquisition. Based on our early experience and different acquisition protocols, nowadays an electrocardiography (ECG)-triggered helical CT angiography of the aortic root and ascending aorta followed by a high-pitch spiral CT angiography from the aortic arch to the femoral bifurcation is performed in all patients. Close collaboration with the local department of radiology is imperative to develop the ideal scan protocol. Using dedicated software, the 3D reconstruction is then derived from these high-quality initial scans [39, 40].

First, suitability for CPB cannulation and safe retrograde perfusion is evaluated on these reconstructions. Minimally invasive mitral valve surgery using retrograde perfusion has been associated with increased risk of stroke [41]. However, in our vision, risk of stroke can be minimalized by pre-operative assessment of the abdominal aorta and peripheral vessels (Figure 5). A recent study by our research group demonstrated approximately 30% of patients to be less suitable for a minimally invasive approach, as we found the following characteristics on CT reconstruction: severe calcification of the abdominal aorta (porcelain aorta), iliofemoral vessel tortuosity, (ascending) aortic elongation and extensive pericardial calcification [39]. These patients were excluded from a minimally invasive approach, as a sternotomy with antegrade perfusion would be safer, avoiding the risk of stroke. Additionally, in severely elongated aortas, we try to avoid aortic occlusion with the trans-thoracic clamp, while we demonstrated aortic elongation to be age-dependent and a risk factor for the development of type A aortic dissection [42, 43].

Figure 5. Three-dimensional anatomical reconstruction of the abdominal aorta and peripheral vessels revealing extensive calcification and tortuosity of the iliofemoral vessels.

CPB, cardiopulmonary bypass.

Of note, one could argue to tailor surgical and perfusion techniques to the individual patient based on CT, as different centers have demonstrated excellent results with antegrade perfusion techniques in MIMVS using axillary artery cannulation or direct aortic cannulation [14, 44, 45]. However, we advocate a standardized approach in all patients undergoing MIMVS, rather than using numerous different strategies.

Second, we determine the strategy for aortic occlusion. Our preferred method for aortic clamping is by use of an endo-aortic balloon (IntraClude, Edwards Lifesciences, Irvine, CA, USA) as it has similar outcome compared to the transthoracic aortic clamp (Chitwood Clamp, Scanlan International, St Paul, MN, USA) and does not require placement of an aortic needle for cardioplegia delivery while this is integrated in the system, making it especially ideal for reoperative mitral valve surgery [46, 47]. Ascending aortic dilatation is evaluated on CT, as the endo-aortic balloon requires an aortic diameter <4cm to safely achieve secure occlusion [48].

Furthermore, the balloon is introduced in a special side port of the femoral arterial cannula and advanced under TEE guidance to its position in the ascending aorta. To facilitate sufficient lumen for introduction of the balloon, a minimal cannula size of 19Ch is required. We determine our cannula size and cannulation side prior to the procedure using dedicated software, which simulates the introduction and advancement of the cannula using iliofemoral vessel diameter calculations (Figure 3, Synapse3D, Fujifilm, Tokyo, Japan).

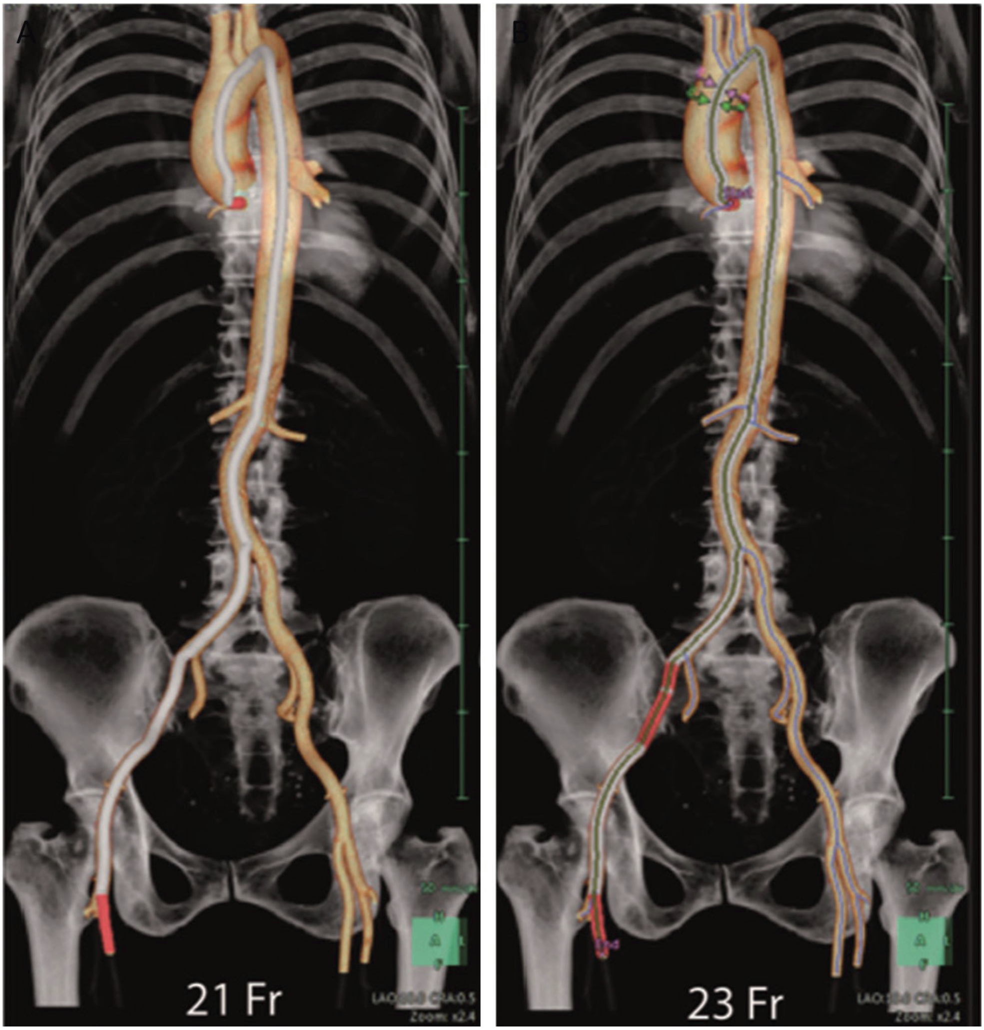

Figure 6. Reconstruction of the iliofemoral vessels and aorta based on CT images for simulation of arterial cannula introduction and advancement.

(A) A 21Ch arterial cannula can safely be introduced in the right femoral artery while (B) the right femoral artery has insufficient luminal diameter for a 23Ch cannula.

Third, the ideal intercostal space for the incision of the mini thoracotomy is determined pre-operatively, based on the level of the left atrium, Waterston's groove and the mitral valve in relation to the height of the right hemi-diaphragm (Figure 7) [49].

Figure 7. Three-dimensional anatomical reconstruction of the thoracic anatomy revealing a high right hemi-diaphragm in relation the mitral valve and the left atrium. Based on this observation, the pre-operative decision was made to enter the thoracic cavity through the 4th intercostal space.

Figure 8. Three-dimensional anatomical reconstruction of the aorta, peripheral vessels and thoracic anatomy, revealing excellent anatomical eligibility for a minimally invasive approach

Figure 8 demonstrates an example of a patient with excellent anatomical features for a minimally invasive approach.

As an additional merit, CT can be used for evaluation of coronary artery disease in young low-risk patients. Of note, coronary CT can only be used to rule out coronary disease [50]. If CT shows no coronary calcifications, coronary angiography is not required. In case of some calcification, CT is still insufficient to quantify stenoses, and additional invasive angiography is warranted [51]. Finally, we observed numerous incidental findings (incidentalomas) on CT. In our clinical practice, CT reveals in approximately 25% of all patients a subclinical incidentaloma, of which one-third are actual malignancies requiring follow-up or intervention, sometimes prior to mitral valve surgery.

FUTURE PERSPECTIVES

With the emergence of minimally invasive and even off-pump beating-heart procedures, patient selection and pre-operative planning will play an increasingly important role in the near future. Most of these off-pump procedures, such as trans-catheter edge-to-edge mitral valve repair [52], trans-catheter (in)direct annuloplasty [53, 54] and surgical beating-heart mitral valve repair [55-57] require intra-procedural TEE-guidance.

First, pre-operative TEE is warranted in these patients, as it is imperative to evaluate the possibility to obtain images of sufficient quality as during the actual procedure. Second, TEE is used to identify suitable patients with eligible valvular pathology for such an approach as described in this review.

Regarding CT, recent advancements in reduction of radiation dosages and contrast media volume will result in an increased use of this imaging modality, making it more available as risk of complications decreases. Currently, cardiac CT is not well-established enough to determine the exact mechanism of valvular dysfunction compared to echocardiography and quantification of coronary artery disease compared to invasive angiography. However, we foresee important developments in these areas, making invasive coronary angiography redundant as it carries a higher complication rate [58]. An important additional merit of CT over conventional echocardiography is that CT can be used to precisely define and measure mitral annular geometry [59, 60] which can facilitate a pre-operative prediction of the ring size for surgical or trans-catheter mitral valve repair. Finally, with recent developments in trans-catheter mitral valve replacement technologies [61, 62], pre-operative assessment of the left ventricular outflow tract (LVOT) and prediction of the neo-LVOT will become mandatory in patients' selection for these procedures, promoting the use of CT in these patients [63].

CONCLUSION

As mitral valve procedures are becoming less invasive, patient selection and pre-operative planning are becoming increasingly important. Using different imaging modalities as CT and echocardiography, precise patient selection could lead to a reduction of complications, as high-risk patients for these operations can be filtered out pre-operatively, potentially resulting in superiority of minimally invasive mitral valve surgery over conventional surgical approaches.

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Chapter 5

Clinical implications of three-dimensional mitral valve modelling, printing and simulation in mitral valve surgery

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ABSTRACT

The continuous trend towards less invasive procedures has increased the complexity of cardiac operations. Routine imaging modalities combined with state-of-the-art reconstruction software can substantially improve preoperative planning and simplify complex procedure by enhancing surgeon's knowledge on patients' specific anatomy. Patient-specific simulation, a combination of three-dimensional mitral valve modelling and printing, could serve as the ideal method for planning of complex mitral valve surgery. In our center, a process for modelling and three-dimensional printing of different mitral valve pathologies for procedural planning and simulation, based on 3D transoesophageal echocardiography, has been developed. In the current report, we present the clinical implications of three-dimensional modelling, printing and simulation in mitral valve surgery.

INTRODUCTION

The continuous trend towards less invasive procedures has increased the complexity of cardiac operations. Minimally invasive techniques require a different set of surgical skills as surgeons work through a smaller incision with long shafted instruments. Minimally invasive mitral valve surgery (MIMVS) has shown to be a safe and effective alternative compared to conventional sternotomy and has become widely accepted in many experienced centers[1,2]. However, not all patients are suitable for a minimally invasive approach. More importantly, not all patients will benefit from a minimally invasive approach. Therefore, adequate patient selection and precise preoperative planning are essential for successful adaptation of minimally invasive techniques[3]. Modern imaging modalities are a mandatory component in patient selection and preoperative planning in cardiothoracic surgery. In mitral valve surgery, preoperative transoesophageal echocardiography (TOE) and computed tomography (CT) angiography increased preoperative knowledge on patient's specific anatomy and pathology. Understanding the complex anatomy of the mitral valvular apparatus is essential for successful repair. Preoperative TOE provides anatomical insight to assess the feasibility of repair and CT is used to evaluate anatomical eligibility for a minimally invasive approach. The introduction of advanced reconstruction software improved the potential to create virtual 3D reconstructions, which can be rotated and segmented into layers. The reconstructions allow surgeons to enhance their understanding of the visuospatial relations between anatomical structures from a surgical view. Currently, virtual reconstructions are limited by being displayed on two-dimensional working stations, and not being displayed in real-time. In contrast, rapid prototyping, a technique used to generate prototype models, allows surgeons to develop a superior understanding of the anatomy and improved operative planning through the ability to interact directly with patient's printed anatomy and pathology.

Since 1980, 3D printing has primarily been used in industrial design and manufacturing. With the introduction of more user-friendly computer-aided design software, 3D printing made its way into the medical field[4]. In addition, the cost of 3D printers and printing materials, in combination with the manufacturing time, have significantly decreased during the recent years, excluding the necessity of outsourcing by clinicians. Rapid prototyping has already shown to be a valuable tool in orthopaedics[5], neurosurgery[6] and plastic surgery[7]. One of the major advantages of 3D printing is the capacity to directly translate a patient specific model into a tangible model. Nowadays, this technique has also emerged in the field of cardiovascular disease and cardiothoracic surgery[8].

Simultaneously with technical improvements in imaging modalities and patient specific modelling, preoperative simulation has gained increasing interest because of the limitations of the apprentice model. Arguments for the rationale for simulation-based training include the European Working Time Directive[9], limiting the working hours of residents and their possibilities to develop their surgical skills intra-operatively[10], more technical procedures (minimally invasive surgery) with steep learning curves[11], operation room efficacy, ethical issues regarding patient safety[12] and a more complex, better informed and more demanding patient population. In the field of cardiac surgery, simulation-based training has been introduced in coronary bypass surgery for vascular anastomosis[13-15], aortic cannulation[16] and mitral valve surgery[17,18], ranging from low- to high-fidelity simulators. Simulation has the potential to reduce traditional learning curves and prevent trial-and-error in actual patients.

Patient-specific simulation, a combination of both 3D modelling and 3D printing, could serve as the ideal planning method in preparation of complex surgery.

In our center, a process for modelling and 3D printing of different mitral valve pathologies for procedural planning and simulation, based on 3D transoesophageal echocardiography, was developed. In this manuscript, we present the clinical implications of 3D modelling, printing and simulation in mitral valve surgery.

The process of rapid prototyping can roughly be divided into four major steps, namely data acquisition, data conversion, mesh refinement and rapid prototyping. Current 3D printing techniques do not allow high-quality printing in flexible, tissue-like materials for simulation purposes. Therefore, models specific for simulation of endoscopic mitral valve repair require 2 additional steps: negative mould fabrication and casting (Figure 1).

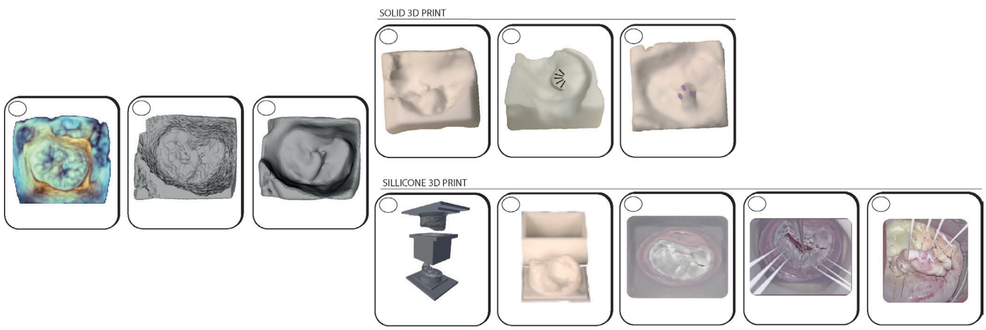

Figure 1. Step-by-step process for solid and silicone 3D print fabrication.

A patient-specific 3D model begins with clinical imaging. In our cases, imaging data were obtained throughout the entire cardiac cycle by 3D TOE using a Philips iE33 device with a 3D TOE probe (Philips Medical Systems, Andover, MA, USA). During data acquisition the mitral valve should be as close as possible to the probe, with minimization of movement to reduce artefacts. The ideal image acquisition possesses a completely dark blood pool with completely bright myocardium and mitral valvular tissue. The current standard ultrasound devices do not allow to directly export the data eligible for printing. Therefore, after a high-quality volumetric 3D image dataset is acquired,

the data is converted to a cartesian Digital Imaging and Communications in Medicine (DICOM) format in QLAB 9.1 (Philips Medical Systems, Andover, MA, USA).
After export, the data is converted to a dynamically 3D reconstructed heart valve dataset using dedicated software (Vesalius3D, PS-Medtech, Amsterdam, Netherlands). Unfortunately, due to quality constrains, it is currently not possible to acquire, reconstruct and print the subvalvular apparatus. Therefore, only the mitral valve annulus and leaflets are reconstructed. In order to capture the coaptation defect itself, the mitral valve is reconstructed in the mid- systolic phase.

Next, the 3D reconstructed valve is exported into a Surface Tessellation Language (STL) file, which is the standard format in 3D printing. Mesh refinements are performed in MeshLab (Istituto di Scienza e Tecnologie dell'Informazione, Pisa, Italy) and afterwards manufactured into a model on a 1:1 scale. During this process, isolated and connected components with diameters smaller than 25% of the maximum diameter are deleted.

Printing is performed using selective laser stereolithography, which is considered the gold standard in 3D biomodel production. In cases where a patient-specific model was fabricated for our high-fidelity simulator two additional steps were required. In addition, for simulation-based training purposes deformable, tissue-mimicking silicone is used to allow suture placement. First, a three-piece negative mould was constructed, after which a tissue-like silicone valve could be casted. A more detailed process for modelling and three-dimensional printing has been described elsewhere[19].

Case presentation
The presented workflow for 3D reconstruction and printing can be used for a plethora of mitral valve pathologies and allowed us to reconstruct and print different mitral valve pathologies. We present 3 cases of clinical implication of mitral valve 3D printing.

Case 1: mitral valve repair for posterior leaflet prolapse and annular dilatation
A 63-year-old man with severe mitral valve regurgitation based on posterior leaflet prolapse and annular dilatation was found eligible for mitral valve surgery. Transthoracic echocardiography showed a normal right and left ventricular function with an end diastolic diameter of 58 millimetres. Transoesophageal echocardiography showed severe mitral valve regurgitation with an eccentric jet based on a P2 prolapse with chordal rupture. Also, a mild prolapse of the P1 segment was found. Echocardiography revealed no aortic insufficiency and a trace of tricuspid valve insufficiency. Computed tomography reconstruction revealed no contraindications for peripheral cannulation and the patient was accepted for minimally invasive mitral valve repair. A three-piece negative mould was created based on imaging acquisition with TOE (). After casting the valve in silicone, the valve was mounted in the simulator for in vitro preoperative planning (Figure 3). Based on simulation, 2 pairs of neochordae were implanted in the P2 region. Additionally, 1 pair of

neochordae was placed at the P1 region and 1 pair at the P3 region. To stabilize the repair, a semi-rigid annuloplasty ring (Medtronic, Dublin, Ireland), size 34, was implanted (Figure 2).

Figure 2. Mitral valve repair for posterior leaflet prolapse and annular dilatation

Figure 3. Silicone model showing posterior leaflet prolapse and annular dilation

Case 2: mitral valve repair for posterior leaflet prolapse

A 64-year-old male with no medical history presented with increasing dyspnoea. A transthoracic echocardiography showed a left ventricular ejection fraction of 68%, left ventricle diastolic diameter of 52 mm, left ventricle systolic diameter of 32 mm and severe mitral regurgitation with an effective regurgitant orifice of 0.53 cm2. The mechanism of regurgitation was a prolapse of the P2 segment of the posterior leaflet. No other valve disease was observed. The patient was discussed in the mitral valve heart and found eligible for minimally invasive mitral valve surgery. A CT scan was performed, which showed no contraindications. A 3D negative mould and silicone casting was performed for preoperative simulation (Figure 4). Based on simulation, the preoperative strategy included 3 pair of neochordae and a stabilizing ring (Figure 5).

Figure 4. Silicone model showing posterior leaflet prolapse (P2 region).

Figure 5. Mitral valve repair for posterior leaflet prolapse

Case 3: transapical off-pump mitral valve repair

An 81-year-old female known with mitral valve regurgitation since 2017 presented at our outpatient clinic with progression of dyspnea. Transthoracic and transoesophageal showed severe MR based on posterior leaflet prolapse due to chordal rupture with a normal right and left ventricular function (Figure 6). Additional coronary angiography showed no coronary artery disease. The patient was discussed in our dedicated mitral valve heart team and was selected for transapical off-pump mitral valve repair using the NeoChord device based on an eligible patient anatomy, eligible valvular pathology and eligible ventricular dimensions in combination with her oncologic medical history and other comorbidities. Based on TOE, an interactive 3D reconstruction was acquired (Figure 6). For transapical off-pump mitral valve repair, a rigid plastic prototype was directly printed using selective laser stereolithography (Figure 7) The patient- specific model was realized in the mid-systolic phase to assess the maximal coaptation defect. The coaptation defect allowed the surgical team to predict the probability of reduction of MR based on sufficient leaflet overlap. In cases with abundant overlap, sufficient tissue can be pulled into the ventricle to create of an adequate coaptation area. Finally, the model can be used intraoperatively to mark the location of the neochord.

Figure 6. Transapical off-pump mitral valve repair

Figure 7. Solid 3D model

DISCUSSION

This report describes the clinical implication of 3D reconstructions, 3D printing and simulation in mitral valve surgery. We developed a standardized workflow for the creation of 3D printed mitral valves. With the help of our step-by-step workflow, it was feasible to create rigid plastic and silicone models of different mitral diseases. All reconstructions were based on 3D TOE, performed during preoperative work-up. The manufactured models assisted in selecting patients for the appropriate intervention by visualization of the exact valve pathology during multi- disciplinary heart team meetings. Additionally, the patient specific mitral valve prints helped to simulate the operation and determine the optimal intraoperative strategy.

Rapid prototyping has emerged in many subdomains in the medical field. Three-dimensional printing is one of the most promising techniques for preoperative planning and is expected to play an important role in personalized medicine in the future. Patient-specific models could subsequently be used to assist in decision making and procedural planning. Selecting the right patient for the right approach could help improve surgical and patient outcomes. As image acquisition is an important basic step for successful 3D printing, close collaboration between radiologist, echocardiologist and cardiothoracic surgeons is of utmost importance. The multidisciplinary valve heart team could be the basis for embankment of the different subdomains[23].

Transoesophageal echocardiography is the cornerstone for our preoperative 3D mitral valve modelling. Compared to other imaging modalities, TOE has the advantages of instant feedback and the ability to directly review the 3D image dataset. Additionally, there is no need for intravenous contrast or radiation exposure, as in computed tomography. Magnetic Resonance Imaging on the other hand, can be time consuming and more expensive. In our center, preoperative 3D TOE is performed by the same imaging cardiologists discussing the patient in the mitral valve heart team, guiding our transapical procedures intraoperatively and assessment of postoperative MR grading after weaning from bypass. Furthermore, other disciplines that use 3D echocardiographic acquisitions, like gynecologist and nephrologist may also benefit from these techniques, while applications are not limited to cardiac surgical procedures. Almost all software is freely available and has an intuitive interface.

Besides the role of rapid prototyping in the preoperative pathway, models are also helpful for training of surgeons and residents. Simulation with patient-specific models can shorten learning curves and ultimately determine intraoperative strategies and prevent intraoperative complications. Furthermore, these could even be used in the beginning of medical school to help students understand anatomy more easily.

Limitations

The accuracy of the 3D printed models used for patient care could raise concern. Current 3D printers can sufficiently print clinically relevant details with a margin of <1 mm. However, as these models are also dependent on post-processing, they are directly linked to operator interpretation and subjected to inter- and intra-observer variability. Standardization and automatization of the workflow is mandatory to make it more reproducible and generally accessible.

One of the major limitations of rapid prototyping is the workaround time. Currently, the average time for fabrication of rigid models, ranges from 4 hours to 1 day. For now, production of silicone models can even take up to 3 days from the image acquisition to the final silicone model. However, with the evolution of 3D printing, we foresee direct printing in silicone to be possible in the near future, shortening production times. Nowadays, the cost for our current models ranges from 15–40 euro for rigid printed models. The expenses for our silicone models, including their negative mould, are around €300, which can be subdivided into €210 for a single mould and €90 for casting.

The current report only shows a small sample of pathologies found in mitral valve surgery. We deliberately choose pathologies which are most common. However, one could argue that these are the most 'simple' repairs, which does not need extensive preoperative planning. The study was intended to give an insight in the possibilities of mitral valve modelling and 3D printing and not to compare the results of 3D printing head-to-head.

CONCLUSIONS

Three-dimensional mitral valve modelling and printing can enhance surgeon's knowledge on patient specific anatomy and facilitate planning of complex surgery. Extensive preoperative planning with patient specific models may directly affect patient selection for the appropriate techniques. Furthermore, simulation-based training with patient specific models can help surgeons and residents to gain proficiency in minimally invasive mitral valve surgery and could ultimately shorten learning curves and improve patient outcomes.

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Chapter 6

Step-by-step guide for endoscopic mitral valve surgery

Jules R Olsthoorn, Samuel Heuts, Saina Attaran, Simon Cornelissen, Jos G Maessen and Peyman Sardari Nia

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ABSTRACT

Minimally invasive mitral valve surgery (MIMVS) is becoming the new standard for mitral valve (MV) operations and has shown to be safe and effective, with less morbidity compared to conventional sternotomy, despite longer cardiopulmonary bypass (CPB) and cross-clamp time. In the current era patients prefer smaller incisions and a shorter rehabilitation period. MV surgery through a limited incision requires a different mind-set due to its high complexity and steep learning curve, especially in a fully endoscopic approach. To achieve success with MIMVS, several new technical skills must be acquired, and a steep learning curve must be overcome. We describe several techniques used in fully endoscopic MV repair and provide a step-by-step guide to set up and start a MIMVS program.

INTRODUCTION

Minimally invasive mitral valve surgery (MIMVS) has gained increasing popularity over the last two decades. In many experienced centers, the minimally invasive approach has become the standard of care for surgical correction of mitral valve (MV) disease, with similar surgical results compared to median sternotomy. Moreover, the limited incision results in reduced postoperative pain, decreased perioperative blood loss and shortening of length of hospital stay[1]. Additionally, for reoperations, MIMVS has proven to result in a lower mortality rate with an equal risk of stroke compared to resternotomy[2]. Furthermore, from a patient's point of view, the minimally invasive approach offers the possibility of a superior cosmetic result and faster rehabilitation[3]. Different techniques have been described for MIMVS ranging from direct vision, endoscopic- assisted, robotic-assisted to full endoscopic approach. In our tertiary referral center, full endoscopic MIMVS is the preferred surgical approach for MV operations with or without tricuspid valve surgery and arrhythmia surgery. The aim of this manuscript is to provide our method of patient. selection and technical details regarding the full endoscopic approach in MV surgery. We also describe our techniques, tips and tricks used for full endoscopic MV repair.

PATIENT SELECTION AND PREOPERATIVE WORKUP

In general, indications and contraindication for endoscopic MV surgery are relative and dependent on the expertise of each surgeon and center. In our center, relative contraindications for elective non-redo MIMVS include: significant mitral annular calcification, large chest with a distance between the MV annulus and right-sided chest wall of more than 25 cm, extensive pulmonary adhesions, more than grade 1+ aortic valve regurgitation, extensive aortic dilatation, extensive abdominal aortic atherosclerosis or small peripheral arterial diameters relative to patients' body mass index (BMI) or an absolute peripheral arterial diameter less than 7 millimetre.

All patients with atrioventricular valve disease and non-significant coronary artery disease referred to our center are primarily discussed in our multidisciplinary MV heart-team, consisting of a dedicated MV surgeon, an interventional cardiologist with expertise in transcatheter mitral repair techniques and an imaging cardiologist. The mechanism of mitral regurgitation is clarified through conventional transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). Additionally, an electrocardiography-triggered computed tomography (CT) angiography of the aortic root and ascending aorta, followed by a high-pitch spiral CT angiography from the aortic arch to the femoral bifurcation is performed to assess eligibility for peripheral cannulation and determine ideal intercostal space (ICS) for a right-sided thoracotomy, as described previously[4]. If not done already, patient's coronary anatomy is fully investigated either with coronary angiography or a CT angiogram and non-surgical lesions are stented if required.

PREPARATION AND ANAESTHETIC SET-UP

After induction of general anesthesia, selective unilateral lung ventilation is achieved with a double lumen endotracheal tube. In our surgical set-up, the patient is placed in supine position on an operating table that can bend. The patient is positioned with the level of incision at the hinge of the flexible table (Figure 1A, B). The right arm is kept in a slightly flexed position, adjacent to the body and the left arm is tucked in next to the body. The chest is marked with an ultraviolet pen, marking the median sternotomy line, right-sided ribs, and intercostal spaces from the second to fifth, level of the diaphragm and the incision. The incision is usually just below the nipple in men and in the infra-mammary fold in women, with degrees of variations depending on each patient's body habitus. External defibrillator pads are placed posteriorly and anteriorly on the chest wall. Pre-procedurally, the sheath for cannulation of the superior vena cava (SVC) is placed by the anesthesiologist during the insertion of the central line (Figure 2). Periprocedural TEE with 2-dimensional (2D) and 3-dimensional (3D) images are used for evaluation of the prolapsing segments, length measurement of the anterior mitral leaflet, annular dimensions, ventricular function, tricuspid valve assessment as well as assessment of hemodynamics during cardiopulmonary bypass (CPB) and surgical results after weaning from CPB.

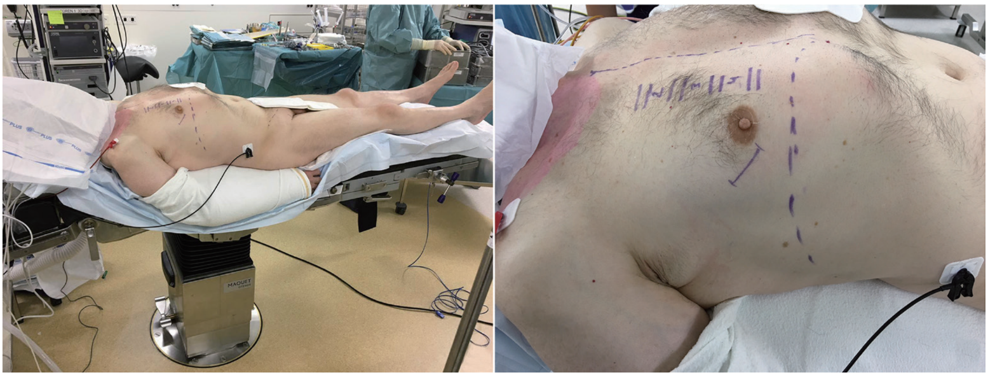

Figure 1. Operative set-up and patient positioning. (A) Patient position. The right arm is fixed in a slightly flexed position, adjacent to the body; (B) the right-sided incision, intercostal spaces, level of the diaphragm and sternum are marked.

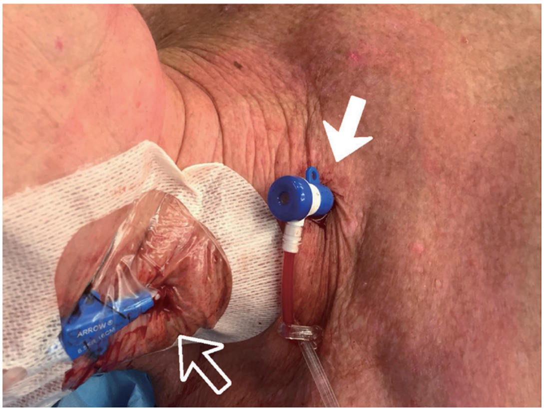

Figure 2. White outlined arrow: central venous line. White arrow: pre-procedurally placed sheath for cannulation of SVC in the innominate vein. SVC, superior vena cava.

Procedure

A right-sided mini-thoracotomy of 4 cm is made in the fourth or fifth intercostal space based on 3D CT reconstruction images. As described earlier, in men, the incision is usually located just below the nipple, while in women the skin incision is made in the infra-mammary fold for cosmetic considerations. An Alexis soft-tissue retractor (Applied Medical, Rancho Santa Margarita, CA, USA) is inserted, preventing extensive rib retraction, and reducing postoperative pain. Visualization is accomplished by a 10 mm 30° 3D endoscope (Karl Storz Endoscopy-America, Culver City, CA, USA) that is placed through a trocar in the same ICS as the mini-thoracotomy. Visualization is optimized by use of dedicated 3D glasses and a 3D monitor, which is placed at eyelevel of the surgeon (Figure 3).

CANNULATION AND CLAMPING

Arterial cannulation options for MIMVS consist of femoral arterial, axillary arterial or direct ascending aortic cannulation[5,6]. In our center, the preferred cannulation strategy consists of peripheral femoral arterial and venous cannulation in the groin under TEE guidance and subsequent use of retrograde perfusion. The CT, made in the preoperative work-up, provides valuable information regarding vessel quality and trajectory and is therefore made in all patients considered eligible for MIMVS. Additionally, dedicated software (Fujifilm Synapse Vincent system, Fujifilm Corporation, Tokyo, Japan), is used to determine the optimal cannula size preoperatively[7]. Preferably, in absence of aorto-iliac atherosclerotic disease and in case of adequate vessel size, the right groin is used. We perform a small 2–3 cm incision horizontally over the femoral vessels around 2 cm below the inguinal ligament. We take extra care to avoid entering the lymph node bundle situated over the femoral sheath by retracting it medially. After the exposure and insertion of the purse strings on femoral vessels, SVC is first cannulated using the sheath that was inserted by the anesthesiologist.

Then the femoral vein is cannulated using the TEE bicaval view. It is important to ensure that both cannulas are placed in the correct position at the entrance of cava in the right atrium for optimal drainage. Afterwards, the descending aorta is visualized with TEE and the femoral artery is cannulated.

In our practice, aortic occlusion is accomplished either with transthoracic aorta clamping (Chitwoord DeBakey- clamp, Scanlan International, Inc., St Paul, MN, USA) or endo-aortic occlusion by use of an endo-aortic balloon (IntraClude, Edwards Lifesciences, Irvine, CA, USA), as described previously[8]. The former is used if the ascending aorta diameter is around 4 cm or more as in these cases endo-aortic balloon occlusion could potentially be unfeasible, resulting in suboptimal myocardial protection[9]. The transthoracic aorta clamp is placed through a separate skin incision in the intercostal space just above and lateral to the mini-thoracotomy incision. In case the external clamp is used, a transaortic needle for cardioplegia delivery is introduced. Endo-aortic balloon occlusion is our preferred strategy since 2017. The triple lumen catheter of the endo-balloon has the advantages of combined cardioplegia delivery, venting, root pressure monitoring and occlusion. In patients referred for reoperations with unsuitable aorta dimensions for endo-aortic balloon occlusion, a third strategy can be used to avoid dissection of the adhesions around the ascending aorta; these patients are cooled to 28 °C and ventricular fibrillation arrest (VF) is induced.

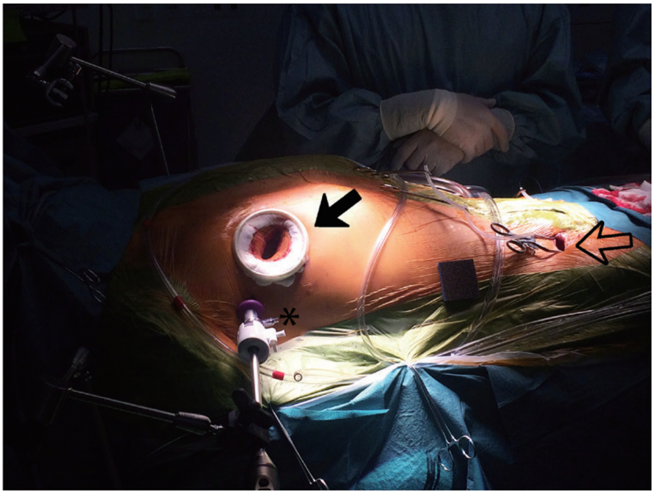

Figure 3. Black outlined arrow: right sided minithoracotomy with soft tissue retractor; asterisk: 3-dimensional (3D) endoscope placed through a trocar in the same intercostal space; black arrow: peripheral cannulation in the right groin.

EXPOSURE

Once on cardiopulmonary bypass, the pericardium can be opened safely. We open the pericardium anterior to the phrenic nerve, starting from the level of the ascending aorta to the level of the diaphragm (Figure 4). Multiple pericardial sutures are placed for retraction of the pericardium to achieve optimal exposure. Before aortic occlusion, a stab incision is made parasternally for the placement of the external part of the atrial retractor (HV retractor, USB Medical, Huntingdon Valley, PA, USA). In case of use of the transthoracic aortic clamp, a sucker is used to lift the transverse sinus to prevent iatrogenic lesions of left atrial appendage while clamping (Figure 4). When conducting this standard maneuver, one should be careful in manipulation of the ascending aorta, as we have observed a case of iatrogenic antegrade type A aortic dissection in our early experience[11]. As mentioned above, in complex reoperations under VF patient is cooled to 28 °C and dissection of the Waterstone's groove is continued (Figure 4). The disadvantages of operating under VF could be a suboptimal exposure of the valve due to backflow.

The left atrium is then opened, and the atrial wall is retracted anteriorly by inserting the blade of the atrial retractor and connecting it to the shaft of the outside table-mounted holder. The blade size can be determined preoperatively, which is based on left atrial volume. A sump sucker connected to an additional vent is placed in the left atrium for adequate drainage of the operation field (Figure 4).

Upon visualization of the MV, nerve hook testing is performed for evaluation of the exact valvular pathology. According to the segmental analysis of Carpentier, the P1 region of the posterior leaflet is used for reference. In case the P1 region is involved in the mechanism of regurgitation, any other unaffected segment or the annular level can be used as the reference point (Figure 5). The principle of valvular analysis is based on confirmation of the pathology as seen on preoperative TEE.

Figure 4. Visual exposure

Figure 5. Mitral valve repair

MV REPAIR

MV repair consists of a plethora of different techniques. In MV prolapse, after a possible resection, neochordae are placed for correction of the prolapsing segments and the coaptation defect. To achieve an optimal result, a coaptation surface of at least 8 to 10 mm is warranted, confirmed by the ink test. In patients with commissural prolapse, papillary muscle reposition can be performed to eliminate the commissural prolapse. For this technique, a single suture with pledgets is placed through the head of the intermediate papillary muscle. The intermediate head is then freed from the anterior head and fixated to the posterior head, resulting in a reduction of the commissure (Figure 5).

Almost all of our mitral repair patients receive artificial neochordae for correction of mitral regurgitation, as described by Falk et al.[13]. These neochordae are placed with respect to the midline of the MV and the papillary muscles, therefore no neochordae should cross the midline. Neochordae are placed through the intermediate heads of the papillary muscles. Neochordae through the posteromedial papillary muscles are placed in backhand position and through the anterolateral papillary muscles in forehand position (Figure 5). The neochordae are fixated on the free edge of the MV leaflet by locking both sutures and knotting the ends in the middle of both insertions. Other techniques for patients with prolapse include triangular and quadrangular resection in patients with Barlow disease and excessive leaflet tissue, the double-orifice technique as described by Alfieri et al.[14] and/or closure of clefts and indentations.

After placement of the neochordae, an annuloplasty ring is implanted to support the repair. Annular ring size is determined by the length of the anterior MV leaflet. As the incision in our center is limited, we do not use conventional ring sizers, but size the valve with a flexible sizer cutout of sterile paper. The annuloplasty sutures are placed according to a suture map and sequence, which is published elsewhere[15]. Briefly, the sutures start clockwise at the posteromedial commissure where one suture is placed in reversed forehand position. Secondly four sutures are placed counterclockwise at the anterior annulus in backhand position. From the anterolateral commissure onwards, three sutures are placed in reversed backhand position. To close the ring four sutures are placed clockwise in forehand position (Figure 5). The suture map allows surgeons to place the sutures without blocking the endoscopic vision. The sutures are tightened with either a knot pusher or an automated fastener (COR- KNOT, LSI SOLUTIONS, Victor, NY USA).

CLOSURE

Once sufficient coaptation is achieved and we are satisfied with the saline test the de-airing process is initiated. In case with endo-aortic balloon occlusion, a vent is placed through the MV, and the patient is positioned in a Trendelenburg position, to start the de-airing process before the atrium is closed. In case with the use of Chitwood clamp, patient is positioned in anti-Trendelenburg position and de-air is achieved through the root vent. Throughout the whole operation, CO2 was insufflated. The atrium is closed with double running 4-0 polypropylene sutures. Before declamping, a pacemaker wire is placed on the anterior wall of the left ventricle. After decannulation, heparin is antagonized for promotion of hemostasis. Before closing, the right lung is once more deflated for a final evaluation of the left atrial suture line for bleeding, after which a single 10mm drain is placed through the camera port.

Figure 6. Tips, tricks, and pitfalls

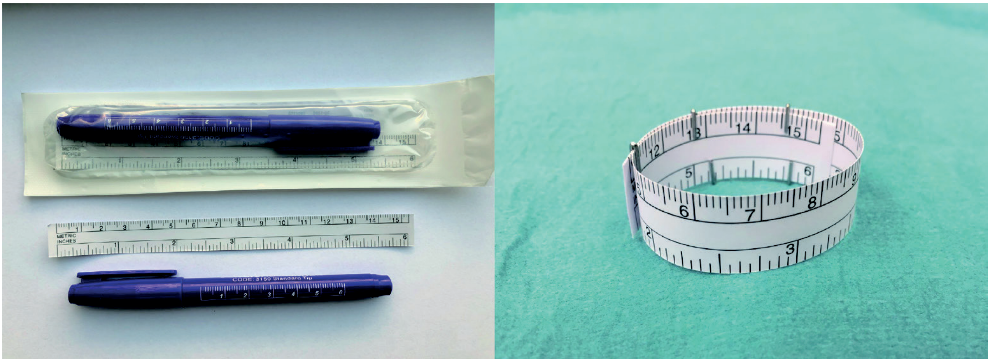

Figure 7. Paper ruler for optimal subvalvular exposure.

TIPS, TRICKS AND PITFALLS

- In patients with an elevated hemi diaphragm a suture at the caudal part of the pericardium can be placed through a tourniquet and retracted out of the patient, thereby lowering the diaphragm without blocking of the endoscopic view for the surgeon (Figure 6).

- In MIMVS, optimal exposure is crucial for a successful procedure. We use a paper ruler for optimal subvalvular exposure. The basis of the ring is a paper ruler (Purple Surgical, Shenley, England), which is folded into a ring and fixed with small vascular clips. The ring is inserted into the MV annulus to retract the leaflets and create maximum visual exposure. The paper ring allows surgeons to visualize the subvalvular apparatus and the ventricular cavity to implant artificial chords more easily (Figures 6,7).

Sizing the annulus with a normal sizer can be difficult in MIMVS due to the limited size of the incision. Therefore, the outline of the sizer is transferred on to paper and trimmed by the scrub nurse prior to incision. These paper sizers can be easily put in to place and resemble the exact same outline as the original sizer (Figures 6,8).

- Saline testing can be used in MV surgery to evaluate the repair intra-operatively. In MV repair for isolated posterior leaflet prolapse, saline testing sometimes shows an unexpected full prolapse of the anterior leaflet, which was not present on preoperative echocardiography. Several intra-operatively maneuvers can counter this phenomenon, such as: pulling down the diaphragm, repositioning of the atrial retractor or forcing down the anterior part of the annuloplasty ring. Despite these maneuvers, some patients still maintain a prolapse of the anterior leaflet during saline testing. When saline testing shows an unexpected prolapse of the anterior leaflet, not present on preoperative echocardiography, no additional surgical techniques should be performed to achieve an excellent postoperative result[17] (Figure 6)

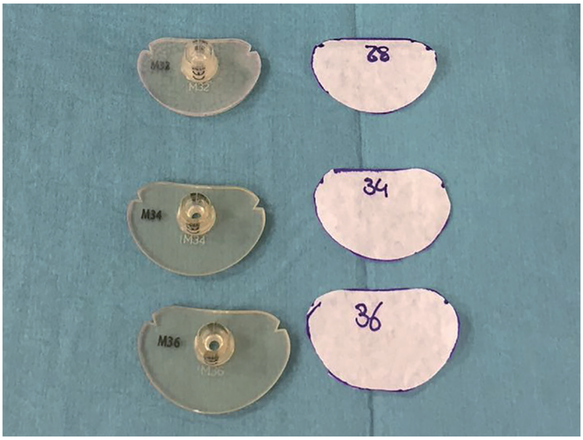

Figure 8. Outlined paper sizers for annuloplasty ring fitted for the minithoracotomy.

ROLE OF TEAM MEMBERS

The role of dedicated heart teams, including scrub nurses, anesthesiologist, perfusionist and cardiologist should not be underestimated[18]. In our center, the day prior to the operation, patients are discussed with the whole team and the team is informed about the surgical approach, cannula sizes and potential technical difficulties. During the operation, the communication between the surgeon, the anesthesiologist and perfusionist is crucial, especially in case of use of the endo-aortic balloon. Additionally, in most cases, the preoperative TEE is performed by the same imaging cardiologist as the intraoperative echocardiogram directly after weaning from bypass, limiting the inter- observer variability, and ensuring an unbiased evaluation of the surgical result.

CONCLUSIONS

Starting a MIMVS program requires a step-by-step approach; correct patient selection and patient preparation especially during the early phases, patience to deal with the learning curve, low threshold in converting to median sternotomy specifically during the initial cases to avoid catastrophe, diligence myocardial protection strategies, teamwork, and strict adherence to the procedural and surgical steps. In addition, surgical techniques used for conventional open surgery cannot be directly adopted in MIMVS due to the increased distance from the chest wall to the MV, the limited operative space, decreased surgical maneuverability, the use of long-shafted instruments, and the need for video assistance. Adaptation of existing techniques combined with extensive preoperative planning and working with dedicated teams could help starting surgeons to select patients for MIMVS, minimalize postoperative complications and improve patient outcomes.

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Chapter 7

Unexpected prolapse of the anterior leaflet during saline testing in mitral valve repair

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ABSTRACT

Objectives

Saline testing is used in mitral valve (MV) surgery to evaluate the repair intra-operatively. Sometimes, saline testing shows a prolapse of the anterior leaflet, not seen on preoperative echocardiography. Our objective was to investigate the incidence, predisposing factors, and consequences of this phenomenon.

Methods

We retrospectively reviewed all consecutive patients undergoing surgery for posterior leaflet prolapse between 2013 and 2017. All data, including intraoperative video recordings of the repair and saline testing, were collected prospectively.

Results

Isolated posterior leaflet repair was performed in 91 patients. In 17 patients (18.7%), saline testing showed an unexpected anterior leaflet prolapse. Patients with unexpected prolapse presented with higher body mass index (BMI) compared to the reference group (27.5 ± 2.3 vs 25.0 ± 4.2, $P = 0.01$). Binomial logistic regression analysis showed BMI, surgical approach, number of prolapsing segments, left ventricular ejection fraction, left ventricular end systolic diameter, and left atrial diameter to be predictive for unexpected anterior leaflet prolapse. In patients with unexpected anterior leaflet prolapse, no adequate saline testing was possible, and repair was accomplished based on correction of the prolapse as seen on a preoperative echocardiogram. In both groups, 100% repair rate was achieved. Predischarge mitral regurgitation grading showed mild or less mitral regurgitation in all the patients in the unexpected prolapse group in comparison with 98.6% of patients in the reference group.

Conclusions

When saline testing shows an unexpected prolapse of the anterior leaflet, not present on preoperative echocardiography, no additional surgical techniques should be performed in order to achieve an excellent postoperative result. Further research is warranted to predict unexpected anterior leaflet prolapse preoperatively.

INTRODUCTION

Mitral valve repair (MVr) has become the preferred method for surgical correction of mitral regurgitation (MR) in degenerative MV disease[1,2] Understanding the complex anatomy of the mitral valvular apparatus and its functional entity is essential for successful repair. Preoperative transthoracic echocardiography (TTE) and additional transoesophageal echocardiography (TOE) provide anatomical characteristics of the different lesions in relation to segmental and functional anatomy, according to the Carpentier classification, in order to assess the feasibility of repair[3]. Even with extensive preoperative planning with TTE and TOE, intraoperative final analysis is crucial for understanding the complex MV pathology and to determine the optimal repair technique. In 49–56% of the patients with degenerative MV disease, the predominant lesion is a prolapse of the posterior leaflet, mainly resulting from chordal rupture[4-7]. Posterior leaflet prolapse can successfully be repaired in most patients with repair rates above 95% and equally high freedom from reoperation[7-8]. Repair rates for MV surgery are shown to be procedural volume related, and the results may vary among cardiac surgeons[9-10]. Several preoperative strategies and intraoperative tests have been proposed to achieve higher repair rates. However, intraoperative assessment of the repair highly relies on visual inspection. Saline testing is the most common technique used to inspect the repaired valve intraoperatively and could simulate the postoperative functional anatomy (Video 1, Part I)[11]. Confirmation of valve competency before closure of the atrium is crucial and will prevent reinstitution of cardiopulmonary bypass (CPB).

Video 1.

(Part I) Normal saline testing and ink testing. (Part II) 3-Dimensional transoesophageal echocardiography showing a flail leaflet of the P2 region of the posterior leaflet. Intraoperative inspection of the mitral valve showing a shift of the ventricular wall with the papillary muscles towards the annulus. Saline testing shows a prolapse of the anterior leaflet, which was not present on the preoperative echocardiogram. Complete repair without correction of the anterior leaflet. Postoperative evaluation with transoesophageal echocardiography.

Although the published data show a high repair rate and long-term durability for repair of degenerative MV regurgitation in experienced hands, the overall repair rate in registry data is much lower, implying that less-experienced MV surgeons fail in repairing the most common valve pathology[12]. In MV repair for isolated posterior leaflet prolapse, saline testing sometimes shows an unexpected full prolapse of the anterior leaflet, which was not present on preoperative echocardiography (Video 1, Part II). This finding may lead inexperienced surgeons to correct the anterior leaflet prolapse, potentially resulting in a suboptimal repair, prolonged operating times, and potential residual MR due to overcorrection and could eventually lead to valve replacement. Experienced surgeons use several intraoperative manoeuvres to counter this phenomenon, such as (i) pulling down the diaphragm, (ii) repositioning the atrial retractor and (iii) forcing down the anterior part of the annuloplasty ring. Despite these manoeuvres, some patients still maintain a prolapse of the anterior leaflet during saline testing (Video 2). A possible explanation for the occurrence of this phenomenon could be the displacement of the ventricle and the subvalvular apparatus in the arrested heart[13].

Video 2.

(I) Unexpected prolapse during saline testing persisting after lowering of the atrial retractor. (II) Unexpected prolapse during saline testing persisting after forcing down the anterior part of the annuloplasty ring.

Our objective was to evaluate the incidence of an unexpected anterior leaflet prolapse in saline testing for isolated posterior leaflet repair, investigate the predisposing factors underlying its occurrence and determine the consequences of surgical repair.

METHODS

In our tertiary referral centre, patients accepted for MV surgery are included in a prospective database. Preoperative variables, intraoperative data, including intraoperative video recordings, and postoperative outcomes are collected prospectively. We retrospectively reviewed all data of patients who underwent MV surgery by a single surgeon (P.S.N.) for degenerative MV disease at our institution from January 2013 to December 2017 (n = 182). Emergency surgery, reoperations and patients who underwent beating heart procedure were excluded (n = 24)[14]. As it is clinically important to evaluate the unexpected anterior leaflet prolapse in isolated posterior MV prolapse, this group forms the focus of the current study. The institutional review board of the Maastricht University Medical Centre approved the study and waived the need for informed consent due to the observational character of the study.

Echocardiography

All patients eligible for MV surgery underwent preoperative TTE to determine the exact MV pathology. In most of the cases, pre-operative TTE was performed at the referral centre in compliance with local agreements and international recommendations[15]. In patients where the mechanism of regurgitation was not clarified on TTE and in all the patients who were eligible for minimally invasive surgery, a TOE was performed. Intraoperative TOE was performed in all patients, prior to incision and post repair to assess the quality of the MV repair and left ventricular function after weaning of CPB, by an imaging cardiologist experienced in MV treatment. Furthermore, all the patients underwent predischarge TTE to assess the quality of the repair and to grade postoperative MR. The severity of MR was graded based on the current international guidelines[16].

Saline testing

After MVr is completed, a 50-cc bulb syringe is filled with heparinized saline which is injected at low pressure through the MV to fill the left ventricle in the arrested heart to mimic the systolic phase. Then, a second injection of saline with higher pressure is given simultaneously with anterograde crystalloid cardioplegia (St. Thomas' cardioplegic solution No. 2, Plegisol, Abbott Laboratories, North Chicago, IL). An optimal result is indicated by a posterior position of the closure line with a symmetrical aspect. In all the patients, saline testing was performed in the same manner by the same surgeon. Additionally, during saline testing, ink testing was used to estimate the length of coaptation[17]. In patients with unexpected prolapse of the anterior leaflet, no adequate saline testing could be performed during pressurization of the left ventricle, and anterior leaflet prolapse occurred, resulting in immediate deflation of the ventricle. In these patients, only the posterior leaflet prolapse was corrected, relying solely on the preoperative TOE, and correction of only the prolapsing segments was performed.

Statistical analysis

Statistical analysis was performed using SPSS 24.0 for Macintosh (SPSS Inc., Chicago, IL, USA). Normality of the continuous variables was tested with visual inspection of the histograms and the Shapiro–Wilk test. Continuous normally distributed data are presented as mean with standard deviation. Continuous non-parametric distributed data are presented as median with inter-quartile range. Frequencies are displayed as absolute numbers and relative percentages. Baseline characteristics and outcomes were compared using the χ^2 test for categorical data and the Fisher's exact test when the minimum expected cell-size assumption did not apply. The student's t-test and Mann–Whitney U-test were performed for continuous parametric and non-parametric data, respectively. Additionally, a binomial logistic regression analysis was performed. Variables for binomial logistic regression analysis were selected based on the baseline difference and theoretical hypothesis. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box–Tidwell procedure. On the basis of this assessment, all continuous independent variables added to the model were found to be linearly related to the logit of the dependent variable. A receiver-operating characteristic analysis was used to determine the diagnostic value of our model. All reported P-values are 2-sided, and P-values of <0.05 are considered statistically significant.

RESULTS

Baseline characteristics

After an analysis of our database, we identified 158 patients with degenerative MV disease. The underlying mechanism of MR was an isolated prolapse of the posterior leaflet in 91 (57.6%) patients, isolated prolapse of the anterior leaflet in 13 (8.2%) patients, commissural prolapse in 3 (1.9%) patients, bileaflet prolapse in 48 (30.4%) patients and calcifications in 3 (1.9%) patients.

Subsequently, a total of 91 patients with isolated posterior leaflet prolapse were included. In 17 (18.7%) patients, saline testing showed an unexpected prolapse of the anterior leaflet (unexpected prolapse group). Mean age was 65.2±7.3 and 65.5±9.6 (P=0.92) in the unexpected prolapse group and the reference group, respectively. Gender was equally distributed between the groups. Biometrics [length, weight, body mass index (BMI), body surface area] showed BMI to be significantly increased in the unexpected prolapse group, with a mean BMI of 27.5±2.3 compared to a mean BMI of 25.0 ± 4.2 in the reference group (P = 0.01). Median logistic EuroSCORE was 2.2 (3.1) and 3.4 (4.4) (P = 0.33) in the unexpected prolapse group and the reference group, respectively. Further characteristics are depicted in Table 1.

Table 1. Baseline characteristics

	Prolapse group (n = 17)	Reference group (n = 74)	P-value
Age (years), mean ± SD[a]	65.2 ± 7.3	65.5 ± 9.6	0.92
Male, n (%)[b]	13 (76.5)	51 (68.9)	0.77
Biometrics			
Length (cm), median (IQR)[c]	175 (9)	174 (12)	0.83
Weight (kg), mean ± SD[a]	82.6 ± 10.4	75.72 ± 16.1	0.10
BMI (kg/m2), mean ± SD[a]	27.5 ± 2.3	25.0 ± 4.2	0.01
BSA, median (IQR)[c]	1.96 (0.17)	1.89 (0.29)	0.12
Medical history			
Logistic EuroSCORE, median (IQR)[c]	2.2 (3.1)	3.4 (4.4)	0.33
Pulmonary hypertension, n (%)[b]	6 (35.3)	32 (43.2)	0.55
Prior cerebral vascular accident, n (%)[d]	2 (11.8)	5 (6.8)	0.61
Preoperative atrial fibrillation, n (%)[b]	3 (17.6)	27 (36.5)	0.16
NYHA classification, n (%)[c]			0.93
I	3 (17.6)	13 (17.5)	
II	8 (47.1)	35 (47.3)	
III	6 (35.3)	23 (31.1)	
IV	0	3 (4.1)	

(a) Independent samples t-test. (b) X^2 test. (c) Mann–Whitney U-test. (d) Fisher's exact test

BMI: body mass index; BSA: body surface area; EuroSCORE: European System for Cardiac Operative Risk Evaluation; IQR: interquartile range; NYHA: New York
Heart Association Functional Classification; SD: standard deviation.
Bold text is statistically significant.

Surgical procedure

Patients in the reference group were more frequently operated on through a sternotomy, n=37 (50.0%), in comparison with the unexpected prolapse group, n = 2 (11.8%). All other patients were operated on through a minimally invasive approach (endoscopically port-access incision). More concomitant surgical procedures were performed in the reference group in comparison with the unexpected prolapse group (20 vs 2 patients). Aortic valve replacement, rhythm surgery and aortic surgery were performed only in the reference group. The median number of prolapsing segments and additionally the median number of artificial neochordae were higher in the unexpected prolapse group in comparison with the reference group 2 (2) vs 1 (0) (P < 0.01) and 6 (1) vs 4 (0) (P < 0.01). Nearly all patients (96.7%) received a semi-rigid annuloplasty ring with no difference in ring size between the groups. The repair rate was 100% for both groups. The surgical procedural details are depicted in Table 2.

Table 2. Surgical procedure

	Prolapse group (n = 17)	Reference group (n = 74)	P-value
Surgical approach[a]			<0.01
Median sternotomy, n (%)	2 (11.8)	37 (50.0)	
Minimally invasive, n (%)	15 (88.2)	37 (50.0)	
Concomitant surgery			
Isolated mitral valve surgery, n (%)[b,c]	15 (88.2)	54 (73.0)	0.23
CABG, n (%)[c]	2 (11.8)	6 (8.1)	0.64
Aortic valve surgery, n (%)[c]	0 (0)	2 (2.7)	0.66
Aortic surgery, n (%)[c]	0 (0)	3 (4.1)	0.53
Tricuspid valve surgery, n (%)[c]	1 (5.9)	4 (5.4)	0.65
AF surgery, n (%)[c]	0 (0)	8 (10.8)	0.34
Cardioplegia			
Cardioplegia volume (ml), median (IQR)[d]	1500 (300)	1550 (1386–1913)	0.47
Surgical technique			
Implantation of neochordae, n (%)[c]	17 (100)	70 (94.6)	0.43
Number of neochordae, median (IQR)[d]	6 (2)	4 (0)	<0.01
Number of prolapsing segments, median (IQR)[d]	2 (2)	1 (0)	<0.01
Annuloplasty ring, n (%)[c]	17 (100)	71 (95.9)	0.53
Annuloplasty ring size (mm), median (IQR)[d]	32 (2)	34 (2)	0.72
Resection, n (%)[c]	0 (0)	11 (14.9)	0.12

(a) X^2 test. (b) Mitral valve repair combined with tricuspid valve repair and/or atrial fibrillation surgery. (c) Fisher's exact test. (d) Mann–Whitney U-test.
AF: atrial fibrillation; CABG: coronary artery bypass grafting.

Pre- and postoperative echocardiography

Mean preoperative left ventricular ejection fraction was 55.9 ± 9.1 in the unexpected prolapse group and 57.9 ± 8.6 (P = 0.40) in the reference group. No significant baseline differences were found in left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left atrial diameter. Pre- and postoperative echocardiographic parameters are summarized in Table 3. Echocardiography with MR grading at discharge was performed in all patients. Predischarge MR grading showed mild or less MR in all the patients in the unexpected prolapse group (n = 17) in comparison with 98.6% (n = 54) of patients in the reference group, with no significant difference between the groups. Only one patient in the reference group had mild-to-moderate residual MR. At a mean follow-up of 6.6 months, all patients in the unexpected anterior leaflet group showed mild (n = 1) or less MR (n = 16).

Table 3. Pre- and postoperative echocardiography

	Prolapse group (n = 17)	Reference group (n = 74)	P-value
Preoperative			
LVEF (%), mean ± SD[a]	55.9 ± 9.1	57.9 ± 8.6	0.40
LVEDD (mm), median (IQR)[a]	56.8 ± 7.3	56.6 ± 7.9	0.92
LVESD (mm), median (IQR)[b]	36.4 (7)	38.0 (7)	0.59
LA diameter (mm), median (IQR)[b]	49.0 (8)	51.4 (8)	0.19
MR severity[b]			0.69
Mild	0	0	
Mild-to-moderate	0	0	
Moderate-to-severe	4 (23.5)	21 (28.4)	
Severe	13 (76.5)	53 (71.6)	
Postoperative			
MR severity[b]			0.79
Absent/trace	13 (76.5)	59 (79.7)	
Mild	4 (23.5)	14 (18.9)	
Mild-to-moderate	0	1 (1.4)	
Moderate-to-severe	0	0	
Severe	0	0	

(a) Independent samples t-test. (b) Mann–Whitney U-test.

LA: left atrial; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter; MR: mitral regurgitation; SD: standard deviation.

Multivariable logistic regression analysis

A binomial logistic regression analysis was performed to ascertain the effects of BMI, surgical approach, number of prolapsing segments, left ventricular ejection fraction, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, and left atrial diameter on the likelihood that patients show an unexpected prolapse during intraoperative saline testing. The logistic regression model was statistically significant, χ^2 (4) = 37.078, P < 0.001. The model explained 54.1% (Nagelkerke R2) of the variance in unexpected anterior leaflet prolapse. Sensitivity was 47.1%, specificity was 95.9%, positive predictive value was 72.7%, and negative predictive value was 88.8%. Of the 7 predictor variables, 6 were statistically significant (Table 4).

Table 4. Multivariable logistic regression analysis for the occurrence of an unexpected anterior leaflet prolapse

	Odds ratio	95% CI	P-value
BMI	1.506	1.116–2.033	0.007
Surgical approach[a]	0.037	0.003–0.383	0.006
Number of prolapsing segments	4.014	1.481–11.372	0.007
LVEF	0.856	0.748–0.979	0.023
LVEDD	1.129	0.973–1.310	0.110
LVESD	0.812	0.676–0.976	0.027
Left atrial diameter	0.873	0.770–0.989	0.033

(a) Surgical approach is for median sternotomy compared to minimally invasive approach.

BMI: body mass index; CI: confidence interval; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter.

DISCUSSION

The phenomenon of unexpected anterior leaflet prolapse in saline testing was found in 18.7% of the isolated posterior leaflet cases. Baseline characteristics demonstrated an increased BMI in the unexpected prolapse group. Binomial logistic regression analysis showed BMI, surgical approach, number of prolapsing segments, left ventricular ejection fraction, left ventricular end-systolic diameter, and left atrial diameter to be predictive for unexpected anterior leaflet prolapse. In all the patients, a posterior leaflet repair was performed without correction of the anterior leaflet, with no differences in postoperative residual MR and with excellent surgical results.

A possible explanation for the occurrence of anterior leaflet prolapse could be displacement of the arrested heart with a shift of the ventricle wall and its papillary muscles towards the annulus, resulting in a prolapse of the anterior leaflet during saline testing. External factors contributing to the displacement of the heart could originate from anatomical characteristics. Habitus, diaphragm elevation, aortic elongation and thorax deformities may all dislocate the heart in an arrested state. We found an increased BMI in patients with unexpected anterior leaflet prolapse. Increased abdominal pressure, similar to that in overweight patients, could contribute to an elevation of the diaphragm in sedated patients with subsequent displacement of the arrested heart. Furthermore, the extensiveness of the disease and the severity of the regurgitating volume, combined with relatively preserved left ventricular dimensions and a slightly reduced ejection fraction, could cause geometric remodelling of the subvalvular apparatus with a shift of the papillary muscles towards the annulus in the arrested heart, resulting in an unexpected anterior leaflet prolapse during saline testing. Additionally, in patients with a prolapse of multiple segments of the posterior leaflet, papillary muscle dysfunction will play a certain role. As papillary muscle functions, in general, seem to follow left ventricular function, patients with a reduced ejection fraction will be more prone to unexpected anterior leaflet prolapse during saline testing[18].

Furthermore, mechanical displacement of the heart could contribute to a shift of the ventricle wall and its papillary muscles. We observed an association between the surgical approach and the incidence of unexpected anterior leaflet prolapse during saline testing in posterior leaflet prolapse. A potential underlying mechanism could be the use of a dedicated atrial retractor in minimally invasive surgery, whereby the atrium is lifted vertically, whereas in sternotomy patients, the atrium is lifted vertically and to the left with rotation of the heart.

In ischaemic MR, 'pseudoprolapse' is described as a factor contributing to early recurrence resulting from the presence of an untreated prolapse of the anterior leaflet[19]. Pseudoprolapse is characterized as a functional prolapse of the anterior leaflet with a prolapse limited to the level of the MV annulus, without deterioration of the leaflets. Pre- and postoperative echocardiography revealed no pseudoprolapse in our cases. In contrast to pseudoprolapse, a full prolapse of the anterior leaflet above the line of the MV annulus was observed during saline testing. On the basis of the literature, we additionally hypothesize that the pressure in saline testing could be higher than in the physiological situation and could overstretch the papillary muscles and chordae tendineae, contributing to a prolapse of the anterior leaflet[20].

An unexpected prolapse of the anterior leaflet could lead to technically more challenging repairs and could eventually result in an inferior surgical outcome with prolonged surgical times. An unexpected prolapse forces the surgeon to perform time-consuming additional manoeuvres. Repositioning of the atrial retractor, pulling down the diaphragm or forcing down the anterior part of the annuloplasty ring will sometimes resolve the anterior leaflet prolapse. In case the prolapse is persistent, surgeons have to determine the optimal length and position of the neochordae based on caliper measurements and their personal experience. However, for less-experienced surgeons, the intraoperative finding of a prolapse of the anterior leaflet could change their operative strategy and eventually lead to repair of the anterior leaflet. This, in turn, could result in a suboptimal repair, prolonged operating times and potentially severe postoperative MR due to overcorrection, which could eventually lead to valve replacement.

Our postoperative echocardiographic observations at discharge showed no significant difference in MR grading between the unexpected prolapse group and the reference group, which therefore, support the strategy of ignoring a prolapse of the anterior leaflet during saline testing that was not present on preoperative TTE or TOE. Only one patient in the unexpected prolapse group showed mild (grade 1) MV regurgitation with a small eccentric jet, of which the severity decreased at last follow-up. At last follow-up, all the patients are in good clinical condition without the recurrence of MR grade 2+. Limitations

We recognize the relatively small sample size and limited follow-up of the current study. Although a larger sample size would enable sufficient statistical power to detect preoperative predictors for unexpected anterior leaflet prolapse, our postoperative results are less likely to be influenced by the potentially underpowered number of patients as no residual MR grade 2+ was found at discharge. Our limited follow-up showed no recurrence of MR, and none of the patients underwent reoperation for failure of MVr. Nevertheless, the retrospective design with its accompanying disadvantages limits the generalizability of our cohort.

When surgeons encounter an unexpected anterior leaflet prolapse during intraoperative saline testing, preoperative echocardiography provides a definite answer regarding anterior leaflet involvement. As operative strategy is dependent on the quality of preoperative echocardiography and subsequently determined by the experience and expertise of the echocardiographist, it plays an important role in decision making and the postoperative outcome. Nowadays, MV surgery is performed in experienced centres with dedicated teams. In our centre, in most of the cases, preoperative TOE is performed by the same imaging cardiologist as the intraoperative echocardiogram directly after weaning from bypass, thereby reducing interobserver variability.

Furthermore, the experience of the surgeon is crucial to recognize an unexpected anterior leaflet prolapse and thus perform a repair of only the posterior leaflet. In the current study, a single experienced surgeon performed the MVrs, which may limit the generalizability of our results.

CONCLUSION

In MVr for posterior leaflet prolapse, intraoperative saline testing for valve competency sometimes shows an unexpected full prolapse of the anterior leaflet, which was not present on the pre-operative echocardiogram. The underlying mechanism could be displacement of the arrested heart, resulting in a prolapse of the anterior leaflet during saline testing. When saline testing shows a prolapse of the anterior leaflet, although it was absent on the preoperative echocardiogram, no additional surgical techniques should be performed for the anterior leaflet in order to achieve excellent surgical results. Further research is warranted to predict unexpected anterior leaflet prolapse preoperatively.

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PART II

POSTOPERATIVE MANAGEMENT AND OUTCOMES

Chapter 8

Antithrombotic therapy after mitral valve repair: VKA or aspirin?

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ABSTRACT

The optimal antithrombotic therapy following mitral valve repair (MVr) is still a matter of debate. Therefore, we evaluated the rate of thromboembolic and bleeding complications of two antithrombotic prevention strategies: vitamin K antagonists (VKA) versus aspirin. Consecutive patients who underwent MVr between 2004 and 2016 at three Dutch hospitals were evaluated for thromboembolic and bleeding complications during three postoperative months. The primary endpoint was the combined incidence of thromboembolic and bleeding complications to determine the net clinical benefit of VKA strategy as compared with aspirin. Secondary objectives were to evaluate both thromboembolic and bleeding rates separately and to identify predictors for both complications. A total of 469 patients were analyzed, of whom 325 patients (69%) in the VKA group and 144 patients (31%) in the aspirin group. Three months postoperatively, the cumulative incidence of the combined end point of the study was 9.2% (95%CI 6.1–12) in the VKA group and 11% (95%CI 6.0–17) in the aspirin group [adjusted hazard ratio (HR) 1.6, 95%CI 0.83–3.1]. Moreover, no significant differences were observed in thromboembolic rates (adjusted HR 0.82, 95%CI 0.16–4.2) as well as in major bleeding rates (adjusted HR 1.89, 95%CI 0.90–3.9). VKA and aspirin therapy showed a similar event rate of 10% during 3 months after MVr in patients without prior history of AF. In both treatment groups thromboembolic event rate was low and major bleeding rates were comparable. Future prospective, randomized trials are warranted to corroborate our findings.

INTRODUCTION

Mitral valve repair (MVr) is recognized as the gold standard for degenerative mitral regurgitation. Compared to mitral valve replacement, repair results in improved survival, better preservation of postoperative left ventricular function and avoidance of the need for long-term anticoagulation treatment[1,2]. The risk of thromboembolic events following MVr varies from 0.4 to 1.6% per year, and reaches 2.5% during the first postoperative month, even with routine anticoagulation therapy[3,4]. However, the appropriate antithrombotic therapy following MVr is still a subject of controversy. Recommendations from international guidelines for the postoperative antithrombotic management have been controversial[5-7], and are based on observational studies without conclusive results, or are provided without references supporting the recommendation[4,8-11].

Consequently, antithrombotic prophylaxis for the prevention of thrombotic events early after MVr varies widely among cardiothoracic surgeons with a vitamin K antagonist (VKA) prescription varying from 46 to 64% in patients with sinus rhythm[12,13]. The risk of thromboembolism secondary to a high incidence of new onset atrial fibrillation (AF) postoperatively and the thrombogenic tendency of the non-endothelialized repair components could motivate surgeons and cardiologists to prescribe VKA therapy for the first months after MVr[14]. However, evidence is limited and more accurate knowledge of the postoperative antithrombotic treatment is required. Based on recent literature and anecdotal reports, we hypothesized that VKA treatment is associated with an increased risk of major bleeding events and no reduction in thromboembolic events[18].

We set out to perform a retrospective observational study to evaluate the rate of thromboembolic and bleeding and complications of two antithrombotic prevention strategies— one with VKA and one with aspirin—occurring within the first three postoperative months.

MATERIALS AND METHODS

Study design and patients

This study was a retrospective observational multicentre cohort study of consecutive adult patients who underwent MVr, to evaluate thromboembolic and bleeding complications of two antithrombotic strategies, VKA and aspirin. Data were collected from the databases of the departments of cardiothoracic surgery of the Leiden University Medical Centre (LUMC), VU University medical centre (VUmc) and Maastricht University Medical Centre (MUMC). Patients who underwent a first MVr with or without concomitant tricuspid valve repair (TVr) between 2004 and 2016 in these three centres were eligible. The postoperative care of these patients often took place in one of 16 affiliated regional hospitals, in which all postoperative medical files were scrutinized for primary and secondary endpoints. Patients were excluded when they underwent other concomitant cardiac procedures than TVr, had previous cardiac surgery or were diagnosed with AF preoperatively. Other concomitant procedures were excluded because these lead to more heterogeneous patient groups. The institutional review board of the LUMC, VUmc and MUMC approved the study protocol and waived the need for informed consent due to the observational design.

Procedures and treatment

MVr was performed at the department of cardiothoracic surgery at the LUMC, VUmc or MUMC and involved implantation of an annuloplasty ring (Edwards Physio I or II mitral ring, Carpentier-Edwards Classic Annuloplasty Ring or Duran AnCore Ring for MVr, and Edwards MC3 tricuspid ring or Carpentier-Edwards Classic Annuloplasty Ring in case of concomitant TVr, Edwards Lifesiences/ Medtronic, USA), and various concomitant techniques (leaflet resections, artificial chorda tendinae implant, chordal transposition, or edge-to-edge technique).

Group A comprised patients from the LUMC and VUmc hospitals, in which therapeutic doses of low-molecular-weight heparin (LMWH) nadroparin were given on the first postoperative day at 7600 IU/ day for patients < 50 kg, 11.400 IU/day for patients 50–70 kg, 15.200 IU/day for patients 70–100 kg and 19.000 IU/day for patients > 100 kg simultaneously with VKA. Treatment with nadroparin was continued until a VKA reached therapeutic levels, as shown by an international normalized ratio (INR) > 2.0 on two consecutive days. VKA therapy was maintained for 6–12 weeks postoperatively and then discontinued at the discretion of the referring cardiologist and occasionally switched to aspirin. The target INR during VKA treatment was 2.0–3.0.

Group B consisted of patients from the MUMC hospital, in which prophylactic doses of nadroparin were started on the first postoperative day at 3750 IU/day for patients < 80 kg, 5700 IU/day for patients 80–100 kg and 7600 IU/day for patients > 100 kg simultaneously with aspirin 80 mg once daily which was continued lifelong in patients with sinus rhythm. Nadroparin was stopped as soon as the patient was fully mobilized. In case of postoperative new onset AF that sustained for more than 24 h, nadroparin and VKA were started analogous to the antithrombotic strategy used in the LUMC and VUmc.

Study endpoints

The primary endpoint of this study was the combined incidence of thromboembolic and major bleeding complications 3 months following MVr. This double endpoint was the basis for determining the net clinical benefit of VKA as compared with aspirin. Since we anticipated a high incidence of postoperative new onset AF, we also compared the primary endpoint in patients who did not develop AF during follow-up as well as in patients who received treatment according to the preferred strategy.

Secondary objectives were to evaluate the incidence rates of thromboembolic and major bleeding events separately and to identify predictors for bleeding and thrombotic complications. All thromboembolic and bleeding events were classified using the criteria for reporting mortality and morbidity after cardiac valve interventions respectively and those of the International Society on Thrombosis and Haemostasis respectively[15,16].

Thromboembolic and bleeding complications occurring on the first postoperative day were not taken into consideration because both antithrombotic therapies were started this day. All suspected bleeding events were independently adjudicated by two expert physicians (F.K. and M.V.) who were blinded to treatment assignment. Disagreement was resolved by consensus.

Predefined candidate predictors for thromboembolic and bleeding events were defined according to the documentation provided by the treating physician, e.g., age, sex, prior arterial or venous thromboembolism, prior PCI, hypertension, history of smoking, preoperative use of anticoagulation therapy, left ventricular ejection fraction (LVEF), concomitant TVr, repeat thoracotomy and new onset AF. The cause of death was verified by reviewing the pathology report. In case autopsy had not been performed, the likely cause of death was verified with the treating physician. All patients were followed and censored at a maximum follow up period of 3 months, the date of last chart documentation, reoperation or outcome events, whichever came first.

Statistical analyses

Means (standard deviation [SD]) and medians (interquartile range [IQR]) to present baseline continuous baseline variables were used. For categorical variables, frequencies and percentages were used. Pearson's $\chi 2$ test was used to compare the distribution of categorical variables, whereas the independent t-tests were used for normally distributed continuous variables. For analysis of primary and secondary objectives, cumulative incidences of bleeding and thromboembolic events of both antithrombotic strategies were estimated according to the Kaplan–Meier methods and presented with two-sided 95% confidence intervals (CI). A Cox proportional hazard model was used to compare both strategies, adjusted for age, gender, and baseline differences.

Backward conditional multivariate Cox-regressions analysis was used to evaluate possible predictors for thrombotic and bleeding events, using variables of clinical importance (age and gender) or that were identified to be relevant predictors ($P < 0.1$) in univariate analysis. Data were analyzed using SPSS version 23 (SPSS, Chicago, IL, USA). A P-value below 0.05 was considered to be significant.

RESULTS

Patients

In the three participating cardiothoracic surgical centers, 809 patients underwent a first isolated MVr between 2004 and 2016. Of these patients, 340 (42%) were excluded for the following reasons: 109 did not receive treatment in one of the affiliated regional hospitals postoperatively (4.9%), 224 had preoperative AF (10%) and seven patients were lost to follow up (0.32%). The remaining 469

(21%) patients were included; 325 patients (69%) in group A and 144 patients (31%) in group B. The baseline characteristics of both groups are shown in Table 1. Their mean age was 61 (SD 12) and 280 patients (60%) were men. Patients in group A underwent concomitant TVr more frequently (22% vs. 4.9%). In group B, a LVEF below 40% and preoperative aspirin use were more present (9% vs. 3.8% and 27% vs. 18% respectively). A total of 220 patients (47%) developed new onset AF after surgery and 35 patients (7.5%) required a repeat thoracotomy.

Antithrombotic treatment

Of the 325 patients in group A, 319 patients (98%) were treated with VKA therapy, four (1.2%) with aspirin therapy and one patient (0.31%) with LMWH (Fig. 1a). In group B, 92 of the 144 patients (64%) received aspirin, 46 patients (32%) VKA because of new onset AF and six patients (4.2%) received other antithrombotic therapy than VKA or aspirin (Fig. 1b). Twenty-three patients (25%) in group B, who received initial aspirin therapy, experienced a single episode of new onset AF.

Table 1. Baseline characteristics of 469 patients who underwent MVr

	Group A: VKA (n = 325)	**Group B: aspirin (n = 144)**
Age at operation, mean ± SD	60 ± 13	62 ± 11
Male, n (%)	195 (60)	85 (59)
Prior ischemic stroke, n (%)	7 (2.2)	8 (5.6)
Prior MI, n (%)	12 (3.7)	4 (2.8)
Prior PCI, n (%)	11 (3.4)	5 (3.5)
Prior VTE, n (%)	11 (3.5)	2 (2.6)
LV ejection fraction < 40%, n (%)	12 (3.8)	13 (9)*
Diabetes, n (%)	17 (5.4)	5 (3.5)
Hypertension, n (%)	149 (47)	74 (51)
COPD, n (%)	29 (8.9)	15 (10)
History of smoking, n (%)	99 (31)	27 (19)
Preoperative anticoagulation use, n (%)		
VKA	12 (3.7)	4 (2.8)
Aspirin	57 (18)	39 (27)*
Clopidogrel	3 (0.90)	2 (1.4)
Dual AP	1 (0.30)	2 (1.4)
Active endocarditis at the moment of surgery, n (%)	24 (7.4)	9 (6.3)
Concomitant TVr, n (%)	72 (22)	7 (4.9)*

SD standard deviation, MI myocardial infarction, PCI percutaneous coronary intervention, VTE venous thromboembolic event, LV left ventricular, VKA vitamin K antagonist, AP antiplatelet, TVr tricuspid valve repair *P-value below 0.05

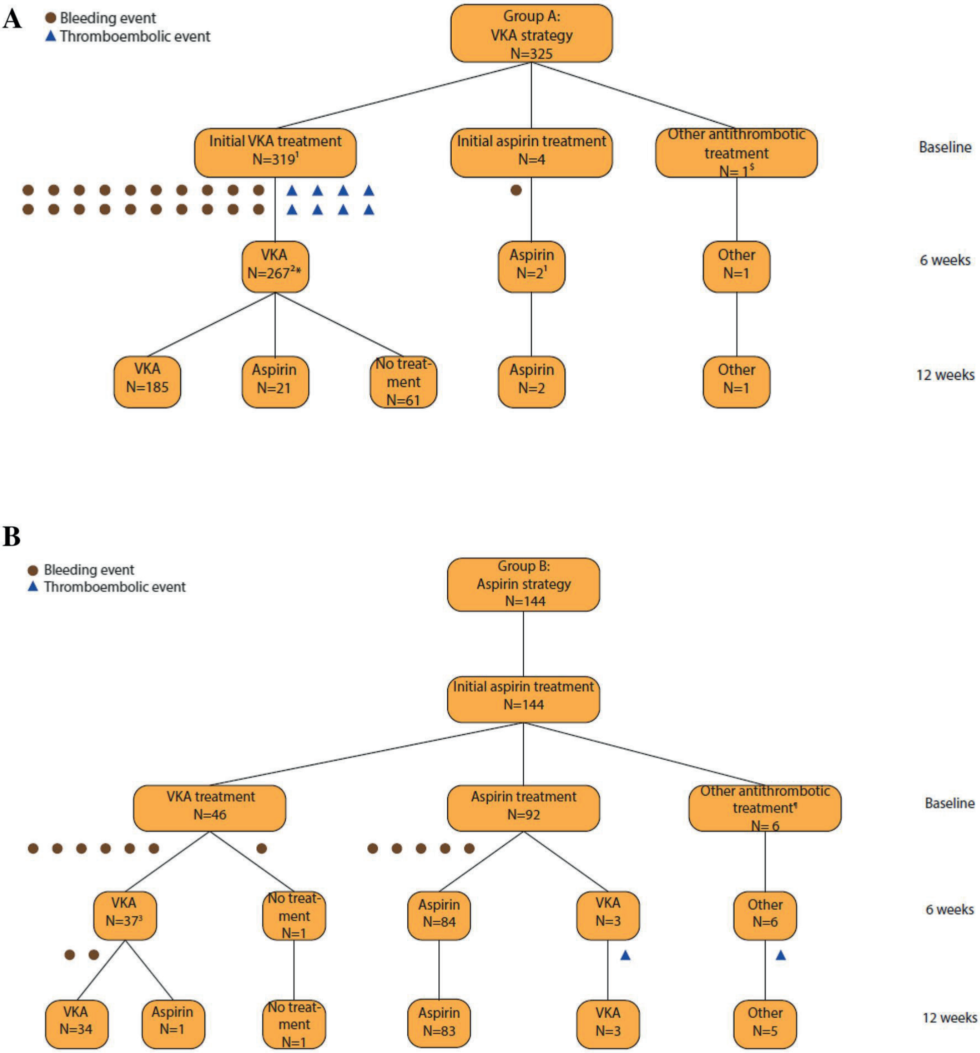

Figure 1. Flowchart of medication use and events of group A: VKA (a) group B: aspirin (b).

[1]1, [2]8, [3]1 patients censored for other reasons than study endpoints. *Data missing in 16 patients. [$]2 patients treated with direct oral anticoagulant (DOAC), 4 patients with clopidogrel, [¶]1 patient treated with low-molecular-weight heparin

VKA versus ASA

Table 2 shows the incidence of thromboembolic and bleeding events in each study group. The primary end point of the study—the composite of thromboembolic and bleeding events—was reached in 29/325 patients in group A (cumulative incidence 9.2%, 95%CI 6.1–12) and in 16/144 patients in group B (cumulative incidence 11%, 95%CI 6.0–17; adjusted hazard ratio (HR): 1.6, 95%CI 0.83–3.1). The composite of thromboembolic and bleeding events in patients without new onset AF occurred in 14/177 patients (cumulative incidence 8.2%, 95%CI 4.1–12) in group A and 5/72 patients in group B (cumulative incidence 8.1%, 95%CI 2.0–14.2; adjusted HR 0.97, 95%CI 0.32–2.9). In patients who received initial treatment according to the preferable strategy, 28/319 patients experienced the primary endpoint in group A and 6/92 patients in group B during the first 3 months, for a cumulative incidence of 9.0% (95%CI 5.9–12) and 6.6% (95%CI 1.5–12) respectively (adjusted HR 0.90, 95% CI: 0.35–2.3).

Table 2. Clinical outcomes within 3 months after MVr

	Group A: VKA (n = 325)	Group B: aspirin (n = 144)
Major bleeding	21 (6.8)[a]	14 (9.1)
Site		
Chest	20	12
GI tract	0	1
Unknown	1	1
Fatal bleeding	1	1
Thromboembolic events	8 (2.6)	2 (1.6)
Type		
Ischemic stroke	4	1
TIA	4	0
Left atrial thrombus	0	1
Fatal ischemic stroke	0	1

GI gastrointestinal, TIA transient ischemic attack, MI myocardial infarction, DVT deep venous thrombosis (a) Numbers in parenthesis are cumulative incidence

Thromboembolism and bleeding

A total of 8/325 thromboembolic events occurred in group A after a median duration of 9 days (IQ 3.3–15) and 2/144 in group B after a median duration of 50 days (IQR 45–50), for a respective cumulative incidence of 2.6% (95%CI 0.84–4.4) and 1.6% (95%CI 0–3.8; adjusted HR 0.82, 95%CI 0.16–4.2). 21/325 patients experienced a major bleeding in group A after a median duration of 12 days (IQR 8–15) and 14/144 patients in group B after a median duration of 11 days (IQR 4.8–20), for cumulative incidences of 6.8% (95%CI 4.1–9.5) and 9.1% (95%CI 4.2–14) respectively (adjusted HR

1.89, 95%CI 0.90–3.9). A total of 89% of the major bleeding events were pericardial tamponades, of which two were fatal (one in each group).

Other observations

During the study period, four patients died (cumulative incidence 0.9%, 95%CI 0–1.9), of whom two died in group A and two in group B. Causes of death were pericardial tamponades (two patients), ischemic stroke and cardiac arrest.

Predictors for thromboembolism and major bleeding

Uni- and multivariate analysis of predictors for thromboembolic and major bleeding events in patients who received initial treatment according to antithrombotic strategy are shown in Table 3. Multivariate analysis revealed that only concomitant TVr was independently associated with an increased risk of bleeding events (odds ratio (OR) 2.8, 95%CI 1.4–5.7) for both groups. For thromboembolic events, no independent predictors were found by multivariate analysis.

Table 3. Predictors for majorbleeding and thromboembolic events in 469 patients who underwent MVr

Predictor	**Major bleeding**		**TE**	
	Univariate RR (95%CI)	**Multivariate RR (95%CI)**	**Univariate RR (95%CI)**	**Multivariate RR (95%CI)**
Age > 60	0.94 (0.48–1.8)		0.71 (0.21–2.4)	
Female	1.2 (0.64–2.4)		0.37 (0.78–1.7)	
Prior ischemic stroke	–		3.1 (0.39–25)	
Prior MI	0.84 (0.12–6.1)		–	
Prior PCI	0.80 (0.11–5.8)		–	
Prior VTE	1.1 (0.15–8.0)		–	
LV ejection fraction < 40%	2.2 (0.78–6.3)		–	
Diabetes	1.9 (0.59–6.3)		–	
Hypertension	1.2 (0.62–2.3)		2.3 (0.61–9.1)	
History of smoking	0.78 (0.36–1.7)		1.5 (0.46–5.3)	
New onset AF	1.7 (0.88–3.4)	1.1 (0.33–4.0)		
Concomitant TVr	2.8 (1.4–5.7)*	2.8 (1.4–5.7)*	2.3 (0.59–8.9)	
Active endocarditis	1.7 (0.6–4.8)	1.5 (0.19–11)		

MI myocardial infarction, PCI percutaneous coronary intervention, VTE venous thromboembolic event, LV left ventricular, AF atrial fibrillation, TVr tricuspid valve repair
*P-value below 0.05

DISCUSSION

VKA and aspirin therapy showed a similar event rate of 10% during the first 3 months after MVr in patients without prior history of AF. In both treatment groups thrombo-embolic event rate was low and major bleeding rates were comparable.

Nearly all bleedings occurred soon after surgery, particularly during the first 2 weeks after MVr. Interestingly, most of these were pericardial tamponades that required repeat thoracotomy. In contrast, the thromboembolic events occurred more dispersed throughout the first 3 months. VKA versus aspirin treatment

We chose a primary combined endpoint of thromboembolic and bleeding rates because both events would have a comparable prognostic effect as both represent an important cause of death and disability after heart valve surgery[17]. A comparison between VKA strategy (group A) and aspirin strategy (group B) revealed no difference in the combined outcome of thromboembolic and bleeding complications as well as for both outcomes separately occurring within 3 months after MVr. As expected, a third of the patients in group B could not follow the aspirin strategy because of new onset AF and received VKA treatment instead of aspirin therapy. Both of these group B treatment groups experienced major bleeding events to a similar extent. However, after exclusion of AF patients in the entire study population as well as analysing patients who received treatment according to the preferable strategy, again no difference in the combined endpoint was found, despite a group B population with solely aspirin use. Of note, three thromboembolic events in the VKA group occurred within the first 4 days during which VKA treatment still had not yet reached therapeutic levels. The observed 3-month cumulative incidence for thrombo-embolic events is in aligned with those reported by previous studies[4,18]. The observed incidence of major bleeding events was slightly higher than described in previous reports, probably due to the adjudication process of postoperative pericardial tamponade[19,20]. Pericardial effusion alongside signs of hemodynamic instability was adjudicated as a pericardial bleeding, whereas these events might not be considered as (major) bleedings in previous studies.

PERSPECTIVE OF INTERNATIONAL GUIDELINES

Recommendations from international guidelines are contradictory to our results, favouring either VKA or aspirin as postoperative thromboprophylaxis 3 months after MVr[5,6,21]. Three former retrospective studies have compared antiplatelet with anticoagulation therapy in patients after MVr[8,9,20,22]. Two studies found no differences in stroke and bleeding rate of early VKA treatment compared with aspirin therapy, suggesting that VKA treatment might not be necessary[20,22]. The largest study to date by Paparella et al. [19] found less bleeding and comparable arterial thromboembolic events in patients treated with aspirin 6 months following MVr. However, in contrast to our study, no data on AF were reported and assigned treatment was mainly chosen by the surgeons' preference. A small study by Aramendi et al. [8]. found a beneficial effect of antiplatelet therapy in preventing thromboembolic events compared with VKA treatment with no increased risk of bleeding. Thus, these four studies suggest aspirin use after MVr. This contradicts the recommendation of VKA use over aspirin by the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology/European Association of Cardiothoracic Surgery (ESC/EACTS) guidelines[6,21]. The ACC/AHA recommendations are based on one observational cohort study which found a high 30-day ischemic stroke incidence of 1.5%, despite VKA treatment[4,21]. The ESC recommendation is provided without references, illustrating the paucity of information[6]. Since recommendations from guidelines are based on retrospective and underpowered studies, the optimal thromboprophylaxis after MVr remains controversial and a frequent matter of debate. However, based on the scarcity of data, our results might suggest a reassessment of the recommendations from international guidelines.

Predictors

In our study, only concomitant TVr was found to be an independent predictor for major bleeding events. Concomitant TVr might have been a more difficult procedure with prolonged cardiopulmonary bypass duration, leading to dysfunction of platelets, which is associated with major cause of excessive bleeding in the early postoperative period[23,24]. Other not predefined predictors, such as surgery duration, preoperative hematologic laboratory values and surgical techniques might also have contributed to the occurrence of early bleeding events. Consistently with earlier findings, no independent predictors were found for thromboembolic events[18]

Clinical perspective

When considering the appropriate antithrombotic treatment after MVr, the thrombotic risk secondary to the endothelialization process and new onset AF could be a good rationale for physicians to prescribe VKA treatment. During the first three postoperative months, the exposure of circulating blood to non-endothelialized repair components can cause thrombus formation and even endocarditis, particularly due to a relatively slower blood flow in the left atrium compared to other parts of the heart. AF is a common postoperative cardiac arrhythmia after MVr occurring in approximately 24–35% of the patients, even after two postoperative weeks[14,25]. In this study we found this incidence of new onset AF to be 47%. VKA treatment, however, has many disadvantages, including need for frequent laboratory monitoring, variability of dose response and drug and food interactions while in contrast aspirin does not require monitoring and dosage adjustments. Consequently, for practical reasons, aspirin might be preferable as antithrombotic treatment compared to VKA in patients with sinus rhythm. Therefore, the choice of antithrombotic treatment in patients without prior history of AF should be individualized based on patient-specific considerations, such as risk factors for AF, compliance with treatment and frailty. Despite the lack of prospective studies specifically evaluating treatment with direct oral anticoagulants (DOACs) in patients with mitral valve repair, subanalysis of DOAC AF trails have showed a similar overall efficacy and safety as compared with VKA in patients with valvular heart disease, including mitral valve repair[26]. However, international guidelines do not recommend the use of DOACs during the first three to six postoperative months in patients with AF[5-7]. Future prospective randomized trials are warranted to provide conclusive results about DOAC treatment in the early postoperative phase after mitral valve repair in patients with and without AF.

Strengths and limitations

The strength of this study is the large cohort of consecutive patients providing novel and clinically relevant data on the antithrombotic strategy after MVr. Moreover, the study population was rather homogeneous, due to the exclusion of concomitant procedures that might lead to different patient groups (i.e., AF, other valve, and coronary atherosclerotic surgery).

Our study had several limitations as well. First, a direct comparison between patients treated with VKA and aspirin would have been preferable, but the high incidence of AF makes such a trial difficult to perform. A large number of patients would be required, in particular patients receiving aspirin. Second, antithrombotic treatment was not randomly allocated due to the retrospective study design. Third, no data was available on individual INR measurements and thus the time during which VKA treated patients were in therapeutic range is unclear. Fourth, we performed a multi-centre study with inherent perioperative variabilities. Ideally, future prospective, randomized clinical trials are warranted to provide evidence-based recommendations for the implementation of appropriate antithrombotic strategy after MVr.

VKA and aspirin therapy showed a similar event rate of 10% during 3 months after MVr in patients without prior history of AF. In both treatment groups thromboembolic event rate was low and major bleeding rates were comparable. Future prospective, randomized trials are warranted to corroborate our findings.

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Chapter 9

Effect of minimally invasive mitral valve surgery compared to sternotomy on short- and long-term outcomes: a retrospective multicentre interventional cohort study based on Netherlands Heart Registration

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ABSTRACT

Objectives

Minimally invasive mitral valve surgery (MIMVS) has been performed increasingly for the past 2 decades; however, large comparative studies on short- and long-term outcomes have been lacking. This study aims to compare short- and long-term outcomes of patients undergoing MIMVS versus median sternotomy (MST) based on real-world data, extracted from the Netherlands Heart Registration.

Methods

Patients undergoing mitral valve surgery, with or without tricuspid valve, atrial septal closure and/or rhythm surgery between 2013 and 2018 were included. Primary outcomes were short-term morbidity and mortality and long-term survival. Propensity score matching analyses were performed.

Results

In total, 2501 patients were included, 1776 were operated through MST and 725 using an MIMVS approach. After propensity matching, no significant differences in baseline characteristics persisted. There were no between-group differences in 30-day mortality (1.1% vs 0.7%, $P = 0.58$), 1-year mortality (2.6% vs 2.1%, $P = 0.60$) or perioperative stroke rate (1.1% vs 0.6%, $P = 0.25$) between MST and MIMVS, respectively. An increased rate of postoperative arrhythmia was observed in the MST group (31.3% vs 22.4%, $P < 0.001$). A higher repair rate was found in the MST group (80.9% vs 76.3%, $P = 0.04$). No difference in 5-year survival was found between the matched groups (95.0% vs 94.3%, $P = 0.49$). Freedom from mitral reintervention was 97.9% for MST and 96.8% in the MIMVS group ($P = 0.01$), without a difference in reintervention-free survival ($P = 0.30$).

Conclusions

The MIMVS approach is as safe as the sternotomy approach for the surgical treatment of mitral valve disease. However, it comes at a cost of a reduced repair rate and more reinterventions in the long term, in the real-world.

INTRODUCTION

Minimally invasive mitral valve surgery (MIMVS) has an established role in the surgical treatment of mitral valve (MV) disease, but it is still not widely adopted. Over the past decades, many high-volume centres have published excellent outcomes, comparing MIMVS to sternotomy[1,2]. These studies, and subsequent meta-analyses, demonstrated no differences in safety, defined as mortality, and efficacy, defined as the recurrence of mitral regurgitation (MR), despite longer cardiopulmonary bypass (CPB) and aortic cross-clamp (X) times. Furthermore, a tendency towards reduced morbidity, with a lower incidence of re- exploration for bleeding, arrhythmia, pneumonia and wound infection, in conjunction with a shorter hospital stay and reduced postoperative pain has been observed [3,4]. In addition, MIMVS has been associated with improved cost-effectiveness[5] and reduced mortality rates in a reoperative setting[6].

Long-term outcome of MIMVS has only been reported by expert single centres[2,7-9] and 1 multicentre British group[10], while most multicentre studies have focused on short-term outcomes[11], resulting in a knowledge gap of long-term real-world data. Therefore, it remains debateable whether the published long-term outcomes are reproducible in real world. As such, the most recent European Society of Cardiology (ESC)/European

Association for Cardiothoracic Surgery (EACTS) guidelines for valvular heart disease do not contain a section on the preferred surgical approach for the treatment of MV disease[12]. However, a consensus statement by The International Society of Minimally Invasive Cardiothoracic Surgery has been published a decade ago, in which some recommendations have been formulated, carried by a low level of evidence[13-15]. Subsequently, many centres remain apprehensive about the development of a minimally invasive programme, due to a presumed steep learning curve coupled with this lack of long-term evidence[16]. Furthermore, as the surgical outcomes are associated with the hospital and surgeon volume[17-19], there is a need for a case load that ensures sufficient volume and continuity. The aim of the current study was to evaluate the short-term and long-term outcomes of patients undergoing MV surgery in the Netherlands, registered in the Netherlands Heart Registration, either through a minimally invasive approach or sternotomy, to provide real-world evidence.

PATIENTS AND METHODS

Source of study data

Data from the national database of the Netherlands Heart Registration (NHR) were used for this study. All patients undergoing cardiac surgery in the Netherlands are collected in this prospective mandatory database. The basis for data collection was reported elsewhere[20]. In short, this prospective database contains a variety of data on cardiac surgical procedures performed in the Netherlands. In addition to demographic factors and type of intervention, the database includes parameters concerning perioperative morbidity and mortality and long-term survival and all risk factors required for the calculation of contemporary risk scores. Participation in this registry was made compulsory by national society decree. Although this database was initiated for the quality evaluation of cardiovascular interventions, its completeness of mandatory preoperative variables enables anonymized long-term follow-up of patients undergoing cardiac surgical interventions. All data were automatically uploaded and anonymized.

Inclusion

Patients were considered for inclusion if they were 18 years and older and underwent isolated primary MV surgery. Isolated MV surgery was defined as mitral valve repair (MVr), or replacement (MVR) combined with tricuspid valve repair/replacement and/or rhythm surgery (pulmonary vein isolation/MAZE procedure) and/or atrial septal closure. Patients undergoing a reoperation or other concomitant interventions were excluded. As robotic surgery is a distinct area within the field of MIMVS, patients undergoing a robotic approach were excluded as well. Minimally invasive surgery was defined as right anterolateral thoracotomy with peripheral cannulation and avoiding sternotomy. No distinctions were made between the length of the incision, or the use of a video-assisted or direct-vision approach.

Study design

The current study is a retrospective multicentre cohort study of prospectively collected data from 16 cardiothoracic centres in the Netherlands. Data were collected for patients undergoing MV surgery between 2013 and 2018, enabling complete long-term follow-up.

Outcomes

All preoperative data and baseline characteristics required for the calculation of the European System for Cardiac Operative Risk Evaluation (EuroSCORE I) were retrieved from the NHR database. Furthermore, short-term outcomes, defined as early mortality (either 30 days or in-hospital), postoperative complications (i.e., peri-operative stroke, vascular complications, myocardial infarction, pneumonia, wound infection, reintubation/prolonged ventilation, re-admission to the intensive care, renal failure, gastrointestinal complications, re-exploration for bleeding and arrhythmia) and duration of hospital stay, were retrieved. Long-term outcomes were defined as long-term survival at 5 years and reintervention for the recurrence of MV disease at 5years. Mortality data were derived from the municipal administration records and were almost complete for all patients. Mitral valve reintervention was retrieved by cross-referencing the registry's database. Both mortality and reintervention follow-up were completed through 1 December 2020.

Missing values

The national database of the Netherlands Heart Registration has an exceptionally high data completeness for baseline characteristics. Unfortunately, 2 non-mandatory variables had a relatively high proportion of missing data: CPB-time (33.1%) and X-time (32.7%). Given the higher levels of missing data for these variables, which clearly exceed >10% and most likely had a non-random distribution, it was inappropriate to apply a multiple imputation method[21].

Statistical analysis

Normality of the continuous variables was tested by visual inspection of the histograms and the Shapiro–Wilk test. Continuous data are presented as mean ± standard deviation (or as median with interquartile range in the presence of skewedness). Categorical data are expressed as frequencies and percentages and were compared using the v2 test. Fisher's exact test was used when the minimum expected cell-size assumption did not apply. Continuous variables were compared using the Mann–Whitney U-test. Covariates, used for the calculation of propensity scores, were identified at baseline analysis. Propensity score matching analyses were used to correct for potential confounders. Propensity scores were estimated using variables identified in a logistic model. Propensity scores were matched using nearest neighbor matching in a 1:1 ratio, replacement was not allowed, and caliper distance was set at 0.02, as advocated by experts in our field[22]. Baseline characteristics were presented both before and after propensity score matching. Standardized mean difference was used to compare the difference in means in units of the pooled standard deviation. A value of >0.10 was considered an index of residual imbalance. Kaplan–Meier survival curves were used to demonstrate long-term survival and freedom from reoperation. Between survival curve differences were assessed using the log-rank test. All reported P-values were two-sided and were considered statistically significant when $P < 0.05$. Statistical analyses of the data were performed using SPSS software (V26, IBM, Armonk, New York, USA) and R Statistics (the R Foundation, Vienna, Austria).

Ethical statement

This is a retrospective study with data of the Netherlands Heart Registration. Therefore, no institutional review board approval was necessary. This study is in line with the institution's ethical policies and standards.

RESULTS

Baseline characteristics

The NHR database contained 2501 patients undergoing MV surgery with a registered surgical approach between 2013 and 2018, of which 1776 were operated through a median sternotomy (MST) and 725 using an MIMVS approach. Patients selected for MIMVS had a significant lower body mass index (24.8 [22.9–27.1] vs 25.6 [23.2–28.0]; P<0.001), a lower rate of diabetes (4.1% vs 8.3%, P<0.001), chronic obstructive pulmonary disease (4.6% vs 10.5%, P < 0.001), extra-cardiac arteriopathy (1.2% vs 3.0%, P = 0.01) and active endocarditis (0.1% vs 1.7%, P<0.001) compared to patients selected for MST. Patients operated through a minimally invasive approach had significantly better left ventricular ejection fraction and lower rate of severe pulmonary artery hypertension. This resulted in a lower median EuroSCORE I (2.99 [1.90–5.36] vs 3.61 [2.08–6.22]; P < 0.001). Baseline characteristics are summarized in Table 1.

Propensity score matching

To correct the differences in baseline characteristics, propensity score matching was performed. Parameters that differed at baseline, i.e., body mass index, diabetes mellitus, chronic obstructive pulmonary disease, extra-cardiac arteriopathy, active endocarditis, left ventricular ejection fraction, pulmonary artery hypertension, EuroSCORE I, and concomitant procedures (tricuspid valve surgery, atrial septal closure and rhythm surgery), were used as covariates for the propensity score matching model. A total of 718 pairs were matched in a 1:1 ratio. After matching, the 2 groups were comparable for all confounders (standardized mean difference <0.10).

Operative characteristics

Of the overall cohort (n = 2501), 1971 patients underwent MVr and 530 patients underwent MVR, resulting in a repair rate of 78.8%. Repair rate for the unmatched MST group was 80.0% vs 75.9% in the MIMVS group (P = 0.02). As the aetiology of mitral valve disease was not registered, this could not be related to the repair rate for either group. Isolated MV surgery was performed in 1598 patients (63.9%). For the matched cohorts, in the MST group, MVr was performed in 581 patients (80.9%) vs 548 patients (76.3%) in the MIMVS group (P=0.04). Concomitant procedures are presented in Table 2. Unfortunately, CPB- and X-time exhibited excessive missing values (32.7% and 33.1%, respectively) and could not be included in the analysis. Operative characteristics are depicted in Table 2.

Short-term outcomes

In the overall cohort (n = 2501), 30-day mortality was 1.3% (n = 33) and stroke occurred in 1.3% of patients (n = 33). For the matched cohorts, 30-day mortality was 1.1% in the MST group, compared to 0.7% in the MIMVS group (P = 0.58). Stroke occurred in 1.1% of patients (n = 8) in the MST group, compared to 0.6% of patients (n = 4) in the MIMVS group (P = 0.25). Mortality and complication rates are depicted in Table 3. One-year mortality was 2.6% in the MST group compared to 2.1% in the MIMVS group (P = 0.60). There were no differences in complications as periprocedural myocardial infarction (P = 0.48), pneumonia (P = 0.99), renal failure (P = 0.20) or vascular complications (P = 0.32). A significantly reduced incidence of postoperative arrhythmia was observed in the MIMVS group (22.4% vs 32.3%, P < 0.001) compared to the MST group. Interestingly, length of hospital stay (LOHS) was shorter in the MST group (6 days [4–8] vs 6 days [5–8], P = 0.001).

Long-term outcomes

Survival

For the overall cohort, the median follow-up was 36 months [20–56], with a 5-year survival rate of 93.6%. For the matched groups, the survival rate at 5 years was 95.0% in the MST group, compared to 94.3% in the MIMVS group (P = 0.49, Fig. 1A).

Table 1. Baseline characteristics

	Total cohort			Matched cohort		
	Sternotomy ***N* = 1776**	**MIMVS** ***N* = 725**	**SMD**	**Sternotomy** ***N* = 718**	**MIMVS** ***N* = 718**	**SMD**
Age, mean (± SD)	64.3 (± 11.7)	64.0 (± 11.7)	-0.025	63.4 (± 12.4)	63.8 (± 11.6)	0.036
BMI, median [IQR]	25.6 [23.2–28.0]	24.8 [22.9–27.1]	-0.166	25.3 [23.1–27.7]	24.8 [22.9–27.2]	-0.054
BSA, median [IQR]	1.93 [1.79–2.06]	1.92 [1.76–2.07]	-0.060	1.93 [1.78–2.05]	1.93 [1.77–2.07]	-0.005
Male sex, *n* (%)	999 (56.3)	413 (57.0)	-0.014	410 (57.1)	411 (57.2)	-0.003
Diabetes, *n* (%)	147 (8.3)	30 (4.1)	-0.208	26 (3.6)	30 (4.2)	0.028
Chronic lung disease, *n* (%)	187 (10.5)	33 (4.6)	-0.287	35 (4.9)	33 (4.6)	-0.013
Extracardiac arteriopathy, *n* (%)	54 (3.0)	9 (1.2)	-0.162	6 (0.8)	9 (1.3)	0.038
Active endocarditis, *n* (%)	31 (1.7)	1 (0.1)	-0.433	1 (0.1)	1 (0.1)	<0.001
Serum creatinine (>200 lm/l), *n* (%)	21 (1.2)	2 (0.3)	-0.173	2 (0.3)	2 (0.3)	<0.001
LV function, *n* (%)						
Good	1195 (67.3)	618 (85.2)	–	616 (85.8)	612 (85.2)	–
Moderate	550 (31.0)	95 (13.1)	-0.529	93 (13.0)	95 (13.2)	0.008
Poor	31 (1.7)	12 (1.7)	-0.007	9 (1.3)	11 (1.5)	0.022
Pulmonary artery pressure, *n* (%)						
Normal	1430 (80.5)	632 (87.2)	–	631 (87.9)	627 (87.3)	–
Moderately increased	238 (13.4)	54 (7.4)	-0.227	55 (7.7)	54 (7.5)	-0.005
Severely increased	108 (6.1)	39 (5.4)	-0.031	32 (4.5)	37 (5.2)	0.031
EuroSCORE I, median [IQR]	3.61 [2.08–6.22]	2.99 [1.90–5.36]	-0.202	3.05 [2.03–5.16]	2.97 [1.89–5.22]	0.026
Tricuspid valve surgery, *n* (%)	495 (27.9)	80 (11.0)	-0.537	78 (10.9)	80 (11.1)	-0.008
Atrial septal closure, *n* (%)	49 (2.8)	23 (3.2)	0.024	23 (3.2)	22 (3.1)	0.009
Rhythm surgery, *n* (%)	373 (21.0)	100 (13.8)	-0.209	103 (14.4)	100 (13.9)	-0.012

BMI: body mass index; BSA: body surface area; EuroSCORE I: European System for Cardiac Operative Risk Evaluation; IQR: interquartile range; LV: left ventricular; MIMVS: minimally invasive mitral valve surgery; SD: standard deviation; SMD: standardized mean difference.

Freedom from reintervention

In the overall cohort, 57 patients were reoperated during long-term follow-up, resulting in a freedom from MV reintervention of 97.7% at 5 years. During the initial procedure, these 57 patients underwent MVR (4 patients, all in the MST group) and MVr (53 patients). Procedures performed during reintervention were re-repair in 17 patients, MVR in 38 patients and a transcatheter procedure in 2 patients.

In the MST group, freedom from reintervention was 98.1% at 5 years (97.9% for the matched group), while this was 96.8% in the MIMVS group (P = 0.001, Fig. 2A). In the subgroup analysis, a significant difference also found in MV reintervention at 5 years when specified to actual isolated MVr (97.4% vs 95.8%, respectively, P = 0.003, Fig. 2A).

Reintervention-free survival. For the overall cohort, the median reintervention-free survival was 25 months [9–47], with a 5-year reintervention-free rate of 93.2%. For the matched groups, he reintervention-free survival rate at 5 years was 92.8% in the MST group, compared to 93.6% in the MIMVS group (P = 0.30, Fig. 1C). In the subgroup analysis, when specified to actual isolated MVr, a reintervention-free survival rate of 93.1% vs 93.8% for MST and MIMVS was found, respectively (P = 0.23, Fig. 2B).

Table 2. Procedural characteristics

Total cohort	**Sternotomy** ***N* = 1776**	**MIMVS** ***N* = 725**	**P-value**	**Sternotomy** ***N* = 718**	**MIMVS** ***N* = 718**	**P-value**
Type of procedure, *n* (%)						
Mitral valve reconstruction	1421 (80.0)	550 (75.9)	0.02	581 (80.9)	548 (76.3)	0.04
Mitral valve replacement	355 (20.0)	175 (24.1)		137 (18.1)	170 (23.7)	
Tricuspid valve reconstruction	492 (27.7)	78 (10.8)	<0.001	75 (10.4)	78 (10.9)	0.80
Tricuspid valve replacement	3 (0.2)	2 (0.3)	0.59	3 (0.4)	2 (0.3)	0.99
Atrial septal closure	49 (2.8)	23 (3.2)	0.58	23 (3.2)	22 (3.1)	0.88
Rhythm surgery	373 (21.0)	100 (13.8)	<0.001	103 (14.3)	100 (13.9)	
Type of prothesis mitral valve, *n* (%)						
Mechanical valve	173 (48.7)	67 (38.3)	0.02	61 (44.5)	67 (39.4)	0.12
Biological valve	178 (50.9)	108 (61.7)		75 (54.7)	103 (60.6)	
Unknown	4 (1.1)	0 (0)		1 (0.1)	0 (0.0)	

MIMVS: minimally invasive mitral valve surgery. Bold denotes statistical significance $p < 0.05$.

Table 3. Postoperative complications and follow-up

	Sternotomy $N = 1776$	**MIMVS** $N = 725$	**P-value**	**Sternotomy** $N = 718$	**MIMVS** $N = 718$	**P-value**
30-Day mortality, *n* (%)	28 (1.6)	5 (0.7)	0.08	8 (1.1)	5 (0.7)	0.58
1-year mortality, *n* (%)	60 (3.4)	15 (2.1)	0.08	19 (2.6)	15 (2.1)	0.60
Overall mortality, *n* (%)	119 (6.7)	42 (5.8)	0.40	36 (5.0)	41 (5.7)	0.64
Follow-up in days, median [IQR]	1135 [491–1706]	427 [239–1093]		1262 [656–1738]	951 [676–1661]	
Hospital stay in days, median [IQR]	5 [4–8]	6 [5–8]	0.001	6 [4–8]	6 [5–8]	0.001
Perioperative myocardial infarction, *n* (%)	10 (0.6)	3 (0.4)	0.77	5 (0.7)	3 (0.4)	0.48
Pneumonia, *n* (%)	42 (2.4)	15 (2.1)	0.65	16 (2.2)	15 (2.1)	0.99
Reintubation due to respiratory insufficency, *n* (%)	14 (0.8)	3 (0.4)	0.42	6 (0.8)	3 (0.4)	0.32
Prolonged intubation (>24 h), *n* (%)	37 (2.1)	6 (0.8)	0.03	18 (2.5)	6 (0.8)	0.02
Re-admission to ICU, *n* (%)	32 (1.8)	8 (1.1)	0.21	9 (1.3)	8 (1.1)	0.99
Cerebrovascular accident, *n* (%)	29 (1.6)	4 (0.6)	0.03	8 (1.1)	4 (0.6)	0.25
Kidney failure, *n* (%)	27 (1.5)	3 (0.4)	0.02	7 (1.0)	3 (0.4)	0.20
Gastro-intestinal complications, *n* (%)	10 (0.6)	4 (0.6)	0.99	4 (0.6)	4 (0.6)	0.99
Vascular complications, *n* (%)	3 (0.2)	1 (0.1)	0.99	3 (0.4)	1 (0.1)	0.32
New-onset arrhythmia, *n* (%)	576 (32.4)	162 (22.3)	<0.001	225 (31.3)	161 (22.4)	<0.001
Reexploration (within 30 days), *n* (%)	93 (5.2)	39 (5.4)	0.89	38 (5.3)	39 (5.4)	0.99
Reintervention, *n* (%)	34 (1.9)	23 (3.2)	0.06	15 (2.1)	23 (3.2)	0.25

ICU: intensive care unit; IQR: interquartile range; MIMVS: minimally invasive mitral valve surgery. Bold denotes statistical significance $p < 0.05$.

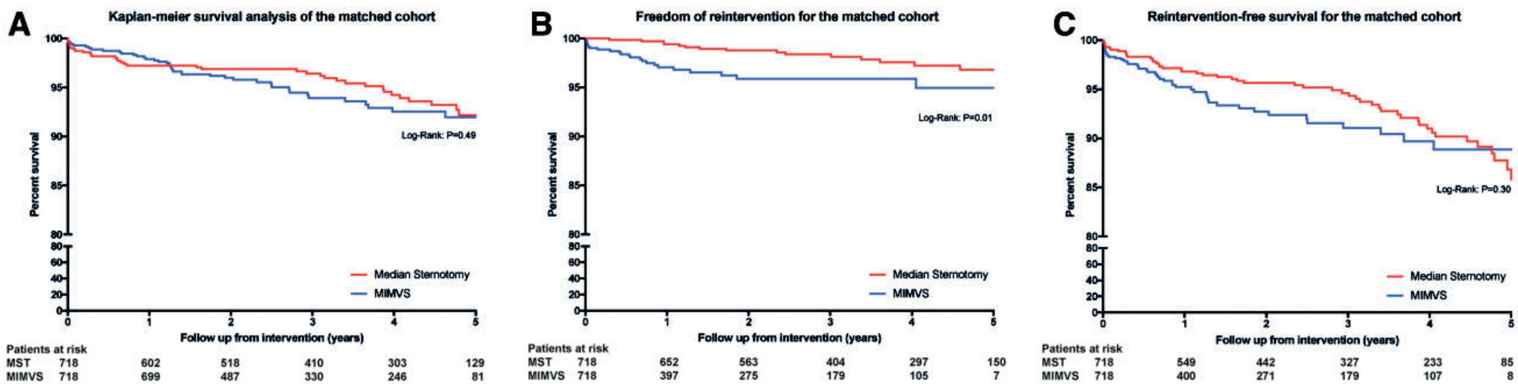

Figure 1. (A) Kaplan–Meier survival analysis of the matched cohort. (B) Freedom of reintervention for the matched cohort. (C) Reintervention-free survival for the matched cohort.

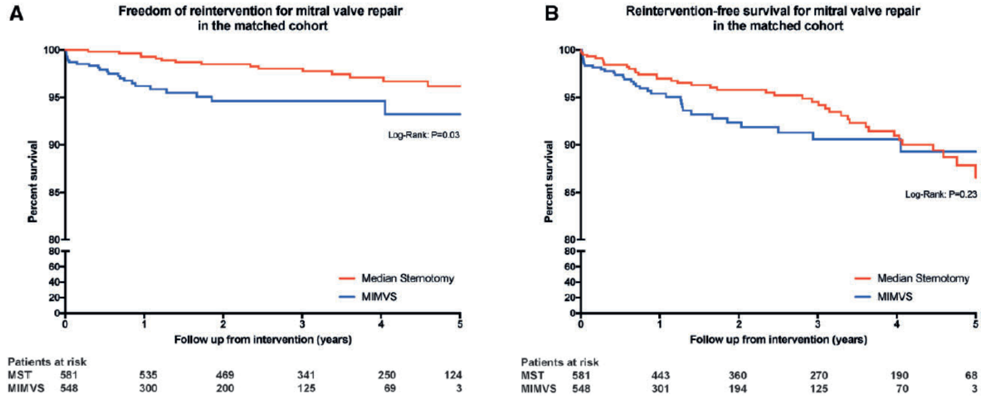

Figure 2: (A) Freedom of reintervention for mitral valve repair in the matched cohort. (B) Reintervention-free survival for mitral valve repair in the matched cohort.

DISCUSSION

This study is the first nationwide multicentred study to investigate the short- and long-term outcomes of MIMVS compared to MV surgery through MST. The most important finding is that MIMVS is as safe as MST in terms of short- and long-term outcomes, based on real-world data.

As is evident by the early results, isolated MV surgery, in all comers with a variety of mitral valve pathologies, is a safe procedure with a 30-day mortality rate of 1.3% for the total cohort (MIMVS and MST). This mortality rate is slightly lower, but in line with previous findings of the Society of Thoracic Surgeons database (2.9% early mortality)[23] and the Netherlands Heart Registration[24]. The difference can be explained by the different era during which these studies were conducted, as early mortality for mitral procedures has improved during the past decades[25], most probably due to an increased penetration of MVr[17]. When comparing an MIMVS approach to MST, we did not find a difference in short-term mortality (0.7% vs 1.1% in the matched cohorts, respectively), demonstrating the safety of MIMVS. Several large single-arm cohort and comparative studies (of which 1 was randomized[26]) have found similar results[8], which were confirmed in meta-analyses[3,4]. In addition, the results of the current Dutch multicentre study are in line with a previous propensity matched multicentre cohort from the UK[10].

For all cardiac surgical procedures, stroke is one of the most feared complications. In earlier comparative studies, this complication seemed to occur more in patients undergoing MIMVS, compared to MST[27], potentially related to the use of retrograde perfusion[28]. With the advent of routine computed tomography scans for the screening of peripheral arterial disease[29], patient selection has improved and the occurrence of stroke as a complication has been diminished[30], irrespective of aortic occlusion techniques[31]. As such, the results of the current study are a reflection of contemporarily used techniques, as stroke rate was low and did not differ between both groups. Interestingly, there was a statistically significant difference in LOHS between the MST and MIMVS groups (6 vs 6 days, respectively, due to distribution P = 0.001). As such, the difference does not seem to be clinically important. Still, a perceived advantage of MIMVS is the faster recovery time, in terms of ventilation duration, intensive care unit stay and LOHS[4]. However, the LOHS found in our study is still comparable to other high-volume centre experiences. As the current study is based on a multi-centre registry, some inter-hospital differences in discharge policies might be expected which could be explanatory for these results. Furthermore, in the minimally invasive group, a larger proportion of bio prosthesis was implanted. These patients had a median age of 74 years [68–78] for median sternotomy and a median age of 77 years [72–81] for MIMVS.

Long-term follow-up of patients surgically treated for mitral disease, especially in the setting of MIMVS, can be challenging, as most of these procedures are performed in tertiary referral institutions. Subsequently, only single-centre experiences have reported long-term survival for patients undergoing MIMVS[1,2]. Therefore, the current study is the first to evaluate and compare the long-term outcomes of MIMVS and MST approaches in the Netherlands. Of note, 5-year survival for the whole cohort was excellent in the Netherlands (93.6%), similar to previous reports[2], and long-term survival did not differ between the matched cohorts, also in line with Grant et al.[10], reporting British results.

In addition to safety, efficacy is as important to confirm the validity of MIMVS as a suitable alternative to MST. In this context, efficacy can be defined as the durability of the operation, which is often presented in literature by repair rate and freedom from mitral reinterventions.

A significant difference in repair rate was found for both the unmatched and matched population (80.0% vs 75.9% and 80.9% vs 76.3%) in favour of MST. The repair rate could unfortunately not be specified for mitral valve pathology. The difference could be a reflection of surgical experience and surgical volume, which is a known factor in the literature. Furthermore, in the analysed cohorts, mitral reintervention at long-term follow-up was increased in the MIMVS group (3.2% vs 2.1%, absolute difference of 8 patients). This difference did not disappear when correcting for isolated mitral repair. Perhaps, reintervention rate might not be an ideal marker of recurrence of mitral disease, as the acceptance for a reintervention potentially only reflects a lower surgical risk profile of the accepted patients. Ideally, recurrence of mitral regurgitation, its aetiology and its grading would be required to analyse actual differences between-group differences in depth.

Although the exact mechanism of recurrence of MV disease cannot be retrieved in the current registry, the observed difference should not be ignored. It may point to the difficulties accompanying the initiation of an MIMVS programme. MIMVS warrants sufficient case volume, as MVr and MIMVS have steep learning curves (75–125 cases) and require a steady patient base ensuring the continuity of 2 MIMVS procedures per week[16,32]. As short- and long-term outcomes are dependent of operator and hospital volume[17,19], these findings should stimulate a trend towards centralization of MIMVS procedures, performed by dedicated MV surgeons[33].

Therefore, we do not promote MIMVS as the preferred approach for all patients undergoing surgery for MV disease. Rather, patient selection for such an approach should be conducted through a standardized process of preoperative planning, minimalizing perioperative risks. Furthermore, we advocate for MIMVS to be performed by dedicated surgeons, optimizing durability and long-term survival.

Limitations

Although the current study design allows for a multicentre evaluation of all comers undergoing MV surgery, some remarks are appropriate. The NHR database was designed for quality evaluation, rather than for research purposes. As such, some important MV disease characteristics were not reported, such as MV disease aetiology, complexity and gradation. In addition, some variables, such as CPB- and X-time, were missing in a relatively large proportion as well. Furthermore, for patients undergoing MVr, no details regarding the repair technique (resection, neochordae or papillary muscle reposition) are registered, which is due to the nature of the registry. The techniques used could have influence on the long-term durability. As the registry was anonymized, and data could not be traced back to surgeons, the influence of surgeon volume could not be assessed. Finally, repair rate for degenerative MR influences short- and long-term outcomes, but its effect could not be evaluated in the current design.

CONCLUSION

The current study is the first nationwide registry to compare the survival of an MIMVS approach to MST for the treatment of MV disease in all comers. No difference in short-term mortality, long-term overall survival or reintervention-free survival was found. MIMVS is associated with a reduced risk of postoperative arrhythmia and prolonged intubation. An increased LOHS, a lower repair rate and an increased risk of reintervention over 5 years were observed for MIMVS. Patient selection, surgical volume and surgical expertise remain crucial.

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APPENDIX

The members of the Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration are as follows:
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Chapter 10

Minimally invasive approach compared to resternotomy for mitral valve surgery in patients with prior cardiac surgery: retrospective multicentre study based on the Netherlands Heart Registration

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ABSTRACT

Objectives

Mitral valve (MV) surgery after prior cardiac surgery is conventionally performed through resternotomy and associated with increased morbidity and mortality. Alternatively, MV can be approached minimally invasively [minimally invasive mitral valve surgery (MIMVS)], but longer-term follow-up of this approach for MV surgery after prior cardiac surgery is lacking. Therefore, the aim of the current study is to evaluate short- and mid-term outcomes of MIMVS versus MV surgery through resternotomy in patients with prior sternotomy, using a nationwide registry.

Methods

Patients undergoing isolated MV surgery after prior cardiac surgery between 2013 and 2018 were included. Primary outcomes were short-term morbidity and mortality and mid-term survival. Cox proportional hazard analysis was used to investigate the association between surgical approach and mortality. Propensity score matching was used to correct for potential confounders.

Results

In total, 290 patients underwent MV surgery after prior cardiac surgery, of whom 205 patients were operated through resternotomy and 85 patients through MIMVS. No significant differences in 30-day mortality (3.4% vs 2%, P = 0.99) were observed between both groups. Five-year survival was 86.3% in the resternotomy group, compared to 89.4% in the MIMVS group (log-rank P = 0.45). In the multivariable analysis, surgical approach showed no relation with mid-term mortality [hazard ratio 0.73 (0.34–1.60); P = 0.44]. A lower incidence of prolonged intubation and new-onset arrhythmia was observed in MIMVS.

Conclusions

MV surgery after prior cardiac surgery has excellent short- and mid-term results in the Netherlands, and MIMVS and resternotomy appear to be equally efficacious. MIMVS is associated with a lower incidence of new-onset arrhythmia and prolonged intubation.

INTRODUCTION

With the ageing population, mitral valve (MV) surgery after priorcardiac surgery is increasingly performed[1], currently comprising 10% of the total case load of surgical MV interventions[2]. Conventionally, cardiac reoperations are performed through a resternotomy with significant perioperative morbidity and mortality[3], as reflected by its incorporation in contemporary surgical risk scores. During resternotomy, dense adhesions can be encountered, which are amenable to severe bleeding, occurringin 7–9% of reoperative procedures[4,5]. Especially in the proximity of cardiac chambers or in the presence of patent bypass grafts, such bleedings can have devastating consequences.

Alternatively, MV surgery after prior cardiac surgery can be performed using a minimally invasive approach [minimally invasive mitral valve surgery (MIMVS)], through a right-sided anterolateral thoracotomy[6,7]. Through this access, many of the potential complications associated with resternotomy can be circumvented, as the left atrium is approached directly from the side, without the need for complete adhesiolysis of the heart. In addition, potentially patent bypass grafts are usually not in the vicinity. Some retrospective studies have demonstrated a beneficial short-term effect of MIMVS in a reoperative setting[7,8] , which was corroborated in a recent meta-analysis by our research group[9], demonstrating superiority of MIMVS in terms of early mortality. Still, these studies comprised relatively small study cohorts and expert single-centre experiences with limited follow-up. As such, longer-term outcomes of MIMVS after prior cardiac surgery remain unknown. The aim of current study is to compare short- and mid-term outcomes of MIMVS versus conventional MV surgery through a resternotomy in patients with prior cardiac surgery, using a multicentre nationwide registry.

PATIENTS AND METHODS

Source of study data

All patients undergoing cardiac surgery in the Netherlands are collected in a prospective mandatory database: the Netherlands Heart Registration (NHR). In short, this prospective database contains a variety of data on all cardiac surgical procedures performed in the Netherlands, including demographic factors, type of intervention, parameters concerning perioperative morbidity and mortality, mid-term survival and all risk factors required for the calculation of contemporary risk scores. All data are anonymized for both patients, surgeons, and centres.

Inclusion

Patients were considered for inclusion if they were 18 years and older, had previous cardiac surgery performed through a median sternotomy and underwent isolated MV surgery for new-onset or recurrent MV disease. Isolated MV surgery was defined as either isolated MV repair (MVr) or

MV replacement (MVR) or MVr/MVR combined with tricuspid valve repair/replacement and/or rhythm surgery (pulmonary vein isolation/MAZE procedure) and/or atrial septal closure. Patients undergoing other concomitant interventions were excluded. As robotic surgery is a distinct area within the field of MIMVS, patients undergoing a reoperative robotic procedure were excluded as well. MIMVS was defined as right-sided anterolateral mini-thoracotomy with peripheral or central cannulation, avoiding (re)sternotomy. No distinctions were made between the length of the incision, or the use of a video-assisted or direct-vision approach.

Study design

The current study is a retrospective multicentre cohort study of prospectively collected data from 16 cardiothoracic centres in the Netherlands. Data were collected for patients with previous cardiac surgery through sternotomy, undergoing MV surgery in the period between January 2013 and December 2018.

Outcomes

Short-term outcomes, defined as early mortality (30-day mortality) and postoperative complications and duration of hospital stay, were retrieved. Definitions regarding postoperative complications are presented in Supplementary Material, S5. Mid-term outcomes were defined as mid-term survival at 5 years. Survival data were derived from the municipal administration records and was completed for all patients. Survival follow-up was completed through December 1, 2020.

Missing values

All mandatory variables for the NHR were complete. However, 2 non-mandatory variables had a relatively high proportion of missing data: cardiopulmonary bypass-time (46%) and aortic cross-clamp time (48%). Given the higher levels of missing data for these variables, which clearly exceed >10% and most likely had a non-random distribution, it was inappropriate to apply a multiple imputation method, impairing analysis of these surgical times.

Statistical analysis

Normality of the continuous variables was tested by the Shapiro–Wilk test. Continuous data are presented as mean ± SD (or as median with interquartile range in the presence of skewedness). Categorical data are expressed as frequencies and percentages (in case of <100 patients, integers were used for the reporting of percentages) and were compared using the v2 test. Fisher's exact test was used when the minimum expected cell-size assumption did not apply. Continuous variables were compared using the Mann–Whitney U-test. Kaplan–Meier survival curves were used to demonstrate mid-term survival. Between survival curve differences were assessed using the log-rank test. Follow up was reported as median in months and interquartile range. The influence of the surgical approach (sternotomy versus MIMVS) on mid-term survival was assessed using the Cox proportional hazards model in the total population. Significant covariates ($P < 0.10$) in the univariable analysis and surgical approach (forced in the model, independent of P-value) were included in a multivariable Cox regression analysis. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs). Proportionality was evaluated using a goodness-of-fit test, in which a P-value of <0.05 demonstrated violation of the proportional hazards assumption. All reported P-values were two-sided and were considered statistically significant when $P < 0.05$. Statistical analyses of the data were performed using SPSS software (V26; IBM Armonk, NY, USA) and R Statistics (the R Foundation, Vienna, Austria).

Propensity score matching

Propensity score matching analyses were performed to compare sternotomy to MIMVS, while correcting for potential confounders. Propensity scores were estimated using covariates identified in binary logistic regression model. Propensity scores were matched using nearest neighbour matching in a 1:1 ratio, replacement was not allowed, and calliper distance was set at 0.1, as advocated by experts in our field. Standardized mean difference was used to compare the difference in means in units of the pooled standard deviation. A value of higher than 0.10 was considered an index of residual imbalance. After matching for baseline differences, data on operative characteristics and outcomes were compared using paired tests, as advocated by experts in our field[10].

Ethical statement

No institutional review board approval was necessary. This study is in line with the institution's ethical policies and standards.

RESULTS

Baseline characteristics

NHR database contained 290 patients undergoing MV surgery after prior cardiac surgery through sternotomy, with a registered surgical approach and known previous cardiac procedure through sternotomy between 2013 and 2018. A total of 205 patients were operated through repeated median sternotomy and 85 patients using an MIMVS approach. Male gender was more frequent in MIMVS (n = 107, 52.2% vs n = 57, 67% P = 0.02). Patients operated through resternotomy were younger (66.0 [54.0–73.5] years vs 70.0 [61.5–74.0] years, P = 0.02). Patients undergoing MIMVS more frequently underwent prior primary MV surgery (n = 47, 22.9% vs n = 36, 42%, P = 0.001). Details regarding the primary procedure in the past are summarized in Supplementary Material, S4. At baseline, no difference in median EuroSCORE I was observed (resternotomy 11.85% [6.39–19.48] vs MIMVS 12.43% [5.97–17.61], P = 0.73). Baseline characteristics of the total population, repeated sternotomy group and MIMVS group are summarized in Table 1

Table 1. Baseline characteristics

	Resternotomy, *N* = 205	MIMVS, *N* = 85	*P*-Value
Age, median [IQR]	66.0 [54.0–73.5]	70.0 [61.5–74.0]	0.02
Male sex, *n* (%)	107 (52.2)	57 (67)	0.02
Diabetes, *n* (%)	33 (16.1)	7 (8)	0.08
Chronic lung disease, *n* (%)	28 (13.7)	9 (11)	0.48
Extracardiac arteriopathy, *n* (%)	23 (11.2)	7 (8)	0.45
Recent myocardial infarction, *n* (%)	4 (2.0)	1 (1)	0.99
Active endocarditis, *n* (%)	9 (4.4)	1 (1)	0.29
Serum creatinine (>200 lm/l)	7 (3.4)	2 (2)	0.99
Prior cardiac procedures[a]			
Prior CABG, *n* (%)	74 (36.1)	42 (49)	0.04
Prior MV intervention	47 (22.9)	36 (42)	0.001
LVEF, median [IQR]	55 [40–55]	55 [40–55]	0.75
Good, *n* (%)	109 (53.2)	51 (60)	0.29
Moderate, *n* (%)	89 (43.4)	32 (38)	0.37
Poor, *n* (%)	6 (2.9)	2 (2)	0.99
Very poor, *n* (%)	1 (0.5)	0 (0.0)	0.99
PA pressure, median [IQR]	25.0 [25.0–31.5]	25.0 [25.0–25.0]	0.002
Normal, *n* (%)	130 (63.4)	72 (85)	<0.001
Moderate increased, *n* (%)	54 (26.3)	8 (9)	0.001
Severe increased, *n* (%)	21 (10.2)	5 (6)	0.24
EuroSCORE I, median [IQR]	11.85 [6.39–19.48]	12.43 [5.97–17.61]	0.73

[a]Patients could have both.
Bold denotes statistical significance.
CABG: coronary artery bypass grafting; IQR: interquartile range; LVEF: left ventricular ejection fraction; MIMVS: minimally invasive mitral valve surgery; MV: mitralvalve; PA: pulmonary artery.

Operative characteristics

In the total cohort (n = 290 patients), 76 patients underwent MVr, 211 patients underwent MVR and 3 patients underwent other procedures (such as paravalvular leak closure), resulting in an overall repair rate of 26.2% (n = 76). When specified for patients without previous MV surgery, the repair rate increased to 33.3% (n = 69). No significant difference in repair rate between repeated sternotomy and MIMVS was observed [n = 59 (28.8%) vs 17 (20%), P = 0.12], even when specified for patients without previous MV surgery [n = 54 (32.4%) vs n = 15 (31%), P = 0.64]. In patients with repeated sternotomy, concomitant tricuspid valve reconstruction was performed in more instances [n = 67 (33.2%) vs n = 10 (12%), P < 0.001]. Other concomitant procedures were presented in Table 2. When performing MVR, in 53.1% of cases (n = 112), a mechanical valve, and in 46.9% (n = 99), a biological valve were implanted. There were no differences in choice of prosthesis for both procedures. Operative characteristics are summarized in Table 2.

Table2. Procedural characteristics of the matched and unmatched groups

	Unmatched			Matched		
	Resternotomy, *N* = 205	**MIMVS, *N* = 85**	***P*-Value**	**Resternotomy, *N* = 80**	**MIMVS, *N* = 80**	***P*-Value**
Type of procedure						
MV repair, n (%)	59 (28.8)	17 (20)	0.12	18 (23)	15 (19)	0.25
MV replacement, n (%)	144 (70.2)	67 (79)	0.14	62 (78)	64 (80)	0.50
Other MV procedures, n (%)	2 (1.0)	1 (1)	0.99	0 (0)	1 (1)	0.99
Tricuspid valve reconstruction, n (%)	67 (33.2)	10 (12)	<0.001	26 (33)	10 (13)	0.005
Atrial septal closure, n (%)	4 (2.0)	3 (4)	0.42	2 (3)	3 (4)	0.99
Rhythm surgery, n (%)	18 (8.8)	4 (5)	0.23	5 (6)	3 (4)	0.69
Type of prosthesis						0.99
Mechanical, n (%)	80 (55.6)	42 (48)	0.29	30 (48)	32 (50)	
Biological, n (%)	64 (44.4)	35 (52)	0.29	32 (52)	32 (50)	
Patients without previous MV surgery	N = 158	N = 49		N = 57	N = 45	
MV repair, n (%)	54 (32.4)	5 (30.6)	0.64	14 (25)	13 (29)	0.99

Bold denotes statistical significance.
MIMVS: minimally invasive mitral valve surgery; MV: mitral valve.

Table 3. Coxregression analysis for investigating the effect of surgical approach on mid-termmortality in the overall population

	Univariable		Multivariable	
	HR (95%CI)	***P*-Value**	**HR (95%CI)**	***P*-Value**
Minimally invasive approach	0.83(0.40–1.70)	0.60	0.73(0.34–1.60)	0.44
Age	1.03(1.00–1.05)	0.09	1.02(0.99–1.05)	0.30
Male sex	1.29(0.67–2.48)	0.46		
Chronic lung disease	1.43(0.60–3.43)	0.42		
Extracardiac arteriopathy	3.35(1.57–7.14)	0.01	2.56(1.16–5.67)	0.02
Recent myocardial infarction	4.12(0.98–17.34)	0.05	2.55(0.44–14.80)	0.30
Serum creatinine (>200 lm/l)	4.80(1.69–13.65)	0.01	3.41(1.14–10.27)	0.03
Active endocarditis	3.46(1.05–11.43)	0.04	2.11(0.49–9.02)	0.32
Diabetes	1.50(0.66–3.45)	0.34		
LVEF <50%	2.23(1.16–4.31)	0.02	1.85(0.95–3.61)	0.07
Pulmon aryartery pressure >30 mmHg	1.53(0.787–2.97)	0.21		
Prior bypass grafting	0.89(0.46–1.73)	0.73		
Prior mitral valve intervention	1.51(0.77–2.94)	0.23		
Mitral valve repair	0.44(0.17–1.12)	0.08	0.53(0.20–1.38)	0.19
Concomitant tricuspid procedure	1.33(0.66–2.64)	0.43		
Concomitant rhythm surgery	0.40(0.05–2.92)	0.37		

Bold denotes statistical significance.
CI: confidenceinterval; HR: hazard ratio; LVEF: left ventricular ejection fraction.

Short-term outcomes

In the overall cohort, 30-day mortality was 3.1%. There were no significant differences in 30-day mortality between repeated sternotomy (n = 7, 3.4%) and MIMVS (n = 2, 2%, P = 0.99). The median length of hospital stay was 7 days ([5.0–13.0] vs 7 days [5.0–11.5] P = 0.98) for repeated sternotomy and MIMVS, respectively. A lower incidence of new-onset arrhythmia (n = 79, 38.5% vs n = 18, 21%, P = 0.004) and prolonged intubation (> 24 hours) was observed in the MIMVS group (n = 14, 6.8% vs n = 0, P = 0.01). No significant differences in other postoperative complications were seen. These postoperative outcomes are depicted in Supplementary Material, S1.

Mid-term outcomes

Survival. The median follow-up of the total cohort was 3.26 [1.68–4.64] years, with a 5-year survival rate of 87.2%. Five-year survival rate was 86.3% in the repeated sternotomy group compared to 89.4% in the MIMVS group (log-rank P = 0.45).

Table 4. Postoperative outcomes of matched cohort

	Resternotomy, *N*=80	MIMVS, *N*=80	*P*- Value
30-Day mortality, *n* (%)	1(1)	2(3)	0.99
Hospital stay in days,median [IQR]	7[4–14]	7[5–12]	0.97
Perioperative myocardial infarction, *n* (%)	1(1)	2(3)	0.99
Pneumonia, *n* (%)	7(9)	3(4)	0.29
Urinary tract infection, *n* (%)	0(0)	0(0)	–
Reintubation due to respiratory insufficiency, *n* (%)	3(4)	0(0)	0.99
Prolonged intubation (>24h), *n* (%)	9(11)	0(0)	0.003
Readmission to ICU, *n* (%)	2(3)	3(4)	0.99
Stroke, *n* (%)	1(1)	1(1)	0.99
Stroke without neurological deficit, *n* (%)	0(0)	1(1)	0.99
Stroke with neurological deficit, *n* (%)	1(1)	0(0)	0.99
Kidney failure, *n* (%)	5(6)	3(4)	0.63
Gastrointestinal complications, *n* (%)	2(3)	0(0)	0.50
Vascular complications, n (%)	2(3)	0(0)	0.50
New-onset arrythmia, n (%)	33(41)	17(21)	0.01
Mediastinitis, *n* (%)	1(1)	0(0)	0.99
Reexploration (within 30 days) , *n* (%)	4(5)	8(10)	0.39

Definitions of postoperative complications are summarized in the Supplementary Material. Bold denotes statistical significance.ICU: intensive care unit; IQR: interquartile range; MIMVS: minimally invasive mitralvalve surgery.

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Cox regression analysis

Univariable analysis showed no influence of surgical approach (i.e., resternotomy or MIMVS) on mid-term mortality. Univariable Cox regression analyses identified age, extra cardiac arteriopathy, recent myocardial infarction, increased serum creatinine (>200 ml/l), active endocarditis and decreased left ventricular function as predictors for late mortality. MVr was identified as protective factor for late mortality. Multivariable analysis showed no influence of surgical approach on mid-term mortality [HR 0.73 (0.34–1.60), P = 0.44]. Only extracardiac arteriopathy (HR 2.56, 95% CI 1.16–5.67, P = 0.02) and increased serum creatinine (HR 3.41, 95% CI 1.14–10.27, P = 0.03) were found to be the independent predictive risk factors for mid-term mortality in MV surgery after prior cardiac surgery. Cox regression analyses are depicted in Table 3. Of note, goodness-of-fit for all included variables indicated proportionality (P > 0.05).

Propensity score matching

To correct for the differences in baseline characteristics, propensity score matching was performed. Age, gender, pulmonary artery pressure, logistic EuroSCORE, and chronic obstructive pulmonary disease were used as covariates for the propensity score matching model. Eighty pairs were matched in a 1:1 ratio. After matching, a residual imbalance remained for diabetes only, which was not considered clinically relevant as diabetes did not show to be a risk factor in univariable and multivariable analyses. All other baseline characteristics showed no residual imbalance (standardized mean difference <0.10). Details on propensity score matching can be found in Supplementary Material, S3.

Comparison matched cohort

Baseline characteristics after propensity matching are summarized in Supplementary Material, S2. Prior MV intervention was more frequently performed in the MIMVS compared to repeated sternotomy [n = 35 (44%) vs n = 23 (29%), P = 0.04]. The repair rate in patients without previous MV surgery was 25% in the repeated sternotomy group and 29% in the MIMVS group respectively (P = 0.99). As seen in the unmatched population, more concomitant tricuspid valve procedures were performed in the sternotomy group (n = 26, 33% vs n = 10, 13%, P = 0.005). In the matched population, no significant difference in 30-day mortality was observed (1% vs 3%, P = 0.99). A lower incidence in prolonged intubation (>24 hours) and new-onset arrhythmia was observed in the MIMVS group (Table 4). Most importantly, regarding midterm follow-up, no significant differences were found in 5-year survival in the propensity-matched cohorts (MIMVS 92.5% vs repeated sternotomy 90.0, log-rank P = 0.661) (Fig. 1).

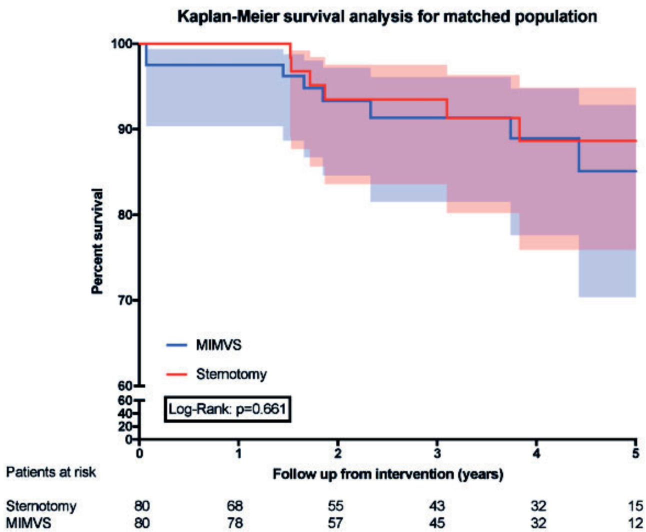

Figure 1. Kaplan–Meier survival analysis of the matched population. MIMVS: minimally invasive mitral valve surgery

DISCUSSION

The current study evaluated the role of a minimally invasive approach for MV surgery after prior cardiac surgery through sternotomy, compared to repeated sternotomy in a multicenter nationwide registry and is the first to establish mid-term followup for this procedure. In addition, as patient data were collected from all centres performing MV surgery in the Netherlands, the current results can be interpreted as contemporary 'real-world data'. Based on these findings, some important conclusions can be drawn.

First, MV surgery, either through resternotomy or MIMVS, is an exceptionally safe reoperative cardiac surgical procedure, as reflected by both unmatched and matched cohorts, with an overall 30-day mortality rate of 3.1%. In retrospective single centre analyses of high-volume expert institutions, mortality rates ranged between 1.2% and 3.0% [11, 12]. However, mortality is reported to range up to 11.1% in the Society of Thoracic Surgeons (STS) database [13], which is based on a multicenter registry, potentially more accurately reflecting real-world results. In accordance with a prior comparison between MIMVS and sternotomy in primary MV surgery of the Dutch national registry, no difference in 30-day mortality regarding surgical approach was observed[14]. Of note, in a previous meta-analysis by our research group, a significant early mortality benefit of the MIMVS approach in a reoperative setting was found[9]. However, the included studies comprised relatively small single-centre experiences and were subjected to potential bias. Furthermore, in the included studies in that meta-analysis, there was a markedly increased use of MVr in the MIMVS group (41% vs 17%).

As MVr is associated with superior short- and long-term outcomes, especially in degenerative MV disease, this might explain the mortality differences in this prior analysis. Interestingly, in the current study, the median preoperative logistic EuroSCORE for the overall cohort (used for the prediction of 30-day mortality) was 12.18%, contrasting the actual reported 30-day mortality rate. However, as EuroSCORE I was introduced in 1999 and the subsequent logarithmic evaluation in 2003, these risk evaluations were based on more historical data, inherently overestimating surgical risk in contemporary patients. For mortality prediction of patients undergoing MV surgery, EuroSCORE II proved superior discriminatory ability compared to both STS score and EuroSCORE I, in a recent analysis[15]. Still, in patients with degenerative mitral regurgitation (MR) operated in a high-volume centre with a high level of expertise in MVr, EuroSCORE II also significantly overestimated actual 30-day mortality[16]. Moreover, in MIMVS, EuroSCORE II overpredicted mortality, potentially limiting its value in this specific patient group[17], undergoing MVr through a minimally invasive approach, especially in a reoperative setting.

In terms of morbidity and complication rate, a low incidence of major postoperative complications for both repeated sternotomy as MIMVS was observed. As known from other large registries and a recent analysis of primary MV surgery[14], MV surgery through a minimally invasive approach is associated with a lower incidence of new-onset postoperative arrythmia compared to sternotomy. This finding is confirmed in the current analysis of patients undergoing reoperative procedures and is potentially explained by less need of adhesiolysis, less cardiac manipulation and a subsequent reduction in inflammation[18]. In addition, in the current analysis, the incidence of prolonged intubation (>24 h) was significantly increased in the matched sternotomy group compared to MIMVS, which might be related to preservation of pulmonary function due to sternal sparing in MIMVS patients. However, these findings have to be appreciated with care, because these parameters are susceptible to various confounding factors.

In the majority of patients referred for MV surgery after prior cardiac surgery, MVR was performed, with an equal distribution of mechanical and biological valve prostheses. The repair rate, when specified for patients without prior MV intervention, is considerably lower (33.3%) compared to the repair rate in primary MV surgery. In a previous analysis of patients undergoing primary MV surgery, repair rate for all-comers approached through sternotomy was 80.0%, while repair rate was 75.9% for MIMVS patients[14]. In contrast to the prior findings in primary MV surgery, we did not observe a difference in surgical approach in terms of repair rate in patients undergoing MV surgery after prior cardiac surgery through sternotomy.

Unfortunately, the current study design, based on predefined parameters of the NHR, did not allow for evaluation of aetiology of MV disease. Subsequently, the proportion of patients with mitral stenosis, ischaemic MR or degenerative MR remains unknown, complicating the correct interpretation of the reported repair rate. In a 2018 analysis of the STS database for patients undergoing MV surgery after prior cardiac surgery, Mehaffey et al. [13] found a significantly higher incidence of mitral stenosis as surgical indication in redo cases compared to primary surgery (36% vs 10%, $P < 0.001$). Although they were also not able to differentiate between MR aetiology, they reported an overall repair rate of 12% in a cohort of 1096 all comers, which is markedly lower compared to the current study findings.

As MV surgery after prior cardiac surgery is increasingly performed[1], mostly due to the ageing population, it is more important than ever to evaluate short- and longer-term results of these different surgical approaches. As an alternative strategy, transcatheter mitral procedures have emerged rapidly, following the successful evolution of transcatheter aortic valve implantation. As MV pathology is more diverse than aortic valve disease, a plethora of devices exist which have the potential to address all different forms of MR. As such, different techniques can be used to perform transcatheter MVr, by chordal replacement or annuloplasty, or MVR in specific cases. Especially transcatheter MV replacement (TMVR) is believed to play an important role in the near future, enabling minimally invasive correction of ischaemic MR or valve-in-valve implantation in failed bioprostheses[19]. Still, both transcatheter MVr and TMVR are currently only applicable in specific subsets of MV patients and require specific conditions related to MV anatomy and left ventricular geometry[20]. Of note, especially longterm outcomes and durability of TMVR and repair are yet to be determined. Therefore, although promising, the exact role and value of transcatheter techniques in the mitral position remains to be defined. When considering such an approach, one most weigh these outcomes to the excellent short- and mid-term results of reoperative surgery, either by MIMVS or sternotomy, as presented in the current study. In that light, patients with new-onset or recurrent MV disease after a previous cardiac surgical procedure through sternotomy, warrant a personalized approach[21], based on extensive preoperative imaging, and should be evaluated in a dedicated MV heart team, incorporating surgeons, interventionalists and imaging cardiologists[22].

Limitations.

The current study has several limitations mostly due the character of the database used. The NHR database was initially designed for quality evaluation (value-based healthcare) rather than for research purposes. Therefore, the retrospective review has an inherent bias, due to selection of patient, patient lost to follow-up and missing data. Of note, these missing data only comprise non-mandatory variables, such as surgical times. For the mandatory variables, data completion was exceptionally high (100%). Some important characteristics were not included, such as information on MV disease characteristics as aetiology, complexity, gradation, and reason for failed repair during first procedures in patients with prior MVr. In addition, no detailed analyses could be performed regarding surgical access (direct vision vs endoscopic), mode of arterial cannulation (femoral, axillary, or direct aortic cannulation) and cardiac preservation (i.e., cooling, cardioplegia). Unfortunately, the database has no information regarding mode of anaesthesia and the use of pain regiment (i.e., intercostal block, erector spinae block), either. Of note, as the database is anonymous, data cannot be traced back to individual centres and surgeons, impairing evaluation of a potential volume-outcome effect. Furthermore, the database includes all surgical procedures performed by 16 cardiothoracic centres in the Netherlands. However, not all centres perform MV surgery after prior cardiac surgery through a minimally invasive approach, therefore the data regarding a minimally invasive approach was only reported by centres with substantial expertise. In line with this, the MIMVS cohort was relatively small, increasing the risk of type 2 error. Then, perhaps most importantly, an analysis of MIMVS versus sternotomy patients is prone to selection bias, as it is possible that patient with a more favourable profile were selected for MIMVS. In an effort to correct for these issues, all consecutive patients undergoing MV surgery after prior cardiac surgery were included and matched using propensity score matching, based on the recommendations by experts in our field[10]. Although this is the least biased method to perform such analyses—matching for known confounders—only randomization can correct for unknown confounders, and results should be interpreted with caution. Finally, as data were collected starting from 2013, simultaneously with the introduction of EuroSCORE II, risk evaluation was evaluated by EuroSCORE I (log), overestimating surgical risk.

CONCLUSION

The current multicentre nationwide study showed excellent outcomes for MV surgery after prior cardiac surgery in the Netherlands, and MIMVS and resternotomy appeared to be equally efficacious. MIMVS is associated with a lower incidence of new onset arrythmia and prolonged intubation. These excellent short- and mid-term results of MV surgery after prior cardiac surgery, regardless of the approach, should be taken into consideration when evaluating transcatheter interventions. Further investigation is necessary to develop contemporary risk score models for MV surgery after prior cardiac surgery.

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APPENDIX 1

Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration

Dr.	S	Bramer	Amphia
Dr.	WJP	van Boven	Amsterdam UMC, locatie AMC
Dr.	ABA	Vonk	Amsterdam UMC, locatie VUmc
Drs.	BMJA	Koene	Catharina Ziekenhuis
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Dr.	G.J.F.	Hoohenkerk	HagaZiekenhuis
Dr.	A.L.P.	Markou	Isala
Drs.	A. de	Weger	Leids Universitair Medisch Centrum
Dr.	P	Segers	Maastricht UMC+
Drs.	F	Porta	Medisch Centrum Leeuwarden
Dr.	R.G.H.	Speekenbrink	Medisch Spectrum Twente
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Drs.	W.W.L.	Li	Radboudumc
Drs.	EJ	Daeter	St. Antonius Ziekenhuis
Dr.	NP	van der Kaaij	UMC Utrecht
Dr.	Y.	Douglas	Universitair Medisch Centrum Groningen

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Supplementary material (S1). Postoperative complications in the unmatched cohort

	Total N=290	Resternotomy N=205	MIMVS N=85	P-value
30-day mortality, n (%)	9 (3.1)	7 (3.4)	2 (2)	0.99
Hospital stay in days, median [IQR]	7.0 [5.0 - 13.0]	7.0 [5.0 - 13.0]	7 .0 [5.0 - 11.5]	0.98
Perioperative myocardial infarction, n (%)	4 (1.4)	2 (1.0)	2 (2)	0.58
Pneumonia, n (%)	19 (6.6)	16 (7.8)	3 (4)	0.30
Urinary tract infection, n (%)	6 (2.1)	6 (2.9)	0 (0)	0.19
Reintubation due to respiratory insufficiency, n (%)	4 (1.4)	4 (2.0)	0 (0)	0.33
Prolonged intubation (>24 hours), n (%)	14 (4.8)	14 (6.8)	0 (0)	**0.01**
Readmission to ICU, n (%)	8 (2.8)	5 (2.4)	3 (4)	0.70
Stroke, n (%)	6 (2.1)	5 (2.4)	1 (1)	0.68
Stroke without neurological defecit, n (%)	2 (0.7)	2 (1.0)	0 (0)	0.99
Stroke with neurological defecit, n (%)	4 (1.4)	3 (1.5)	1 (1)	0.99
Kidney failure, n (%)	14 (4.8)	11 (5.4)	3 (4)	0.76
Gastro-intestinal complications, n (%)	2 (0.7)	2 (1.0)	0 (0)	0.99
Vasculair complications, n (%)	3 (1.0)	3 (1.5)	0 (0)	0.56
New-onset arrythmia, n (%)	97 (33.4)	79 (38.5)	18 (21)	**0.004**
Mediastinitis, n (%)	1 (0.3)	1 (0.5)	0 (0)	0.99
Reexploration (within 30 days), n (%)	22 (7.6)	14 (6.8)	8 (9)	0.45

ICU: intensive care unit, IQR: interquartile range. Definitions of postoperative complications are summarized in Supplementary materials

Supplementary material (S2). Baseline characteristics in the matched population

	Resternotomy N=80	**MIMVS N=80**
Age, mean (±SD)	66.7 ± 10.7	66.2 ± 11.2
Age, median [IQR]	69.5 [61.0 -75.8]	69.0 [60.3 - 74.0]
Male sex, n (%)	51 (64)	52 (65)
Diabetes, n (%)	14 (18)	7 (9)
Chronic Lung Disease, n (%)	9 (11)	8 (10)
Extracardiac arteriopathy, n (%)	8 (10)	7 (9)
Recent myocardial infarction, n (%)	1 (1)	1 (1)
Active endocarditis, n (%)	3 (4)	1 (1)
Serum creatinine (>200um/L)	3 (4)	2 (3)
Prior cardiac procedures#		
Prior CABG, n (%)	27 (34)	38 (48)
Prior mitral valve intervention	23 (29)	35 (44)
LVEF, median [IQR]	55 [40 - 55]	55 [40 - 55]
Good, n (%)	46 (58)	49 (61)
Moderate, n (%)	33(41)	29 (36)
Poor, n (%)	1 (1)	2 (3)
Very poor, n (%)	-	-
PA pressure, median [IQR]	25 [25 - 25]	25 [25 - 25]
Normal, n (%)	61 (77)	67 (84)
Moderate increased, n (%)	15 (19)	8 (10)
Severe increased, n (%)	4 (5)	5 (6)
EuroSCORE I, median [IQR]	12.29 [7.65 - 17.36]	12.38 [5.96 -17.89]
#patients could have both		

CABG: Coronary Artery Bypass Grafting, LVEF: Left ventricular ejection fraction, LV: left ventriclar, PA: pulmonary artery, MIMVS: miminally invasive mitral valve surgery, IQR: interquartile range

Supplementary material (S3). Pre- and post-matching Standard Mean Difference

	Pre-matching Standard Mean Difference	Post-matching Standard Mean Difference
Age	0,413	-0,040
Gender	0,314	0,026
Pulmonary artery pressure	-0,252	0,035
Left Ventricular function	-0,118	-0,089
Chronic Lung Disease	-0,099	-0,040
Extracardiac arteriopathy	-0,108	-0,045
Recent myocardial infarction	-0,071	0,000
Serum creatinine	-0,070	-0,082
Diabetes	-0,284	-0,316
EuroSCORE I	-0,305	-0,054

Supplementary materials (S4). Detailed information prior surgery

Procedures	Sternotomy (n=205)	MIMVS (n=85)
Isolated CABG (%)	36 (18%)	14 (17%)
CABG with concomitant surgery (%)	38 (19%)	27 (32%)
Isolated AV surgery (%)	3 (2%)	6 (7%)
Isolated MV surgery (%)	12 (6%)	9 (11%)
Isolated aortic surgery (%)	7 (3%)	2 (2%)
Aortic surgery with concomitant valvular surgery (%)	1 (1%)	9 (11%)
Double valve surgery (%)	14 (7%)	6 (7%)
Triple valve surgery (%)	1 (1%)	0
Other/non-specified (%)	93 (45%)	12 (14%)

Supplementary material (S5). Definitions of postoperative complications

Perioperative myocardial infarction

Increase and/or decrease in one or more cardiac biomarkers (preferably troponin) by at least one value above the 99th percentile of the upper limit where at least one of the following symptoms is present:

- Symptoms consistent with ischemia (chest pain; nausea/vomiting/perspiration; shortness of breath due to left ventricular failure; dizziness/lightheadedness/syncope), and/or
- New significant ST-segment or T-wave abnormalities or bundle branch block, and/or
- Develop pathological Q waves on the electrocardiogram, and/or
- Imaging new loss of viable myocardial tissue or new wall movement disorders, and/or
- Identification of intracoronary thrombus at angiography or autopsy.

Pneumonia

Lung infection/pneumonia with positive sputum cultures.

Urinary tract infection

Infection with positive urine culture.

Reintubation due to respiratory insufficiency

Respiratory failure requiring reintubation.

Prolonged intubation (>24 hours)

Ventilation for more than 24 hours.

Readmission to ICU

Readmission to the Intensive Care Unit (ICU) or Post Anesthesia Care Unit (PACU) after initial discharge from the IC/PACU. This does not include a stay in the Medium Care (MC).

Stroke

The combined endpoint of stroke without neurological deficit and stroke with neurological deficit

Stroke without neurological deficit

A neurologist has determined that a central neurological deficit (CVA) during the postoperative period has occurred, but with no residual injury at discharge.
This also concerns a Transient Ischemic Attack (TIA)

Stroke with neurological deficit

A neurologist has determined that a postoperative stroke during the hospitalization of the current intervention has occurred (excluding TIA).
CVA = permanent neurological dysfunction diagnosed by a neurologist as due to focal ischemia of the brain, spinal cord, or retina, caused by an acute infarction of the neurological tissue due to thrombosis, embolism, systemic hypoperfusion or bleeding.

Kidney failure

Renal failure occurs if one or more of the following STS criteria are met during the postoperative period

- Renal replacement therapy (dialysis, CVVH) which was not initiated preoperatively
- Highest postoperative creatinine value > 177 µmol/L and doubling of the preoperative value (as preoperative value: the value of the creatinine on which the EuroSCORE is calculated).

Gastro-intestinal complications

Bleeding: gastrointestinal bleeding requiring therapy such as transfusion, scope or surgery. Other: intestinal ischemia, acalculous cholecystitis.

Vascular complications

The occurrence of any vascular complications during hospitalization, diagnosis according to the VARC-2 definitions, from the start of the current intervention (including peroperative vascular complications and excluding stroke).

New-onset arrhythmia

All forms of de novo rhythm problems requiring treatment (such as resuscitation in connection with asystole, new onset atrial fibrillation / flutter for which specific intervention (defibrillation, medication) is necessary). Below is not considered: a spontaneously transient period of atrial fibrillation, without any consequence for the patient.

Mediastinitis

Deep sternal wound infection (mediastinitis) within 30 days. Includes muscle, sternum, mediastinum and is positive if one or more of the following criteria is present:

- Surgical drainage / sternum refixation in deep sternum wound infection
- Positive wound cultures.
- AB therapy due to the sternum wound.

This includes a deep sternal wound infection that occurred after the patient was discharged from that hospital.

Reexploration (within 30 days)

Rethoracotomy within 30 days due to a complication of the current intervention. This also includes rethoracotomies performed after the patient has been discharged. This concerns the first rethoracotomy after the initial closing of the thorax. This applies to all causes, with the exception of opening the sternum in due to mediastinitis or refixation of the sternum.

Chapter 11

Does Concomitant Tricuspid Valve Surgery Increase the Risks of Minimally Invasive Mitral Valve Surgery? A Multicentre Comparison Based on Data from The Netherlands Heart Registration.

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on behalf of the Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration‡

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ABSTRACT

Objectives

Mitral valve (MV) disease is often accompanied by tricuspid valve (TV) disease. The indication for concomitant TV surgery during primary MV surgery is expected to increase, especially through a minimally invasive surgical (MIS) approach. The aim of the current study is to investigate the safety of the addition of TV surgery to MV surgery in MIMVS in a nationwide registry.

Methods

Patients undergoing atrioventricular valve surgery through sternotomy or MIS between 2013 and 2018 were included. Patients undergoing MV surgery only through sternotomy or MIS were used as comparison. Primary outcomes were short-term morbidity and mortality and long-term survival. Propensity score matching was used to correct for potential confounders.

Results

The whole cohort consisted of 2698 patients. A total of 558 patients had atrioventricular double valve surgery through sternotomy and 86 through MIS. As a comparison, 1365 patients underwent MV surgery through sternotomy and 689 patients through MIS. No differences in 30- and 120-day mortality were observed between the groups, both unmatched and matched. 5-year survival did not differ for double atrioventricular valve surgery through either sternotomy or MIS in the matched population (90.1% vs 95.3%, Log-Rank p=0.12). A higher incidence of re-exploration for bleeding (n=12 (15.2%) vs n=3 (3.8%), P=0.02) and new onset arrhythmia (n=35 (44.3%) vs. n=13 (16.5%), P<0.001) was observed in double valve surgery through MIS. Median length of hospital stay (LOHS) was longer in the minimally invasive double valve group (9 days [6 - 13]) compared to sternotomy (7 days [6-11]; P=0.04).

Conclusion

No differences in short-term mortality and 5-year survival was observed when tricuspid valve was added to MV surgery in MIS or sternotomy. The addition of tricuspid valve surgery is associated with higher incidence of re-exploration for bleeding, new onset arrhythmia. A longer LOHS was observed for MIS compared to sternotomy.

INTRODUCTION

Mitral valve (MV) regurgitation is the second most common valvular heart disease in Western world.[1] Although mitral stenosis (MS) and mitral regurgitation (MR) are distinct mitral pathologies, their effect on left atrial pressure, pulmonary hypertension and subsequent right ventricular (RV) afterload are equitable.[2] As such, MV pathology significantly affects the RV and its accompanying structures, amongst others the tricuspid valve (TV). Secondary basal RV dilatation often results in TV leaflet tethering, TV annular dilatation, leaflet malcoaptation and in many cases, secondary tricuspid regurgitation (TR). [3] Interestingly, in 62.5% of patients diagnosed with significant TR, its actual cause was perceived to be the left-sided valve disease.[4] Due to this inseparable link between the atrioventricular valves, it is imperative to adequately evaluate the anatomy and function of the TV, when surgery for MV disease is indicated. As the prevalence of MV disease and MV surgery is increasing[5], this also applies to the presence or prevention of secondary TR. Indeed, current guidelines do not only recommend concomitant TV surgery when secondary severe TR is present, but also in moderate TR accompanied by TV dilatation (> 40mm).[6,7] Moreover, new evidence – not yet incorporated in guidelines - even suggests to perform concomitant TV repair (TVr) in patients with mild TR and significant TV dilatation[8], as many patients with TV dilatation eventually progress to severe TR and subsequent RV failure, irrespective of durable MV surgery.

Based on these developments, the indication for concomitant TV surgery during primary MV surgery is expected to increase. For isolated MV surgery, minimally invasive mitral valve surgery (MIMVS) has proven to be a safe and effective alternative to sternotomy, in terms of mortality, complication rate and efficacy.[9] However, data is scarce on the outcomes of concomitant TV surgery during MIMVS, and surgeons may be apprehended to perform concomitant TV surgery during MIMVS due to the associated increased cardiopulmonary bypass (CPB)- and aortic clamping times.[10,11] Therefore, the current study aims to investigate the outcomes of the addition of TV surgery to MV surgery performed through sternotomy and through a minimally invasive surgical (MIS) approach, using a nationwide multi-centre registry.

PATIENT AND METHODS

Study design

The current retrospective multicentre cohort included patients between January 2013 and December 2018 from 16 cardiothoracic centers in the Netherlands. In order to evaluate the outcomes of the addition of TV surgery to MV surgery performed through sternotomy and through MIS, two separate questions were formulated:

- *Does the addition of concomitant TV surgery add additional risk of mortality to MIMVS (safety)?*
- *Are there differences in short- and mid-term outcomes between double atrioventricular valve surgery performed through sternotomy or MIS (safety and efficacy)?*

Therefore, the study population was divided in four subgroups, namely

- (1) MV surgery through sternotomy; Sternotomy MV (SM)
- (2) MV + TV through sternotomy; Sternotomy DV (SDV)
- (3) MV surgery through anterolateral mini thoracotomy: MIMVS
- (4) MV + TV surgery through anterolateral mini thoracotomy; MIDVS.

Source of study data

The data of the current study are retrieved form the nationwide mandatory prospective database of the Netherlands Heart Registration (Nederlandse Hart Registratie, NHR). Results on primary MV and reoperative MV surgery from this nationwide registry were previously reported by our research group[12]. All data are anonymized for both patients, surgeons, and centres. All mandatory variables for the NHR registry were complete. However, two non-mandatory variables had a relatively high proportion of missing data: cardiopulmonary bypass-time and aortic cross clamp time Given the higher levels of missing data for these variables, which clearly exceed >10% and most likely had a non-random distribution, it was inappropriate to apply a multiple imputation method, impairing analysis of these surgical times.

Inclusion

Adult patients operated for mitral valve surgery and patients with double atrioventricular valve surgery were included. Mitral valve surgery was defined as either isolated MV repair (MVr) or isolated replacement (MVR) or MVr/MVR with rhythm surgery (pulmonary vein isolation/MAZE procedure) and/or atrial septal closure. Double atrioventricular valve surgery was defined as MV surgery with either tricuspid valve repair (TVr) as tricuspid valve replacement (TVR) with or without rhythm surgery (pulmonary vein isolation/MAZE procedure) and/or atrial septal closure. Patients undergoing other concomitant interventions were excluded. Minimally invasive surgery (MIS) was defined as right-sided anterolateral thoracotomy with peripheral cannulation, avoiding (re) sternotomy. Robotic mitral valve surgery were excluded.

Outcomes

Short-term outcomes, defined as early mortality (30-day mortality, 120-day mortality) and postoperative complications and duration of hospital stay, were retrieved. Definitions regarding postoperative complications are presented in the Appendix. Mid-term outcomes were defined as mid-term survival at 5 years. Survival data were derived from the municipal administration records and was completed for all patients. Survival follow-up was completed through December 1st 2020.

Statistical analysis

Normality of the continuous variables was tested by visual inspection of the histograms and the Shapiro–Wilk test. Continuous data are presented as mean ± standard deviation or as median with [interquartile range] in the presence of skewness. Categorical data are expressed as frequencies and percentages and were compared using the χ^2 test and Fisher's Exact test when the minimum count was not met. Continuous variables were compared using the t-test in case of normality and the Mann-Whitney U-test in case of skewed data. Kaplan-Meier survival curves were used to demonstrate mid-term survival and the Log-Rank test was applied to assess differences.

Propensity-score matching analyses were performed to compare minimally invasive double atrioventricular valve surgery to minimally invasive mitral valve surgery and double atrioventricular valve surgery through sternotomy. Propensity scores were estimated using covariates identified at baseline differences. Propensity scores were matched using nearest neighbour matching in a 1:1 ratio, replacement was not allowed, with a 0.01 calliper. Baseline characteristics were presented before and after propensity score matching. Standardized mean difference (SMD) were used to compare the difference in means in units of the pooled standard deviation. A value higher than 0.10 was considered an index of residual imbalance.

All reported p-values were 2-sided and were considered statistically significant when $p<0.05$. Statistical analyses were performed using SPSS software (V28, IBM, Armonk, New York, USA) and R Statistics (the R Foundation, Vienna, Austria).

DATA AVAILABILITY STATEMENT

The Netherlands Heart Registration provided the data underlying this article by permission of the participating hospitals. Data will be shared upon reasonable request to the corresponding author with the permission of the Netherlands Heart Registration.

ETHICAL STATEMENT

No individual centre institutional review board approval was necessary for this retrospective study. This study is in line with the institution's ethical policies and standards.

RESULTS

Minimally invasive double valve surgery compared to minimally invasive single valve surgery

Patient referred for MIDVS were older (73 [67 - 77] vs. 64 [56 - 72]; P<0.001) and less frequently male (n=34 (39.5%) vs n=415 (60.2%); P<0.001) compared to MIMVS (Table 1). A higher incidence of diabetes (n=9 (10.5) vs. n=26 (3.8); P=0.01) was observed in the MIDVS group. Overall, the logistic EuroSCORE was significantly higher in the MIDVS group (5.5 [4.2 - 7.7] vs 2.9 [1.8 - 5.5]; P<0.001). In the MIMVS group more MVr was performed (n=511 (74.2) vs n=54 (62.8); P=0.03) resulting in a higher repair rate (77.4%

Table 1. Baseline characteristics of all unmatched subgroups

	Sternotomy		Minimally invasive		P-value		
	MV	MV + TV	MV	MV + TV	SMV vs SDV	MIMVS vs MIDVS	SDV vs MIDVS
	N=1365	N=558	N=689	N=86			
Age, median [IQR]	64 [55 - 72]	70 [62 - 75]	64 [56 - 72]	73 [67 - 77]	**<0.001**	**<0.001**	**<0.001**
Male sex, n(%)	792 (58.0)	281 (50.4)	415 (60.2)	34 (39.5)	**0.002**	**<0.001**	0.06
Diabetes, n(%)	122 (8.9)	46 (8.2)	26 (3.8)	9 (10.5)	0.63	**0.01**	0.49
Chronic Lung Disease, n(%)	134 (9.8)	74 (13.3)	30 (4.4)	8 (9.3)	**0.03**	0.06	0.31
Extracardiac arteriopathy, n(%)	46 (3.4)	26 (4.7)	12 (1.7)	1 (1.2)	0.18	0.99	0.24
Recent myocardial infarction, n(%)	7 (0.5)	9 (1.6)	3 (0.4)	0 (0)	**0.02**	0.99	0.62
Active endocarditis, n(%)	34 (2.5)	0 (0)	2 (0.3)	0 (0)	**<0.001**	0.99	-
Serum creatinine (>200um/L)	15 (1.1)	11 (2.0)	2 (0.3)	0 (0)	0.13	0.99	0.38
LVEF, median [IQR]	55 [50 - 60]	55 [40 - 55]	55 [55 - 55]	55 [50 -55]	**<0.001**	0.65	**0.004**
Good, n(%)	978 (71.6)	298 (53.4)	586 (85.1)	64 (74.4)	**<0.001**	**0.01**	**<0.001**
Moderate, n(%)	375 (27.5)	239 (42.8)	91 (13.2)	23 (24.4)	**<0.001**	**0.01**	**0.001**
Poor, n(%)	12 (0.9)	20 (3.6)	12 (1.7)	1 (1.2)	**<0.001**	0.99	0.34
Very poor, n(%)	0 (0)	1 (0.2)	0 (0)	0 (0)	0.29	-	0.99
PA pressure, median [IQR]	25 [25 - 25]	25 [25 - 40]	25 [25 - 25]	25 [25 - 25]	**<0.001**	0.07	**0.005**
Normal, n(%)	1145 (83.9)	374 (67.0)	607 (88.1)	69 (80.2)	**<0.001**	0.04	**0.01**
Moderately increased, n(%)	157 (11.5)	122 (21.9)	48 (7.0)	10 (11.6)	**<0.001**	0.12	**0.03**
Severely increased, n(%)	64 (4.6)	62 (11.1)	34 (4.9)	7 (8.1)	**<0.001**	0.20	0.41
Prior cardiac surgery, n(%)	93 (6.8)	65 (11.6)	44 (6.4)	6 (7.0)	**<0.001**	0.82	0.20
Logistic EuroSCORE, median [IQR]	3.4 [2.1 – 6.0]	5.3 [3.2 - 8.8]	2.9 [1.8 - 5.5]	5.5 [4.2 - 7.7]	**<0.001**	**<0.001**	0.49

MV = mitral Valve, TV= tricuspid valve, SMV= sternotomy mitral valve, SDV= sternotomy double valve, MIMVS= minimally invasive mitral valve surgery, MIDVS= minimally invasive double valve surgery, PA= pulmonary artery, LVEF= left ventricular ejection fraction, LV= left ventricular, SD= standard deviation, IQR=inter quartile range vs 63.7%; P=0.01) (Table 2). No differences in 30-day mortality (n=0 (0) vs n=5 (0.7); P=0.99) and 120-day mortality (n=1 (1.2) vs n=7 (1.0); P=0.99) were observed (Supplementary Data; Table 1). A longer median hospital stay (9 days [6 - 13] vs 6 days [5- 8]; P<0.001), a higher incidence of new onset arrythmia (n=39 (45.3) vs n=134 (19.4); P<0.001) and higher need for re-exploration of bleeding (n=12 (14.0) vs n=30 (4.4); P=0.001) was observed for MIDVS in the unmatched population compared to MIMVS (see Supplementary).

Propensity score matching was performed for covariates that differed at baseline, i.e., age, gender, and diabetes. A total of 79 pairs were matched in a 1:1 ratio. After matching, the 2 groups were comparable for all confounders (standardized mean difference <0.10); Table 3; supplementary Figure 1).

In the matched population no significant difference in 30-day and 120-day mortality were found. (Table 4) The higher incidence of new onset arrhythmia and higher need for re-exploration of bleeding for MIDVS persisted after matching.

Minimally invasive double valve surgery compared to sternotomy double valve surgery
Patient referred for MIDVS were older (73 [67 - 77] vs. 70 [62 - 75]; P<0.001) compared to patients undergoing SDV (Table 1). A higher incidence of moderate LV function and moderately increased pulmonary artery pressures were observed in sternotomy patients. No significant difference in logistic EuroSCORE were observed (SDV 5.3 [3.2 - 8.8] vs MIDVS 5.5 [4.2 - 7.7]; P=0.49). In the SDV group more MVr was performed (n=425 (76.2) vs n=54 (62.8); P=0.01) resulting in a higher repair rate (81.3% vs 63.7%; P<0.001) (Table 2). No difference in 30-day mortality (n=0 (0) vs n=13 (2.3); P=0.23) and 120-day mortality (n=20 (3.5) vs n=1 (1.2); P=0.34) were observed (Supplementary data; Table 1). Furthermore, no difference in postoperative complications, besides a higher incidence of re-exploration for bleeding (12 (14.0) vs. n= 38 (6.8), P=0.02) was observed in the MIDVS group (Supplementary data; Table 1). Five-year survival rate was 95.3% in the MIDVS group, compared to 90.1% in the SDV group (Log-Rank P=0.12). Kaplan-Meier curves are shown in **Figure 1A**.

Propensity score matching was performed with parameters that differed at baseline, i.e., age, gender, left ventricular ejection fraction and pulmonary artery pressure. A total of 75 pairs were matched in a 1:1 ratio. After matching, the 2 groups were comparable for all confounders (standardized mean difference <0.10); Table 3 and supplementary Figure 2).

After matching no difference in 30-day and 120-day mortality were found and the postoperative complication rates were similar between the groups. The median length of hospital stay was longer in the MIDVS group (9 days [6 - 13] vs 7 days [6 - 11]; P=0.04) in the SDV group. (Table 4) Kaplan Meier analyses in the matched population showed no significant difference between MIDVS and SDV (94.7% vs 93.3%, Log-Rank P=0.62 **Figure 1B**).

Table 2. Procedural characteristics of all unmatched subgroups

	Sternotomy		Minimally invasive		P-value		
	MV	**MV + TV**	**MV**	**MV + TV**	**SMV vs SDV**	**MIMVS vs MIDVS**	**SDV vs MIDVS**
	N=1365	**N=558**	**N=689**	**N=86**			
Type of procedure							
MV repair, n(%)	1046 (76.6)	425 (76.2)	511 (74.2)	54 (62.8)	0.83	**0.03**	**0.01**
MV replacement, n(%)	319 (23.4)	133 (23.8)	178 (25.8)	32 (37.2)	0.83	**0.03**	**0.01**
TV reconstruction, n(%)	-	554 (99.3)	-	84 (97.7)	-	-	0.19
TV replacement, n(%)	-	4 (0.7)	-	2 (2.3)	-	-	0.19
Atrial septal closure, n(%)	37 (2.7)	14 (2.5)	20 (2.9)	5 (5.8)	0.80	0.13	0.16
Rhythm surgery, n(%)	216 (15.8)	170 (30.5)	83 (12.0)	20 (23.3)	<0.001	**0.01**	0.17
Type of prothesis MV							
Mechanical, n(%)	161 (50.6)	71 (53.4)	76 (42.7)	7 (21.9)	0.59	**0.03**	**0.001**
Biological, n(%)	154 (48.4)	61 (45.9)	102 (57.3)	25 (78.1)	0.62	**0.03**	**0.001**
Unknown, n(%)	3 (0.9)	1 (0.8)	0 (0)	0 (0)	0.99	-	0.99
Repair Rate							
Primary surgery, n(%)	(1011/1272) 79.5%	(401/493) 81.3%	(499/645) 77.4%	(51/80) 63.7%	0.38	**0.01**	**<0.001**
Redo surgery, n(%)	(35/93) 37.6%	(24/65) 36.9%	(12/44) 27.3%	(3/6) 50%	0.92	0.35	0.67

MV = mitral Valve, TV= tricuspid valve, SMV= sternotomy mitral valve, SDV= sternotomy double valve, MIMVS= minimally invasive mitral valve surgery, MIDVS= minimally invasive double valve surgery

Table 3. Baseline characteristics of the matched subgroups

	MIDVS N=79	MIMVS N=79	Prematching SMD	Postmatching SMD	MIDVS N=75	SDV N=75	Prematching SMD	Postmatching SMD
(*,#)) Age, median [IQR]	73.0 [67.0 - 76.0]	73.0 [67.0 - 76.0]	-0.71	0.01	73.0 [67.0 - 77.0]	72.0 [67.0 - 77.0]	-0.41	0.05
(*,#) Male sex, n (%)	30 (38.0)	32 (40.5)	-0.42	-0.05	33 (44.0)	37 (49.3)	0.22	0.09
(*) Diabetes, n (%)	2 (2.5)	3 (3.8)	-0.35	0.07	9 (12.0)	8 (10.7)	-0.08	-0.05
Chronic Lung Disease, n (%)	7 (8.9)	7 (8.9)	-0.24	0.00	8 (10.7)	9 (12.0)	0.12	0.04
(#) Extracardiac arteriopathy, n (%)	1 (1.3)	1 (1.3)	0.04	0.00	1 (1.3)	1 (1.3)	0.17	0.00
Active endocarditis, n (%)	0 (0)	0 (0)	0.05	0.00	0 (0)	0 (0)	-	-
Recent myocardial infarction, n (%)	0 (0)	0 (0)	0.07	0.00	0 (0)	1 (1.3)	0.13	0.10
Serum creatinine (>200um/L)	0 (0)	0 (0)	0.05	0.00	0 (0)	1 (1.3)	0.14	0.10
(#) LVEF, median [IQR]	55 [55 - 55]	55 [55 - 55]	0.14	-0.04	55 [48 - 55]	55 [50 - 55]	-0.28	-0.01
Good, n (%)	61 (77.2)	64 (81.0)			53 (70.7)	46 (61.3)		
Moderate, n (%)	17 (21.5)	13 (16.5)			21 (28.0)	27 (36.0)		
Poor, n (%)	1 (1.3)	2 (2.5)			1 (1.3)	2 (2.7)		
(#) PA pressure, median [IQR]	25 [25 - 25]	25 [25 - 25]	-0.28	0.01	25 [25 - 25]	25 [25 - 35]	0.18	0.04
Normal, n (%)	64 (81.0)	63 (79.7)			58 (77.3)	53 (70.7)		
Moderately increased, n (%)	8 (10.1)	9 (11.4)			10 (13.3)	15 (20.0)		
Severely increased, n (%)	7 (8.9)	7 (8.9)			7 (9.3)	7 (9.3)		
Prior cardiac procedures			-0.02	-0.05			0.15	0.00
Prior cardiac surgery, n (%)	5 (6.3)	4 (5.1)			6 (8.0)	6 (8.0)		
Logistic EuroSCORE, median [IQR]	5.2 [4.2 - 7.4]	5.5 [3.2 – 8.0]	-0.61	-0.01	5.4 [4.2 - 7.6]	5.9 [3.8 - 8.6]	0.07	0.02

(*) Matching covariates MIDVS to MIMVS, (#) Matching covariates MIDVS to SDV, MV = mitral Valve, TV= tricuspid valve, SMV= sternotomy mitral valve, SDV= sternotomy double valve, MIMVS= minimally invasive mitral valve surgery, MIDVS= minimally invasive double valve surgery, PA= pulmonary artery, LVEF= left ventricular ejection fraction, LV= left ventricular, SD= standard deviation, IQR=inter quartile range

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Table 4. Postoperative complications of the matched subgroups

	MIDVS N=79	MIMVS N=79	P-value	MIDVS N=75	SDV N=75	P-value
30-day mortality, n(%)	0 (0)	0 (0)	-	0 (0)	1 (1.3)	0.99
120-day mortality, n(%)	1 (1.3)	0 (0)	0.99	1 (1.3)	2 (2.7)	0.71
Hospital stay in days, median [IQR]	8 [5 - 11]	7 [5 - 8]	0.08	9 [6 - 13]	7 [6 - 11]	**0.04**
Perioperative myocardial infarction, n(%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Pneumonia, n(%)	1 (1.3)	3 (3.8)	0.62	1 (1.3)	3 (4.0)	0.62
Urinary tract infection, n(%)	1 (1.3)	0 (0)	0.99	0 (0)	0 (0)	-
Reintubation due to respiratory insufficiency, n(%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Prolonged intubation (>24 hours), n(%)	2 (2.5)	1 (1.3)	0.99	2 (2.7)	1 (1.3)	0.99
Readmission to ICU, n(%)	1 (1.3)	1 (1.3)	0.99	1 (1.3)	1 (1.3)	0.99
Stroke, n(%)	0 (0)	1 (1.3)	0.99	0 (0)	1 (1.3)	0.99
Stroke with neurological deficit, n(%)	0 (0)	1 (1.3)	0.99	0 (0)	1 (1.3)	0.99
Stroke without neurological deficit, n(%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Kidney failure, n(%)	0 (0)	0 (0)	-	1 (1.3)	2 (2.7)	0.99
Gastro-intestinal complications, n(%)	1 (1.3)	0 (0)	0.99	1 (1.3)	0 (0)	0.99
Vascular complications, n(%)	1 (1.3)	0 (0)	0.99	1 (1.3)	0 (0)	0.99
New-onset arrhythmia, n(%)	35 (44.3)	13 (16.5)	**<0.001**	33 (44.0)	27 (36.0)	0.32
Deep sternal wound infection, n(%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Re-exploration (within 30 days), n(%)	12 (15.2)	3 (3.8)	**0.02**	9 (12.0)	5 (6.5)	0.26
Reintervention, n(%)	5 (6.3)	6 (7.6)	0.76	5 (6.7)	3 (4.0)	0.72
Reintervention in primary mitral valve repair, n(%)	5 (9.8)	6 (10.9)	0.85	5 (10.9)	3 (4.9)	0.29

SDV= sternotomy double valve, MIMVS= minimally invasive mitral valve surgery, MIDVS= minimally invasive double valve surger

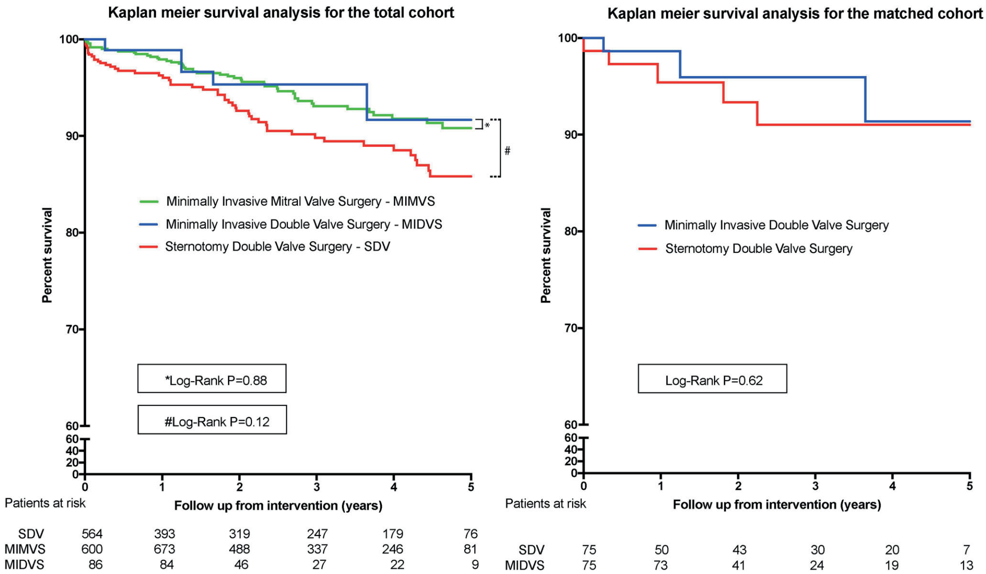

Figure 1. Kaplan–Meier survival analysis for the total cohort and for the matched cohort. MIDVS, minimally invasive double valve surgery; MIMVS, minimally invasive mitral valve surgery; SDV, sternotomy double valve.

DISCUSSION

The current study investigated the safety and efficacy of minimally invasive double atrioventricular valve surgery. As such, the study aim was divided into two research questions: does the addition of TV surgery add risk to a MIMVS procedure? And second, are there differences in outcomes between approaches (i.e., sternotomy or minimally invasive) for double atrioventricular valve surgery? Due to the relatively low incidence of double valve surgery through MIS, a multi-centre nationwide registry was realized, reflecting real-world outcomes. The main findings of the current study are that concomitant TV surgery did not increase the risk of mortality as a concomitant surgical procedure, and that there were no differences in terms of safety and efficacy between MIS and sternotomy for surgical correction of double atrioventricular valve disease, despite a higher incidence of re-exploration for bleeding and new – onset arrhythmias.

Mitral valve disease, right ventricular dysfunction and secondary TR are inseparably related. Although MV disease can be considered the culprit of secondary TR in many cases, the mere surgical resolution of MV disease (either MR or MS), does not necessarily eliminate the risk of future TR progression. Even in cases of mild TR during primary isolated MV surgery, TR is reported to progress to a severe class, also in case of a durable MV repair or replacement.[13] However, outcomes of TR progression vary in literature, and might also be related to the aetiology of initial MR.[14,15] Still, re-operative surgery for severe symptomatic isolated TR carries significant morbidity and mortality rates[16], with a potentially prohibitive surgical risk, resulting in reduced survival of this patient group. Especially the latter observation has lowered the threshold for concomitant TV surgery during primary MV surgery. A recent robust randomized clinical trial by the Cardiothoracic Surgical Trials Network (CTSN), compared concomitant TV repair during the index procedure to isolated MV surgery in patients with degenerative MV disease and moderate TR or mild-to-moderate TR and TA dilatation (>40mm).[17] Although 2-year mortality did not differ between groups, there was a significant difference in the composite endpoint consisting of mortality, reoperation and extensive progression of TR, favouring a concomitant procedure. Of note, the observed difference was mainly driven by a marked reduction in TR progression in the concomitant group. Also, not incorporated in the composite outcome, permanent pacemaker implantation rate was surprisingly high in the concomitant group (14.1% versus 2.5%), which is known to influence progression of heart failure and long-term survival.[18,19] Still, with the expected increase in MV disease and the lowering of the threshold for indication of concomitant TV repair, a significant rise in double atrioventricular valve surgery in the near future is expected. An important - but yet to be elucidated – observation in the current study was a reduction in repair rate in the concomitant MIMVS group (77.4% versus 63.7%). Unfortunately, the NHR database does not include MV disease entity (i.e., MS or MR) and does not differentiate between MR aetiologies, complicating adequate interpretation of repair rate as an outcome. Another important finding was the increased rate of re-explorations in the group undergoing double valve surgery, which could be explained by the additional incision and suture line in the right atrium. Still, derived from the results of the current study, surgeons should not be apprehended by a potentially elevated surgical risk to performed additional TV surgery during the index procedure, as morbidity and mortality rates and 120-day survival were equal in both the unmatched and matched groups.

When an indication for concomitant TV and MV surgery is set by the heart-team, the question arises which approach (i.e., through sternotomy or MIS) is more appropriate in this setting. As the mere addition of TV surgery inherently leads to longer cardiopulmonary bypass (CPB) and aortic cross clamping (ACC) times, this is an issue worth considering, particularly in the case of MIS. Indeed, MIS is perceived to be technically more demanding than valvular surgery performed through sternotomy, resulting in prolonged CPB and ACC times, especially in the early stages of program initiation.[20] Until now, only high-volume expert centres have evaluated their results of minimally invasive double valve surgery compared to sternotomy. These single-centre experiences demonstrated that double valve surgery can be performed as safely through MIS, without differences in operative result or morbidity and mortality rates, despite longer CPB and ACC time.[21] These findings were confirmed in a recent meta-analysis of observational studies.[22] Interestingly, the study by Akin et al. evaluated long-term survival as well, demonstrating no differences in long-term follow-up between both approaches.[21] Still, it remains difficult to extrapolate these findings to real-world practice, as these studies comprised (expert) single-centre experiences. Subsequently, the current study was initiated with data from a nationwide registry, allowing for an adequate multi-centre interpretation of surgical results. We found no differences in terms of short-term mortality and 5-year survival in the unmatched and matched groups. Although there were no differences in terms of complications after matching either, a significant longer duration of hospitalization in the minimally invasive group was observed, in accordance with prior results of this nationwide registry for isolated MV surgery.[9] Whether this remarkable difference is related to the surgical approach or to inter-hospital discharge protocol differences, remains to be elucidated. Based on these findings, a MIS approach is as safe and effective as double valve surgery through sternotomy, confirmed by the excellent 5-year survival rates of 95.3% and 90.1% in the unmatched population and 94.7% vs 93.3% in the matched population, respectively.

Of note, the current findings should not be interpreted as an unambiguous decision for MIS in all patients with an indication for double valve surgery. MIS in general, and with use of peripheral CPB in particular, requires adequate patient selection to, amongst others, evaluate presence of extensive peripheral arterial disease. Subsequently, we advocate for a standardized process of pre-operative planning, specifically minimizing peri-operative risk associated with MIS.

Limitations

Although the multicentre character of the current registry allows for a real-world evaluation of outcomes of atrioventricular double valve surgery, several limitations should be addressed. First, only a modest number of patients undergoing combined MV, and TV surgery were operated through MIS. Also, as patients could not be traced backed to the participating centres, a possible inclusion bias exists as hospital and operator volume remain unclear. Furthermore, although propensity score matching was performed to correct for known confounders, this method cannot balance unknown confounders, potentially leaving some form of selection bias. Finally, given its retrospective nature, the registry was subjected to some missing data, such as CPB and ACC times. Although we could not assess differences in the surgical times, the expected increased CPB and ACC time in the concomitant groups did not result in clinical sequelae, as demonstrated by our data. As the registry does not contain any information on the actual approach of the mitral valve (left atriotomy or transseptal approach) for patients operated through sternotomy, the higher incidence of new onset arrhythmia compared with sternotomy should be interpreted with care.

CONCLUSION

The current multicenter nationwide study presented the outcomes of minimally invasive double atrioventricular valve surgery. No differences in short-term mortality and 5-year survival compared to both minimally mitral valve surgery and double valve surgery through sternotomy were found. A higher incidence of re-exploration for bleeding and postoperative arrhythmia and longer hospital stay was observed in the minimally invasive double valve group compared to minimally invasive single valve surgery. Patient selection remains crucial with the expected increase in double valve surgery.

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APPENDIX 1

Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration

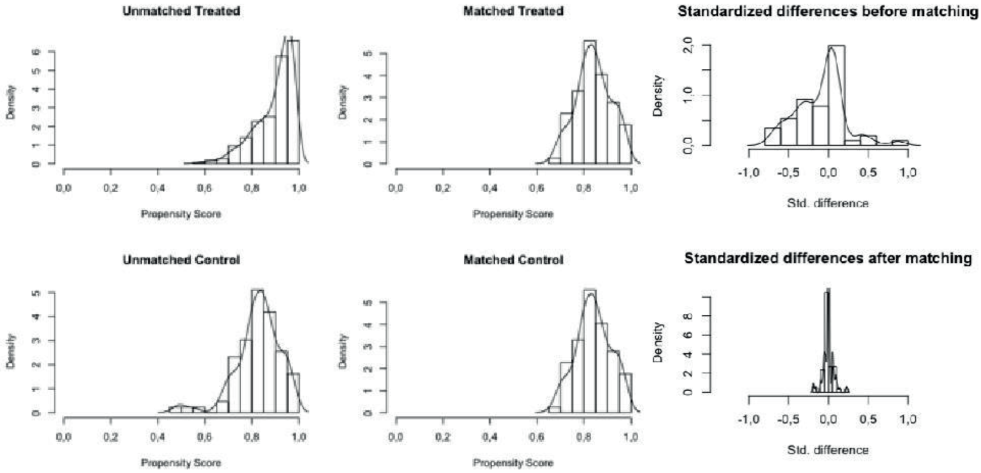
Dr.	S	Bramer	Amphia
Dr.	WJP	van Boven	Amsterdam UMC, locatie AMC
Dr.	ABA	Vonk	Amsterdam UMC, locatie VUmc
Drs.	BMJA	Koene	Catharina Ziekenhuis
Dr.	J.A.	Bekkers	Erasmus MC
Dr.	G.J.F.	Hoohenkerk	HagaZiekenhuis
Dr.	A.L.P.	Markou	Isala
Drs.	A. de	Weger	Leids Universitair Medisch Centrum
Dr.	P	Segers	Maastricht UMC+
Drs.	F	Porta	Medisch Centrum Leeuwarden
Dr.	R.G.H.	Speekenbrink	Medisch Spectrum Twente
Dr.	W	Stooker	OLVG
Drs.	W.W.L	Li	Radboudumc
Drs.	EJ	Daeter	St. Antonius Ziekenhuis
Dr.	NP	van der Kaaij	UMC Utrecht
Dr.	Y.L.	Douglas	Universitair Medisch Centrum Groningen

SUPPLEMENTARY MATERIALS

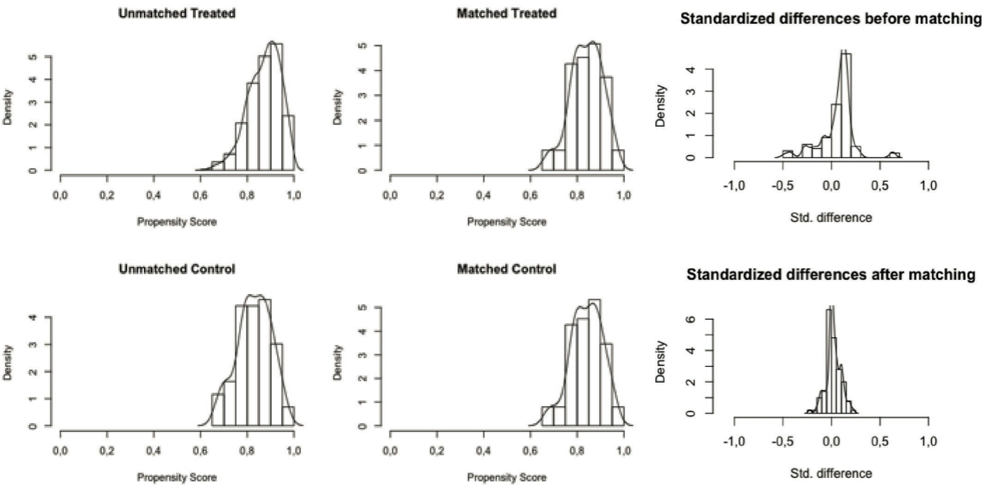
Supplementary table 1. Postoperative complications of all unmatched subgroups

	Sternotomy		MIMVS		P-value		
	MV	MV + TV	MV	MV + TV	SMV vs SDV	MIMVS vs MIDVS	SDV vs MIDVS
	N=1365	N=558	N=689	N=86			
30-day mortality, n (%)	22 (1.6)	13 (2.3)	5 (0.7)	0 (0)	0.29	0.99	0.23
120-day mortality, n (%)	36 (2.6)	20 (3.6)	7 (1.0)	1 (1.2)	0.25	0.99	0.34
Hospital Stay in days, median [IQR]	6 [4 - 8]	8 [6 - 11]	6 [5- 8]	9 [6 - 13]	**<0.001**	**<0.001**	**<0.001**
Perioperative myocardial infarction, n (%)	9 (0.7)	4 (0.7)	5 (0.7)	0 (0)	0.99	0.99	0.99
Pneumonia, n (%)	32 (2.3)	23 (4.1)	15 (2.2)	1 (1.2)	**0.03**	0.99	0.23
Urinary tract infection, n (%)	18 (1.3)	7 (1.3)	9 (1.3)	1 (1.2)	0.91	0.99	0.99
Reintubation due to respiratory insufficiency, n (%)	9 (0.7)	8 (1.4)	3 (0.4)	0 (0)	0.11	0.99	0.61
Prolonged intubation (>24 hours), n (%)	29 (2.1)	19 (3.4)	4 (0.6)	2 (2.3)	0.11	0.14	0.99
Readmission to ICU, n (%)		20 (3.6)	7 (1.0)	1 (1.2)		0.99	0.34
Stroke, n (%)	24 (1.8)	9 (1.6)	4 (0.6)	0 (0)	0.82	0.99	0.62
Stroke with neurological deficit, n (%)	15 (1.1)	4 (0.7)	4 (0.6)	0 (0)	0.44	0.99	0.99
Stroke without neurological deficit, n (%)	9 (0.7)	5 (0.9)	0 (0)	0 (0)	0.56	-	0.99
Kidney failure, n (%)	19 (1.4)	17 (3.0)	3 (0.4)	1 (1.2)	**0.02**	0.38	0.49
Gastro-intestinal complications, n (%)	7 (0.5)	5 (0.9)	3 (0.4)	1 (1.2)	0.35	0.38	0.58
Vasculair complications, n (%)	4 (0.3)	2 (0.4)	0 (0)	1 (1.2)	0.99	0.11	0.35
New-onset arrhythmia, n (%)	437 (32.0)	194 (34.8)	134 (19.4)	39 (45.3)	0.24	**<0.001**	0.06
Deep sternal wound infection, n (%)	0 (0)	3 (0.5)	0 (0)	0 (0)	**0.02**	-	0.99
Re-exploration (within 30 days), n (%)	67 (4.9)	38 (6.8)	30 (4.4)	12 (14.0)	0.10	**0.001**	**0.02**
Reintervention, n (%)	51 (3.7)	23 (4.1)	35 (5.1)	5 (5.8)	0.69	0.80	0.41
Reintervention for patients with primary mitral valve repair, n (%)	42 (4.0)	23 (5.4)	32 (6.3)	5 (9.3)	0.24	0.38	0.23

MV = mitral Valve, TV= tricuspid valve, SMV= sternotomy mitral valve, SDV= sternotomy double valve, MIMVS= minimally invasive mitral valve surgery, MIDVS= minimally invasive double valve surgery



Supplementary Figure 1. Matching output of minimally invasive double valve surgery compared to minimally invasive single valve surgery



Supplementary Figure 2. Matching output of minimally invasive double valve surgery compared to sternotomy double valve surgery

Definitions of postoperative complications

Perioperative myocardial infarction
Increase and/or decrease in one or more cardiac biomarkers (preferably troponin) by at least one value above the 99th percentile of the upper limit where at least one of the following symptoms are present:
Symptoms consistent with ischemia (chest pain; nausea/vomiting/perspiration; shortness of breath due to left ventricular failure; dizziness/lightheadedness/syncope), and/or
New significant ST-segment or T-wave abnormalities or bundle branch block, and/or
Develop pathological Q waves on the electrocardiogram, and/or
Imaging new loss of viable myocardial tissue or new wall movement disorders, and/or
Identification of intracoronary thrombus at angiography or autopsy.

Pneumonia
Lung infection/pneumonia with positive sputum cultures.

Urinary tract infection
Infection with positive urine culture.

Reintubation due to respiratory insufficiency
Respiratory failure requiring reintubation.

Prolonged intubation (>24 hours)
Ventilation for more than 24 hours.
Readmission to ICU
Readmission to the Intensive Care Unit (ICU) or Post Anesthesia Care Unit (PACU) after initial discharge from the IC/PACU. This does not include a stay in the Medium Care (MC).

Stroke
The combined endpoint of stroke without neurological deficit and stroke with neurological deficit

Stroke without neurological deficit
A neurologist has determined that a central neurological deficit (CVA) during the postoperative period has occurred, but with no residual injury at discharge.
This also concerns a Transient Ischemic Attack (TIA)

Stroke with neurological deficit
A neurologist has determined that a postoperative stroke during the hospitalization of the current intervention has occurred (excluding TIA).
CVA = permanent neurological dysfunction diagnosed by a neurologist as

due to focal ischemia of the brain, spinal cord, or retina, caused by
an acute infarction of the neurological tissue due to thrombosis, embolism,
systemic hypoperfusion or bleeding.

Kidney failure

Renal failure occurs if one or more of the following STS criteria are met during the postoperative period

Renal replacement therapy (dialysis, CVVH) which was not initiated preoperatively

Highest postoperative creatinine value > 177 µmol/L and doubling of the preoperative value (as preoperative value: the value of the creatinine on which the EuroSCORE is calculated).

Gastro-intestinal complications

Bleeding: gastrointestinal bleeding requiring therapy such as transfusion,
scope or surgery.

Other: intestinal ischemia, acalculous cholecystitis.

Vascular complications

The occurrence of any vascular complications during hospitalization,
diagnosis according to the VARC-2 definitions, from the start of the current intervention
(Including peroperative vascular complications and excluding stroke).

New-onset arrhythmia

All forms of de novo rhythm problems requiring treatment (such as
resuscitation in connection with asystole, new onset atrial fibrillation / flutter for which
specific intervention (defibrillation, medication) is necessary). Below is not
considered: a spontaneously transient period of atrial fibrillation, without any
consequence for the patient.

Mediastinitis

Deep sternal wound infection (mediastinitis) within 30 days. Includes muscle, sternum,
mediastinum and is positive if one or more of the following criteria is present:

Surgical drainage / sternum refixation in deep sternum wound infection

Positive wound cultures.

AB therapy due to the sternum wound.

This includes a deep sternal wound infection that occurred after the patient
was discharged from that hospital.

Re-exploration (within 30 days)

Rethoracotomy within 30 days due to a complication of the current intervention. This
also includes rethoracotomies performed after the patient has been discharged.

This concerns the first rethoracotomy after the initial closing of the thorax. This applies to all causes, with the exception of opening the sternum in due to mediastinitis or refixation of the sternum.

Chapter 12

Patient-reported outcomes in minimally invasive mitral valve surgery compared to sternotomy based on the multicenter registry of the Netherlands Heart Registration.

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on behalf of the Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration

Submitted

ABSTRACT

Background

The aim of surgical treatment of mitral valve disease is to reverse heart failure and its related symptoms and restore life expectancy and quality of life (QoL). In mitral valve surgery, QoL has not been studied extensively, especially regarding the surgical approach. As such, the current study aimed to evaluate QoL after mitral valve surgery through full sternotomy and a minimally invasive approach (MIMVS).

Methods

The current study was a retrospective analysis of prospectively collected data, using a multicenter nationwide registry in the Netherlands. Quality of life was measured using the 12- and 36-item short form surveys, before surgery and postoperatively at 1 year. Logistic regression analyses were performed to evaluate the independent predictors for loss of QoL.

Results

The current study included 485 patients undergoing mitral valve surgery (full sternotomy: n=276, and MIMVS: n=209). Overall, patients experienced a significant increase in physical component score (56 [42-75] vs 74 [57-88], $p<0.001$) and mental component score at 1-year (63 [52-74] vs 70 [59-86], $p<0.001$). There were no significant differences in QoL increase between the surgical approaches (full sternotomy and MIMVS both $p<0.001$ for physical and mental improvement) at 1 year. Predictors for loss of physical and mental QoL were baseline QoL scores and new onset of arrhythmia.

Conclusion

In this multicenter cohort, mitral valve surgery is associated with significant improvement in physical and mental QoL, regardless of surgical approach. There were no significant differences in QoL improvement between the surgical approaches at 1-year.

INTRODUCTION

Severe mitral valve (MV) disease, comprising both severe mitral stenosis (MS) and regurgitation (MR), is associated with a reduced life expectancy, significant morbidity, and development of symptoms affecting daily life[1,2]. Consequently, the aim of surgical treatment of MV disease is to restore life expectancy, reverse the development of heart failure, resolve symptoms, and improve quality of life (QoL). Although QoL has been evaluated previously in the surgical treatment of MV disease, these studies mainly focused on differences in QoL between mitral valve repair (MVr) and replacement (MVR), trans-catheter procedures and conservative treatment[3], and in some instances, differences in QoL between biological and mechanical prostheses[4]. Indeed, especially MVr is associated with improved QoL compared to MVR[5,6], although conflicting evidence exists[7]. In the case of the implantation of a valve prosthesis, the choice of prosthesis does not seem to influence QoL[4].

Patient-reported outcomes measures (PROM) play an increasingly important role in decision-making, especially in the light of the aging population, increasing incidence of high-risk procedures, and the advent of trans-catheter and minimally invasive techniques. For surgical procedures on the MV, minimally invasive MV surgery (MIMVS) has proven to be a valuable alternative to a full sternotomy (FS) approach, with comparable short-term outcomes[8], and equivalent long-term survival[9,10]. By circumventing FS and its associated drawbacks, MIMVS has the potential advantage – especially in the re-operative setting[11] – of a reduced complication rate, an enhanced recovery and, potentially, an improved QoL. Still, there is only scarce data on patient-reported outcomes, illustrated by one single-center analysis evaluating QoL difference between the FS and MIMVS approaches[12]. Therefore, in the current study, we aim to evaluate QoL following MV surgery in patients undergoing FS or MIMVS using a nationwide registry.

METHODS AND MATERIALS

Source of study data

The Netherlands Heart Registration (NHR) was described in detail before[9,13]. In short, reporting of interventions to the NHR is compulsory, using a variety of mandatory and non-mandatory parameters, including patient characteristics, intervention variables and outcomes.

Inclusion

Although most parameters are mandatory to report, QoL assessment has not been a mandatory parameter to report. Consequently, not all patients in the current registry completed both pre- and postoperative QoL assessment between 2013-2018.

In the current study, all adult patients undergoing elective isolated primary (i.e., non-reoperative) MV surgery with (1) a registered approach (i.e., FS or MIMVS) *and* (2) pre- and postoperative QoL assessment (>50% completed) between 2013-2018 were included. Inherently, this implies only 1-year survivors were included. Isolated MV surgery was defined as truly isolated MV surgery, or MV surgery in combination with tricuspid valve (TV) procedures, ablative surgery for atrial arrhythmia, and/or atrial septal defect (ASD) closure. Patients undergoing robot-assisted procedures were excluded.

Between 2013 and 2018, 5394 patients underwent MV surgery in the Netherlands, of which 2914 had a registered approach (FS or MIMVS). Patients undergoing reoperative surgery were excluded from the current analysis (n=413). Of the 2501 patients undergoing primary surgery with a registered surgical approach, 485 patients completed both pre- and postoperative QoL assessment (exclusion of 2016 non-responders, flowchart in Supplementary Material 2).

Study design

The current study is a retrospective multicenter cohort study of prospectively collected registry data from 11 Dutch cardiothoracic centers, included between 2013-2018.

Quality of life assessment

In the NHR database, both the 12-item and 36-item short form survey (SF-12 and SF-36 respectively) are included, for which the specific questions can be found elsewhere [14, 15]. The SF-36 was developed in the early 1990's, objectively assessing health-related QoL [15]. In the SF, QoL is divided in a physical component score (PCS) and mental component score (MCS). For PCS and MCS, these scores are assessed in subdomains (physical functioning, role physical, bodily pain, and general health, for PCS, and social functioning, role emotional, vitality, and mental health, for MCS).

In a later era, the SF-36 was reduced to a shortened 12-item form (SF-12) incorporating 12 identical questions of the SF-36, assessing the same specific subdomains. Several studies have confirmed that outcomes of both surveys were virtually identical, for cardiac and non-cardiac patients [14, 16]. As such, both surveys can be used interchangeably.

In the NHR database, the SF-36 was used by 10 centers, while 1 center reported QoL based on the SF-12. Furthermore, QoL was assessed directly before surgery, and at 1-year after surgery (between 10-14 months postoperatively).

Outcomes

Primary outcomes were pre- and postoperative (1-year) QoL (PCS and MCS) in absolute points for both component scores, and differences in stratified QoL changes between both approaches. Although definitions of stratified changes in SF-scores should be based on standardized mean differences in the dataset[17], a large study of randomized trials defined corresponding raw SF score cut-offs of 0-4 points for a small effect, 4-10 points for a moderate effect, and >10 points for a large effect [17]. As such, for the current study, the minimal clinically important difference (MCID) was defined as >5 points difference. Consequently, changes in QoL were stratified in reduced QoL (≥5 points decrease), similar QoL (<5 points difference), or increased QoL (≥5 points QoL).

The secondary aim was to evaluate predictors of a reduction of QoL (≥5 points decrease in PCS or MCS), amongst others based on major postoperative complications (defined as stroke, myocardial infarction, renal failure, or vascular complications), re-exploration for bleeding, and length of hospital stay (LOHS).

Statistical analysis

Continuous data were presented as means and standard deviations or medians with 25th and 75th percentile, when appropriate. Based on the distribution of continuous data, Student's T test or Mann-Whitney U test was used for unrelated comparisons, while the paired T-test or Wilcoxon signed rank test was used for paired samples. Categorical data were presented as absolute numbers and percentages (%) and compared using the χ2-test (unpaired, in case of n<5 Fisher's exact test), or McNemar test (for paired samples). Sensitivity analyses were performed for patients undergoing mitral valve repair specifically (as repair itself is associated with improved QoL[5,6]). Furthermore, responders and non-responders were compared to evaluate potential selection bias.

To evaluate potential predictors for a reduction in QoL, a univariable logistic regression model was applied based on the available data. In this model, a clinically relevant reduction of QoL (defined as >5 points decrease) was used as the dependent variable. In univariable analysis, baseline and procedural characteristics, and important postoperative complications were tested. When p<0.20 in univariable analysis, this covariate was included in the multivariable model [18], in which p<0.05 was considered statistically significant, as for all other analyses. Results of the logistic regression models were presented as odds ratio (OR) and corresponding 95% confidence intervals (CI). Model discrimination was tested in a receiver operating characteristic (ROC) analysis, of which an area under the curve <0.7 indicated poor discrimination, 0.7–0.8 acceptable discrimination and >0.8 excellent discrimination. Hosmer-and-Lemeshow (H-L) tests were performed to evaluate goodness-of-fit.

All statistical analyses were performed using SPSS software (V27, IBM, Armonk, NY, USA).

Data availability statement

Data will be shared, upon reasonable request to the corresponding author, with the permission of the Netherlands Heart Registration.

Ethical statement

As data was provided anonymously, institutional review board approval was not warranted for this retrospective study. This study is in line with all institutions' ethical policies and standards.

RESULTS

Baseline characteristics

In total, 485 patients were included, whom completed both pre- and postoperative QoL assessment. A comparison between responders and non-responders is presented in Supplementary Material 3. In general, non-responders had higher operative risk (as defined by logistic EuroSCORE), primarily driven by an increased rate of concomitant tricuspid valve surgery.

Responders were divided in the FS group (n=276, 56.9%) and MIMVS group (n=209, 43.1%). Baseline characteristics were presented in Table 1. Patients undergoing FS showed a tendency towards a higher mortality risk, based on a logistic EuroSCORE (3.24 [2.08-5.61] vs 2.76 [1.94-5.10], p=0.05)

Table 1. Baseline and procedural characteristics of all included patients, subdivided into FS and MIMVS groups.

	Total (n=485)	**FS** (n=276)	**MIMVS** (n=209)	**p-value**
Baseline				
Age (years)	66.0 [58.0-72.0]	66.0 [58.0 - 72.0]	65.0 [58.0 – 72.0]	0.48
Female sex (%)	190 (39.2%)	102 (37.0%)	88 (42.1%)	0.25
BMI (kg/m^2)	25.7 [23.2-28.0]	25.6 [23.1-27.8]	25.7 [23.5-28.4]	0.23
Diabetes Mellitus (%)	20 (4.1)	14 (5.1)	6 (2.9)	0.23
LVEF > 50% (%)	395 (81.4)	218 (79.0)	177 (84.7)	0.11
COPD (%)	35 (7.2)	27 (9.8)	8 (3.8)	**0.01**
Peripheral arterial disease (%)	8 (1.6)	6 (2.2)	2 (1.0)	0.48
Endocarditis (%)	3 (0.6)	3 (1.1)	0 (0.0)	0.26
Recent myocardial infarction (<90 day, %)	2 (0.4)	2 (0.7)	0 (0)	0.51
Procedure				
MVr (%)	391 (80.6)	226 (81.9)	165 (78.9)	0.42
MVR (%)	94 (19.4)	50 (18.1)	44 (21.1)	0.42
Rhythm surgery (%)	97 (20.0)	76 (27.5)	21 (10.0)	**<0.001**
ASD closure (%)	15 (3.1)	11 (4.0)	4 (1.9)	0.19
TV surgery (%)	57 (11.8)	50 (18.1)	7 (3.3)	**<0.001**
Mortality risk				
EuroSCORE (log)	3.07 [2.08-5.38]	3.24 [2.08 - 5.61]	2.76 [1.94 - 5.10]	0.05

Continuous variables were presented as median and [25th-75th percentile].

ASD: atrial septal defect, BMI: body mass index, COPD: chronic obstructive pulmonary disease, EuroSCORE: European system for cardiac operative risk evaluation, FS: full sternotomy, LVEF: left ventricular ejection fraction, MIMVS: minimally invasive mitral valve surgery, MVr: mitral valve repair, MVR: mitral valve replacement, PAD: peripheral arterial disease, TV: tricuspid valve.

Pre- and postoperative quality of life

In the overall cohort, patients undergoing MV surgery (n=485) experienced a significant increase in the physical component score (56 [42-75] vs 74 [57-88], p<0.001) and mental component score at 1-year (63 [52-74] vs 70 [59-86], p<0.001). Table 2 presents the overall physical and mental component scores, with a subdivision per specific domain.

Both FS and MIMVS patients experienced an increase in physical QoL (57 [43-73] vs 73 [57-88] and 56 [38-75] vs 75 [57-88], both p<0.001). For mental QoL, similar results were observed (66 [52-78] vs 73 [62-89] and 63 [51-69] vs 69 [56-81], both p<0.001).

Table 2. Pre- and postoperative quality of life of mitral valve patients, based on SF-12 and SF-36 questionnaires

	Preoperative	Postoperative	p-value
		Total (n=485)	
PCS	56 [42-75]	74 [57-88]	<0.001
Subdomains			
Physical functioning	30 [50-80]	85 [50-100]	
Role physical			
Bodily pain	38 [19-69]	63 [38-88]	
General health	90 [67-100]	100 [75-100]	
	50 [45-70]	60 [50-80]	
MCS	63 [52 – 74]	70 [59 – 86]	<0.001
Subdomains			
Vitality	50 [31-75]	63 [50-50-75]	
Social functioning	75 [50-100]	88 [75-100]	
Role emotional	67 [25-100]	75 [50-100]	
Mental health	65 [50-85]	75 [55-90]	
		FS (n=276)	
PCS	57 [43-73]	73 [57-88]	<0.001
Subdomains			
Physical functioning	60 [39-85]	85 [60-95]	
Role physical			
Bodily pain	25 [9-56]	50 [25-88]	
General health	89 [59-100]	100 [78-100]	
	60 [50-75]	68 [50-85]	
MCS	66 [52-78]	73 [62-89]	<0.001
Subdomains			
Vitality	56 [38-75]	63 [50-75]	
Social functioning	75 [50-100]	88 [75-100]	
Role emotional	50 [25-92]	75 [25-100]	
Mental health	80 [65-90]	85 [70-93]	

Table 2. Continued

		MIMVS (n=209)	
PCS	56 [38-75]	75 [57-88]	<0.001
Subdomains			
Physical functioning	50 [25-75]	75 [50-100]	
Role physical			
Bodily pain	50 [25-75]	75 [50-100]	
General health	100 [75-100]	100 [75-100]	
	50 [25-50]	50 [50-75]	
MCS	63 [51-95]	69 [56-81]	<0.001
Subdomains			
Vitality	50 [25-75]	50 [25-75]	
Social functioning	75 [50-100]	75 [50-100]	
Role emotional	75 [50-100]	88 [63-100]	
Mental health	50 [38-63]	63 [50-75]	

FS: full sternotomy, MCS: mental component score, MIMVS: minimally invasive mitral valve surgery, PCS: physical component score.

Differences in quality of life change following sternotomy and MIMVS

Clinically important changes in QoL can be appreciated in Figure 1, demonstrating similar results for FS and MIMVS regarding PCS and MCS as well, with an important increase in QoL for both approaches.

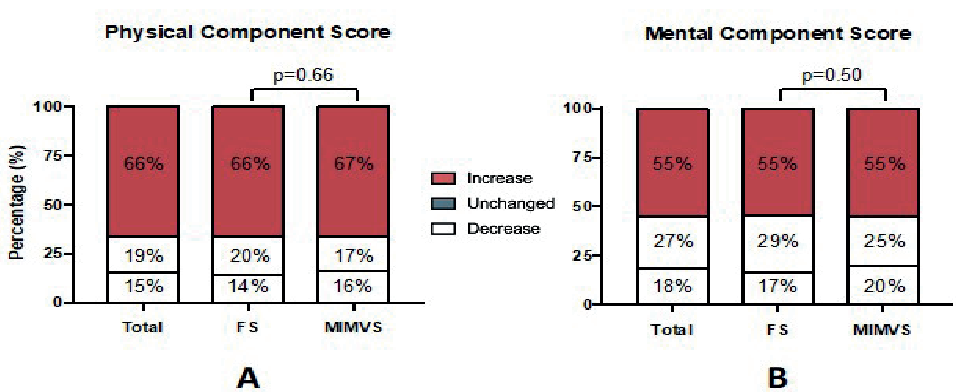

Figure 1. Clinically important changes in QoL for PCS (A) and MCS (B), for the overall cohort, and stratified for patients undergoing FS and MIMVS.
FS: full sternotomy, MCS: mental component score, MIMVS: minimally invasive mitral valve surgery, PCS: physical component score.

Subgroup analysis for isolated mitral valve repair

Subgroup and sensitivity analysis were performed for MVr patients (total n=391 [80.6%], FS n=226 [57.8%], MIMVS n=165 [42.2]), confirming the robustness of the observed results (significant improvements in physical and mental QoL for both cohorts). These data are presented in Supplementary Material 4 and 5.

Predictors of loss of quality of life

Potentially Important baseline, operative and clinical outcomes related to QoL assessment were used for regression analyses. A uni- and multivariable logistic regression model was realized for physical QoL (Table 3), resulting in the identification of a significant association between decrease of QoL and baseline physical component score per point increase (OR 1.05 95%CI 1.03-1.06), and new onset arrhythmia (2.58, 95% CI 1.42-4.72). Receiver-operating characteristic analysis confirmed good discrimination of the model (AUC=0.75), and H-L test confirmed goodness-of-fit (p=0.66).

A similar model was realized for mental QoL (Table 4), identifying baseline mental component score per point increase (OR 1.03, 95%CI 1.02-1.05) and LOHS per additional day (OR 1.09, 95%CI 1.03-1.14) to be associated with a decrease in mental QoL at 1-year. For this model, discrimination was poor, as demonstrated by an AUC of 0.65 in ROC-analysis, but H-L test confirmed goodness-of-fit (p=0.96).

Table 3. Uni- and multivariable logistic regression analysis for a decrease in PCS.

	Univariable		Multivariable	
Covariates	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
MIMVS	1.18 (0.72 - 1.95)	0.52	1.54 (0.86 - 2.75)	0.15
Female gender	0.68 (0.40 - 1.15)	0.15	1.07 (0.59 - 1.91)	0.83
Age	0.99 (0.97 - 1.01)	0.40		
LVEF <50%	0.58 (0.27 - 1.20)	0.14	0.80 (0.36 - 1.76)	0.58
Diabetes mellitus	0.99 (0.28 - 3.49)	0.99		
COPD	0.94 (0.35 - 2.50)	0.90		
PHT	1.30 (0.53 - 2.97)	0.60		
Peripheral arterial disease	0.80 (0.10 - 6.63)	0.84		
MVr	1.26 (0.65 - 2.46)	0.49		
Rhythm surgery	0.67 (0.34 - 1.33)	0.26		
ASD closure	1.43 (0.39 - 5.19)	0.59		
TV surgery	1.07 (0.50 - 2.28)	0.87		
Baseline PCS	1.05 (1.03 - 1.06)	**<0.001**	1.05 (1.03 - 1.06)	**<0.001**
LOHS	1.01 (0.95 -1.07)	0.86		
Major complications	1.58 (0.66 - 3.78)	0.31		
New onset arrythmia	1.71 (1.03 - 2.87)	**0.04**	2.58 (1.42 - 4.72)	**<0.01**
Reexploration for bleeding	1.02 (0.99 - 1.05)	0.27		

ASD: atrial septal defect, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, LOHS: length of hospital stay, MIMVS: minimally invasive mitral valve surgery, MVr: mitral valve repair, OR: odss ratio, PCS: physical component score, TV: tricuspid valve.

Table 4. Uni- and multivariable regression analysis for a decrease in MCS.

	Univariable		Multivariable	
Covariates	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
MIMVS	1.26 (0.79 - 1.99)	0.33	1.45 (0.89 - 2.36)	0.13
Female gender	1.16 (0.72 - 1.85)	0.54		
Age	0.99 (0.97 - 1.01)	0.31		
LVEF <50%	1.16 (0.65 - 2.07)	0.61		
Diabetes mellitus	1.53 (0.54 - 4.33)	0.42		
COPD	0.93 (0.38 - 2.31)	0.87		
PHT	1.18 (0.52 - 2.67)	0.69		
Peripheral arterial disease	0.64 (0.08 - 5.27)	0.68		
MVr	1.21 (0.66 - 2.22)	0.54		
Rhythm surgery	0.72 (0.39 - 1.33)	0.30		
ASD closure	0.31 (0.41 - 2.42)	0.27		
TV surgery	0.96 (0.46 - 1.97)	0.90		
Baseline MCS	1.03 (1.02 - 1.05)	**<0.001**	1.03 (1.02 - 1.05)	**<0.001**
LOHS	1.00 (0.95 - 1.06)	0.91		
Major complications	1.23 (0.52 - 2.94)	0.64		
New onset arrhythmia	1.06 (0.65 - 1.75)	0.81		
Reexploration for bleeding	0.98 (0.90 - 1.06)	0.55		

ASD: atrial septal defect, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, LOHS: length of hospital stay, MIMVS: minimally invasive mitral valve surgery, MCS: mental component score, MVr: mitral valve repair, OR: odss ratio, TV: tricuspid valve.

DISCUSSION

The current study is the first multi-center registry to comprehensively evaluate QoL after mitral valve surgery in general, and the surgical approach in particular. Overall, patients improve significantly in terms of physical and mental QoL. However, we observed no differences in QoL changes between surgical approaches at 1-year.

Patient-reported outcomes are becoming increasingly important in monitoring medical care outcomes, and at least as important as measuring more objective process-measured outcomes. As the patient's perspective can be regarded as a subjective opinion, it is imperative to measure these PROMs using the most objective modalities. For the assessment of QoL, the SF-36 – and later on SF-12 – was originally developed, incorporating not only health perception using physical measures, but also metrics for social, emotional and mental wellbeing [19]. Although physical and mental health are inseparably related, their outcome scores are reported separately using the SF-scales. Consequently, a differentiation can be made between outcomes on a physical and a mental level.

Indeed, in the current study, overall, patients improved significantly in terms of physical QoL. This applied to patients undergoing both MIMVS and FS approaches. Although this improvement was a result of an increase in physical QoL over every physical subdomain, it was most notable in patients' *physical functioning* and *physical role*. These findings imply patients are able to perform all types of physical functioning more vigorously with less health-related limitations[19]. In MV disease patients, this is most likely related to a reduction in MR/MS-associated dyspnea[5]. Of note, as bodily pain is usually not associated with MV disease, this does not seem to play an important role in the pre-operative phase. Also 1 year after surgery, bodily pain is low and comparable between the MIMVS and FS approach, confirming previously findings at 1-year in patients undergoing FS MV surgery[20]. However, differences in pain outcomes between both approaches could potentially be present in the shorter-term[12], however the current study design did not allow for shorter-term QoL evaluation.

Similar statistically significant – but less pronounced – differences were found for an increase in mental QoL at 1-year, overall. In the current registry, both FS and MIMVS were associated with an increase in mental QoL at 1 years. Although patients did improve in terms of mental health, this was less notable for *social functioning* and the *emotional role*, implying some residual difficulties with work and daily activities as a result of emotional problems [19]. However, the important improvements in mental QoL are in line with previous studies, demonstrating a significant reduction in anxiety and posttraumatic stress after undergoing MV surgery, compared to conservatively treated patients[21]. Of note, in another prior study, lower *mental* QoL was associated with an increased dissatisfaction regarding the sternotomy scar[12], but this did not seem to play an important role in the current registry.

In order to evaluate which patients might benefit less – in terms of QoL – from either surgical approach, regression analyses were performed for a loss of QoL. New onset arrhythmia and baseline QoL were associated with a significant decrease in QoL (≥5 points). Indeed, especially postoperative atrial fibrillation, which is common after cardiac surgery in general and MV surgery in particular[22], is reported to have an important influence on QoL [23]. Also, the latter finding implies that higher baseline SF scores are associated with a 1-year reduction in QoL. Although this might seem confusing, this paradoxical finding can more easily be explained in MV surgery. Indeed, in the current era, MV surgery is even indicated in asymptomatic patients when MR is severe, and repair is likely[24]. Consequently, this important patient group generally does not experience any impairment in daily life pre-operatively but might be subjected to a relative reduction in longer-term QoL after surgery, in a trade-off to a restored life expectancy. Although these findings are only hypothesis-generating, from a mental perspective, such asymptomatic individuals might not regard themselves as a 'patient' prior to surgery, while the surgery transformed them into life-long cardiovascular patients requiring extensive follow-up and medical treatment.

Given the increasing importance of the patient's point of view, QoL assessment should be considered in all studies evaluating cardiac surgical procedures in general, and less invasive or trans-catheter mitral valve procedures in particular. Although the SF-scoring surveys are widely available, other – more MV disease specific – questionnaires exist, evaluating heart-failure related QoL, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ), more closely related to functional capacity and heart-failure symptoms[25]. Still, such valve disease-specific questionnaires might be difficult to implement on a national level, as they are less likely to result in a homogeneous nationwide QoL assessment of cardiac surgical procedures. Finally, especially on a study-level, more objective measures of physical QoL and activity could be considered, such as the use of pre- and postoperative accelerometers or smartwatches[26,27].

Limitations

Unfortunately, QoL assessment was non-mandatory to register in the NHR. Therefore, only a selected number of patients completed both pre- and postoperative SF-forms, subjecting the results to potential selection bias. This potential bias extents to the exclusive inclusion of (i) responders and (ii) 1-year survivors, as only these patients completed both pre- and postoperative QoL assessment (survivorship bias). A comparison between responders and non-responders revealed an elevated operative risk in non-responders, driven by an increased rate of concomitant surgery. Regarding potential survivorship bias, it is not perceived that the exclusion of non-survivors with pre-operative QoL evaluation would influence results, as short- and long-term mortality was similar between FS and MIMVS patients in this registry, as reported previously[9].

The current registry did not allow for incorporation of shorter-term (i.e., 3- and 6-month) QoL outcomes. Hypothetically, shorter-term differences could be present between the surgical approaches[12], although conflicting evidence exists in related cardiac surgical procedures[28]. Finally, the results of the regression analyses should be interpreted with caution as AUC was suboptimal, especially for the MCS regression analysis, and CIs were relatively wide.

CONCLUSION

Mitral valve surgery is associated with a significant improvement in mental and physical QoL, regardless of the surgical approach. Future research could focus on the standardized incorporation of QoL assessment in studies evaluating less invasive or trans-catheter mitral procedures, to evaluate their effectiveness from a patient-reported perspective, in addition to objective clinical outcomes.

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SUPPLEMENTARY MATERIAL

Supplementary Material 1. Members of the Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration

Dr. Bramer	Amphia Hospital Breda
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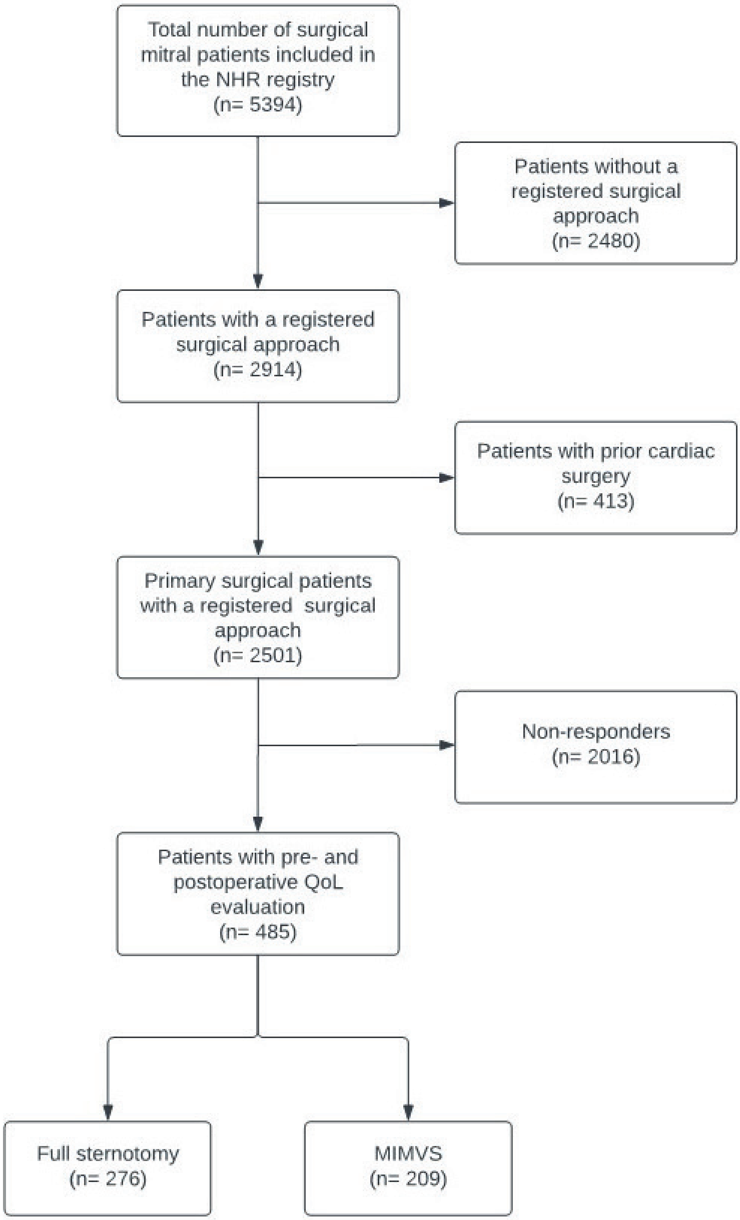

Supplementary Material 2. Flowchart for patient inclusion.

MIMVS: minimally invasive mitral valve surgery, NHR: Netherlands Heart Registration, QoL: quality of life.

Supplementary Material 3. Subgroup and sensitivity analysis for pre- and postoperative stratified QoL of patients undergoing mitral valve repair.

	Responder (n=485)	Non-responder (n=2016)	p-value
Baseline			
Age (years)	66.0 [58.0-72.0]	66.0 [57.0 – 73.0]	0.87
Female sex (%)	190 (39.2)	899 (44.6)	**0.03**
BMI (kg/m^2)	25.7 [23.2 – 28.0]	25.3 [23.0 – 27.7]	**0.04**
Diabetes Mellitus (%)	20 (4.1)	157 (7.8)	**0.01**
LVEF > 50% (%)	395 (81.4)	1421 (70.5)	**<0.001**
COPD (%)	35 (7.2)	185 (9.2)	0.17
Peripheral arterial disease (%)	8 (1.6)	55 (2.7)	0.17
Endocarditis (%)	3 (0.6)	29 (1.4)	0.15
Recent myocardial infarction (<90 day, %)	2 (0.4)	14 (0.7)	0.48
Procedure			
MVr (%)	391 (80.6)	1579 (78.3)	0.27
MVR (%)	94 (19.4)	433 (21.5)	0.31
Other procedure (%)	0 (0)	1 (0.1)	0.99
Unknown (%)	0 (0)	3 (0.1)	0.99
Rhythm surgery (%)	97 (20.0)	376 (18.7)	0.50
ASD closure (%)	15 (3.1)	57 (2.8)	0.75
TV surgery (%)	57 (11.8)	518 (25.7)	**<0.001**
Mortality risk			
EuroSCORE (log)	3.07 [2.08-5.38]	3.47 [2.08 - 6.03]	**0.01**

Supplementary Material 4. Subgroup and sensitivity analysis for pre- and postoperative absolute QoL of patients undergoing mitral valve repair.

	Preoperative	Postoperative	Increase/Decrease	p-value
		FS (n=226)		
PCS	58 [46-75]	73 [59-88]	Increase	<0.001
MCS	67 [53-79]	73 [62-90]	Increase	<0.001
		MIMVS (n=165)		
PCS	59 [42-81]	75 [63-88]	Increase	<0.001
MCS	63 [53-69]	69 [59-81]	Increase	<0.001

FS: full sternotomy, MCS: mental component score, MIMVS: minimally invasive mitral valve surgery, PCS: physical component score.

Supplementary Material 5. Subgroup and sensitivity analysis for pre- and postoperative stratified QoL of patients undergoing mitral valve repair.

	Total (n=391)	FS (n=226)	MIMVS (n=165)	p-value
PCS				0.50
Decreased (%)	61 (15.6)	31 (13.7)	30 (18.2)	
Unchanged (%)	80 (20.5)	48 (21.2)	32 (19.4)	
Increased (%)	250 (63.9)	147 (65.0)	103 (62.4)	
MCS				0.61
Decreased (%)	73 (18.7)	41 (18.1)	32 (19.4)	
Unchanged (%)	105 (26.9)	65 (28.8)	40 (24.2)	
Increased (%)	213 (54.5)	120 (53.1)	93 (56.3)	

FS: full sternotomy, MCS: mental component score, MIMVS: minimally invasive mitral valve surgery, PCS: physical component score.

PART III

OUTCOMES IN INTERNATIONAL LITERATURE

Chapter 13

Right minithoracotomy versus median sternotomy for reoperative mitral valve surgery: a systematic review and meta-analysis of observational studies

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SUMMARY

Reoperative mitral valve surgery (MVS) through a median sternotomy (ST-MVS) can be particularly challenging due to dense adhesions and is known to carry a substantial risk of injuries to vascular structures. These injuries occur in 7–9% of cases and are associated with increased mortality rates. A valid alternative that could avoid the risks associated with redo ST-MVS is the right anterolateral minithoracotomy (MT-MVS) approach. The aim of this study was to quantify the effects of MT-MVS compared with those of ST-MVS on morbidity and mortality among patients who underwent prior cardiac surgery through a sternotomy. The MEDLINE and EMBASE databases were searched through 1 November 2017. Data regarding mortality, stroke, reoperation for bleeding and length of hospital stay were extracted and submitted to a meta-analysis using random effects modelling and the I2-test for heterogeneity. Six retrospective observational studies were included, enrolling a total of 777 patients. In a pooled analysis, MT-MVS demonstrated reduced mortality rates compared to a stand- ard sternotomy [odds ratio (OR) 0.41, 95% confidence interval (CI) 0.18–0.96; P = 0.04]. MT-MVS was, moreover, associated with reduced length of hospital stay [difference between the means was -3.81, 95% CI -5.53 to -2.08; P < 0.0001) and reoperation for bleeding (OR 0.32, 95% CI 0.10–0.99; P = 0.0488). The incidence of stroke was similar (OR 1.51, 95% CI 0.65–3.54; P = 0.34), all in the absence of heterogeneity. In conclusion, reoperative minimally invasive MVS through a minithoracotomy is a safe alternative to standard sternotomy, with reduced mortality rates, length of hospital stay and reoperations for bleeding and a comparable risk of stroke. However, because the existing literature provided limited, low-quality evidence, more methodologically rigorous randomized controlled trials are needed.

INTRODUCTION

Redo cardiac surgery has been associated with increased mortality rates compared to primary surgery[1,2]. Cardiac redo procedures are traditionally performed through a repeat median sternotomy (ST). For the past decade, reoperative mitral valve surgery (MVS) has become more common, representing over 10% of all mitral valve procedures in the USA[3,4]. However, redo MVS performed through an ST (ST-MVS) can be particularly technically challenging and is known to carry a substantial risk of injuries to patent coronary artery bypass grafts and vascular structures that lie directly substernally and can adhere to the sternum. Resternotomy may furthermore be demanding in patients with (healed) mediastinitis, prior thoracic radiotherapy and dense adhesions or other complications from prior surgery[5-7]. These injuries to cardiac structures occur in 7 to 9% of resternotomies[3,8,9] and are reported to be an independent risk factor for in-hospital death[3]. A valid alternative to repeated conventional ST-MVS would be a minimally invasive approach through a right anterolateral minithoracotomy (MT)[5,10]. An incision of <10cm is made in the 4th or 5th intercostal space, the goal being to minimize surgical trauma compared to that of a full ST or thoracotomy (20 cm)[11,12]. MT-MVS can be performed either under direct or video-assisted vision, with the use of long-shafted instruments in both situations. Primary MT-MVS is, besides being associated with less surgical trauma, believed to result in diminished pain, blood loss and need for transfusions, which translates into reduced length of hospital stay (LOHS)[13]. In addition, with MT-MVS, one could avoid the risks associated with resternotomy. Despite these advantages, no general consensus exists on the approach of choice for redo MVS. This consensus should ideally arise from well-designed randomized controlled trials and comprehensive literature reviews that compare redo MT- and ST-MVS among patients with a prior ST. However, to date such data are only available from non-randomized studies, in the form of 2 best evidence topics[14,15] and 1 small narrative subreview[16]. Therefore, an overview and analysis of the available comparative data, which may aid in determining the optimal approach for redo MVS, are needed.

The aim of this report was to review all published observational studies that compare redo MVS through a MT and a conventional median ST approach among patients with prior cardiac surgery through a ST, with mortality as the primary outcome measure. Secondary outcome measures include stroke, reoperation for bleeding, LOHS, wound infection and red blood cell (RBC) transfusions. In order to draw more useful and robust conclusions regarding these outcome metrics, data from individual studies were collected and analysed using meta-analytical techniques.

MATERIALS AND METHODS

Methods of the analysis, outcome measures and inclusion criteria were specified in advance and documented in a protocol. The review and meta-analysis were conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[17]. Risk of bias in individual studies and across studies was not assessed, because retrospective observational studies are generally known for possessing a certain level of bias.

Eligibility criteria

Types of participants.

Participants aged 18 years and above who presented with mitral valve disease requiring surgery and who underwent at least 1 previous cardiac surgical procedure through a median ST were considered for inclusion. No exclusions were made based on the indication of primary ST (e.g., coronary artery bypass graft, aortic valve replacement).

Types of interventions.

Studies that compared the MT (also denoted as 'port access') and the median ST approach for reoperative MVS were considered. Studies in which cardiac procedures were performed concomitantly with the initial mitral valve repair or replacement were also assessed for eligibility. The MT approach was defined as a ≤10 cm right anterolateral incision in the 4th or 5th intercostal space to acquire surgical exposure. No difference was made between video-assisted or direct vision MT; however, studies utilizing robotic telemanipulation such as the Da Vinci robot were excluded because telemanipulation forms a totally different area within minimally invasive MVS. If the report did not define the thoracotomy approach as either mini or full, the authors were contacted for clarification. Redo ST was defined as MVS in which the previous ST incision was re-entered and cardiac exposure was obtained by an oscillating saw to complete the ST.

Type of primary outcome measure.

The primary outcome measure was mortality, reported as in-hospital death, 30-day mortality rate or death as an early postoperative complication.

Types of studies.

Observational studies comparing MT and ST for reoperative MVS after a previous median ST were examined for eligibility. Studies reporting combined data for mitral and aortic valve reoperations were considered only if mitral valve data were presented separately. Studies reporting primary operations were excluded.

Literature search

Potentially eligible studies were identified by searching the elec- tronic MEDLINE and EMBASE databases through PubMed and Ovid, respectively. No unpublished data were obtained. The search was limited to the English language, human subjects and studies published after 2000, because the latter provide the best evidence for current practice. No publication status restrictions were imposed. The last search was run on 1 November 2017. In addition, a cross-reference and related-articles search was con- ducted as a check of rigour. The search strategy was first applied to the electronic MEDLINE database and combined the following MeSH and free terms: 'mitral valve', 'mitral valve insufficiency', 'mitral valve prolapse' AND 'thoracotomy', 'minithoracotomy', 'port access' AND 'ST' AND 'reoperation', 'reoperative' and 'redo'. This search was subsequently adapted for EMBASE. Reports origi- nating from the electronic search were screened for eligibility based on their titles and abstracts. Subsequently, full texts of po- tentially eligible reports were read and carefully assessed according to the eligibility criteria. Studies meeting these criteria were included for review and, if applicable, for quantitative synthesis (meta-analysis). Study selection was conducted in a non-blinded standardized manner by 2 independent reviewers. Potential inter-reviewer disagreements were resolved by consensus.

Data collection

For this review, a data extraction sheet was developed and pilot-tested on 3 randomly selected included studies, whereupon the sheet was refined accordingly. Data extraction was performed by 1 review author. The second author validated the correctness of the tabulated data. Potential inter-reviewer disagreements were resolved by consensus. Studies reporting their continuous variables as mean and standard deviation (SD) were extracted without conversion. Variables denoted as median and interquartile range or standard error of the mean were first converted, as described elsewhere[18,19]. Data were extracted from each included report on (i) general study characteristics: study design, enrolment period, country, setting, in- and exclusion criteria, baseline characteristics and statistical methods; (ii) characteristics of participants: number of patients, mean age (years), gender (male/female), previous surgery and preoperative characteristics such as Society of Thoracic Surgeons (STS) score or EuroSCORE, ejection fraction, New York Heart Association class and several comorbidities; (iii) intervention characteristics: mean time to redo surgery (years), cannulation site, clamping technique, myocardial protection method, concomitant procedures, repair rate in redo surgeries (mitral valve repair versus replacement), conversion to ST (redo MT-MVS only), cardiopulmonary bypass (CPB) and clamping time; (iv) primary outcome measure: death, either reported as 30-day mortality, in-hospital death or early postoperative death; (v) secondary outcome measures: stroke, reoperation for bleeding, LOHS, wound infection and RBC transfusions. If outcome measures were reported in any other way than stated and could not be converted, data were assumed to be not available. In addition, it must be noted that the authors did not discriminate between minor differences in surgical procedures.

Statistical analysis

Odds ratios (ORs) were used to assess dichotomous outcome measures. The difference in means (MD) was used for continues variables, which were made on the same scale among all studies. If not, the standardized difference was used. Obtained ORs were interpreted as risk ratios. In addition, an OR or MD less than 1 favours MT over ST for MVS. Statistical analyses were performed using Review Manager (RevMan v5.3, Cochrane Collaboration, Oxford, UK). For this analysis, the random effects model with a 95% confidence interval (CI) was used when there was a substantial risk of heterogeneity, originating from the non-randomized nature of the included studies. In addition, because risk profiles and selection criteria differed between centres, the random effects model was favoured. The I2-test for heterogeneity was conducted to assess variability across studies that could not be due to random error alone. High I2-values indicated that the observed variability among studies could not be explained by chance (i.e., a consequence of clinical and/or methodological di- versity). Heterogeneity was deemed to be substantial and considerable if I2 >50% and I2 >75%, respectively with P-value <0.10 [18]. No additional analyses were conducted.

RESULTS

Study selection

A total of 6 studies were identified for inclusion in this review and meta-analysis. The MEDLINE and EMBASE database search provided a cumulative number of 250 citations. In addition, 1 citation was obtained via a cross-reference and related-article search. Of these, 84 duplicates were discarded. Another 151 papers were eliminated because their title and abstract clearly did not meet the eligibility criteria. Full texts of the remaining 16 articles were assessed in detail for eligibility. Of these, 10 reports did not meet the criteria as described. Reasons for exclusion were no comparison between MT and median ST (n = 6), results for mitral valve reoperation were not separately reported (n = 3) and the main text for 1 study was in Japanese that could not be translated into English (n = 1). In addition, no unpublished relevant studies were obtained (flowdiagram, Fig. 1).

STUDY CHARACTERISTICS

Methods

All 6 studies finally selected for inclusion were retro- spective single-centre observational studies published in English. All studies were conducted in the USA, Canada, Japan or South Korea. The main inclusion criterion encompassed patients who received a MT or median ST for mitral valve disease with at least 1 prior cardiac surgical procedure through a median ST. Overall, studies enrolled patients who were operated on between 1985 and 2011.

Participants

A total number of 777 participants were included for review. These were subdivided in an MT (n=237; 31%; mean age 62.8 ± 14.0 years) and an ST (n = 540; 69%; mean age 60.1 ± 14.8 years) group. The number of subjects per individ- ual study ranged from 35 to 287 [20–25] (Table 1). Previous operations as well as preoperative patient characteristics are presented in Table 2. STS scores [25] and EuroSCOREs [23] were both only reported in 1 paper each, whereas others mainly reported ejection fraction, New York Heart Association class and comorbidities such as diabetes mellitus and hypertension.

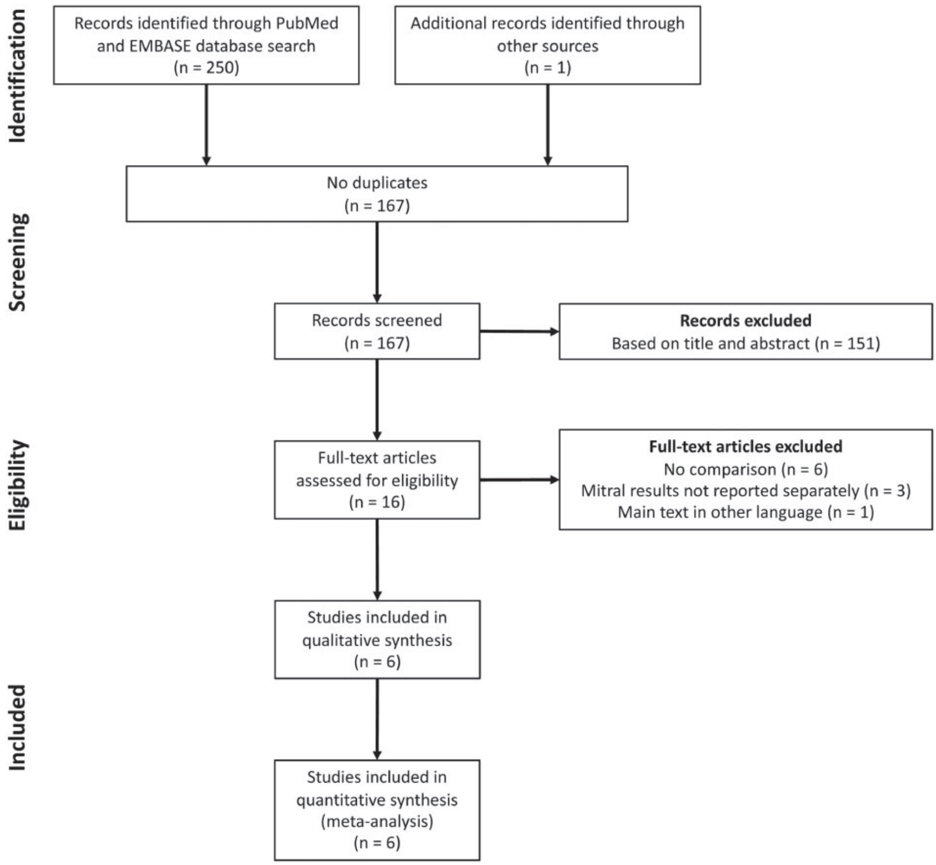

Figure 1. Study selection procedure shown in a PRISMA flow diagram.

Intervention

Patients underwent surgery through a MT, initiated through a right anterolateral incision in the 4th or 5th intercostal space or a median ST approach, both aimed at repairing or replacing the diseased mitral valve. In some subjects, concomitant surgery was performed. Bolotin et al.[21] and Kim et al.[22] excluded participants who received such concomitant proce- dures in general whereas others only excluded those receiving any concomitant procedure other than tricuspid repair[20,23]. Two reports excluded those who received concomitant procedures that were not amenable to a minimally invasive approach [24,25]. Mean time to redo surgery was reported only by Kim et al.[22], whereas cannulation site, clamping technique, myocar- dial protection method, repair rate in redo surgeries (MVP/MVR), conversion of redo MT-MVS to ST-MVS, CPB and clamping time were described by at least 3 studies each (Table 2).

Outcomes

All studies reported the number of deaths, either as 30-day mortality rate, in-hospital deaths, or deaths of early postoperative complications. In addition, all secondary outcome measures investigated in this review were assessed at least by 1 study each. Other outcomes investigated by different researchers, but not of interest for this review, were time in the intensive care unit, arrhythmias, chest tube output and several others[20-25].

Synthesis of results

See Table 1 for all primary and secondary outcome measures. Death, stroke, reoperation for bleeding and wound infection were described as the number of events and as percentage of the group total, whereas LOHS was denoted as mean and SD. Wound infection and RBC transfusions were excluded from the meta-analysis because these outcomes were only reported in 2 or fewer studies each, and forest plots yield little value and may be seriously biased. Wound infections were reported by Vallabhajosyula et al.[24] and Losenno et al.[25] and occurred in 0.5% (1) and 3.3% (3) of patients who received ST-MVS (220 and 92), respectively. No wound infections were reported for either MT group. RBC transfusion data were reported by Losenno et al.[25], encompassing 132 patients. Overall, 63% (25) and 79% (73) of patients required such blood products in the MT (40) and ST (94) group, respectively. Intraoperative conversion from redo MT-MVS to ST-MVS was described by Bolotin et al.[21], Vallabhajosyula et al.[24] and Losenno et al.[25] (Table 2) and occurred in 0.7% (1) of patients. In addition, data for CPB times were available for all included studies. The mean CPB time was 177±64 and 169±74min for MT- and ST-MVS, respectively (Table 2). Figures 2–5 present results of each meta-analysis performed, including measures of heterogeneity and 95% CIs. Data comparing deaths following MT- and ST-MVS were available for all 6 studies and were included for quantitative synthesis [20–25]. A total of 2.5% (6) and 8.9% (48) of patients who underwent an MT and an ST mitral valve reoperation (237 and 540; total 777) died, respectively. These percentages reveal a trend towards a reduced number of deaths of patients who had MT-MVS. Analysis confirmed this trend and showed (Fig. 2) that the MT approach was associated with a significantly reduced number of deaths compared to ST-MVS (OR 0.41, 95% CI 0.18–0.96; P=0.04). In add- ition, evidence for heterogeneity was absent (I2 = 0%, P=0.62). Quantitative synthesis for stroke incidence was based on 4 of the analysed studies[20,23-25]. Overall, stroke occurred in 5.1% (9) and 3.4% (17) of patients who underwent MT- and ST-MVS (177 and 494, total=671), respectively. Moreover, analysis revealed (Fig. 3) that the MT approach was not significantly associated with a higher occurrence of stroke (OR 1.51, 95% CI 0.65–3.54; P = 0.34) in the absence of heterogeneity (I2 = 0%, P = 0.86).

Table 1. Principal data and outcomes of interest from individual studies

Study	Country	Study design	Study period	Group (MT/ST)	Participants (total (male/female))	Age (years)	Mortality (events (%))	Stroke (events (%))	LOHS (days)	RFB (events (%))	Wound infection (events (%))	RBC transfusion (patients (%))
Burfeind *et al.* [20]	USA	Retrospective observational study	1996–2001	MT	60 (33/27)	60 ± 14	0 (0)	4 (7)	NA	1 (2)	NA	NA
			1985–1997	ST	155 (42/113)	58 ± 16	21 (14)	7 (5)	NA	8 (5)	NA	NA
Bolotin *et al.* [21]	USA	Retrospective observational study	January 1996–June 2003	MT	38 (-/-)	68 ± 2	2 (5)	NA	7 ± 6	NA	NA	NA
				ST	33 (-/-)	63 ± 2	2 (6)	NA	11 ± 6	NA	NA	NA
Kim *et al.* [22]	South Korea	Retrospective observational study	September 2007–December 2010	MT	22 (4/18)	46 ± 15	0 (0)	NA	16 ± 6	0 (0)	NA	NA
				ST	13 (5/8)	45 ± 16	1 (8)	NA	20 ± 17	2 (15)	NA	NA
Hiraoka *et al.* [23]	Japan	Retrospective observational study	January 2006–September 2011	MT	10 (5/5)	68 ± 15	0 (0)	1 (10)	18 ± 8	0 (0)	NA	NA
				ST	27 (18/9)	63 ± 15	1 (4)	1 (4)	22 ± 13	2 (7)	NA	NA
Vallabhajosyula *et al.* [24]	USA	Retrospective observational study	1988–2001	MT	67 (32/35)	64 ± 13	2 (3)	2 (3)	11 ± 15	0 (0)	0 (0)	NA
				ST	220 (99/121)	61 ± 15	13 (6)	7 (3)	14 ± 12	3 (1)	1 (0.5)	NA
Losenno *et al.* [25]	Canada	Retrospective observational study	September 2000–August 2014	MT	40 (28/12)	68 ± 14	2 (5)	2 (5)	8 ± 7	1 (3)	0 (0)	25 (63)
				ST	92 (38/54)	62 ± 13	10 (11)	2 (2)	12 ± 10	6 (7)	3 (3)	73 (79)

Data are expressed as absolute number, percentages or as mean ± SD.

LOHS: length of hospital stay; MT: minithoracotomy; NA: not available; RBC: red blood cell; RFB: reoperation for bleeding; SD: standard deviation; ST: median sternotomy; USA: United States of America.

Table 2. Supplementary data of interest from individual studies

Study	Group	Previous surgery (%)	Mean time to redo surgery (years)	Preoperative patient characteristics	Cannulation site	Clamping technique	Myocardial protection	Clamping time (min)	CPB time (min)	MVP/ MVR (%)	Conversion to sternotomy (number of patients)
Burfeind *et al.* [20]	MT	MVS (60)	NA	LVEF (45 ± 9%) and mean NYHA (3.4)	FV-FA/AscA	Endoclamp (45%)	VF (55%) and additional percutaneous retrograde cardioplegia (33%)	NA	208 ± 76	NA	NA
	ST	MVS (83)	NA	LVEF (54 ± 13%) and mean NYHA (3.5)	IVC and SVC-AscA	NA	VF (5%) and cardioplegia (95%)	NA	157 ± 53	NA	
Bolotin *et al.* [21]	MT	NA	NA	LVEF (46 ± 12%) and mean NYHA (2.7)	FV and JV-FA		Hypothermia (26°C) and VF	NA	160 ± 65	42/58	0
	ST	NA	NA	LVEF (55 ± 11%) and mean NYHA (2.6)	NA	NA	NA	NA	157 ± 54	9/91	
Kim *et al.* [22]	MT	MVP (59), MVR (9), MVR + TVP/AVR (9), MVP + TVP (5) and other (18)	12 ± 9	LVEF (61 ± 9%), hypertension (5%) and diabetes mellitus (5%)	FV-FA	Transthoracic clamp	Moderate hypothermia and antegrade cardioplegia	91 ± 27	171 ± 47	77/23	NA
	ST	MVP (46), MVP + TVP (8), MVR (8), MVR + TVP/AVR (8), CABG (8), AVR (8) and other (22)	10 ± 9	LVEF (45 ± 16%), hypertension (39%) and diabetes mellitus (23%)	IVC and SVC-AscA	NA	NA	102 ± 57	210 ± 103	100/0	
Hiraoka *et al.* [23]	MT	MVP (50), redo MVR (10), AVR (10) and CABG (30)	NA	LVEF (47 ± 19%), mean NYHA (1.3 ± 0.5) and EuroSCORE (4.8 ± 2.0)	FV and JV-FA/AA		Hypothermia (27–30°C) and VF	90 ± 7 (VF-time)	145 ± 25	0/100	NA
	ST	MVP (33), MVR (19), redo MVR (4), AVR (11), CABG (4), Bentall (4) and other (25)	NA	LVEF (64 ± 9), mean NYHA (1.3 ± 0.7) and EuroSCORE (3.8 + 2.4)	FV and SVC-FA	Aortic cross-clamp	Antegrade cardioplegia	84 ± 19	135 ± 28	0/100	
Vallabhajosyula *et al.* [24]	MT	MVP (78), MVR (19) and MVP + MVR (3)	NA	LVEF (54 ± 12%), NYHA ≥2 (63%), hypertension (61%) and diabetes mellitus (13%)	FV and SVC-FA (97%)/AA (3%)	Endoclamp (81%) and Chitwood clamp (7%)	Hypothermia, antegrade cardioplegia (88%) and VF (12%)	104 ± 38	153 ± 42	NA	1
	ST	MVP (41), MVR (53) and MVP + MVR (6)	NA	LVEF (54 ± 17%), NYHA ≥2 (69%), hypertension (55%) and diabetes mellitus (17%)	Central aortic cannulation (95%) and FA (5%)	Aortic cross-clamp (100%)	Antegrade and retrograde cardioplegia	130 ± 71	172 ± 83	NA	
Losenno *et al.* [25]	MT	Isolated MVR/MVP (18), MVR/MVP ± other valve ± CABG (13), CABG (50), AVR/repair ± aortic ± CABG (18) and other (18)[a]	NA	Mean NYHA (3.3), STS score (15 ± 11) and diabetes mellitus (28%)	FV and JV-FA/AA		Hypothermia (28–30°C), VF	123 ± 37 (VF-time)	201 ± 63	20/80	0

Study	Group	Previous surgery (%)	Mean time to redo surgery (years)	Preoperative patient characteristics	Cannulation site	Clamping technique	Myocardial protection	Clamping time (min)	CPB time (min)	MVP/ MVR (%)	Conversion to sternotomy (number of patients)
	ST	Isolated MVR/MVP (62), MVR/ MVP ± other valve ± CABG (17), CABG (11), AVR/ repair ± aortic ± C-ABG (5) and other (10)[a]	NA	Mean NYHA (3.3), STS score (15 ± 11) and diabetes melli-tus (15%)	IVC and SVC-AscA	Aortic cross-clamp	Combination of ante-grade and retrograde blood cardioplegia (100%)	105 ± 46	180 ± 75	9/91	

Data are expressed as absolute number, percentages or mean ± SD.

aTotal >100%; some patients received >1 previous surgery.

AA: axillary artery; AscA: ascending aorta; AVR: aortic valve replacement; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; FA: femoral artery; FV: femoral vein; IVC: inferior vena cava; JV: jugular vein; LVEF: left ventricular ejection fraction; MT: minithoracotomy; MVP: mitral valve plasty; MVR: mitral valve replacement; MVS: mitral valve surgery; NA: not available; NYHA: New York Heart Association; SD: standard de-viation; ST: median sternotomy; STS: Society of Thoracic Surgeons; SVC: superior vena cava; TVP: tricuspid valve plasty; VF: ventricular fibrillation.

Reoperation for bleeding data were available for 5 observational studies, encompassing 706 patients [20, 22–25]. These sub- jects were subdivided into an MT and an ST group (199 and 507, respectively) in which reoperation for bleeding was required in 1.0% (2) and 4.1% (21) of cases, respectively. Initially (Fig. 4), MT-MVS was not significantly associated with a reduction in reoperations due to postoperative bleeding (OR 0.32, 95% CI 0.10–0.99; P = 0.05). However, Review Manager (RevMan v5.3) depicts rounded P-values in its forest plots, so a 4-decimal, commaseparated file was created and exported. This file revealed a P- value of 0.0488 by which MT-MVS was deemed to be significantly associated with a reduced need for reoperation for bleeding. No significant heterogeneity was detected within this comparison (I2 = 0%, P = 0.96).

Data regarding LOHS were reported in 5 studies, which included 562 subjects[21-25]. LOHS data were presented on an identical scale among all studies so the difference in means was used. Mean LOHS for MT- and ST-MVS (177 and 385) was, respectively, 10.5±11.0 days and 14.0±11.7days. A meta-analysis (Fig. 5) demonstrated that MT-MVS was significantly related with a lower LOHS compared to patients receiving MVS through a median ST (MD -3.81, 95% CI -5.53 to -2.08; P<0.0001). There was no evidence of heterogeneity (I2 = 0%, P = 1.00).

DISCUSSION

Summary of evidence

This systematic review examined whether the MT approach reduces the number of deaths compared to a conventional me- dian ST among patients who received reoperative MVS and underwent prior cardiac surgery through a median ST. Stroke, reoperation for bleeding, LOHS, wound infection and RBC transfusions were added to this comparison as secondary outcome measures. Six non-randomized observational studies that met the eligibility criteria were included for review. The total number of patients was 777, with 237 in the MT group and 540 in the conventional ST group. Forest plots (Figs 2–5) revealed no heterogeneity for all outcome measures subjected to quantitative synthesis. Subsequently, homogeneity across studies was by Holzhey et al.[26], adverse events, including death, are highly dependent on the surgeon's experience in minimally invasive MVS. Furthermore, the authors described the influence of a learn- ing curve, which comprises 75–125 procedures. Therefore, reported mortality rates with MT were assumed to be an overestimation compared to those from high volume centres, because all included studies[20-25] reported fewer than 75 minithoracotomies over a period exceeding 1 year at their respective institutions.

MT-MVS was associated with a trend (in 3 of 4 studies) towards an increased, although not significant, risk of stroke (Fig. 3). Nevertheless, such embolic events remain a substantial concern when considering reoperative surgery through a MT. The trend in stroke risk may be explained by the observed differences in method for CPB across intervention groups. Retrograde perfusion was most frequently used across all 4 MT groups who reported stroke data [20, 23–25] compared to the ST groups, where 3 of the 4 studies mainly performed antegrade perfusion (AP) via central cannulation of the ascending aorta [20, 24, 25] (Table 2). In gen- eral, antegrade ascending aorta perfusion is not used during MT- MVS because the addition of the arterial cannula through the small 3- to 10-cm incision may impede or even prohibit adequate exposure compared to femoral artery exposure, which is easily achieved. Nevertheless, Murzi et al.[27] revealed that retrograde perfusion (compared to AP) was an independent risk factor for stroke (OR 4.28, P = 0.02) in patients who underwent MVS through a MT. Subsequently, AP via the axillary or subclavian artery was preferred over femoral cannulation in patients with peripheral vascular disease for MT-MVS. Axillary or subclavian artery cannulation for MT-MVS was only performed in a minority of cases in 3 studies. Vallabhajosyula et al.[24] performed this type of perfusion in 3% of cases; in contrast, Losenno et al.[23] and Hiraoka et al.[25] only performed axillary AP, depending on individual patient risk factors for atheroembolism and for elderly patients, respectively. Another concern that may contribute to the trend towards increased risk of stroke is inadequate deairing of cardiac cavities before closure. This trend may also be due to the restricted access in minimally invasive MVS, according to Botta et al.[14]. Subsequently, surgeons should utilize CO_2 insufflation[28,29] and venting[30,31] procedures to mitigate this intracavity air in order to prevent embolic events.

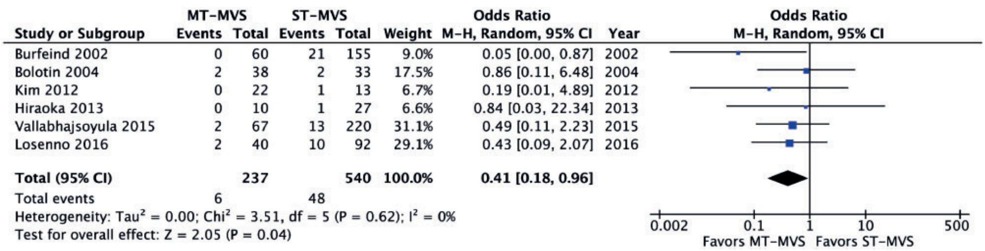

Figure 2. Comparison between redo MT-MVS and ST-MVS for the outcome death. CI: confidence interval; MT-MVS: minithoracotomy mitral valve surgery; ST-MVS: median sternotomy mitral valve surgery.

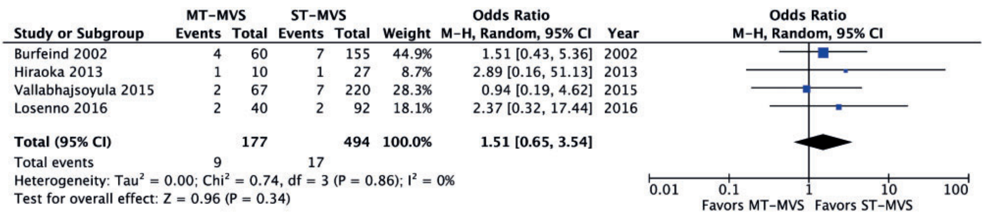

Figure 3. Comparison between redo MT-MVS and ST-MVS for the outcome stroke. CI: confidence interval; MT-MVS: minithoracotomy mitral valve surgery; ST-MVS: median sternotomy mitral valve surgery.

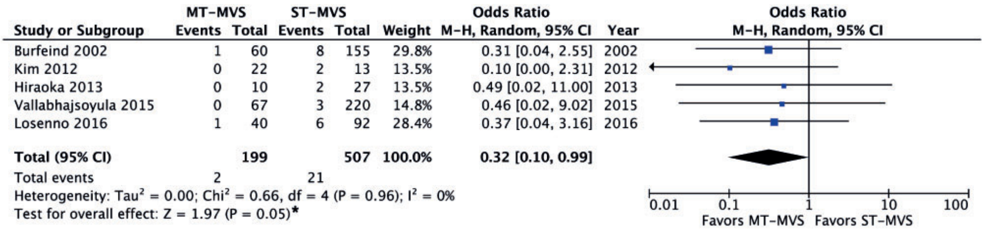

Figure 4. Comparison between redo MT-MVS and ST-MVS for the outcome reoperation for bleeding. *P = 0.0488. CI: confidence interval; MT-MVS: minithoracotomy mitral valve surgery; ST-MVS: median sternotomy mitral valve surgery.

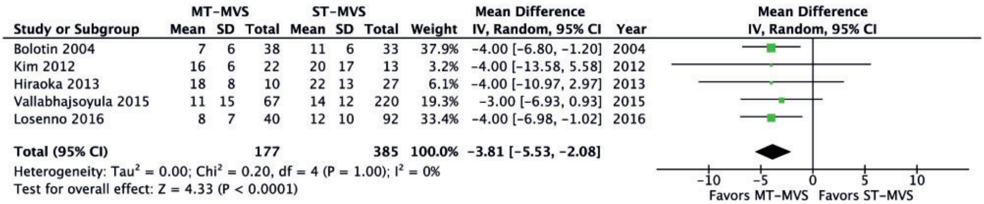

Figure 5. Comparison between redo MT-MVS and ST-MVS for the outcome length of hospital stay. CI: confidence interval; MT-MVS: minithoracotomy mitral valve surgery; SD: standard deviation; ST-MVS: median sternotomy mitral valve surgery

In Fig. 5, a homogeneous trend towards reduced LOHS for MT-MVS is seen. This trend was also demonstrated by meta-analysis; reoperation through a MT was significantly associated with a lower LOHS compared to patients who had ST-MVS, in the absence of any heterogeneity. The mean LOHS was 3.81 days shorter for MT-MVS. This more rapid patient recovery may be attributed to the minimally invasive nature of a MT approach, which yields less tissue trauma. This faster recovery was also described by Iribarne et al.[32,33] for first-time operations. In addition, reoperation due to postoperative bleeding was also expected to be lower as a result of reduced wound surface and less tissue trauma with MT-MVS. Moreover, because MT-MVS utilized retrograde perfusion, no aortic and right atrial cannula- tions were required, which translated into fewer surgical seams and a reduced risk of postoperative bleeding. This observation was confirmed by analysis (Fig. 4) and consistently translates into diminished blood loss and need for transfusion. However, be- cause transfusion outcomes were reported only in 1 study, quan- titative synthesis was not performed. The same applies to wound infections, which were reported in 2 studies. Nevertheless, zero wound infections were observed for MT-MVS compared to 4 for ST-MVS[24,25].

Among the included studies, only 2 reported use of preoperative computed tomography (CT) scans to address potential procedural difficulties or contraindications. Vallabhajosyula et al. [24] performed a CT scan out of concern for significant disease, where- as Hiraoka et al.[23] even performed an additional magnetic resonance imaging scan systematically. The added value of this pre- operative imaging was previously described elsewhere by Heuts et al.[34] and may potentially prevent procedural complications.

Apart from the proposed MT approach for redo MVS, several other techniques are currently evolving to circumvent the sub- stantial risks associated with redo ST, such as mitral transcatheter valve-in-valve (MTVIV) and valve-in-ring implantations. Both may be particularly useful for redo surgery patients with high risk or multiple comorbidities after failed mitral bioprosthesis or failed mitral valve repair, respectively. Implantation of these transcatheter, balloon-expandable valves may be performed via a transseptal or transapical approach, whereby the latter is performed through a left anterior MT in the 5th or 6th intercostal space. Despite the fact that a transseptal approach may be less invasive, it is believed to be more technically challenging, by which MTVIV is mainly performed transapically. Nevertheless, the safety and feasibility of transvenous transseptal MTVIV are currently being evaluated by the prospective clinical MITRAL trial (Mitral ImpLantation of TRAnscatheter vaLves) and will potentially be used more frequently in the future[35]. Overall, these percutaneous MTVIV and valve-in-ring implantations have demonstrated excellent haemodynamic performance with low perivalvular regurgitation and transvalvular gradient in feasibility studies[36-39]. In the current European Society of Cardiology/ European Association for Cardio-Thoracic Surgery 2017 guidelines for the management of valvular heart disease, these approaches were considered to be a reasonable alternative to redo operations for high-risk patients[40].

In summary, MT-MVS is a safe alternative for ST-MVS, with reduced mortality rates, reduced LOHS, lower incidence of reoperation for bleeding and comparable risk of stroke. Nevertheless, the trend towards increased risk of stroke may remain a substan- tial concern when considering reoperative MVS through a MT.

LIMITATIONS

Several limitations in this systematic review and meta-analysis should be addressed. The meta-analysis combined data across studies to estimate deaths and secondary outcomes. However, the main limitation of this analysis was the heterogeneity of risk profiles and selection criteria between centres. In addition, 3 different definitions of death were used, which could have led to bias. This systematic review only included retrospective observational studies because no randomized controlled trials have yet been published on this topic. Such observational studies are, however, more prone to confounding. In addition, the number of reports included was small, primarily because of the scarcity of comparative studies. The number of subjects within each MT group was also small and ranged from 10 to 67 compared to relatively larger ST groups, potentially limiting the level of evidence.

CONCLUSIONS

This meta-analysis is the first performed to test the differences between reoperative minimally invasive MVS through a right MT versus conventional median ST after prior cardiac surgery. The existing literature provided limited data but demonstrated significant differences with regards to mortality, LOHS and reoperation for bleeding, all in favour of MT-MVS. These benefits were evi- dent despite the comparable risk of stroke. Moreover, because the current evidence is of insufficient quality, this review could function as a base for more methodologically rigorous random- ized controlled trials.

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Chapter 14

Right Anterolateral Thoracotomy Versus Sternotomy for Resection of Benign Atrial Masses: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective

Primary benign cardiac tumors are rare disease entity that predominantly originate from the atria. Benign masses can induce heart failure, arrhythmia, or thromboembolic events. Therefore, surgical excision is often indicated. Current guidelines on the preferred approaches for resection (i.e., median sternotomy [MST] or right anterolateral thoracotomy [RAT]) are lacking. The aim of the current meta-analysis was to evaluate all studies comparing RAT to MST for excision of benign atrial masses in terms of safety, efficacy, and complications.

Methods

The PubMed and EMBASE databases were searched through 9 June 2020. Data regarding mortality, complications, recurrence, ICU stay, and length of hospital stay were extracted and submitted to meta-analysis using random effects modelling. Heterogeneity was assessed by the I2 test.

Results

Four retrospective observational studies were included, including 196 patients (RAT n = 97, MST n = 99). Mortality was 0% in both groups. Recurrence was <1% in the RAT group and 0% in the MST group. Complication rate tended to be lower in favor of the RAT group. Furthermore, RAT was associated with lower length of ICU stay (–17.7 hr, $P = 0.01$) and hospital stay (–4.0 days, $P < 0.001$). No significant differences in cardiopulmonary bypass ($P = 0.09$) and cross-clamp times ($P = 0.15$) were observed.

Conclusions

The RAT approach is as safe and effective as MST for the excision of benign atrial masses. Moreover, RAT is associated with a reduced complication rate and a reduced duration of hospitalization and could be considered as the preferred approach in anatomically suitable patients.

INTRODUCTION

Primary cardiac tumors are a relatively rare disease entity, with an incidence of approximately 0.02% in the general population.[1,2] The overwhelming majority of these tumors are of benign origin and originate from the atria, predominantly the left atrium (LA).[1,3] Of these benign masses, cardiac myxomas are the most frequently encountered entities tumors on pathological examination.[4] Additionally, lipoma, papillary fibroelastoma, fibroma, and hemangioma are observed within the spectrum of benign cardiac masses.[5] The clinical manifestation of myxoma is predominantly asymptomatic, it affects females more often than males and occurs at a relatively young age (mean age 56 years).[6] Patients can suffer from a wide variety of symptoms that range from minor fatigue to severe dyspnea, arrhythmia, and even stroke.[7] Although cardiac tumors are usually encountered as an incidental finding in asymptomatic patients, surgical excision is usually indicated because they can induce heart failure and can even cause arrhythmia and thromboembolic events.8 However, guidelines for surgical indications, treatment and preferred approaches are lacking, due to a paucity in comparative data.[9] Historically, median sternotomy (MST) has been the standard approach for excision of these masses. For the past decades, minimally invasive cardiac surgery (MICS) has emerged as an accepted approach for a variety of cardiac procedures such as mitral valve surgery, aortic valve surgery, and surgery for arrhythmia.[10–12] The rise of MICS has mainly been driven by its potential benefits, such as decreased length of intensive care unit (ICU) and hospital stay, decreased surgical trauma with reduced need for blood transfusion, and increased patient cosmetics and satisfaction. The advantages of MICS have mainly been studied in mitral valve surgery, where comparable efficacy was demonstrated without compromising patient safety.[13] In line of these findings, it would be equitable to hypothesize that benefits of MICS might also apply for patients undergoing excision of atrial masses, especially because of the presumed short operating time. However, given the low incidence of benign cardiac masses and single-center experiences with relatively small patient cohorts, data supporting the potential superiority of such an approach are lacking. The aim of the current meta-analysis is to review all published observational studies that compare benign atrial mass resection through a right anterolateral thoracotomy (RAT) and conventional MST in order to evaluate safety, efficacy, and potential superiority in terms of hospitalization and complications of such a minimally invasive approach.

METHODS

A local review protocol was drafted prior to initiation. The current systematic review and meta-analysis was written in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14]

Eligibility Criteria

Types of participants

Patients aged above 18 years with an atrial and presumed benign mass, who underwent a first-time cardiac surgical procedure were considered for inclusion. All cardiac tumors in any other location than atrial (e.g., ventricular) were excluded. Patients who underwent concomitant procedures (e.g., coronary artery bypass grafting, aortic valve surgery) that cannot be performed through a right-sided minimally invasive approach were excluded as well.

Types of interventions

Studies comparing a minimally invasive approach (defined as RAT with central or peripheral cannulation and avoiding sternotomy) to MST for the resection of benign atrial masses were considered for inclusion. Concerning the RAT approach, no distinctions were made between the incision length, cannulation site, or the use of a video-assisted or direct-vision approach. Studies including patients undergoing robotic surgery were excluded as telemanipulation is considered to encompass a different area of MICS.[15]

Types of outcome measures

The primary outcome was all-cause mortality defined as in-hospital death or death within 30 days following surgery. Secondary outcomes were complications such as stroke, wound infection, atrial arrhythmias, pneumonia, reoperation for bleeding, conversion to sternotomy (for RAT patients), and ICU and length of hospital stay (LOHS).

Types of studies

All observational and randomized studies comparing RAT to MST for excision of presumed benign atrial masses were examined for eligibility. Studies reporting combined data were solely considered if outcomes on atrial mass excisions were presented separately. The same accounted for studies reporting on any concomitant procedures.

Search and Study Selection

A systematic search was performed using the electronic MEDLINE and PubMed Central databases through Embase (Supplemental Table 1, Supplemental Table 2). Additionally, a cross-reference and related-article search was performed. Only articles reported in the English language were considered. No publication date restrictions were imposed. All searches were performed by an experienced author (JD) that was previously trained by a certified librarian. The last search was run on June 9th, 2020. Studies were screened for eligibility based on their title and abstract. Subsequently, full texts of potentially eligible reports were comprehensively assessed according to the predefined eligibility criteria. Studies adhering to these criteria were included for review and if possible, for meta-analysis. Two independent reviewers (JD, SH) carried out study selection in a nonblinded standardized manner. Potential inter-reviewer disagreements were resolved by consultation of a third author (JO).

Data Collection

Data extraction was performed by two authors (JD, SH). Potential inter-reviewer disagreements were resolved by consultation of a third author (JO). Studies reporting continuous variables as mean and standard deviation (SD) were extracted as such, while those reported in any other way were first converted applying the methods by Wan et al.[16] The following data were extracted: (a) general study characteristics (study design, enrolment period, country, and setting), (b) characteristics of participants (number of patients, age, gender, and preoperative characteristics such as left ventricular function), (c) intervention characteristics (arterial and venous cannulation site, clamping technique, cardioplegia route, concomitant procedures, conversion rate to sternotomy, and cardiopulmonary bypass [CPB] and cross-clamp time), (d) primary outcome measure (death, either reported as 30-day mortality or in-hospital death), (e) secondary outcomes (stroke, wound infection, atrial arrhythmia, pneumonia, reoperation for bleeding, conversion to sternotomy, ICU stay, and LOHS).

SUMMARY MEASURES AND SYNTHESIS OF RESULTS

Meta-analyses were conducted by RevMan v5.3 for Macintosh (Cochrane Collaboration, Oxford, UK) using the random-effects model with inverse variance or Mantel-Haenszel method and I2 test of heterogeneity. An I2 value larger than 50% in conjunction with a P <0.10 indicated the presence of statistically significant heterogeneity among studies. Risk ratios (RR) were used to compare dichotomous outcome measures. Continuous variables were compared using the difference in means (MD) if reported similarly among studies. If not, the standardized mean difference (SMD) was used. A MD or SMD less than zero or a RR <1.0 was interpreted to favor the RAT approach. A P value <0.05 was considered statistically significant. Subgroup analyses were not prespecified and conducted in the presence of significant heterogeneity.

Risk of Bias Across Studies

Nonrandomized studies were judged on risk of bias in individual studies using the ROBINS-I tool[17], by 2 independent reviewers (JD, SH). The presence of publication bias was evaluated both visually and statistically by jamovi v0.9 for Macintosh (MAJOR software package add-on, the jamovi project, Sydney, Australia). A funnel plot of the primary outcome measure was created and Egger's test as well as Begg's and Mazumdar's test were conducted. A P value <0.05 was considered statistically significant.

RESULTS

Study Selection

The MEDLINE and Embase databases were searched using the predefined terms, producing a total number of 256 publications. Additional, 1 publication was acquired by cross-reference searches. After exclusion of duplicates (n = 74), 182 articles were screened based on title and abstract, where after 12 articles remained for full-text assessment. These articles were assessed in detail and 8 more articles were excluded. Reasons for exclusion were nonatrial masses (n = 4), robotic surgery (n = 1), results not reported separately (n = 2), and hemisternotomy as minimally invasive technique (n = 1). Finally, 4 studies were included for qualitative and quantitative synthesis (Fig. 1).[18–21]

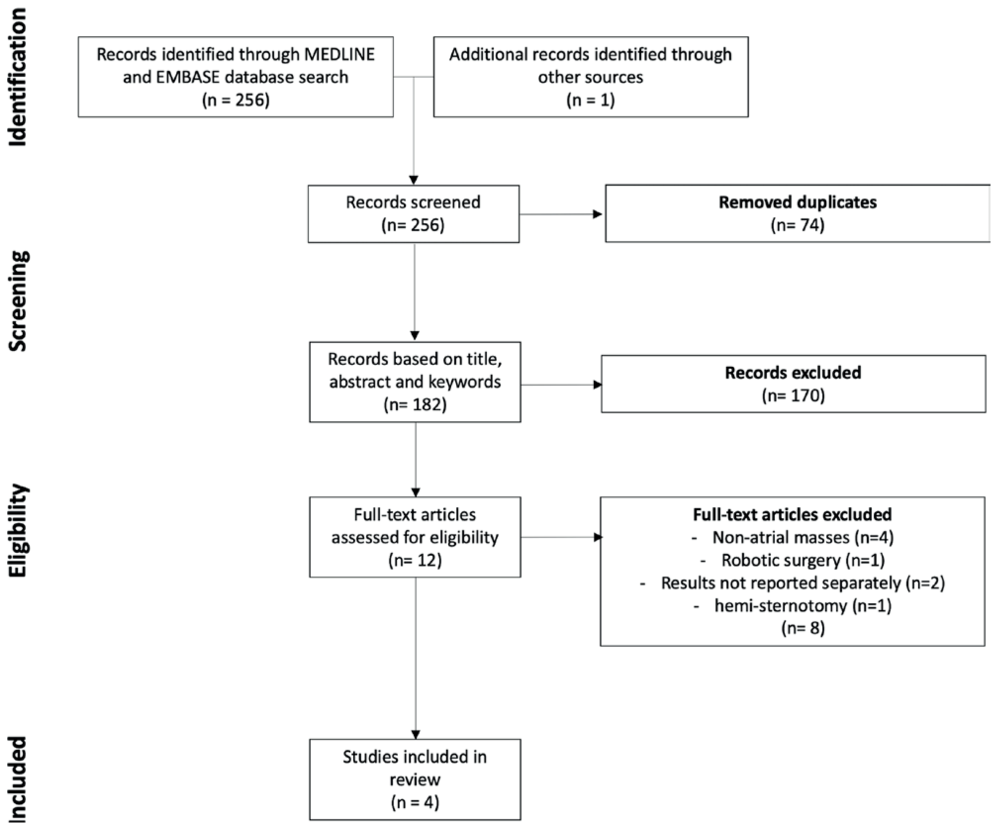


Figure 1. PRISMA flow- chart.

STUDY CHARACTERISTICS

Methods

All studies were written in the English language and comprised retrospective single-center observational cohorts that were conducted in Canada[18], China[19,20] or Japan.[21] Studies were published between 2015 and 2018, retrospectively including patients operated between 2001 and 2017

Participants

Baseline characteristics of both groups per study are presented in Table 1. Cumulatively, 196 patients were included and subdivided into a RAT (n = 97, 49%) and MST group (n = 99, 51%). The cumulative number of patients per study ranged from 23 to 6619[21] patients. Mean age ranged from 48 to 69 years in the RAT group and 52 to 63 years in the MST group. The RAT group included 68 females (70%) compared to 72 females (73%) in the MST group. Body mass index was only reported in 3 studies, as well as left ventricular ejection fraction (Table 1).[18,20,21]

Table 1. Study and Patient Characteristics.

Study	Country	Study design	Study period	Group	Participants (M/F)	Age, y	Body mass index, kg/m^2	Preoperative EF, %	Preoperative neurological events	Follow-up time
Deng et al. (2017)	China	Retrospective observational	Mar 2012 to Aug 2015	RAT	40 (13/27)	48 ± 11	NR	NR	2 (5%)	12 months
				MST	24 (5/19)	52 ± 4	NR	NR	0	12 months
Dong et al. (2018)	China	Retrospective observational	Jan 2009 to Jun 2015	RAT	30 (6/24)	56 ± 7	21.7 ± 1.8	61 ± 7	3 (10%)	12 months
				MST	36 (9/27)	54 ± 6	22.6 ± 2.1	59 ± 6	3 (8%)	12 months
Ellouze et al. (2018)	Canada	Retrospective observational	Oct 2011 to Dec 2017	RAT	20 (6/14)	61 ± 12	26 ± 4	60 ± 6	7 (45%)	111 ± 105 days
				MST	23 (9/14)	56 ± 12	25 ± 6	57 ± 7	6 (26%)	570 ± 577 days
Sawaki et al. (2015)	Japan	Retrospective observational	Sep 2001 to Feb 2014	RAT	7 (4/3)	69 ± 8	23.4 ± 2.4	69 ± 5	2 (29%)	4.7 ± 3.7 y
				MST	16 (4/12)	63 ± 18	23.9 ± 4.1	68 ± 7	1 (6%)	4.7 ± 3.7 y

Abbreviations: EF, ejection fraction; F, female; M, male; MST, median sternotomy; NR, not reported; RAT, right anterolateral thoracotomy.
Data presented as mean ± SD or frequency.

Intervention

Inclusion criteria of studies were patients requiring excision of benign atrial masses, either through a minimally invasive approach (defined as RAT, either with peripheral or central cannulation) or through MST with central cannulation. Considerations regarding patient selection were merely mentioned by Dong et al., stating that patients were chosen based on "specialist selection."[20] In the RAT group, arterial cannulation was achieved through femoral cannulation in all studies, while 1 study did not report on arterial cannulation site in the MST group,[19] but this was perceived to be in the ascending aorta. Several techniques for venous cannulation were used in the RAT group, of which femoral (with or without an additional jugular cannula) was most prevalent. In the RAT group, aortic occlusion technique was reported by 3 studies.[18,20,21] In these studies, 2 reported to have exclusively used a transthoracic aortic crossclamp,[20,21] while 1 study reported on 1 case of endoaortic balloon exclusion (Table 2).[18] Three studies compared RAT to MST for excision of benign cardiac masses exclusively.[18,20,21] Deng et al. reported on outcomes of RAT versus MST for excision of benign cardiac masses and the correction of atrial septal defects or mitral/tricuspid valve repair.[19] However, the results for mass excision were reported separately, which resulted in the inclusion of this study.

Table 2. Operative Data.

Study	Group	Myxoma location	Concomitant procedures	Arterial cannulation site	Venous cannulation site	Clamping technique	Cardioplegia route	Cross-clamp time, min	CPB time, min	Conversion to sternotomy
Deng et al. (2017)	RAT	LA (*n* = 38, 95%), RA (*n* = 2, 5%)	None	Fem	Fem	NR	Antegrade	45 ± 17	125 ± 29	NR
	MST	LA (*n* = 17, 71%), RA (*n* = 7, 29%)	None	NR	NR	—	NR	34 ± 16	59 ± 5	—
Dong et al. (2018)	RAT	LA (*n* = 30, 100%)	NR	Fem	Fem (*n* = 30), additional JV (*n* = 30)	Cross-clamp	Antegrade	50 ± 6	88 ± 10	0
	MST	LA (*n* = 36, 100%)	NR	AscA	Bicaval	—	NR	48 ± 6	84 ± 8	—
Ellouze et al. (2018)	RAT	LA (*n* = 18, 90%), RA (*n* = 2, 10%)	Maze (*n* = 1, 5%)	Fem	Fem (*n* = 20), additional JV (*n* = 9)	Endoclamp (*n* = 1), cross-clamp (*n* = 19)	Antegrade	37 ± 15	64 ± 18	0
	MST	LA (*n* = 19, 83%), RA (*n* = 4, 17%)	Maze (*n* = 2, 9%)	AscA	Bicaval	—	Antegrade (*n* = 23), additional retrograde (*n* = 6)	38 ± 20	54 ± 25	—
Sawaki et al. (2015)	RAT	LA (*n* = 6, 86%), RA (*n* = 1, 14%)	None	Fem	Fem	Cross-clamp	Antegrade	52 ± 27	109 ± 35	0
	MST	LA (*n* = 13, 82%), RA (*n* = 2, 13%), AS (*n* = 1, 6%)	None	AscA	Bicaval	—	Antegrade	49 ± 21	88 ± 25	—

Abbreviations: AS, atrial septum; AscA, ascending aorta; CPB, cardiopulmonary bypass; Fem, femoral; JV, jugular vein; LA, left atrium; MST, median sternotomy; NR, not reported; RA, right atrium; RAT, right anterolateral thoracotomy.
Data presented as mean ± SD or frequency.

Outcomes

All included papers reported on the primary outcome, mortality. Other outcomes were at least reported by 1 study each.

Risk of Bias Within Studies

Of the 4 nonrandomized studies, 3 were judged to possess a moderate risk of bias,18,20,21 while 1 study was judged to have serious risk of bias (Supplemental Fig. 1, Supplemental Fig. 2).[19] The largest share in bias resulted from potential confounding that was most probable for Deng et al.[19]

SYNTHESIS OF RESULTS

The extracted data on primary and secondary outcomes are presented in Table 2 and Table 3. As the event rates for mortality and complications were extremely low, these were withheld from quantitative synthesis. Furthermore, as blood loss was reported by only 1 study, it was not included in qualitative synthesis.[18] Conversion to sternotomy was admitted to qualitative synthesis, as this complication was solely reserved for the RAT group. As there was excellent reporting with acceptable heterogeneity for CPB time, cross-clamp time, ICU stay, and LOHS, these outcomes could be included in quantitative analyses.

Qualitative Synthesis of Results

Mortality was reported by all studies and was 0% for both the RAT and MST groups.[18–21] Stroke was reported by 3 studies and was also 0% for both groups.[19–21] Three studies described wound infections and showed an incidence of 3% (n = 2) in the MST group and 0% in the RAT group.[18,20,21] Atrial arrhythmias were reported by 3 studies and occurred in 9% (n = 6) patients in the RAT group versus 16% (n = 12) in the MST group.[18,20,21] Pneumonia was solely described by Dong et al., and was 0% in both groups.[20] Three studies presented data on reoperation for bleeding, which was 0% in the RAT group and 1% (n = 1) in the MST group.[18,20,21] Total amount of intraoperative blood loss was only reported by Ellouze et al., and was 106 ± 95 ml in the RAT group versus 339 ± 270 ml in the MST group.[18] Intraoperative conversion to sternotomy in patients undergoing RAT approach was reported by 3 studies and was 0%.[18,20,21] The location of benign masses, reported by all studies, were in the LA in 95% of RAT patients (n = 92) and the right atrium (RA) in 5% of RAT patients (n = 5). For the MST group, the masses were originating from the LA in 86% of cases (n = 85), the RA in 13% of cases (n = 13), and within the atrial septum in 1 patient (1%).[18–21]

On pathological examination, which was reported by 2 studies,[20,21] all masses proved to be a myxoma in the RAT group, while 92% (n = 48) of masses were myxoma in the MST group. Other benign masses were thrombus, hemangioma, or hamartoma.[21] On long-term follow-up, late recurrence was <1% (n = 1) in the RAT group and 0% in the MST group, which was reported by all studies.[18–21] All data included in the qualitative synthesis are summarized and presented in Table 2 and Table 3.

Table 3. Outcomes.

Study	Group	LOHS, days	ICU stay, hr	VT, hr	CVA	WI	Arrhythmia	Pneumonia	Reoperation for bleeding	Blood loss, mL	Recurrence	Pathological examination	30-day mortality
Deng et al. (2017)	RAT	10.0 ± 3.5	17.7 ± 5.0	6.5 ± 2.4	0	NR	NR	NR	NR	NR	0	NR	0
	MST	15.1 ± 1.1	49.9 ± 3.2	6.4 ± 0.5	0	NR	NR	NR	NR	NR	0	NR	0
Dong et al. (2018)	RAT	5.0 ± 1.6	29.2 ± 6.5	NR	0	0	1 (3%)	0	0	NR	0	myxoma (*n* = 30, 100%)	0
	MST	8.3 ± 2.3	43.5 ± 6.9	NR	0	0	2 (6%)	0	0	NR	0	myxoma (*n* = 36, 100%)	0
Ellouze et al. (2018)	RAT	5.7 ± 3.0	39.6 ± 28.8	3.9 ± 1.4	NR	0	4 (20%)	NR	0	106 ± 95	1 (5%)	NR	0
	MST	7.1 ± 2.0	54.2 ± 43.2	5.0 ± 2.4	NR	2 (9%)	8 (35%)	NR	1 (4%)	339 ± 270	0	NR	0
Sawaki et al. (2015)	RAT	10.4 ± 1.5	24.3 ± 9.7	4.7 ± 1.1	0	0	1 (14%)	NR	0	NR	0	myxoma (*n* = 7, 100%)	0
	MST	17.5 ± 5.6	30.6 ± 19.5	12.4 ± 16.7	0	0	2 (13%)	NR	0	NR	0	myxoma (*n* = 12, 75%), thrombus (*n* = 2, 13%), hemangioma (*n* = 1, 6%), hamartoma (*n* = 1, 6%)	0

Abbreviations: CVA, cerebrovascular accident; ICU, intensive care unit; LOHS, length of hospital stay; NR, not reported; MST, median sternotomy; RAT, right anterolateral thoracotomy; VT, ventilation time; WI, wound infection.
Data presented as mean ± SD or frequency.

Quantitative Synthesis of Results

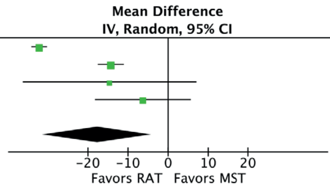
Figure 2 demonstrates results of the meta-analysis for ICU stay and LOHS. Both outcomes were reported as raw MD because ICU stay (hours) and LOHS (days) were reported uniformly by all studies with a clearly defined T0 (day of surgery). Mean ICU stay ranged from 18 to 39 hr in the RAT group compared to 30 to 54 hr in the MST group. Raw MD was −17.7 hr in favor of the RAT group, which was statistically significant (95% confidence interval [CI] −31.3 to −4.1, P = 0.01]. However, significant heterogeneity was noted (I 2 = 97%, P < 0.001). Mean LOHS ranged 5 to 10 days in the RAT group compared to 7 to 18 days in the MST group. Raw MD was −4.0 days in favor of the RAT group, which was statistically significant (95% CI −5.9 to −2.1, P < 0.001). Again, significant heterogeneity was noted (I 2 = 85%, P < 0.001). Figure 3 presents the results of the meta-analysis for CPB and aortic cross-clamp times. Again, as all studies reported uniformly on these outcomes (in minutes) with a clearly defined T0, data were depicted as raw MD. Mean CPB time ranged from 64 to 125 min in the RAT group compared to 54 to 88 min in the MST group. However, there was no statistically significant difference between the groups (P = 0.15). For this outcome, significant heterogeneity was found (I 2 = 98%, P < 0.001). Mean aortic cross-clamp time ranged from 37 to 52 min in the RAT group compared to 34 to 49 min in the MST group. Again, this difference was not statistically significant (P = 0.09). Finally, for this outcome there was no significant heterogeneity (I 2 = 29%, P = 0.24).

It was not possible to construct a funnel plot of the primary outcome, as there were no fatal events in either group. Therefore, the presence of publication bias was deemed highly unlikely.

a

Study or Subgroup	RAT Mean	RAT SD	RAT Total	MST Mean	MST SD	MST Total	Weight	Mean Difference IV, Random, 95% CI
Deng et al., 2017	17.67	4.95	40	49.88	3.21	24	29.6%	−32.21 [−34.21, −30.21]
Dong et al., 2018	29.2	6.5	30	43.5	6.9	36	29.3%	−14.30 [−17.54, −11.06]
Ellouze et al., 2018	39.6	28.8	20	54.24	43.2	23	16.9%	−14.64 [−36.34, 7.06]
Sawaki et al., 2015	24.3	9.7	7	30.6	19.5	16	24.2%	−6.30 [−18.26, 5.66]
Total (95% CI)			**97**			**99**	**100.0%**	**−17.72 [−31.33, −4.11]**

Heterogeneity: $Tau^2 = 162.05$; $Chi^2 = 97.81$, df = 3 (P < 0.00001); $I^2 = 97\%$
Test for overall effect: Z = 2.55 (P = 0.01)



b

Study or Subgroup	RAT Mean	RAT SD	RAT Total	MST Mean	MST SD	MST Total	Weight	Mean Difference IV, Random, 95% CI
Deng et al., 2017	9.97	3.54	40	15.13	1.06	24	27.8%	−5.16 [−6.34, −3.98]
Dong et al., 2018	5	1.6	30	8.3	2.3	36	29.0%	−3.30 [−4.24, −2.36]
Ellouze et al., 2018	5.7	3	20	7.09	2	23	25.7%	−1.39 [−2.94, 0.16]
Sawaki et al., 2015	10.4	1.5	7	17.5	5.6	16	17.5%	−7.10 [−10.06, −4.14]
Total (95% CI)			**97**			**99**	**100.0%**	**−3.99 [−5.86, −2.12]**

Heterogeneity: $Tau^2 = 2.90$; $Chi^2 = 20.23$, df = 3 (P = 0.0002); $I^2 = 85\%$
Test for overall effect: Z = 4.19 (P < 0.0001)

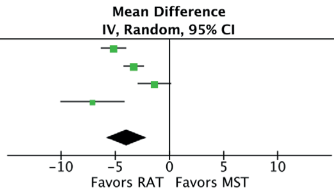


Figure 2. Forest plots for length of intensive care unit stay (a) and length of hospital stay (b). MST, median sternotomy; RAT, right anterolateral thoracotomy.Publication Bias Assessment

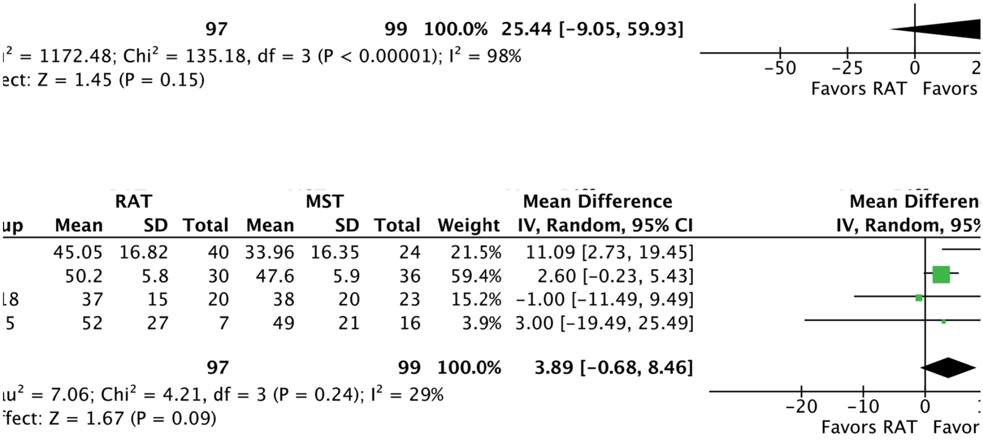


Figure 3. Forest plots for cardiopulmonary bypass time (a) and aortic cross- clamp time (b). MST, median sternotomy; RAT, right anterolateral thoracotomy.

DISCUSSION

To the best of our knowledge, this is the first study that systematically reviewed all published observational studies comparing benign atrial mass resection through a RAT and conventional MST approach. In principle, a less invasive surgical approach should not be preferred at the expense of safety and efficacy. For myxoma resection, safety can be defined as mortality and morbidity, while efficacy can be defined as recurrence rate. Therefore, in this meta-analysis, mortality rate was prespecified as the primary outcome. As demonstrated, surgical excision of benign atrial masses, either through RAT or MST, is a safe procedure as mortality rate in both groups was 0%. Additionally, major morbidity was low, with a stroke rate of 0% for both approaches. These low rates could be the result of underpowering, given the inclusion of a relatively small numbers of patients. Still, these numbers are confirmed in the literature in single-arm studies as reported by Vroomen et al.,[22] Obrenović-Kirćanski et al.,[23] and Keeling et al.[24] with an early mortality rate ranging between 0% and 2%. Furthermore, low mortality and morbidity rates can also be explained by the absence of risk factors as these patients are generally considered a low-risk patient group due to their young age and preserved cardiac function.[6]

Not all complications were reported by all studies, and definitions of these complications differed between the reporting studies. As their rate was relatively low as well, they were not included for meta-analysis. Still, all reported complications had a tendency to occur less in the RAT group, without any conversions to sternotomy. As prolonged aortic cross-clamp and CPB times are known to negatively influence postoperative outcomes,25 these times were evaluated as well. For both groups, these surgical times were relatively short and did not significantly differ between approaches.

Based on these findings, we conclude that the RAT approach is as safe as the MST approach for atrial mass resection. As radical resection is imperative, there should be no trade-off in recurrence rate. Again, as recurrence rate was extremely low, this outcome was not included for quantitative synthesis. In the current review, recurrence rate in the RAT group was <1% and 0% in the MST group. However, prior studies have described recurrence rates ranging from 3% to 22% for sporadic tumors and familial myxomas independent of surgical approach.[26,27] Reasons for recurrence vary from incomplete resection or tumor spread during first surgery to regrowth in another location[28] whereby the latter is mostly seen in patients with Carney complex.[29] Given the low recurrence rates in both groups, we conclude that a minimally invasive approach is as efficacious as a conventional approach. As our data demonstrated the RAT approach to be as safe as an MST approach, we aimed to compare secondary outcomes such as complications, ICU stay, and LOHS in order to evaluate the potential benefit of a minimally invasive approach. In our analysis, ICU stay and LOHS was notably reduced for RAT. However, significant heterogeneity was observed, as described by the I2 test. Still, by mere visual assessment of the forest plots, differences in surgical times are observed between studies, but are all in favor of a minimally invasive approach (Fig. 2). These observed differences between studies could potentially be explained by different hospital protocols for ventilation times, postoperative echocardiographic assessment, or transfer to referral hospitals.[30] Although significantly shorter hospitalization was observed for the minimally invasively treated patients, the real objective of such an approach is a faster rehabilitation and return to work. Generally, patients with benign cardiac masses are relatively young, which makes a quick recovery and return to work even more important. The included studies did not evaluate these outcomes. However, previous studies comparing minimally invasive approaches to MST for mitral valve surgery have demonstrated patients treated by minimally invasive manner achieve faster rates of independent ambulation,[31] and return to work or study more rapidly.[32] In perspective, starting with a RAT approach for benign mass resection could also enhance surgical skills for other minimally invasive cardiac procedures. The most prevalent cardiac surgical procedure through a right-sided minimally invasive approach with peripheral CPB is minimally invasive mitral valve surgery (MIMVS). Still, the learning curve for this procedure is relatively long, with an estimated number of 75 to 125 operations before overcoming this learning curve.[33] Given the similarity in both approaches for MIMVS and myxoma resection, and the short aortic cross-clamp and CPB times associated with myxoma resection through a RAT approach, implementation of this procedure in the MIMVS learning curve could potentially reduce the case volume load needed to overcome the earlier perceived threshold. Finally, we would like to emphasize that we do not advocate a minimally invasive approach for all patients undergoing atrial mass resection. Especially peripheral CPB cannulation can be unsuitable for certain types of patients with extensive peripheral arterial disease. We believe patient selection for a minimally invasive approach is crucial for success and should depend on surgical experience, patient characteristics, and anatomical eligibility.[34] None of the studies reported any information about the inclusion criteria for patient allocation to a minimally invasive approach, most likely due to the retrospective methodology. Only Dong et al. reported, selection for minimally invasive surgery was chosen by specialist recommendation.

In all studies minimally invasive approaches were combined peripheral cannulation through the femoral artery, and none of the studies reported any information about preoperative computed tomography angiography for selection of patients for retrograde perfusion.

LIMITATIONS

A modest number of studies and patients were included in the current meta-analysis. However, due to the low incidence of benign atrial masses, such a patient number would be difficult to accumulate in prospective manner. Regarding the study methodology, none of the included studies were randomized controlled trials. Again, this type of study would be challenging to conduct given the inherent disease epidemiology. Another limitation of this analysis includes the selection criteria for minimally invasive surgery with heterogeneity in risk profiles, on which most of the studies did not report. Finally, in contrast to full sternotomy, minimally invasive surgery can be performed using several strategies (i.e., under direct vision or fully endoscopically and with antegrade or retrograde perfusion). As all these strategies were included in the RAT group in the current analysis, a possible difference in outcome due to surgical strategy could not be investigated.

CONCLUSIONS

Benign atrial masses have a relatively low incidence and occur mostly in relatively young patients. In the current meta-analysis, we demonstrated benign atrial mass resection to be a safe procedure. Furthermore, a minimally invasive approach through a right anterolateral thoracotomy proved to be as safe and effective as a conventional approach through median sternotomy. As a minimally invasive approach was associated with reduced complication rate and duration of hospitalization, it could be considered as the preferred approach in anatomically suitable patients.

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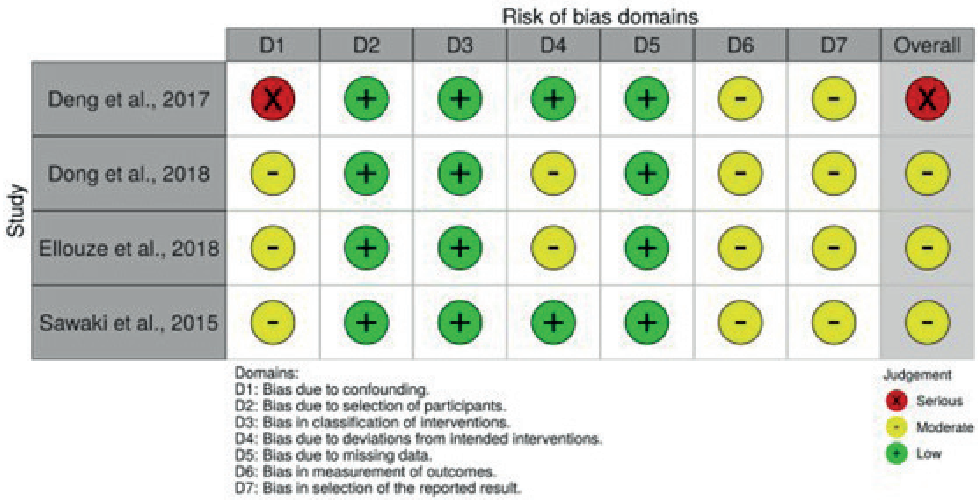
SUPPLEMENTAL MATERIAL

Supplemental Table 1. MEDLINE & PubMed Central

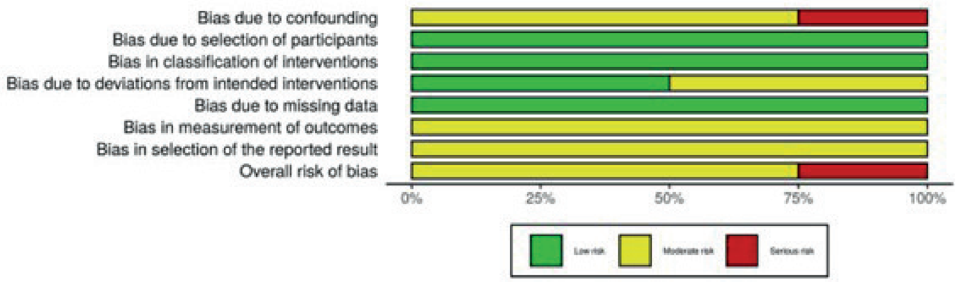
Overview		
Database	MEDLINE & PubMed Central	
Platform	PubMed	
Date of search	June 9th, 2020	
Number of results	92	
Syntax guide		
Mesh	Medical subject headings	
tiab	Words in title or abstract	
*	Truncation	
Search	**Query**	**Items found**
#1	"myxoma"[Mesh]	7,232
#2	myxom*[tiab] OR angiomyxom*[tiab] OR benign mass*[tiab] OR cardiac mass*[tiab] OR benign tumor*[tiab] OR benign tumour*[tiab] OR cardiac tumor*[tiab] OR cardiac tumour*[tiab] OR atrial mass*[tiab] OR atrial tumor*[tiab] OR atrial tumour*[tiab]	37,335
#3	#1 OR #2	38,462
#4	"minimally invasive surgical procedures"[Mesh]	513,769
#5	minimal* invasiv*[tiab] OR thoracotom*[tiab] OR minithoracotom*[tiab] OR mini-thoracotom*[tiab]	28,521
#6	#4 OR #5	534,265
#7	"sternotomy"[Mesh]	2,389
#8	sternotom*[tiab]	9,749
#9	#7 OR #8	10,658
#10	#3 AND #6 AND #9	92

Supplemental Table 2. Embase

Overview		
Database	Embase	
Platform	Embase	
Date of search	June 9th, 2020	
Number of results	164	
Syntax guide		
/exp	EMtree keyword with explosion	
:ab,ti	Words in title or abstract	
*	Truncation	
Search	**Query**	**Items found**
#1	'myxoma'/exp	11,383
#2	'myxom*':ab,ti OR 'angiomyxom*':ab,ti OR 'benign mass*':ab,ti OR 'cardiac mass*':ab,ti OR 'benign tumor*':ab,ti OR 'benign tumour*':ab,ti OR 'cardiac tumor*':ab,ti OR 'cardiac tumour*':ab,ti OR 'atrial mass*':ab,ti OR 'atrial tumor*':ab,ti OR 'atrial tumour*':ab,ti	47,088
#3	#1 OR #2	49,902
#4	'minimally invasive surgery'/exp	41,265
#5	'minimally invasive procedure'/exp	56,336
#6	'minimal* invasiv*':ab,ti OR 'thoracotom*':ab,ti OR 'minithoracotom*':ab,ti OR 'mini-thoracotom*':ab,ti	132,919
#7	#4 OR #5 OR #6	149,565
#8	'sternotomy'/exp	19,858
#9	'sternotom*':ab,ti	14,214
#10	#8 OR #9	23,967
#11	#3 AND #6 AND #10	164



Supplemental Figure 1. Risk of Bias Assessment Per Study



Supplemental Figure 2. Risk of Bias Assessment Overall

Chapter 15

General Discussion

DISCUSSION

This thesis describes a personalized approach for patients with mitral valve (MV) disease in general and patients undergoing minimally invasive mitral valve (MIMVS) procedures in particular. The MV remains one of the most complex valve pathologies in cardiac surgery. The wide variety in MV pathology and different stages of disease has resulted in a more diverse landscape of treatment modalities. Combined with a paradigm shift towards a minimally invasive approach to reduce surgical trauma to patients. In that light, patient selection is more complex than ever. Since the first MV procedure performed in 1923, the field of MV surgery changed completely. Mitral valve surgery transformed from a classical approach – through sternotomy - towards minimally invasive procedures, an evolution which is expected to continue in the coming years. This shift from conventional surgery towards less invasive surgical procedures is mainly due to a more demanding patient population, an increase in technical possibilities and the advent of trans-catheter procedures performed by interventional cardiologists, which pushes the surgical community to be innovative in this respect. As an advantage, these less invasive approaches even allow treatment of patients initially deemed too high of a risk, as many of these approaches avoid substantial surgical trauma and the use of cardiopulmonary bypass (CPB). As a result of these developments, a tailored made approach for each individual patient is warranted, which requires an extensive multidisciplinary deliberation. Therefore, the most important dilemma for patients, cardiologists and cardiothoracic surgeons remains to select the right patient, for the right technique and approach, at the right time. As such, personalized medicine is the objective in MV disease.

The concept of personalized medicine can be divided in three separate phases: the pretreatment phase, a personalized treatment phase and a post treatment phase (Figure 1). However, in this concept surgeons should not exclusively focus on the operation itself but concentrate on the whole process of treatment from the pre-treatment phase to the post-treatment phase. Embedded in personal medicine is the strive to work with dedicated teams throughout the treatment.

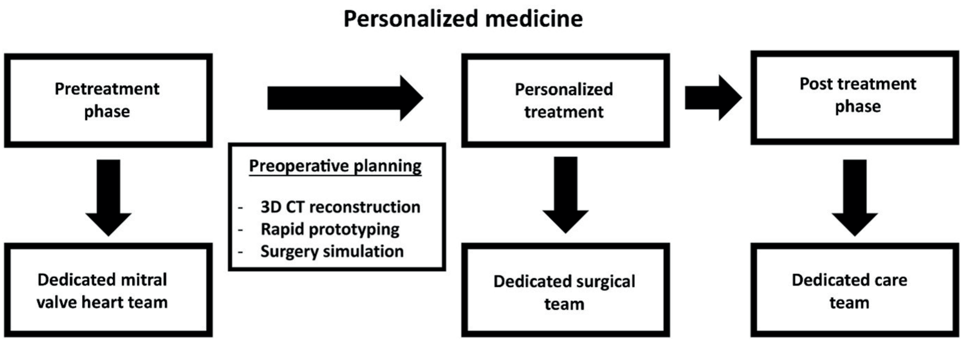


Figure 1. The concept of personalized medicine

PRETREATMENT PHASE

The pretreatment phase starts when the patient presents to the general practitioner and is referred to a cardiologist. When after precise evaluation of the patient's history, symptomatic status, and proper physical examination, the diagnosis of MV dysfunction is suspected, transthoracic echocardiography (TTE) is performed to confirm the diagnosis. Echocardiography is the key technique used to confirm the diagnosis of MV disease, as well as to assess its etiology, severity, repairability and other associated valvular and ventricular dysfunction.[2, 3] If a cardiologist considers the valve dysfunction to be noteworthy, the patient can be referred to one of the sixteen tertiary cardiothoracic centers for evaluation in the heart team. In the Netherlands, the heart team approach for cardiovascular disease (CVD) has been integrated into daily practice, as recommended by current guidelines for valvular heart disease (VHD). [4, 5] Although there might be institutional practice differences between the heart teams in the Netherlands, every patient undergoing any complex cardiac intervention will pass through the heart team. Historically, the heart team consist of a cardiologist and cardiothoracic surgeon, which on a rotational basis discuss patients and determine whether additional diagnostic procedures are required and set a potential indication for an intervention. In the conventional circumstances of a general heart team, the rotational basis would not necessarily bring the required expertise together for the treatment of patients with MV disease. Still, the varying nature of MV pathology, the integrative approach to its assessment, the importance of timing of interventions, the variability in treatment options and the operator dependence of its outcome, makes the decision-making crucial for the individual patient. This complexity resulted in the concept of a dedicated mitral valve heart team. In this concept, the mitral valve heart team consist of a cardiac thoracic surgeon specialized in MV surgery, an imaging cardiologist subspecialized in MV imaging, and an interventional cardiologist dedicated to transcatheter treatment of the mitral- and tricuspid valve, ideally accompanied by a cardiologist with a heart-failure specialization. In high-risk patients, an anesthesiologist, intensivist and perfusionist can join this multidisciplinary discussion.

Multidisciplinary decision-making has been well established in various fields of medicine, especially in the treatment of patients with cancer. [6, 7] In different patient populations, an association between multi-disciplinary care teams and improved survival is observed. [8] Consequently, the concept of the heart team has gained interest considering the emergence of new therapeutic options in different subspecialities in cardiac surgery. [9] Although the heart team approach to CVD is apparently intuitive and has a class I indication in recent guidelines[4], actual scientific supporting evidence regarding its role in different subdomains, the composition of the team and its effect based on comparative data, is still lacking. In literature, the implementation of such a dedicated mitral valvular team has not described previously. In chapter 2, we present the initial findings of this dedicated mitral valve heart team. During the one-year study period one hundred and fifty-eight patients were included prospectively. The concept of a dedicated heart team is not merely a weekly meeting of medical experts in MV disease but extends by initiation of a standardized diagnostic pathway for all patients with MV disease, independent of etiology and severity. The identification of the etiology and underlying lesions that result in MV dysfunction is of particular importance for managing decisions; patients with degenerative mitral regurgitation (DMR) should be differentiated from those with other forms of MV disease such as rheumatic, functional mitral regurgitation (FMR) or mitral valve stenosis (MS).[11] In patients with isolated MV disease, which is defined as MV disease with or without indication for concomitant tricuspid valve (TV) intervention, rhythm surgery or atrial septal defect (ASD) closure, without contraindications, a CT angiography of the heart and aorta is performed to assess anatomical eligibility for a minimally invasive approach using peripheral cannulation.

As a merit of this dedicated approach, cardiologists can consult the MV heart team in any phase of the disease. Therefore, not only the patients referred for interventions are discussed, but cardiologist can also refer their patients for evaluation of the severity of MV disease. The heart team provides guidance for additional imaging and determines a follow-up strategy in cases without indication for intervention. The early referral strategy is illustrated by the number of patients who were treated conservatively due to an insufficient grade of MR for intervention (42%) in the first study (Chapter 2). These patients remain under surveillance of both the referring cardiologist but also the heart team keeps track of those patients, until they reach an actual indication for intervention. Earlier referral should be encouraged if a patient develops symptoms or worsens before the next planned visit.

In literature surgical intervention for severe MR is usually triggered by the occurrence of symptoms, declining left ventricle (LV) function, significant LV enlargement, or the development of atrial fibrillation (AF) or severe pulmonary hypertension. [12] Emerging data suggest a wide clinical practice gap in appropriate referral of patients with guideline-defined indications for surgical intervention. [13] Mirabel et al. found that 49% of patients with symptomatic MR of various etiologies from the Euro Heart Survey were denied surgical referral. [14] Advanced age, co-morbidities, and an abnormal ejection fraction were the arguments used to deny referral surgery. Furthermore, approximately 300 cardiologists were surveyed in Canada, of which nearly 40% of those cardiologists indicated that they would wait for the ejection fraction to fall below 40% or wait for symptoms to occur before referring an asymptomatic patient for surgery with severe MR. [15] One of the objectives of the dedicated MV heart team is to stimulate earlier referral by cardiologist for evaluation of the MV pathology and to determine, together, the adequate strategy. In this way the heart team extends beyond the boundaries of the treating hospital but includes the referring hospitals. This is a significant change in strategy, especially as in Chapter 3 it was observed that patients who did not following the advice of the heart team, had the worst survival at 5 years. Furthermore, in our study, we found that patients treated by a dedicated MV heart team had significantly higher survival rates compared to a general heart team. It remains unclear whether this is a consequence of centralization and increasing center and individual experience and volume, or the tendency to operate earlier on patients, but it strengthens our believe in the proposed approach, whereby the referring cardiologist is integrated.

Furthermore, MV disease also affects the left ventricle and increases left atrial pressure, which result in pulmonary hypertension and subsequent increases in right ventricular (RV) afterload. As such, MV pathology ultimately also affects the RV and the TV, which can lead to tricuspid regurgitation (TR). As the prevalence of MV disease and MV surgery is increasing16, this also applies to the presence and prevention of secondary TR. Current guidelines do not only recommend concomitant TV surgery when secondary severe TR is present, but also in moderate TR accompanied by TV dilatation of more than 40 millimetres[4]. New evidence even suggests performing concomitant TV repair in patients with mild TR and significant TV dilatation, as many patients with TV dilatation eventually progress to severe TR and subsequent RV failure, irrespective of durable MV surgery.[17] These finding have yet to be incorporated in current guidelines but should already be integrated in the deliberation in the MV heart team.

Subspecialized heart teams will become increasingly integrated in daily practice in the future. Cardiac surgery is a medical domain in which surgeons, more than in other medical fields, specialize is one or two domains (i.e., coronary, aorta, rhythm, mitral- and tricuspid valve or congenital) after their general cardiac surgical training. Therefore, one might argue that a surgeon who do not operate on patients with MV disease should not discuss patients with MV pathology. Even when guidelines are followed, MV disease is the most heterogeneous valvular pathological condition with extreme individual anatomical variations, and the variety of repair techniques makes the quality of care extremely operator dependent.

Concurrent with changes in technique and approaches, patient demands have changed. Given the durable results of MV repair in degenerative disease, even asymptomatic MR carries an indication for surgery.[18] Compared with conservative management, early surgery is associated with significant long-term reductions of cardiac mortality and cardiac events in asymptomatic severe MR.[19] However, asymptomatic patients are often younger of age and will subsequently have other demands than the traditional patient groups.[20] In these patients, cosmesis could play a more important role, as well as a rapid recovery with a reduced time to get back to daily (working) activities. Both patients and their referring physicians are attracted to a less-invasive option for the surgical treatment of MV disease, especially when patients are asymptomatic. These demands require surgeons to decrease surgical trauma by a minimally invasive approach and the challenge of course is how to ensure high standards of mitral reconstructive surgery as the field moves toward earlier intervention. We believe that preoperative planning plays an important role to comply with these current demands. Through preoperative planning, advantages of this minimally invasive technique can be more pronounced with less perioperative complications.

Preoperative planning

After the indication for intervention is determined, additional work-up can be performed to assess which approach is most suitable for each individual patient. In Chapter 4, we describe our process of preoperative planning with the use of multimodality imaging. In all patient's, electrocardiography, chest x-ray, echocardiography, and CT with anatomical reconstructions, are performed. Moreover, in complex cases, the MV can be printed through a process of three-dimensional (3D) reconstruction and printing, which can be used for preoperative simulation. This process aids to determine the eligibility of patients for a minimally invasive approach and determine the surgical strategy (repair vs replacement).

Echocardiography

Echocardiography is the diagnostic method of choice to assess patients with MV disease. [21, 22] Transthoracic echocardiography is the main tool to assess MV pathology in day-to-day practice. Although it is the routine examination for MV disease, TTE is not reliable enough to provide the surgeon with the essential anatomic pre-operative information. [23] The role of intraoperative TEE has therefore increased tremendously. Today intraoperative TEE has a class I indication for surgical MV reconstruction for evaluation of MV pathology, graduation of MR and detection of potential risk factors as well as post-repair assessment. [24]

As minimally invasive and even off-pump techniques for MV repair become more popular, image guidance by intraoperative TEE will play an essential role in the peri-operative period. A dedicated imaging cardiologist interested and experienced in valvular heart disease is an essential component of the dedicated heart team; their role expands from preoperative evaluation, particularly in the high-risk patient, to medical optimization, interaoperative guiding and conformation of the repair, to follow-up in the postoperative period. This involvement will improve the outcomes in both ways, as imaging cardiologist will further understand surgical considerations (from a surgeon's point of view).

Furthermore, mitral valve surgeons should become experts in echocardiography themselves. The preoperative imaging is the basis on which the surgical plan, with the preferred repair technique, should be based. The intraoperative visualization and nerve hook testing should merely be for conformation of the preoperative findings. The importance of a surgeon's knowledge on preoperative imaging is highlighted in chapter 7.

Computed tomography

The standard workup for MIMVS to assess eligibility includes a CT and computed tomography angiography (CTA). Recent advancements in reduction of radiation dosages and contrast media volume for CT have resulted in an increased use of this imaging modality, making it more available as risk of complications decreases. 25 In an international consensus statement, preoperative CT is already recommended, although not yet supported by substantial scientific evidence. [26] Since aortic occlusion is accomplished with either an internal endoaortic balloon or external cross clamp, ascending aortic disease must be ruled out. Furthermore, CT can be helpful to determine the level of the MV in relation to the thoracic cavity to decide the right intercostal space (ICS) for the mini thoracotomy incision. Although MIMVS can be performed with central cannulation techniques, most surgeons prefer peripheral cannulation. [27] Planning for this approach requires thorough knowledge of the peripheral vascular anatomy. In addition to the standard workup, we use 3D reconstruction models to allow the surgeon to have an optimal preoperative surgical view of the operating field to foresee any potential difficulties or complications. Coronary angiography is recommended for the assessment of coronary artery disease (CAD) when surgery or an intervention is planned, to determine if concomitant coronary revascularization is recommended. [28] Owing to its high negative predictive value, coronary CT may be used to rule out CAD in patients who are at low risk of atherosclerosis. [29] Therefore, we foresee important developments in these areas, making invasive coronary angiography redundant as it carries a higher complication rate. Currently, cardiac CT is not well-established enough to determine the exact mechanism of valvular dysfunction compared to echocardiography. Although the merit of CT over conventional echocardiography is that CT can be used to precisely define and measure mitral geometry, which can facilitate a preoperative prediction of the ring size for surgical or trans-catheter mitral valve repair. Indeed, in trans-catheter mitral valve replacement technologies, preoperative assessment of the left ventricular outflow tract (LVOT) and prediction of the neo-LVOT are mandatory in selection of patients for these procedures.

The reduction of radiation dosages, which is currently almost comparable with a chest x-ray, may change the preoperative work-up of all cardiac procedures.[30] However, current studies with non-contrast CT did not influence the surgical approach nor the incidence of perioperative stroke compared with standard of care. [31]

Interestingly, as CT is usually not limited to the evaluation of the organ of interest, incident findings in other organs are inevitable, so-called incidentalomas. In the initial study presented in Chapter 2, in 27% of cases an incidentaloma was found, of which 33% were actual carcinomas requiring further follow-up and/or treatment. Although not the primary aim of the investigation, incidentalomas do have clinical impact for both patients and physician and might influence the timing and planning of treatment. With an increase usage of CT, there might also be an increase in incidentaloma.

Three-dimensional reconstruction

Routine imaging modalities (TEE, CT) combined with state-of-the-art reconstructions can substantially improve preoperative planning and simplify complex procedure by enhancing surgeon's knowledge on patients' specific anatomy. Understanding the complex anatomy of the MV apparatus is essential for successful repair. The introduction of advanced reconstruction software resulted in an improvement of virtual 3D reconstructions, which can be rotated and segmented into layers. Several studies in both cardiac as in thoracic surgery have shown a change in surgical strategy after extensive three-dimensional reconstruction. [32-34] In the future virtual reality and artificial intelligence could allow even better 3D visualization of the complex anatomy. [35, 36]

Three-dimensional printing

Rapid prototyping, a technique used to generate prototype models, allows surgeons to develop a better understanding of the anatomy and could improve operative planning through the ability to interact directly with patient's printed anatomy and pathology. The process of 3D printing remains complex and is reliable on the quality of imaging acquisition.[37] The last years the quality of TEE and CT improved significantly, which in turn increase the quality of 3D printing. However, the process of 3D printing should still be seen as work-in-progress, as the accuracy of the 3D printed models used for patient care raises concerns. Current 3D printers can sufficiently print clinically relevant details with a margin of <1 mm. As the leaflets of the MV are extremely thin, printing the MV remains challenging. Furthermore, as the geometry of the valve is depended on the phase of the cardiac cycle, the prints should be adapted to the pathology. Additionally, the process remains time-consuming and costly.

Simulation and training

Historically, surgeons were trained in an apprentice model with trial and error in actual patients.[38] However, ethical issues regarding patients' safety and a more complex, better informed and more demanding patient population require alternative methods for training surgeons and surgical residents. Furthermore, the European Working Time Directive, limits the working hours of residents and their possibilities to develop their surgical skills intra operatively. [39] Patient-specific simulation, a combination of 3D printing and simulation, will become more apparent. Simulation-based training is proven to be an effective tool in training surgical skills and may subsequently allow training of residents to achieve proficiency in basic skills within shorter training periods, whereas practicing surgeons can be swiftly trained in novel techniques. [40, 41] For adequate training of surgeons and residents a high-fidelity simulator is required, to provide objective, real-time, and reproducible feedback, which can be used to guide skills development and assess the level of proficiency.[42]

Mitral valve surgery, especially MIMVS, is known for the steep learning curve. Holzhey et al. investigated the learning curves of 17 individual surgeons during a 17-year study period with 3907 procedures at the beginning of their transition to MIMVS and found that around 75-125 procedures are required to overcome the learning curve. [43] Interestingly, they also found that a minimal number of 2 procedures per week are required to maintain adequate results. Simulation cannot cover all aspects of a surgical procedure; however, the most important aspect is, that it has the potential to mimic an important detail of a complex procedure. Surgeons can practice this part of the procedure over and over, until satisfactory results are achieved. It can provide the operator with detailed feedback, without trial and error in patients. Although simulation seems intuitive, the current literature on improved outcomes in cardiac surgery after simulation is scarce. However, two systematic reviews reported that simulation-acquired surgical skills in other surgical fields, are transferable to the operative setting, which may consequently enhance surgical performance. [44, 45]

PERSONALIZED TREATMENT

In chapter 6, we describe the surgical set-up for MIMVS. This approach forms the basis of all procedures in our current studies. In our center, MIMVS is performed through a right anterolateral mini thoracotomy with use of peripheral cardiopulmonary bypass through the femoral vessels. Aortic occlusion can either be achieved by use of a transthoracic clamp or endo-aortic occlusion balloon. In patients referred for reoperations with unsuitable aorta dimensions for endo-aortic balloon occlusion, a third strategy can is used to avoid dissection of the adhesions around the ascending aorta. These patients are cooled to 28 °C and ventricular fibrillation arrest is induced.
In patients with degenerative MV disease, mitral valve repair (MVr) should be performed, as it has proven to result in superior survival compared to mitral valve replacement (MVR).[10, 46] Around 50% of patients, the predominant lesion is a prolapse of the posterior mitral valve leaflet (PML), most of the times resulting from chordal rupture. 47 A PML prolapse can successfully be repaired in 95% of cases, with equally high freedom from reoperation. [48] Mitral valve repair consists of a plethora of different techniques. In MV prolapse, with or without additional leaflet resection, neochordae can be placed for correction of the prolapsing segments and coaptation defects. To achieve an optimal result, a coaptation surface of at least 8 to 10 mm is warranted.[49] Several preoperative strategies and intraoperative tests have been proposed to achieve higher repair rates. [50 51] However, intraoperative assessment of the repair highly relies on visual inspection. Saline testing with concurrent ink testing is the most common technique used to inspect the repaired valve intraoperatively and could simulate the postoperative functional anatomy. [52]

Interestingly, during our initial experience with MIMVS, we discovered a new phenomenon, during saline testing (Chapter 7). When injecting saline into the LV, no pressure build-up was possible, as there was no coaptation between the anterior and posterior leaflet. Initially, the underlying mechanism was not fully understood, and was deemed as a residual prolapse of the anterior mitral valve leaflet (AML). In an early case, this led to the unjustified surgical correction of the AML and suboptimal repair. Eventually, the mechanism was unravelled, which comprised a so-called pseudoprolapse of the AML secondary to a change of LV geometry during surgery. Moreover, as this pseudoprolapse is absent on pre-operative echocardiography, it is imperative for surgeons to meticulously study the preoperative imaging and determine which segment is involved in the process of MR. Consequently, when there is no AML prolapse on the preoperative echocardiography, it will probably be caused by the change in geometry of the arrested heart and no additional repair is necessary. Indeed, during surgery, patients are sedated, and muscle relaxant are administered, causing the diaphragm to relax and elevate towards the thoracic cavity. Unexpected AML prolapse probably can be explained based on 3 components—the anterior mitral annulus, the AML and the subvalvular structures which are shared by the MV and LVOT. Unexpected AML prolapse occurs when external forces cause these 3 components of the MV to lose their functional harmony.

Such an unexpected AML prolapse makes valve repair in these patients even more complex. The valve cannot be tested intraoperatively, and surgeons must determine the optimal length of the neochordae based on other reference points, such as the native chordae. Therefore, surgeons should meticulously study the preoperative imaging and become experts in echocardiography themselves. After ring implantation, the valve height should be related to the annuloplasty ring as this marks the upper limit of the MV annulus. In these cases, the P1 segment of the PML can be used as reference, like in valve inspection proposed by Carpentier. [53]

Dedicated care teams

Patients undergoing surgery often see numerous health care providers, which may lead to substantial variation and even introduces the potential for disparate levels of patient care. Therefore, dedicated care teams should be structurally imbedded in the personalized treatment of patients with mitral valve disease. This is should not only be limited to the cardiologist and cardiac surgeon, but also includes the nurses on the ward and OR.

Dedicated surgical teams have found to reduce surgical times and room times in patients with adolescent idiopathic scoliosis. [54] Surgical times decreased by 13%, and room times by 11%, in 590 cases between 2006 and 2015. This reduction is attributed to a reduction in delays and distractions as well as increased experience with the flow of the operation. In MV surgery this finding was confirmed for robotic MV repair. After initiation of a totally endoscopic robotic MV repair programme, Loulmet et al. found that a dedicated team allows one to address the entire spectrum of pathological complexity and provides consistent results despite increase in complexity of the pathology. [55] This dedication should not be limited to the preoperative and intraoperative teams, but postoperative critical care management should be an integral part of cardiac surgery that contributes directly to clinical outcomes.

Centers of excellence in mitral valve surgery

The current European guidelines advocate the initiation of Heart Valve centres to improve outcomes for patients with VHD by concentration of care. [4] The main goal is to deliver optimal quality of care with a patient-centred approach. Indeed, the relationship between case volume and outcomes for surgery is undeniable. As an example, for MV repair, Badhwar et al. found an important association between hospital and surgeon volume for 30-day and 1-year mortality in isolated MV surgery for primary MR in the United States. [56] Interestingly, only 53% percent of all centres in the United States performed 25 or more MV procedures per year. In the state of New York, the median annual surgeon volume of any mitral operation was 10 (range 1 to 230), with a mean repair rate of 55%. In the subgroup of patients with degenerative disease, the mean repair rate was 67%, with a range of 0% to 100%. [57] It is difficult to master and sustain skills in mitral valve surgery when a cardiac surgeon on average performs fewer than 10 mitral valve procedures per year, especially as mitral valve surgery requires a large number of cases per year to acquire and maintain the skills necessary to consistently provide good results. Low-volume cardiac surgeons also have a much greater likelihood of replacing rather than repairing a valve that is ostensibly repairable. A study by Chikwe et al. confirmed that individual surgeon volume is a determinant of not only MV repair rates, but also freedom from reoperation and survival. These findings are confirmed by LaPar et al, showing significant variation in the performance of MVr and MVR for MR. [58] Average annual surgeon volume was more closely related to MV repair rate than institutional volume, with an increased likelihood for performance of MVr among surgeons performing >20 procedures annually. For transcatheter therapy, the relation between volume and outcomes is more complex. Barker et al, found no relationship between trans-catheter MV procedural centre volume and outcomes. [59] However, operator experience was associated with improvements in procedural success, procedure time, and procedural complications. [60]

The aim of minimally invasive surgery is to decrease patient burden, reduce complications and facilitate a more rapid recovery, while maintaining a perfect surgical result. However, many studies have shown this result to be compromised when the procedure is performed in a non-standardized manner, on an individual surgeon level, as well as an institutional level. Consequently, procedures with such a steep learning curve may be performed with better results at hospitals with high procedural volume and experience, as advocated by current guidelines.

While even a low-volume surgeon in a low-volume hospital may be performing at a very high level of excellence, with excellent quality metrics and long-term outcomes, there are little data regarding the long-term success of the repair and patient outcome beyond what is published from a select group of high-volume academic centers. Furthermore, currently no literature is available to confirm the association between centre volume and outcomes for minimally invasive mitral valve surgery specifically.

It is likely, however, that in addition to experiencing higher replacement rates, a patient operated on by a less experienced surgeon also will face an increased risk of complications and a nondurable valve repair. Therefore, the primary component of a center of excellence is a dedicated team including a group of surgeons who received advanced fellowship training in (minimally invasive) mitral surgery. Other criteria for a centre should include mitral valve surgery volume requirements (center and surgeon), dedicated mitral valve teams including a heart team, appropriate periprocedural imaging capabilities and a willingness to provide patients and referring doctors' data regarding expected outcomes based on the center's recent experience, including repair rates, mortality rates, stroke rates and evidence of the likelihood of repair durability.

Postoperative treatment phase

In the postoperative phase, patients should be initially carefully monitored on the intensive care. Protocols for Enhanced recovery after surgery (ERAS) have already been implemented in different surgical disciplines and represent one of the most important recent advancements in perioperative medical care. [61, 62] In general surgery, and especially colorectal surgery, major advantages in terms of gastrointestinal morbidity, healthcare associated infections and earlier hospital discharge have been demonstrated for ERAS. [63, 64] Like in general surgery, ERAS can be introduced to improve patients' outcomes in MV surgery. ERAS protocols in cardiac surgery are still in a premature stage. Several factors influence fast recovery which are not necessarily linked to a reduction of surgical trauma. The first step takes place even before surgery, with an improvement of the preoperative physical and mental status (e.g., training of the cardio-pulmonary capacity and optimization of the nutritional status). This shift towards a modification of the intraoperative management by standardized minimally invasive surgery will contribute towards faster recovery. Early extubation (within 6 hours after surgery) is safe and can improve outcome. 65 In contrast, prolonged (>24h) mechanical ventilation after cardiac surgery is associated with higher morbidity, mortality, and increased costs. 66 Furthermore, a multimodal, opioid-sparing, pain management plan is recommended postoperatively. Optimizing postoperative pain control accelerates normalization of quality of life and functionality for patients. As illustrated, such interventions are relatively simple to implement but require standardization and differ slightly from standard cardiac surgical care, underlying the importance of a dedicated care team, also incorporating anaesthetists and intensivists.

As another example, the optimal antithrombotic therapy following MV repair is still a matter of debate. Even in the Netherlands, inter-hospital difference in antithrombotic therapy is apparent. In chapter 8, two different antithrombotic treatment regimens were studied, namely vitamin K antagonists (VKA) and aspirin. The risk of thromboembolic events following MV repair ranges from 0.4 to 1.6% per year, and reaches 2.5% during the first postoperative month, even with routine anticoagulation therapy. [67, 68] In a retrospective observational multicentre cohort study the two antithrombotic treatment regimens were compared. The primary outcome was a composite of thromboembolic and bleeding complications. Vitamin K antagonists and aspirin therapy showed a similar event rate of 10% during the first 3 months in patients without prior history of AF. In both treatment groups, thromboembolic event rate was low and major bleeding rates were comparable. Nearly all bleedings occurred in the subacute phase following surgery, particularly in the first 2 weeks. In contrast, the thromboembolic events occurred more dispersed throughout the first 3 months. VKA treatment, however, has many disadvantages, including the need for frequent laboratory monitoring, variability of dose response and drug and food interactions. In contrast, aspirin does not require monitoring and dosage adjustments. Consequently, for practical reasons, aspirin might be preferred to VKA as antithrombotic treatment in patients undergoing MVr. Still, the choice of antithrombotic treatment in patients without prior history of AF should be individualized based on patient-specific considerations.

Quality of life

In addition to improvement in prognosis and survival, an important aspect is patient reported quality of life (QoL). This aspect is important for both symptomatic and asymptomatic patients. In symptomatic patients, surgery is initially triggered by the onset of symptoms which resulted in referral to a cardiologist. Presumably, these patients have a decreased QoL prior to surgery and after surgery this QoL will expectedly increase, helping to return patients back to their normal daily activities. In asymptomatic patients, this is more complex, as these patients will have a presumably 'normal' QoL. Surgery in these patients is initiated to prevent secondary complications. In chapter 9 we investigated the differences in QoL between MIMVS and conventional surgery through sternotomy, in which a total of 485 patients were included. Both sternotomy and MIMVs showed significant increases in physical health and mental health status after surgery. Reduced baseline QoL score and new postoperative arrythmia were the most important factors influencing QoL. Surgical approach did not influence the QoL. However, the study was subjected to inherent limitations as it comprises a retrospective evaluation of potentially selectively included data and QoL was only evaluated after 1 year. The effect of surgical approach on the postoperative QoL could be more pronounced in the immediate phase after surgery, as the goal of MIMVS is to reduce surgical trauma to enhance rehabilitation. Huang et al, suggests that the totally endoscopic approach is superior to the median sternotomy approach in terms of pain intensity, aesthetic appearance, and health-related quality of life.[69]

Outcomes in the Netherlands

All patient undergoing cardiac surgery in the Netherlands are registered in the Netherland Heart Registration (NHR). Participation in the registry is mandatory by national decree of the board of cardiothoracic surgeons (Nederlandse Vereniging voor Thoraxchirurgie; NVT). The database is very robust and audited for obligatory data. Mitral valve surgery is the second most performed cardiac valve surgery in the Netherlands. In 16 centres, between 2016 and 2020, a total of 3008 MV procedures were performed. Interestingly, there is wide variability in surgical volume between centres, with a total 5-year case load ranging between 82 and 552 cases-per-centre. In the overall data, a 120-day mortality of 4.3% and a one-year mortality of 5.3% are observed. [70]

In chapter 10, the results of MIMVS and classical open sternotomy in the Netherlands are presented. This study included all patients with a registered surgical approach and compared outcomes in term of mortality, morbidity, and long-term survival during a 5-year study period. A total of 2501 patients, of which 725 underwent MIMVS and 1776 sternotomy were included. Our study found overall excellent results for MV surgery in the Netherlands with a 30-day mortality of 1.3%, a repair rate around 78.8%, a 5-year survival rate of 93.6% and a 5-year freedom from mitral valve reintervention of 97.7%, unparalleled in international literature. Unfortunately, in this study we could not explore differences between high- and low volume centres and distinguish between valve pathology. The study found a higher repair rate in sternotomy and freedom from MV reintervention in favour of sternotomy. The repair rate could unfortunately not be specified for MV pathology. The observed difference might reflect surgical experience and surgical volume, which is a known factor in literature and mentioned earlier. Although the exact mechanism of recurrence of MV disease cannot be retrieved using the current registry, the observed differences should not be ignored. It may point to the difficulties accompanying the initiation of an MIMVS programme. This study also reflects the importance of patient selection for such an approach. Although we could not distinguish in volume per surgeon or centre, we hypothesize when MIMVS is performed by dedicated surgeons, durability and long-term survival are optimized.

The published data from the STS database, as mentioned earlier, shows a 30-day mortality rate of 2.9% (2016) and 2.0% (2018), with a repair rate overall of 57.4% (2016) and 65.6% (2018). The reason why results in the Netherlands are still debatable. However, we belief centralisation of care is an important aspect through which a higher standard of care is achieved. In the Netherlands, the Netherlands Heart Registry was initially initiated for value-based health care. Further improvement of quality and patient safety can be achieved only by measuring patient-relevant outcomes and sharing and adopting each other's best practices. On a yearly basis individual center outcomes (repair rate, complications including stroke, myocardial infarction, reeploraxtion for bleeding and reintervention rate with follow-up) for mitral valve surgery are published. Discrepancy in outcomes acts as a trigger for individual heart centres to review their current care process. The participating heart centres are motivated to understand where this discrepancy originates from and how they can improve their outcomes. It aims not only to focus on the results of an individual treatment or specialization, but also on the results of the integrated care for patient groups, both inside and outside the hospital. This overview is needed to improve outcomes for patients with MV disease and stimulates a shift from specialist and intervention-oriented care to patient and disease management-oriented care, which is the corner aspect of personalized medicine. The performance of the full cycle of care can be evaluated, which starts with a Heart Team discussion.

Tricuspid valve Disease

Parallel to an increase in complexity of MV surgery, an increase in indications for concomitant TV surgery is expected as well. In chapter 12 we investigated the safety and efficacy of minimally invasive double atrioventricular valve surgery. The main findings of the current study were that concomitant TV surgery did not increase the risk of mortality as a concomitant surgical procedure, and that there were no differences in terms of safety and efficacy between a minimally invasive approach and sternotomy for surgical correction of double atrioventricular valve disease, despite a higher incidence of re-exploration for bleeding and new – onset arrhythmias. With the expected increase in MV disease and the lowering of the threshold for indication of concomitant TV repair, a significant rise in double atrioventricular valve surgery in the future is expected, which can be treated safely and effective through both sternotomy and a minimally invasive approach. This important finding is not yet incorporated in the current guidelines but should already be incorporated in the heart team discussion.

Mitral valve reoperation

With the aging population, reoperative MV surgery is increasingly performed, currently comprising 10% of the total case load of surgical MV interventions. Reoperative MV surgery is conventionally performed through resternotomy and is associated with significant morbidity and mortality. Alternatively, reoperative MV can be approached minimally invasively, but long-term follow-up of this approach for reoperative MV surgery is lacking. In chapter 11, we aimed to study the short- and mid-term outcomes of reoperative MIMVS versus sternotomy in a multi-center nationwide registry. The study showed, that reoperative MV surgery, either through resternotomy or MIMVS, is an exceptionally safe reoperative cardiac surgical procedure, as reflected by both unmatched and matched cohorts, with an overall 30-day mortality rate of 3.1%. MIMVS is as safe and effective as resternotomy and is associated with a lower incidence of new-onset arrhythmia and prolonged intubation. Interestingly, the current study outperformed the current risk-score models and therefore warrants the need for alternative risk score models for (reoperative) mitral valve surgery.

As an alternative strategy, trans-catheter mitral procedures have emerged rapidly, following the successful evolution of trans-catheter aortic valve implantation (TAVI). As MV pathology is more diverse than aortic valve disease, a plethora of devices exist which have the potential to address all different forms of MR. Especially trans-catheter mitral valve replacement (TMVR) is believed to play an important role in the future, enabling minimally invasive correction of ischemic MR or valve-in-valve implantation in failed bioprosthetic valves. Still, both trans-catheter MV repair and TMVR are currently only applicable in specific subsets of MV patients and require specific conditions related to MV anatomy and left ventricular geometry. Long-term outcomes and durability of TMVR and repair are yet to be determined. These new surgical techniques and strategies need scientific analysis and evaluation of sufficiently large patient cohorts with respect to equality, possible superiority or even inferiority compared to established therapies. Therefore, although promising, the exact role and value of trans-catheter techniques in the mitral position remains to be defined. When considering such an approach, one must balance these outcomes to the excellent short- and long-term results of reoperative MV surgery presented by the current study, either through MIMVS or sternotomy. Patients with new-onset or recurrent MV disease after a previous cardiac surgical procedure through sternotomy, warrant a personalized approach.

In conclusion, currently no comparable data on a national basis have been published previously for both primary as reoperative MIMVS in a multicentre setting. The Netherlands Heart Registration showed excellent results of mitral valve surgery in the Netherlands. For primary surgery, after propensity matching for baseline characteristics and concomitant procedures, excellent and comparable results for both sternotomy and MIMVS in terms of mortality and perioperative complications were found. However, for patients who underwent MIMVS a lower repair rate and a slight, but significantly lower freedom from reintervention at 5 years was observed. Despite several limitations of the registry, the observed differences should not be ignored. Keeping in mind the steep learning curves and a postulated number of 2 MIMVS procedures per week to ensure high-quality treatment, the low mean number of MV procedures per centre per year in the present studies highlights an important point of improvement. Furthermore, highlighted by the editorial of Dr Müller, as from a patient's perspective the real world is not depicted by a national registry. 71 It might be true on a national basis but not in a specific local/regional environment. The patient's real world is where the specific patient receives his/her treatment. To accommodate for these differences, centralisation of treatment of MV disease is required with the commitment of a well-informed patient population. Only with excellent results can surgery compete with interventional techniques and be the best offered treatment to patients.

Outcomes in literature

To evaluate the international results of reoperative mitral valve surgery, a systematic review was performed as well. As redo cardiac surgery has been associated with increased mortality rates compared to primary surgery, the outcomes of reoperative mitral valve surgery were investigated in a meta-analysis (Chapter 13). A total of 6 studies were included with a total of 777 patient. The existing literature provided limited data but demonstrated significant differences with regards to mortality, LOHS and reoperation for bleeding, all in favour of a minimally invasive approach. These benefits were evident despite the comparable risk of stroke. This study also confirms our results for reoperative mitral valve surgery in the Netherlands.

Cardiac myxoma

Patients with myxoma cordis represent a relative scarce subset of patients requiring surgery. The overwhelming majority of these benign tumours originate from the atria. Guidelines for surgical indications, treatment and preferred approaches are lacking, due to a paucity in comparative data. Traditionally these patients were operated through median sternotomy, like in MV disease. However, the strive to reduce surgical trauma also applies for patients with myxoma, which are mostly found in asymptomatic young patients. Given the low incidence of benign cardiac masses and single-centre experiences with relatively small patient cohorts, data supporting the potential superiority of such an approach for cardiac myxoma were lacking. Therefore, in chapter 14, all published observational studies that compared benign atrial mass resection through a right anterolateral thoracotomy and conventional median sternotomy were analysed to evaluate safety, efficacy, and potential superiority in terms of hospitalization and complications of such a minimally invasive approach. In total, 4 retrospective observational studies representing 196 patients were included. In this meta-analysis, an equal safety and efficacy of right anterolateral thoracotomy compared to sternotomy for resection of benign atrial masses were observed. The minimally invasive approach is as safe and effective as sternotomy for the excision of benign atrial masses. Moreover, a minimally invasive approach is associated with a reduced complication rate and a reduced duration of hospitalization and could be considered as the preferred approach in anatomically suitable patients. In perspective, starting with a minimally invasive approach for benign mass resection could also enhance surgical skills for other minimally invasive cardiac procedures, like MIMVS.

CONCLUSION

The prevalence of mitral valve disease will continue to increase with an ageing population, which in turn increases the annual case load of surgeons. Mitral valve surgery remains one of the most challenging procedures due to the heterogeneity of disease entities, the plethora of treatment modalities, the required annual case volume, and a more demanding patient population. A high-standard of care, for both open and minimally invasive procedures, with excellent overall outcomes (survival, repair rate, freedom-from-reoperation) is achievable. Patients should be treated on an individualized basis by dedicated teams. Surgeons should rise above their (sub)speciality and be involved throughout the whole process. They should not merely perform their 'trick' but overview the process needed to improve outcomes for patients with MV disease and stimulate a shift from specialist and intervention-oriented care to patient and disease management-oriented care. Mitral surgery will improve when surgeons become experts in mitral valve echocardiography, heart-failure treatment, and transcatheter mitral valve interventions.

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Chapter 16

English Summary

SUMMARY

The current thesis addresses the concept of personalized medicine in mitral valve surgery, investigating the individual phases of patient selection and preoperative planning as well as perioperative care, particularly for patients undergoing minimally invasive mitral valve surgery.

The first part of this thesis focuses on patient selection and preoperative planning for mitral valve surgery. Although intuitive, there is no supportive data of the use of the heart team in decision making for cardiovascular disease. The rationale for a dedicated mitral valve heart team is based on evidence in which dedication and experience in mitral valve surgery is associated with improved outcomes. A general heart team would not necessarily bring together the required expertise for the treatment of patients with mitral valve disease. Therefore, in our first study (**Chapter 2**) we present the initiation of a dedicated mitral valve heart team, consisting of an interventional cardiologist, cardiac surgeon, and imaging specialist with expertise in interventional imaging, all focused on mitral valve disease. In this study more insight into our strategy for clinical decision-making and treatment allocation is provided. Furthermore, the study demonstrated the short-term clinical outcomes of all consecutive patients with mitral valve disease referred to our hospital patients within one year.

In **Chapter 3** a comparative study, using a historical cohort (the general heart team) is presented. In this retrospective study, patients treated for mitral valve disease - based on a dedicated heart team decision - showed a significantly higher survival, independent of the allocated treatment, mitral valve pathology and baseline characteristics. With the advent of new transcatheter technologies and the complexity and variability of mitral valve pathology, the establishment of dedicated mitral heart teams seems warranted.

Minimally invasive mitral valve surgery has still not been widely adopted as standard approach for surgical treatment of mitral valve disease due to a lack of consistent supporting evidence. In our philosophy, extensive pre-operative planning, using different imaging modalities, has the potential to reduce perioperative complications. This philosophy is outlined in the review in **Chapter 4**, presenting an overview of current literature on this topic, together with our institution's experience in this field. Routine imaging modalities combined with state-of-the-art reconstruction software have the potential to substantially improve and simplify complex procedure by enhancing surgeon's knowledge on patients' anatomy. Indeed, patient-specific simulation, a combination of three-dimensional mitral valve modelling and printing, could serve as the ideal method for planning of complex mitral valve surgery. In **Chapter 5** the clinical implications of three-dimensional modelling, printing and simulation in mitral valve surgery is presented. In adjunction, starting a MIMVS program requires a step-by-step approach which is presented in **Chapter 6**.

The seamless connection between the pre- and intra-operative evaluation of mitral valve disease and surgery is illustrated by **Chapter 7**. Currently, saline testing is the most used method to evaluate the repair intra-operatively. In the earlier experience we encountered an unexpected anterior mitral leaflet (AML) prolapse during saline testing, which made it impossible to test the valve intraoperatively. In **Chapter 7** we evaluated the incidence of such an unexpected AML prolapse, which was found to be as high as 18.7% in isolated posterior leaflet cases. Body mass index, surgical approach (MIMVS), number of prolapsing segments, left ventricular ejection fraction, left ventricular end-systolic diameter, and left atrial diameter showed to be predictive for unexpected anterior leaflet prolapse. When saline testing shows an unexpected prolapse of the anterior leaflet, not present on preoperative echocardiography, no additional surgical techniques should be performed in order to achieve an excellent postoperative result, illustrated by **Chapter 7's** outcomes.

The second part of this thesis focusses on the postoperative management and the outcomes in the Netherlands. The optimal antithrombotic therapy following mitral valve repair is still a matter of debate. In **Chapter 8,** the rate of thromboembolic and bleeding complications between vitamin K antagonists and aspirin were compared. Three months after mitral valve repair, a similar event rate of 10% for the primary outcome was observed, in patients without a prior history of AF. No significant differences were observed in thromboembolic rates as well as in major bleeding rates. Therefore, aspirin might be preferable as antithrombotic treatment compared to VKA in patients with sinus rhythm.

Although still not widely adopted, MIMVS is being performed increasingly. However, large comparative studies on short- and long-term outcomes are lacking. In **Chapter 9** we compared short- and long-term outcomes of patients undergoing MIMVS versus median sternotomy in the Netherlands. We found no between-group differences in 30-day mortality and 5-year survival. The incidence of perioperative stroke was comparable, and an increased rate of postoperative arrhythmia was observed in median sternotomy. The current nationwide study showed MIMVS to be as safe as the sternotomy. However, MIMVS is associated with a reduced repair rate and may be subjected to more reinterventions in the long term. Unfortunately, the repair- and reintervention rate could not be specified for mitral valve pathology.

In addition to the study in **Chapter 9**, **in Chapter 10** we aimed to evaluate short- and mid-term outcomes of MIMVS versus MV surgery through resternotomy in patients with prior sternotomy, in the Netherlands. The current multicenter nationwide study showed excellent outcomes for MV surgery after prior cardiac surgery in the Netherlands, and MIMVS and resternotomy appeared to be equally efficacious. However, MIMVS was associated with a lower incidence of new onset arrythmia and prolonged intubation. These excellent short- and mid-term results of MV surgery after prior cardiac surgery, regardless of the approach, should be considered as a benchmark in reoperative mitral valve surgery, particularly when evaluating the implementation of transcatheter interventions.

The indication for concomitant tricuspid valve surgery during primary MV surgery is expected to increase. In **Chapter 11** we investigated the safety of the addition of TV surgery to MV surgery in MIMVS in a nationwide registry. No differences in short-term mortality and 5-year survival compared to both minimally mitral valve surgery and double valve surgery through sternotomy were found. A higher incidence of re-exploration for bleeding and postoperative arrhythmia and longer hospital stay was observed in the minimally invasive double valve group compared to minimally invasive single valve surgery.

The aim of surgical treatment of mitral valve disease is to reverse heart failure and its related symptoms, and to restore life expectancy and quality of life. In **Chapter 12**, we aimed to evaluate quality of life after mitral valve surgery through full sternotomy and a minimally invasive approach (MIMVS). Overall, patients experienced a significant increase in physical score and mental score at 1-year. There were no significant differences in quality of life increase between sternotomy and MIMVS. Predictors for loss of physical and mental quality of life were baseline quality of life scores and new onset of arrhythmia.

The last part of this thesis addresses the outcomes of minimally invasive reoperative mitral valve surgery and minimally invasive resection of benign atrial masses. In **Chapter 13,** a systematic review and meta-analysis of six retrospective observational studies is presented, comprising 777 patients. Reoperative minimally invasive MVS through a minithoracotomy seemed to be a safe alternative to standard sternotomy, with reduced mortality rates, length of hospital stay and reoperations for bleeding and a comparable risk of stroke. In addition, primary benign cardiac tumors are a rare disease entity. Current guidelines on the preferred approaches are lacking. In **Chapter 14**, a meta-analysis is presented to evaluate all studies comparing a minimally invasive approach compared with median sternotomy for excision of benign atrial masses in terms of safety, efficacy, and complications. A minimally invasive approach proved to be as safe and effective as median sternotomy for the excision of benign atrial masses. Moreover, a minimally invasive approach is associated with a reduced complication rate and a reduced duration of hospitalization and could therefore be considered as the preferred approach in anatomically suitable patients.

Chapter 17

Nederlandse Samenvatting

SAMENVATTING

De huidige thesis bestudeert het concept van een gepersonaliseerde (chirurgische) behandeling (personalized medicine) voor patiënten met mitraliskleplijden. In deze thesis worden de verschillende fasen van personalized medicine (patiëntenselectie, preoperatieve planning en perioperatieve zorg) individueel belicht met bijzondere aandacht voor patiënten die in aanmerking komen voor een minimaal invasieve mitralisklepoperatie.

Het eerste gedeelte van dit proefschrift focust op het selecteren van patiënten en de preoperatieve planning van mitralisklepchirurgie. In de meeste centra worden beslissingen omtrent de behandeling van hart- en vaatziekten voor een individuele patiënt genomen door een zogenaamd hartteam. Dit hartteam heeft een wisselende samenstelling van interventie/ beeldvormende cardiologen en cardiothoracaal chirurgen met ieder hun eigen subspecialisme. Een gespecialiseerd hartteam gericht op slechts één patientpopulatie is in de praktijk nog niet gangbaar. De wisselende samenstelling van een dergelijk algemeen hartteam zorgt derhalve noodgedwongen voor het ontbreken van de vereiste expertise voor de behandeling van patiënten met een mitralisklepaandoening. In hoofdstuk 2 presenteren we de initiatie van een dedicated (aangewezen) mitralisklep hartteam, bestaande uit een interventiecardioloog, een cardiothoracaal chirurg en een beeldvormend cardioloog, allen gespecialiseerd in mitralisklepaandoeningen. In deze studie wordt meer inzicht gegeven in de klinische besluitvorming en de behandelstrategie. Daarnaast presenteert deze studie de kortetermijn-klinische resultaten van alle patiënten met een mitralisklepaandoening. In hoofdstuk 3 wordt een vergelijkende studie gepresenteerd waarbij de resultaten van een algemeen hartteam worden vergeleken met het mitralisklep hartteam. Deze retrospectieve studie toont een significant betere overleving van patiënten met mitraliskleplijden, wanneer zij in het mitralisklep hartteam worden besproken. Deze significant hogere overleving is onafhankelijk van de patiëntkarakteristieken, de mitraliskleppathologie en de toegewezen behandeling. Derhalve, met de komst van de nieuwe transkathetertechnologieën en de complexiteit en variabiliteit van mitraliskleppathologie, lijkt de initiatie van speciale mitralisklep hartteams gerechtvaardigd.

Minimaal invasieve mitralisklepchirurgie wordt vandaag de dag nog niet aanvaard als de standaardbenadering voor de chirurgische behandeling van mitraliskleplijden, vanwege het ontbreken van consistent wetenschappelijk bewijs. In onze filosofie heeft uitgebreide preoperatieve planning, waarbij gebruik wordt gemaakt van verschillende beeldvormende modaliteiten, het potentieel om perioperatieve complicaties te verminderen. In hoofdstuk 4 wordt een overzicht gegeven van de huidige literatuur op het gebied van preoperatieve planning. Wanneer routinematige beeldvormende modaliteiten (CT, TTE, TEE) worden gecombineerd met moderne reconstructiesoftware kunnen geavanceerde driedimensionale (3D) modellen worden gecreëerd. Deze 3D-modellen hebben het potentieel om complexe procedures, zoals mitralisklepchirurgie, aanzienlijk te vereenvoudigen en te verbeteren, doordat het de kennis van de chirurg over de individuele patiënt vergroot. In navolging daarvan kan, wanneer deze 3D-modellen worden gecombineerd met 3D-printing, een patiënt specifiek geprint model worden vervaardigd. In hoofdstuk 5 worden de klinische implicaties van driedimensionale mitralisklepmodellen, het printen van deze modellen en het gebruik van deze modellen bij simulatie gepresenteerd.

Het starten van een minimaal invasief mitraalklep programma vergt een gestandaardiseerde werkwijze. In hoofdstuk 6 wordt een stapsgewijze benadering gepresenteerd voor minimaal invasieve mitraalklepchirurgie.

Uitgebreide preoperatieve planning met transthoracale echocardiografie, eventueel aangevuld met transoesofagiale echocardiografie, helpt chirurgen bij het bepalen van de juiste strategie (reparatie versus vervanging) ten aanzien van de mitralisklep. Intraoperatief blijft het testen van de mitralisklep, door het inspuiten van zoutoplossing in de linker ventrikel (zgn. Watertest), de meest gebruikte methode om de mitralisklep te beoordelen. In de eerdere casuïstiek werd, tijdens de watertest een onverwachte prolapse van het anterieure mitralisklepblad gezien. Hierdoor bleek het onmogelijk om de klep intraoperatief te testen. In hoofdstuk 7 evalueren we de incidentie van zo'n onverwachte prolapse van het anterieur mitralisklepblad. In 18,7% van alle patiënten die verwezen zijn met een geïsoleerde posterieure prolapse bleek dit fenomeen aanwezig bij de watertest. Body mass index, een minimaal invasieve benadering, het aantal prolaberende segmenten, linker ventrikel ejectiefractie, linker ventrikel eind systolische diameter en linker atrium diameter bleken voorspellend te zijn voor deze onverwachte bevinding van het anterieure klepblad. Echter, wanneer een onverwachte prolapse van het anterieure klepblad optreedt, die niet aanwezig is op preoperatieve echocardiografie, dienen geen aanvullende chirurgische technieken te worden uitgevoerd om een uitstekend postoperatief resultaat te bereiken.

Het tweede deel van dit proefschrift richt zich op het postoperatieve beleid en de uitkomsten in Nederland. De optimale antitrombotische therapie na mitralisklepreparatie is nog steeds een punt van discussie. In hoofdstuk 8 wordt het aantal trombo-embolische complicaties en bloedingscomplicaties vergeleken tussen vitamine K antagonisten en acetylsalicylzuur. Drie maanden na de mitralisklepreparatie werd een vergelijkbare incidentie van 10% voor de primaire uitkomst (combinatie van trombo-embolische en bloedingscomplicaties) waargenomen bij patiënten zonder atriumfibrilleren. Er werden geen significante verschillen waargenomen in het aantal trombo-embolieën evenmin in het aantal ernstige bloedingen. Acetylsalicylzuur heeft daardoor de voorkeur als antitrombotische behandeling in vergelijking met vitamine K antagonisten bij patiënten in sinusritme.

Hoewel minimaal invasieve technieken in mitralisklepchirurgie nog niet op grote schaal worden toegepast, zien we wel een toenemende trend. Echter ontbreken er grote vergelijkende studies over de korte- en langetermijnuitkomsten. In hoofdstuk 9 worden de korte- en langetermijnuitkomsten van patiënten die een minimaal invasieve procedure ondergaan vergeleken met een mediane sternotomie in Nederland. Er werden geen verschillen gevonden tussen beide groepen in zowel 30-dagen mortaliteit als 5-jaars overleving. De incidentie van een perioperatief herseninfarct was vergelijkbaar en een verhoogde incidentie van postoperatieve aritmieën werd waargenomen bij een mediane sternotomie. Deze landelijke studie toont aan dat minimaal invasieve mitralisklepchirurgie net zo veilig is als een sternotomie. Een minimaal invasieve benadering gaat echter wel gepaard met een lager herstelpercentage van de mitralisklep en verhoogde kans op een reoperatie op de lange termijn. Helaas kan het herstelpercentage- en de incidentie van reoperaties niet worden gespecificeerd voor de desbetreffende mitraliskleppathologie.

Naast de studie in hoofdstuk 9 waarbij de uitkomsten van primaire mitralisklepoperaties worden vergeleken, worden in hoofdstuk 10 de korte- en middellange termijn resultaten van een minimaal invasieve benadering versus resternotomie geëvalueerd, bij patiënten na een eerdere sternotomie. Deze landelijke multicenter studie laat uitstekende resultaten zien van mitralisklepchirurgie na een eerdere hartoperatie in Nederland. Minimaal invasieve mitralisklep chirurgie en resternotomie bleken even effectief. Minimaal invasieve mitralisklep chirurgie wordt echter wel geassocieerd met een lagere incidentie van nieuwe postoperatieve ritmestoornissen en een langdurige intubatie. Deze uitstekende korte- en middellange termijn resultaten van mitralisklepchirurgie na eerdere hartchirurgie, ongeacht de benadering, moeten worden beschouwd als een maatstaf voor reoperatieve mitralisklepchirurgie, vooral bij het evalueren van transkatheterinterventies.

De indicatie voor een gelijktijdige tricuspidalisklep procedure tijdens primaire mitralisklepchirurgie zal naar verwachting worden aangepast en hierdoor neemt het aantal dubbelklep ingrepen toe. In hoofdstuk 11 onderzoeken we de veiligheid wanneer tricuspidalisklepchirurgie aan mitralisklepchirurgie wordt toegevoegd tijdens minimaal invasieve mitralisklepchirurgie. In deze landelijke multicenter registry worden geen verschillen gevonden in de korte termijn mortaliteit en de 5-jaarsoverleving. Een hogere incidentie van re-exploratie voor bloedingen, postoperatieve aritmieën en een langer verblijf in het ziekenhuis wordt waargenomen bij minimaal invasieve dubbelklepchirurgie, in vergelijking met minimaal invasieve enkelvoudige klepchirurgie.

Het doel van de chirurgische behandeling van mitralisklepaandoeningen is het tegengaan van hartfalen en de bijbehorende symptomen, evenals het herstellen van de levensverwachting en de kwaliteit van leven. In hoofdstuk 12 evalueren we de kwaliteit van leven na mitralisklepchirurgie, zowel voor patiënten behandeld via een volledige sternotomie alsmede een minimaal invasieve benadering. Over het algemeen ervaren patiënten na 1 jaar een significante toename in de fysieke score en mentale score. Er zijn geen significante verschillen in de toename van de kwaliteit van leven tussen een sternotomie en een minimaal invasieve benadering. Voorspellers voor verlies van fysieke en mentale kwaliteit van leven, waren baseline scores voor kwaliteit van leven en het optreden van nieuwe postoperatieve ritmestoornissen.

Het laatste deel van dit proefschrift behandelt de uitkomsten van minimaal invasieve mitralisklep reoperaties en minimaal invasieve resectie van goedaardige atriale tumoren. In hoofdstuk 13 wordt een systematische review en meta-analyse gepresenteerd van zes retrospectieve observationele studies, met in totaal 777 patiënten. Reoperatieve minimaal invasieve mitralisklepchirurgie door middel van een mini thoracotomie leek een veilig alternatief voor een standaard sternotomie met een lagere mortaliteit, kortere opnameduur in het ziekenhuis, lagere indicentie van reoperaties voor bloedingen en een vergelijkbaar risico op een beroerte.

Primair goedaardige harttumoren is een zeldzame ziekte entiteit. Huidige richtlijnen over de voorkeursbenaderingen ontbreken. In hoofdstuk 14 wordt een meta-analyse gepresenteerd om alle studies te evalueren die een minimaal invasieve benadering vergelijken met een mediane sternotomie voor excisie van goedaardige atriale tumoren in termen van veiligheid, werkzaamheid en complicaties. Een minimaal invasieve benadering blijkt even veilig en effectief te zijn als een mediane sternotomie voor de excisie van goedaardige atriale massa's. Bovendien gaat een minimaal invasieve benadering gepaard met een verminderd aantal complicaties en een kortere ziekenhuisopnameduur. Daarom zou een minimaal invasieve benadering beschouwd kunnen worden als de voorkeursaanpak bij anatomisch geschikte patiënten.

Chapter 18

Impact paragraph

IMPACT PARAGRAPH

Two thousand twenty three marks the 100th year anniversary after the world's first successful surgical treatment of valvular heart disease. The pioneering work by dr Elliot Culter in 1923 changed the field of mitral valve surgery tremendously. In the beginning, only valvular commissurotomy, and afterwards valve replacement, were performed. However, nowadays we strive to repair the mitral valve, especially in degenerative mitral valve disease. Continues with a change in the surgical approach (repair instead of replacement), a persuasion to reduce surgical trauma to patients was observed. Since the late 1990's, and onwards, a paradigm shift towards video-assisted mitral valve surgery is observed, which is progressively adopted worldwide.

This thesis centers on the improvement of outcomes in patients referred for mitral valve disease in general, by providing evidence for the concept of personalized medicine in mitral valve surgery. As such, the individual phases of patient selection and preoperative planning as well as perioperative care are investigated, with an emphasis on the adoption of minimally invasive mitral valve surgery.

Mitral valve disease is one of the most complex valvular pathologies in the field of cardiothoracic disease, due to the heterogeneity of mitral valve dysfunction and the plethora of treatment modalities. In order to provide excellence in the quality of care, cardiothoracic surgeons should not merely focus on the technical aspect of a procedure, but improve all aspects from decision-making, procedural planning, to postoperative care. Indeed, patients do not only undergo an operation, but a complete treatment process, initiated at the moment of diagnosis and continuing until rehabilitation.

First, the prevalence of mitral valve disease is expected to increase with the ageing population, augmenting the annual case load for cardiologists, and in turn cardiothoracic surgeons. As such, in the coming decades, there may be a focus-shift towards the individual treatment of patients by dedicated care teams. Subspecialization (i.e., cardiologists and cardiac surgeons specializing in mitral valve disease) will therefore be essential for the future of cardiac surgery. The era of cardiac surgeons performing all types of cardiac procedures will consequently remain in the past. This paradigm shift from specialist and intervention-oriented care to patient and disease management-oriented care may be initiated with the formulation and standardization of the dedicated (mitral valve) heart team. Although current guidelines on valvular heart disease advocate for the implementation of the heart-team, actual supporting evidence is lacking. The current thesis provides the first scientific evidence for a survival benefit, when patients are allocated to any mitral treatment modality by the dedicated mitral valve heart-team. Eventually, we expect dedicated valvular heart teams to become the standard of care in daily practice. As a start, the European Societies of Cardiology and Cardiothoracic Surgery emphasize the establishment of Heart Valve Centers, for treatment of complex valve disease. The main purpose of such heart valve centers is to deliver optimal quality of care with a patient-centered approach. A dedicated valvular heart

team will become a mandatory aspect, which may eventually be endorsed or even be obliged by patient associations, national associations and/or health insurers.
With the emergence of minimally invasive procedures, pre-operative planning will play an increasingly important role, especially in off-pump beating-heart and transcatheter procedures. The modalities of pre-operative planning presented in this thesis can be used to identify ideal patients for a minimally invasive approach. This could likely result in a decrease in peri-operative complications and suboptimal valve repair, leading to a reduction of costs for increased length of hospital stay, re-admissions and re-interventions.

In surgery, mitral valve repair is dependent on the understanding of the valvular pathology, which is a complex interplay between the annulus, leaflets, papillary muscles with chordae and the left ventricle. Transthoracic and –esophageal echocardiography remain the golden standard and to improve the durability of mitral valve repair, the focus must shift towards meticulously understanding the valve, with surgeons becoming experts in interpretation of these images. In the preoperative phase three-dimensional-reconstructions, printing and simulation can provide direction, as it will help to determine the optimal repair strategy. During surgery, surgeons should highly rely on their preoperative interpretation of the echocardiography and merely use the intraoperative inspection to confirm their findings. Mitral valve repair will further improve with virtual modifiable reconstructed patient-specific geometry models. Virtual modifiable mitral valve models are feasible, as proven by several publications.[1-3] These models allow surgeons to simulate and determine the optimal repair techniques (resection, neochordae) prior to surgery with quantification of the outcome. In the future, artificial intelligence can even be used to train algorithms with a large number of imaging datasets, to determine the optimal repair strategy.

Any specialized procedure in the surgical spectrum will be subjected to centralization. This might particularly apply to the treatment of mitral valve disease, given its diverse presentation and plethora of treatment modalities. For centralization of care, capability, and willingness to provide patients, referring doctors, national- and international societies and health care insurance, data regarding (expected) outcomes, based on the center's recent experience, including repair rates, mortality rates, stroke rates and evidence of the likelihood of repair durability. In the Netherlands these outcomes are collected in the Netherlands Heart Registry, which provides a contemporary benchmark for mitral valve surgery. The transparent depiction on both preoperative and intraoperative characteristics as postoperative outcomes provides the opportunity to investigate mitral valve surgery and minimally invasive mitral valve surgery in the Netherlands. Furthermore, it also provides the community with data, which may function as a benchmark for new technologies and treatment modalities. For instance, it will help to determine whether a transcatheter approach for the mitral valve in a redo-setting is justified compared to reoperative mitral surgery.

In the postoperative phase, selected patients (without atrial fibrillation) can safely be treated with acetylsalicylic acid solely. The results for our study might suggest a reassessment of the recommendations from international guidelines. From a patient's perspective this will eliminate the need for frequent laboratory monitoring and variability of dosage. Furthermore, when a subset of patients no longer require laboratory monitoring this will reduce health care cost.

Improving outcomes of mitral valve surgery is multifactorial and multidisciplinary. In summary, the current thesis facilitates standardization of patient selection for various mitral valve procedures, aids to improve intra-operative outcomes, and provides a benchmark for upcoming innovative mitral valve interventions. As such, the current thesis may be interpreted transitional between the era of conventional cardiac surgery and the age of patient-specific disease management.

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Chapter 19

List of publications

LIST OF PUBLICATIONS

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Chapter 20

About the author

Ikigai 生き甲斐

Acknowledgements (Dankwoord)

Music playlist

ABOUT THE AUTHOR

Jules Robin Olsthoorn was born on 3 November 1992 in Eindhoven.

After attending primary school in Eindhoven, he moved to Son en Breugel with his parents and two sisters. During his youth, he played for two high-level hockey clubs and won several prizes together with his friends. He attended secondary school in Eindhoven (Atheneum, Lorentz Casimir Lyceum, Eindhoven, The Netherlands). After graduation for secondary school, he took a gap year for voluntary work in an orphanage in Port Elisabeth, South Africa. In 2011 he started with the Bachelor program of Medicine at the faculty of Health, Medicine and Life Sciences at the University of Maastricht. During his bachelor he started as a student-research assistant at the department of Cardiology of the Maastricht University Medical Center under supervision of dr Kietselaer. Furthermore, he founded two companies in merchandise and online marketing. During his medical educational program, he was the treasurer of Taskforce QRS Maastricht and the Netherlands; a foundation providing secondary school children in basic life support to improve outcomes of out of hospital cardiac arrest.

In the 4th year of medical University, he joined the research team headed by dr Peyman Sardari Nia, which formed the basis of this thesis. After graduation from the Faculty of Health, Medicine and Life Sciences of the Maastricht University he was registered as a medical doctor on 1 January 2019. Afterwards, he started working as a resident at the Department of Cardiothoracic Surgery of the Catharina Hospital in Eindhoven. After four months he was accepted for the residency program as a cardiac surgeon in training led by dr Bart van Straten and dr Joost ter Woorst. He continued his scientific work combined with his clinical activities. He had the honors to give several presentations regarding his scientific work during several international meetings (EACTS 2018, 2022 & 2023, Mitral Conclave 2017, 3D Printing Hospitals Forum 2023). During his surgical training he gained a profound interest in minimally invasive aortic valve, aortic and mitral valve surgery.

In 2022, together with his colleague and friend, Sameul Heuts, he won the European Resident Competition in Milan. After winning the European final, he participated in the international resident competition in San Diego during the Society of Society of Thoracic Surgeons meeting 2023, in which they finished second. In 2023 he joined the Resident Board of the European Association of Cardiothoracic Surgery (EACTS).

IKIGAI

生き甲斐

The Japanese Concept of Finding Purpose in Life

The word "ikigai" is a Japanese term that has gained popularity in recent years, especially in the Western world. It is often referred to as "the reason for being" and is seen as a key element in achieving happiness and fulfillment in life. The word "ikigai" is made up of two Japanese words: "iki," meaning "life," and "gai," meaning "value" or "worth." So, when translated, the word "ikigai" means the value or worth of one's life.

The concept of ikigai has been around in Japanese culture for centuries and is deeply rooted in their traditional values. It is seen as the intersection between four key elements: what you love, what you are good at, what the world needs, and what you can be paid for. In other words, ikigai is the point where your passions, skills, mission, and vocation meet. Finding one's ikigai is considered to be the ultimate goal in life, as it provides a sense of purpose and satisfaction.

The idea of ikigai is often associated with the idea of a long and fulfilling life. This is due to the fact that people who have found their ikigai tend to have a positive outlook on life and a strong sense of purpose. This can lead to a longer lifespan, as they are less likely to experience stress, depression, and other mental health issues. In addition, people who have found their ikigai tend to be more active and engaged in their community, which can lead to a stronger social network and a more fulfilling life.

So, how can one go about finding their ikigai? The first step is to take a good look at your own values and interests. Ask yourself what you love doing and what you are good at. Then, consider what the world needs, and what you can be paid for. Once you have a good understanding of these four elements, you can begin to explore how they intersect and how you can use this information to create a sense of purpose and direction in your life.

DANKWOORD

Dit proefschrift is gedurende een periode van ruim 6 jaar tot stand gekomen. Het was een zeer intensieve periode, waarbij ik mijn wetenschappelijke activiteiten trachten te combineren met coschappen en uiteindelijk de opleiding tot cardiothoracaal chirurg, vrienden, familie en mijn aanwezigheid thuis. Het is een periode geweest waarin ik niet alleen geleerd heb valide en betrouwbaar onderzoek te doen, maar ook mezelf op persoonlijk en professioneel vlak verder heb ontwikkeld. Het was een periode met ups en downs, maar zeker de moeite waard. Deze thesis was niet mogelijk geweest zonder de ondersteuning van vele individuen die zorgden voor wijze raad en steun in deze periode. Een aantal mensen wil ik graag in het bijzonder bedanken.

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MUSIC PLAYLIST

Scan the spotify qr code and listen to the music

Chapter	Title	Artist
Chapter 1	Turn On The Lights Again	Fred Again X Swedisch House Mafia (feat Future) – Maddix Techno Remix
Chapter 2	Bee Alright	Lady Bee, Jebroer, Boaz van de Beatz
Chapter 3	Say It Right	Macon, Enny-Mae
Chapter 4	It's Plenty	Burna Boy
Chapter 5	De Leven	Sef
Chapter 6	Numb / Encore	JAY-Z, Linkin Park
Chapter 7	Get It Crackin - Sefa Remix	Re-Style, Sefa
Chapter 8	Echo	Big2, Antoon
Chapter 9	Africa	TOTO
Chapter 10	Una Mattina	Ludovico Einaudi
Chapter 11	Een Vriend	John West, Mike Peterson
Chapter 12	Pookie	Aya Nakamura
Chapter 13	Good Times	Outsiders, The Darkraver
Chapter 14	Sky and Sand	Paul Kalkbrenner, Fritz Kalkbrenner
Chapter 15	De Wereld	Goldband
Chapter 16	Lose Yourself	Eminem
Chapter 17	Sultans of Swing	Dire Straits
Chapter 18	Money on My Mind	Dirtcaps & The Million plan
Chapter 19	Push Up	Creeds
Chapter 20	Delilah (pull me out if this)	Fred again.., Delilah Montagu

SENT FROM MY IPHONE