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[REVIEW ARTICLE]

Transcatheter mitral valve replacement — a new option for a selected group of patients?

[Running title: **Transcatheter mitral valve replacement**]

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Abstract

Mitral regurgitation (MR) is the second most common valvular disease. Symptomatic MR is associated with a poor prognosis. Cardiac surgery is recommended in the severe form of the disease. If the surgical risk is high or functional mitral regurgitation repair/replacement

cannot be combined with aorto-coronary bypass graft surgery, a transcatheter edge-to-edge valve repair should be considered. Currently, there is no recommended procedure in patients with severe symptomatic MR, high cardiac surgical risk, and low probability of success or contraindications to the percutaneous edge-to-edge treatment. A recent alternative is the mitral valve implantation using a transapical approach or through the interatrial septum. Currently, the only CE-marked transcatheter bioprothesis valve using transapical approach and implanted without extracorporeal circulation support is the Tendyne valve. This paper discusses the safety, clinical efficacy and cost effectiveness of this valve and the size of the target population in Poland. The clinical efficacy was evaluated in a study of 100 patients with severe symptomatic MR. The total 2-year mortality was 39%. The hospitalisation rate due to heart failure decreased from 1.3 events/year prior to the surgery to 0.51. MR was not recorded in 93.2% of the survivors. An economic analysis accounting for the survival, health-related quality of life, and the risk of hospitalisation due to heart failure showed that the Tendyne system is cost-effective compared to pharmacological treatment: the incremental cost-utility ratio equalled 93,324–110,696 PLN, depending on the approach, clearly below the official threshold in Poland. The annual number of eligible patients was estimated at 60.

Keywords: mitral regurgitation, mitral valve implantation, Tendyne, cost-effectiveness

INTRODUCTION

This paper is a summary of the discussions held at two advisory board meetings of experts in interventional cardiology and cardiac surgery from the leading Polish centres experienced in the treatment of patients with mitral regurgitation (MR). The aim of the paper is to identify the potential place of so far the only CE-marked transcatheter mitral valve replacement system — Tendyne (Abbott, USA; central picture) in the treatment of MR in Poland, to determine the likely target characteristics of patients, to discuss available evidence on clinical efficacy and system profitability, and to approximate the size of the potential target population.

MITRAL REGURGITATION — EPIDEMIOLOGY

Mitral regurgitation is the second most common valvular disease (after aortic stenosis). In the valvular disease registry of the European Society of Cardiology (ESC), patients with MR constituted 21.3% of all patients with severe valvular pathology, and in two thirds of cases it was primary valvular regurgitation [1]. In a recent British study, the incidence rate of moderate to severe mitral regurgitation was 3.5% in the population > 65 years of age remaining under the care of general practitioners [2].

AETIOLOGY AND PATHOGENESIS OF MITRAL REGURGITATION

The mitral valve is composed of two leaflets, anterior and posterior, connected by lateral and medial commissures. The posterior leaflet is smaller, but it occupies 2/3 of the mitral ring circumference. According to the Carpentier segmentation, there are three segments of the posterior leaflet (P1–P3), usually separated by leaflet indentations. Three corresponding segments of the anterior leaflet are defined (A1–A3) [3]. The base of both leaflets is connected to the saddle-shaped fibrous ring, which is a part of the heart structure. Primary chordae tendineae connect the free edges of the leaflets with two papillary muscles: the anterolateral and posteromedial. In addition, secondary and tertiary chordae tendineae run from the papillary muscles to the ventricular surface of the leaflets. The described structures together with the left ventricular (LV) and left atrium myocardium form the so-called mitral complex, and their interaction is responsible for the normal function of the valve [4].

Mitral regurgitation is characterised by a very diverse aetiology and mechanism, which affects the eligibility and selection of surgical treatment methods. Primary (called also: organic) regurgitation is caused by damage to the component(s) of the mitral complex. In highly developed countries, degenerative changes are most commonly responsible for primary valve regurgitation: mucoid degeneration of the leaflets (mitral valve prolapse) and fibroelastic deficiency; in underdeveloped countries, rheumatic aetiology predominates. Infective endocarditis, nonspecific inflammatory processes, age-related mitral ring calcification, and congenital mitral valve defects may also be responsible for the development of primary mitral regurgitation.

Secondary (called also: functional) mitral regurgitation is due to damage and remodelling of the left ventricle or enlargement of the left atrium with mitral ring dilation and impairment of its function. The basic differences between secondary ventricular and atrial regurgitation include, in addition to the enlargement of the corresponding heart chamber, the

position of the mitral valve leaflets and the direction of the regurgitation jet. In the case of regurgitation resulting from left ventricular dilatation and dysfunction, systolic leaflet restriction (increased coaptation depth and mitral valve tenting) is observed. The regurgitation jet is usually central. The eccentric regurgitation jet may occur in case of a “pseudoprolapse” of the tethered anterior leaflet (seagull sign) or it may be associated with segmental wall motion abnormalities causing asymmetric leaflet restriction. In regurgitation caused by the enlargement of the left atrial cavity (e.g. in the course of atrial fibrillation), the depth of coaptation (distance from the annulus line to the coaptation point) in systole is usually normal and the regurgitation jet is centrally directed. The shape of regurgitant orifice in both types of secondary MR is usually elyptical, and the regurgitation severity may be variable depending on the loading conditions.

CLINICAL MANIFESTATION AND PROGNOSIS OF PATIENTS WITH MITRAL REGURGITATION

Acute mitral valve regurgitation causes a sudden increase in left atrial pressure and a decrease in cardiac output, resulting in pulmonary oedema and/or cardiogenic shock. This is a life-threatening condition that requires urgent surgery. In some cases with high surgical risk, transcatheter repair or replacement is also possible.

The chronic form of organic mitral regurgitation may initially be asymptomatic. The dominant auscultatory symptom of the defect is a systolic murmur heard over the apex of the heart radiating to the left axillary area but may be silent in patients with poor left ventricular (LV) contractility. The progression of the disease leads to the occurrence of supraventricular and ventricular arrhythmias (including atrial fibrillation) and dyspnoea — initially on exertion, and in the advanced stage at rest. Symptoms of the underlying disease, i.e. ischaemic or non-ischaemic cardiomyopathy or atrial fibrillation dominate in the secondary mitral regurgitation.

Symptomatic MR is associated with a poor prognosis, particularly in patients with depressed LV function and in patients not eligible for surgical treatment. According to the results of the Euro Heart Survey, the one-year survival of patients with severe mitral regurgitation who were eligible for surgical treatment was 96%, while that of patients treated conservatively (representing almost half of the study group) was 89% ($p = 0.02$ for the difference in proportions) [5]. In another single-centre study with the participation of over

1,000 patients with severe mitral regurgitation and heart failure who did not undergo surgery, the 1-year mortality rate was 20% and the 5-year mortality rate was 50%. Among patients who survived, the percentage of hospitalisations due to heart failure increased from 41% in the first year of follow-up to 90% after 5 years [6].

DIAGNOSTIC EVALUATION

The first-line imaging method for assessing the mechanism and severity of the defect is transthoracic echocardiography. Recommendation of the European Association of Cardiovascular Imaging proposed qualitative, semi-quantitative and quantitative criteria for valve regurgitation, as well as structural data regarding the left ventricular and left atrial cavities [7]. The qualitative criteria include the morphology of the valve with the assessment of the systolic position of the leaflets and the search for the coaptation defect, the cross-sectional area of the regurgitation jet in the colour Doppler echocardiography, the diameter of the flow convergence zone (PISA, proximal isovelocity surface area) and the density of the regurgitation jet signal in the continuous-wave Doppler. The semi-quantitative criteria include the width of the vena contracta, the systolic retrograde flow in the pulmonary veins, the mitral inflow profile with the dominant E wave, and the ratio of the mitral inflow volume to the left ventricular outflow tract flow as measured by pulsed-wave Doppler. The quantitative assessment of the defect consists of the effective regurgitant orifice area (EROA), regurgitation volume (RV) and regurgitation fraction (RF). Based on the quantitative echocardiography criteria, chronic mitral regurgitation can be described as mild, moderate or severe; or a four-degree scale can also be applied: grade 1 (mild insufficiency), grade 2 (moderate insufficiency), grade 3 (moderate-to-severe insufficiency) and grade 4 (severe insufficiency) [8]. Quantitative criteria for severe mitral regurgitation (regardless of the aetiology of the defect) are: EROA > 0.4 cm^2, RV > 60 mL and RF > 50%. [9] In patients with elyptical shape of the regurgitant orifice vena contracta should be measured in two views and averaged and the threshold of EROA > 0.3 cm^2, RV > 45 mL may be considered. In the case of difficulties in visualising the valve, discrepancies between transthoracic echocardiography and the clinical condition of the patient and before planned percutaneous treatment, imaging diagnostics should be expanded to include transoesophageal echocardiography. Magnetic resonance imaging, which assesses the volume of the mitral regurgitation jet and the degree of left ventricular remodelling, could also be helpful.

RECOMMENDATIONS OF SCIENTIFIC SOCIETIES REGARDING THE SURGICAL TREATMENT OF MITRAL REGURGITATION

Current recommendations for the management of patients with mitral regurgitation include the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines and the 2020 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of Patients With Valvular Heart Disease [9, 10]. Both guidelines discuss recommendations for patients with primary and secondary regurgitation separately.

According to the ESC/EACTS guidelines, surgical valve repair is recommended in severe primary mitral regurgitation if permanent effects of such procedure can be expected (Class I-B recommendation). Surgery is recommended in symptomatic patients who are not at high surgical risk [Class I-B recommendation]. Surgery is recommended in asymptomatic patients if left ventricular dysfunction is present [left ventricular end-systolic diameters (LVESD) ≥ 40 mm and/or left ventricular ejection fraction (LVEF) ≤ 60%] (Class I-B recommendation). In asymptomatic patients with preserved left ventricular (LV) function (LVESD < 40 mm and LVEF > 60%), surgery should be considered if atrial fibrillation secondary to mitral regurgitation or pulmonary hypertension [systolic arterial pulmonary pressure (SPAP) at rest > 50 mmHg] is observed (Class IIa-B recommendation). Surgical valve repair should also be considered in asymptomatic patients with LVEF > 60% and LVESD < 40 mm and a low risk of surgery if significant left atrial enlargement (volume rate ≥ 60 mL/m^2 or atrial diameter ≥ 55 mm) is present, provided that the procedure is performed at the reference centre and permanent repair is likely (Class IIa-B recommendation).

In symptomatic patients who, according to the Heart Team, are ineligible for surgery or bear high risk of conventional surgery, transcatheter edge-to-edge valve repair can be considered [11]. These patients must meet echocardiographic and clinical criteria for eligibility for this type of procedure, and the procedure cannot be considered futile (Class IIb-B recommendation) [12].

In the case of secondary mitral regurgitation, surgical treatment is recommended only in patients with severe disease, in whom symptoms persist despite conservative treatment compliant with the recommendations (including the use of cardiac resynchronisation therapy, if appropriate), and the decision to perform the procedure is made by the Heart Team (Class I-B recommendation).

In patients requiring surgical treatment for other indications [undergoing coronary artery bypass grafting (CABG) or another heart surgery], cardiac valve surgery is also recommended (Class I-B recommendation). In patients considered by the Heart Team ineligible for a surgery, percutaneous coronary intervention (PCI) should be considered if revascularisation or transcatheter aortic valve implantations (TAVI) with a significant aortic valve defect is required, and then, if severe valve regurgitation persists, the transcatheter edge-to-edge valve repair should be performed (Class IIa-C recommendation).

If there is no concomitant coronary artery disease or another heart disease requiring surgical treatment, the transcatheter edge-to-edge valve repair should be considered in symptomatic patients (Class IIa-B recommendation) — such treatment has a higher class of recommendation than a classic cardiac surgery based on the results of the COAPT study [11]. If, according to the Heart Team, a symptomatic patient is an appropriate candidate for surgery, valve surgery may be considered (Class IIb-C recommendation).

In symptomatic patients from the high risk group who are disqualified from surgery and do not meet the criteria for response to the transcatheter valve repair, the Heart Team may, in selected cases, consider percutaneous edge-to-edge treatment or another transcatheter valve intervention, if the treatment is possible and justified, after considering the indications for other therapeutic methods (use of a ventricular assist device or heart transplantation) (Class IIb-C recommendation).

The 2020 ACC/AHA Guidelines recommendation for intervention in the case of chronic primary mitral regurgitation do not differ significantly from European guidelines. In symptomatic patients, surgical treatment of the defect is recommended, indicating valve repair as the optimal method of treatment (Class I recommendation). In asymptomatic patients with normal left ventricular systolic function, the probability of successful and permanent valve repair has been precisely determined — the probability of the absence of residual regurgitation jet is > 95% with the expected mortality of < 1% when the procedure is performed in a specialised centre for the treatment of valvular defects. Then mitral valve repair is justified (Class IIa recommendation). According to American recommendations, mitral valve surgery may be considered regardless of the probability of successful and permanent repair in asymptomatic patients with severe primary mitral regurgitation and normal left ventricular systolic function but a progressive increase in its size or decrease in the ejection fraction in at least three consecutive imaging examinations (Class IIb recommendation). The guidelines also specify the indications for the transcatheter edge-to-

edge repair. This procedure is justified in patients with severe primary valve regurgitation in New York Heart Association (NYHA) Class III or IV, high or very high surgical risk, if the anatomy is favourable for repair and the patient's life expectancy is at least one year (Class IIa recommendation). In the case of secondary severe valve regurgitation associated with left ventricular dysfunction (LVEF < 50%), the transcatheter repair using the edge-to-edge method is recommended in patients with symptoms in the functional Class II–IV despite optimal recommended pharmacotherapy for heart failure, and favourable valve anatomy in the echocardiography, LVEF in the range of 20–50%, LVESD ≤ 70 mm and pulmonary artery systolic pressure ≤ 70 mmHg — COAPT study criteria (Class IIa recommendation). However, in patients with severe secondary valve regurgitation without other indications for surgical treatment, American recommendations are based on persistent clinical manifestations (NYHA Class III or IV) despite optimal pharmacotherapy for heart failure. In this group of patients, valve surgery may be considered (Class II-B recommendation).

MITRAL VALVE IMPLANTATION USING THE TRANSAPICAL APPROACH

As can be seen by analysing the guidelines of scientific societies cited above, there is currently no recommended treatment for patients with severe symptomatic MR, high cardiac surgical risk and low probability of success of percutaneous edge-to-edge treatment or with contraindications to this type of a procedure. An alternative therapy method that has emerged in recent years is the mitral valve implantation using a transapical approach or through the interatrial septum [13].

The introduction of this treatment method into clinical practice was a much greater challenge than the use of TAVI. The main difficulties were due to much larger dimensions of the mitral ring, which is also saddle-shaped rather than flat. The non-rigid tissue of the mitral annulus and surrounding structures does not provide sufficient resistance when anchoring the valve, which operates under conditions of high systolic pressure of the left ventricle. Moreover the valve should be wide enough to allow unrestricted passage of blood from the atrium to the ventricle during relaxation phase of the cardiac cycle. An additional problem is the risk of obstruction of the left ventricular outflow tract (LVOT) caused by the prosthesis itself or by the forward displacement of the anterior leaflet of the native mitral valve. Axial implantation is required at an appropriate level to seal the entire circumference of the saddle-shaped orifice and to avoid paravalvular leakage.

In recent years, several systems for transcatheter mitral valve replacement have been tested in clinical trials, including: CardiaQ (Edwards Lifesciences, Irvine, CA, USA), Tiara (Neovasc Inc., Richmond, Canada), Twelve (Intrepid, Medtronic, MN, USA), AltaValve (4C Medical, Apple Grove, MN, USA), HighLife Mitral (HighLife SAS, Paris, France) and Tendyne™ (Abbott, MN, USA) [14]. Currently, the only transcatheter mitral bioprosthesis implanted in a beating heart, without the use of extracorporeal circulation support, that has the CE mark is the Tendyne valve (Abbott Cardiovascular, Plymouth, MN, USA). The Tendyne system is a transcatheter transapical bioprosthesis implantation system intended for the treatment of native mitral valve diseases, and it has been designed to address the anatomical aspects listed above. The trileaflet valve from the porcine pericardium is attached to a double stent made of nitinol. The external stent is adjusted to the shape of the orifice, with appropriate flattening on the base of the anterior leaflet to reduce the risk of LVOT obstruction (LVOTO).

The valve is connected via a wire (tether) to a plate placed outside the apex of the left ventricle (ventricular pad). The tether, together with the ventricular pad, stabilises and anchors the implant, preventing its displacement towards the atrium.

The valve requires surgical access through the left minithoracotomy. A 4–6 cm incision allows for identification and exposition of the left ventricular apex.

Thanks to unique tether design Tendyne system enables full retrievability through duration of procedure and also secures reliable fixation in the desired position, together with apical pad placed over ventricular access site. Despite potential disadvantages of transapical access, the system gives a high-level control throughout the implantation, with possibility of repositioning and retrieving the valve. Unlike other solutions, this option represents an important aspect of the system.

Tendyne System enables also correct positioning in the mitral anatomy thanks to the possibility of valve’s rotation to comply with the native mitral valve anatomy. This adoption to the natural mitral ring annulus rotation is defined upfront during screening and procedural planning process and can be corrected during the implantation itself.

The Tendyne valve is available in two profiles (SP — standard profile and LP — low profile) which, together with dedicated anterior-posterior (AP) and annular perimeter dimensions, give the option to choose between 13 different valve sizes. According to the sizing chart, the system allows to address anatomies ranging from 26.4 to 41.3mm (AP

distance) and 96–143 mm (based on perimeter). The broad selection of sizes allows for proper selection of the device it order to minimize paravalvular leak but also — to minimize left ventricular outflow tract obstruction.

Cardiac imaging using three-dimensional transoesophageal echocardiography (3D TEE) and dynamic computed tomography provides necessary pre and intraprocedural guidance and is of paramount importance. The selection of the prosthesis is based on computer modelling, taking into account additional individual anatomical features (e.g. presence of calcifications, thickness and shape of the interventricular septum, length of the anterior mitral valve leaflet).

Based on the modelling mentioned, apical access site is defined to secure the orthogonal annular trajectory of the valve. In majority of the cases, the orthogonally calculated access site is moved from the true apex, which plays an indicative navigation point during the procedure.

The implantation itself is mainly guided by TEE imaging, with occasional support of fluoroscopy, to evaluate implantation accuracy, valve position and sealing. It is also recommended to measure LVOT gradient in order to mitigate LVOTO and react properly with reposition or retrieving the valve.

The clinical experience of using the Tendyne transcatheter transapical mitral bioprosthesis implantation system is growing. The first results of a prospective assessment of the effectiveness and safety of the procedure using the Tendyne technology in a group of patients with mitral regurgitation and high surgical risk included data on 30 patients [15]. The study enrolled patients from eight study sites in Australia, the United States and Norway between November 2014 and March 2016.

Inclusion criteria for the study included: age over 18 years, primary or secondary mitral regurgitation (stage 3 or 4), clinical manifestations (NYHA class ≥ 2). Exclusion criteria included: decreased left ventricular ejection fraction < 30%, left ventricular end-diastolic dimension > 70 mm, significant ring or mitral valve leaflet calcification, severe tricuspid regurgitation, previous mitral or aortic valve surgery or transcatheter mitral valve intervention, systolic pressure in the pulmonary artery ≥ 70 mmHg and severe right ventricular dysfunction with symptoms of right ventricular heart failure. In the case of patients with resynchronisation therapy, qualification was possible 3 months after the

implantation of the resynchronisation system, and in patients after acute coronary syndrome upon 30 days after the event.

The primary endpoint during the 30-day follow-up period was effective device implantation and absence of deaths due to cardiovascular reasons, stroke and device dysfunction. Pre-specified secondary endpoints included: severity of regurgitation, changes in the left ventricular size, change in NYHA functional class, 6-minute walk test (6MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores.

The primary safety endpoint was the absence of serious adverse events, including cardiovascular death, disabling stroke of the central nervous system, myocardial infarction, re-intervention for valve-related dysfunction, life-threatening bleeding and renal failure requiring dialysis. Other prespecified variables were rehospitalisation due to heart failure and re-intervention in the case of valve dysfunction at any time during follow-up.

The presented results included, as already mentioned, data from 30 patients at an average age of 75.6 ± 9.2 years, of whom 83.3% were men. The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) value ranged between 5.7–7.3%. The majority of patients (76.7%) had secondary mitral regurgitation, grade 4 (93.1%) and grade 3 (6.9%).

The Tendyne valve was successfully implanted in 28 (93.3%) patients, completely eliminating mitral regurgitation (transvalvular and paravalvular) in 27 of them. During the 30-day follow-up period, one death due to hospital-acquired pneumonia and respiratory failure was recorded. Successful device implantation free from cardiovascular death, stroke, and device dysfunction in 30-day follow-up was achieved in 86.7% of cases.

An extended analysis of the first 100 patients treated with the Tendyne system as part of the global feasibility study was published two years later [16]. The inclusion and exclusion criteria of patients and the analysed endpoints were consistent with the study discussed above. Between November 2014 and November 2017, patients from 24 centres (13 in the United States, 3 in Australia and 8 in Europe) were enrolled in the study.

The average age of patients was 75.4 ± 8.1 years, and 69% were male. Approximately 89% of patients had secondary mitral regurgitation grade 3 or 4 in 99% of them. NYHA Class III or IV patients accounted for 66% of the entire study group. Bioprothesis was implanted in 97 out of 100 patients, eliminating mitral regurgitation in 96 of them, resulting in 96% success rate for the entire cohort. The average follow-up period was 13.7 months. Overall, there were 26 deaths during the entire follow-up period, 6 of which occurred within the first 30 days. All-

cause death-free survival after 1 year of follow-up was 72.4%. Most deaths were due to cardiovascular causes (85%). Additionally, 20 patients were re-hospitalised due to heart failure.

Reduction in mitral regurgitation after the Tendyne system implantation was maintained during the follow-up period. Regurgitation was not observed in 95.3% of patients after 6 months, and in 98.4% of patients after 1 year of follow-up. Patients who survived showed a significant improvement in symptoms and quality of life. Within one year, 88.5% of patients remained in NYHA Class I or II in comparison to 34% at baseline ($p < 0.0001$). There was also a significant improvement in the 6MWT (after 12 months: $p = 0.011$), with the greatest improvement observed in the first 3 months after the procedure. During a yearly follow-up, the KCCQ score increased by 5 points in 81.3% and by 10 points in 73.4% of surviving patients.

In the two-year follow-up, the overall mortality rate of the first 100 patients was 39% [17]. The rate of hospitalisation for heart failure decreased from 1.3 events/year before the procedure to 0.51 events/year at the two-year follow-up after the procedure ($p < 0.0001$). After 2 years, no MR was recorded in 93.2% of surviving patients. There was also continued improvement in the clinical condition of patients (81.6% of them were in NYHA Class I or II) and their quality of life. At the same time, no structural dysfunctions in the Tendyne valve were observed after 2 years.

An interesting retrospective study has been recently published comparing the efficacy of procedures using the Tendyne system with edge-to-edge repair using the MitraClip system (Abbott Structural Heart, Santa Clara, CA, USA) or the PASCAL system (Edwards Lifesciences, Irvine, CA, USA) in patients with symptomatic mitral regurgitation considered ineligible for surgical treatment or patients classified as high-risk based on the Heart Team assessment [18]. The study included 63 patients who underwent computed tomography between April and October 2019 and were considered eligible for the Tendyne system. Finally, the procedure was performed in 17 patients and in the remaining 46 patients percutaneous valve repair was performed using the edge-to-edge method. Patients undergoing bioprosthesis implantation were characterised by a higher transvalvular gradient and valve morphology unsuitable for the transcatheter edge-to-edge repair (TEER) therapies. The use of the Tendyne system reduced the grade of valve regurgitation to less than 1+ in 94.1% of patients (assessed at discharge from the hospital) and was associated with a greater reduction in the left ventricular end-diastolic volume in the 30-day follow-up compared to the

MitraClip/Pascal system. However, 30-day mortality was higher in the Tendyne group, while mortality between the 30th day and one year after the procedure was comparable in both analysed groups.

Worth mentioning is that TMVR therapy with the Tendyne valve may also have a future role in the treatment of patients with MR and severe mitral annular calcification (MAC). This population represents a great challenge for surgical treatment, due to inability to suture the valve correctly. First experience in 20 patients with MR and severe MAC showed that the use of the Tendyne valve was associated with encouraging acute outcomes (technical success in 95% patients, 100% elimination of MR, no procedural mortality, and 30-day mortality of 5%), and clinical improvement. Currently, a dedicated MAC cohort is a part of the Tendyne SUMMIT pivotal clinical trial that remains ongoing (https://clinicaltrials.gov/ct2/show/NCT03539458) [19].

COST-UTILITY ANALYSIS

An attempt was made to assess the economic validity of using the Tendyne system in the form of the cost-utility analysis from the perspective of the public payer in Poland in a 10-year framework after the procedure. The analysis took into account the impact of the use of the Tendyne system on overall survival, on the quality of life reflected by the NYHA Class, and on the reduction in the risk of hospitalisations caused by exacerbation of heart failure. Pharmacological treatment was used as the comparator.

No randomised controlled trials comparing the Tendyne system with pharmacological treatment have been published so far. The data on deaths within two years after the Tendyne treatment is available [16, 17]. In the economic analysis, it was necessary to determine the clinical benefits in the longer term to fully reflect the clinical effects achieved. Survival curves were extrapolated using the Weibull distribution.

Due to the lack of data for the comparison group, the following approach was used. The COAPT study [11] assessed the safety and effectiveness of the procedure using the MitraClip system in patients with heart failure and secondary MR. The characteristics of the patients largely overlap with those treated with the Tendyne system [17] (Tab. 1). Hence, it was assumed that the clinical effect from the COAPT study, i.e. the hazard ratio (HR) of 0.62, 95% CI = (0.46–0.82), can be related to the expected benefit of the Tendyne system. Based on the HR parameter, the survival curve for the pharmacologically treated group was secondarily

estimated. Figure 1 shows the obtained survival curves for the Tendyne system and the pharmacologically treated group. It is important to acknowledge a substantial difference in the LVEF between the two studies [11, 17], which could have had a favourable impact on the outcomes obtained for the Tendyne system.

According to experts, in the case of pharmacological treatment, if the Tendyne system is not used, there will be a need for an average of two hospitalisations per year due to exacerbations of heart failure. The analysis conservatively limited the savings horizon to the first year. Three possible types of hospitalisation were considered and survey data regarding their expected structure were collected. The hospitalisation codes and their respective cost and structure were as follows: E50 Acute or decompensated heart failure — treatment in a cardiac intensive care unit with the cost of 17,000 Polish zloty (PLN) and 75% structure, E52 Advanced heart failure with the cost of 5,593 PLN (up to 28 days assumed) and 12.5% structure and E53G Heart failure with the cost of 4,184 PLN (at least 3 days assumed) and 12.5% structure.

The structure of the NYHA Class according to the Muller (2021) study was taken into account [17]. The baseline distribution of classes was assumed throughout the entire period in the pharmacotherapy group, assuming that the patients' condition did not change over the entire analysis horizon. The results reported at 1, 12, and 24 months of follow-up were used in the Tendyne group. It was assumed that the benefits were visible from the moment of treatment and increased evenly in the following months. It was assumed that after the 24th month of follow-up, the patients' condition remained stable until the end of the analysis horizon. While this assumption only approximates the actual clinical situation, it corresponds to the assumption made for the pharmacotherapy arm, which also did not model the deterioration of NYHA Classes beyond the most recent available data. Table 2 shows the distribution of individual NYHA Classes for individual time points along with the health state utility values (adapted from [20]).

In an additional variant of the analysis, the overall score obtained in the Kansas City Cardiomyopathy Questionnaire — overall score (KCCQ-OS) questionnaire was used in the Muller (2021) study [17], which was converted into utility values based on the approach according to [21]:

$$0.44 + 0{,}0035 * (\text{KCCQ-OS})$$

The result was utility values after 1, 12 and 24 months of follow-up for the Tendyne group, and baseline values were assumed for the pharmacotherapy group (Tab. 3).

The total cost of using the Tendyne system was assumed to be PLN 144,000 including the cost of the device and the cost of carrying out the procedure by the healthcare provider (according to the information for the ratio of costs of the device and the entire procedure for the MitraClip system). Since the costs of pharmacotherapy are negligible compared to the costs of this system, they were omitted in this analysis. The average cost of one avoided hospitalisation is PLN 13,972 (based on the weighted average of individual hospitalisations due to acute or decompensated heart failure — treatment in a cardiac intensive care, advanced heart failure and heart failure).

The analysis used an annual discount rate of effects of 3.5% (costs are limited to the first year of the analysis). The result was that the use of the Tendyne system is PLN 97,056 more expensive than pharmacotherapy and provides additional clinical outcomes: 1.31 life years gained (LYG), 1.24 quality-adjusted life years (QALYs) in the NYHA-based approach, and 1.05 QALYs in the KCCQ-OS-based approach. The additional cost of a unit of effect, i.e. the incremental cost-effect ratio (ICER, for the analysis by LYG) is PLN 88,578/LYG and the incremental cost-utility ratio (ICUR, for the analysis by QALY) is PLN 93,324/QALY for the NYHA Class-based approach and PLN 110,696/QALY ICUR for the KCCQ-OS-based approach. The ICER and ICUR values are clearly below the profitability threshold in Poland (as at 31 October 2023 — PLN 190,380/LYG or PLN/QALY) (Tab. 4).

POPULATION SIZE ESTIMATION

Shall Tendyne technology be available in Poland, 10% to 20% of patients who were initially qualified for transcatheter mitral intervention will be considered by Heart Teams as eligible for Tendyne valve. Assuming the number of patients considered as TEER eligible amounts to 400 per year, and assuming an average eligibility for Tendyne of 15%, we get a target population of 60 patients per annum. Taking into account the cost of the procedure and the savings from avoided hospitalisations, the annual cost sums to PLN 7 million.

Summary

The presented data indicate high clinical effectiveness and cost-effectiveness of the transapical mitral bioprosthesis implantation method (Tendyne system) in a selected group of patients who suffer from severe mitral regurgitation. Careful qualification of the patient by a

multidisciplinary team based on modern imaging examinations is fundamental to the success of the procedure. Due to their complexity, these procedures should be performed in a few specialised centres with extensive experience in percutaneous treatment of mitral regurgitation and in interventional procedures using the apical approach.

Conflict of interests: A. Gackowski declares proctoring and lecture honoraria from Abbott and from Edwards Lifesciences. M. Grygier is a proctor for Abbott and reports speaker's or consulting honoraria from Abbott, Medtronic, Edwards Lifesciences, and 4cMedical. M. Grabowski declares speaker honoraria from Abbott Medical. M. Jakubczyk and M. Niewada are co-owners of HealthQuest, a consultancy receiving payments from Abbott.

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Central illustration. The Tendyne system

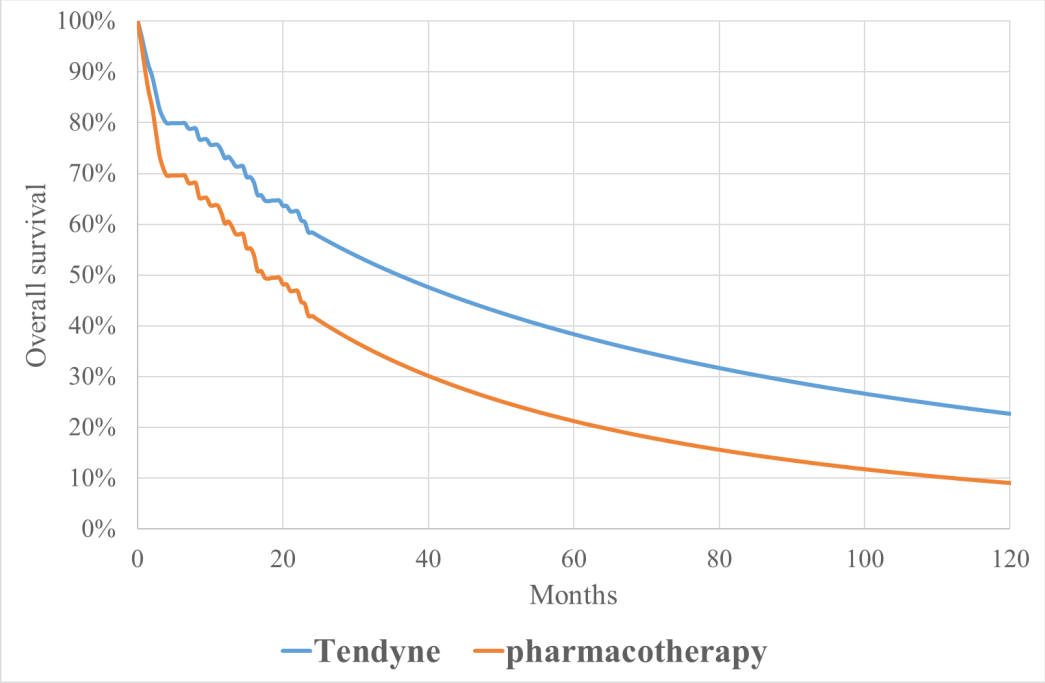

Figure 1. Overall survival — original data from the Muller (2021) study and extrapolation (after 24 months)

Table 1. Comparison of the baseline characteristics of patients in the Muller (2021) and COAPT studies [11, 17]

Parameter		**Muller (2021)**	**COAPT**
Age, years (SD)		74.7 (± 8.0)	72.8 (± 10.5)
Sex, male, %		69%	61.5
STS-PROM, % (SD)		7.8 (± 5.7)	8.5 (± 6.2)
NYHA, %	Class I	0	0
	Class II	34	35.4
	Class III	62	54
	Class IV	4	10.6
MR severity, %	3+	99	55.3
	4+		44.7
LVEF (SD)		46.4 (± 9.6)	31.3 (± 9.6)

LVEF — left ventricle ejection fraction; MR — mitral regurgitation; NYHA — New York Heart Association; SD — standard deviation; STS-PROM — Society of Thoracic Surgeons — Predicted Risk of Mortality

Table 2. Distribution of NYHA Classes and average utility values

NYHA class	**Utility**	**Muller (2021)**			
		At baseline	**30 days**	**1 year**	**2 years**
NYHA I	0.858	0%	17%	33%	33%
NYHA II	0.761	34%	60%	56%	49%
NYHA III	0.646	62%	18%	10%	18%
NYHA IV	0.458	4%	5%	2%	0%
Average utility values		0.6774	0.7422	0.7759	0.7722

NYHA – New York Heart Association

Table 3. Estimated utility values based on the KCCQ — Muller (2021) study

Source	**Muller (2021)**			
Time	**At baseline**	**At 30 days**	**After 1 year**	**After 2 years**
KCCQ	48.6	58.6	71.5	67.2
Utility	0.6101	0.6451	0.6903	0.6752

KCCQ — The Kansas City Cardiomyopathy Questionnaire

Table 4. Summary of economic analysis results

Category	**TMVI**	**Pharmacological treatment**	**Incremental results**
QALY (using NYHA)	3.01	1.77	1.24
QALY (using KCCQ-OS)	2.64	1.59	1.05
LYG	3.92	2.61	1.31
Total cost, PLN	144,000.00	27,944.25	116,055.75
ICUR (using NYHA), PLN	n/a	n/a	93,324
ICUR (using KCCQ-OS), PLN	n/a	n/a	110,696
ICER, PLN	n/a	n/a	88,578

ICER — incremental cost-effectiveness ratio; ICUR – incremental cost-utility ratio; LYG — life-years gained; PLN — Polish zloty; QALY — quality-adjusted life years; TMVI — transcatheter mitral valve implantation