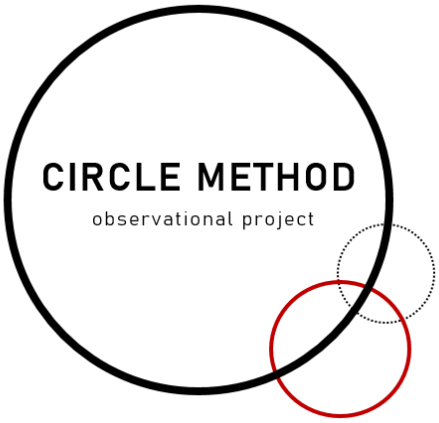
# The Circle Method Observational Project

Circle method for sizing and positioning in bicuspid valves




*Non-interventional, retrospective, multicenter international data collection to validate circle method for sizing and positioning in bicuspid aortic valves*

***– Project Description –***

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## 1 SYNOPSIS

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|---|---|
| **Title** | The Circle Method Observational Project - Circle method for sizing and positioning in bicuspid valves |
| **Background** | The bicuspid aortic valve (BAV) is the most common heart valve abnormality and is associated with a number of cardiac complications, including infective endocarditis, aortic dissection, aortic dilatation, and the development of severe aortic stenosis (AS). Due to its anatomical characteristics BAV has been considered a contraindication to transcatheter aortic valve implantation (TAVI), a standard treatment of AS. However, several recent trials have presented promising results indicating TAVI to be a safe alternative to surgery for low risk patients and more patients with BAV have been considered for TAVI.<br><br>There are several sizing techniques for TAVI in BAV, including an annular sizing, a supra-annular sizing, and a balloon sizing, yet there is still no consensus on the most appropriate technique. Although annular sizing remains the major approach in most patients with BAV, some BAV anatomies may profit from the supra-annular sizing. Recently published consensus for sizing and positioning the balloon-expandable Edwards SAPIEN 3 transcatheter heart valve (THV) in BAV describes the anatomical features that influence sizing optimization (1). The novel circle technique has also been proposed in the presence of the unique anatomical factors and sizing at the supra-annular level. This method is particularly helpful for visually identifying anatomic features, indicating the sealing zone at the commissures, visually reassuring of the size and position, and treating patients with large annuli. Currently, there are limited data validating the circle method for identifying sizing and positioning for TAVI in BAV patients. |
| **Aim** | To validate the circle method for sizing and positioning of SAPIEN 3 THV, using circles to simulate the SAPIEN 3 TAVI at 0, 3, 6, and 9 mm in 3mensio above and below the coronary arteries. |
| **Trial design** | Retrospective, non-interventional, 3mensio based analysis in 3 centers (Berlin, Katowice and Cambridge) and at least 60 eligible patients. |

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| **Patients** | **Inclusion Criteria**:<br>• Patients with bicuspid aortic valves undergoing aortic valve replacement with a balloon expandable valve (SAPIEN 3 / Ultra)<br>• Computed Tomography data available |
| **Primary objectives** | To assess whether patients with bicuspid aortic valves that received a SAPIEN 3 / Ultra THV suffered from fewer complications<br>• if valve size was identical to the one determined using the circle method<br>compared to<br>• a case where circle method derived valve size is different from the actually implanted valve |
| **Secondary objectives** | To develop recommendations on how to size the valve using the circle method. |
| **Exploratory research questions / endpoints** | We aim to assess whether patients with bicuspid aortic valves that received a SAPIEN 3 / Ultra THV suffered from fewer complications<br>• if valve size was identical to the one determined using the circle method<br>*compared to*<br>• a situation where circle method derived valve size is different from the actually implanted valve<br>Complications are defined as:<br>• Death<br>• Stroke<br>• Paravalvular Leakage (PVL)<br>• Pacemaker implantations<br>• Coronary occlusion<br>• Malposition<br>• Fistula to right ventricular outflow tract (RVOT)<br>• Annulus rupture<br>• Sinus sequestration<br>• Valve embolisation |
| **Schedule** | Baseline, Intervention, Discharge, 30 days, 3 months/12 months (according to availability, all retrospective) |

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| **Quality assurance / CoreLab** | A CoreLab with the 3mensio Software and the most recent update as of January 2021 will be available to assess the CT data matching each patient. The two CoreLab physicians will independently assess the CT data based on the manual provided in the appendix. These data will be collated with the clinical dataset to assess correlations between measurements and complications / outcomes. |
| **Statistics** | No pre-specified statistical analyses, explorative approach. |
| **Sample size** | Given the limited data for sizing and positioning with the circle method in BAV patients, we aim to include at least 60 patients for this pilot study. |

# 2 INTRODUCTION

## 2.1 CLINICAL BACKGROUND

The bicuspid aortic valve (BAV) is the most common heart valve abnormality, affecting 0.4% to 2.25% of the general population and up to 6% of patients with severe aortic stenosis (AS) (2). Although BAVs do not usually pose any risks at birth and during early life, they are associated with a number of cardiac complications during the adulthood, including AS, infective endocarditis, aortic dilatation, and aortic dissection (3). Progressive regional calcification is also common in BAVs and is identical to that occurring in tricuspid aortic valves (TAV).

Transcatheter aortic valve replacement (TAVI) has become a standard treatment option for patients with severe AS who are considered high risk for surgical aortic valve replacement (4-6). The presence of BAV has been considered a contraindication to TAVI due to BAV's anatomical features (large annulus, calcified raphe, aortic root dilatation, and horizontal aorta) that may adversely impact procedural outcomes (7). Consequently, patients with BAV have constantly been excluded from the major randomized trials involving TAVI, despite promising results from a series of registries and observational reports (8-11). However, in light of the evidence from recent trials indicating TAVI to be a safe alternative to surgery for low risk patients, more patients with BAV are now being considered for TAVI (12-15).

Due to the existing knowledge gap on TAVI in BAV patients, several issues, including sizing and positioning of the device, remain unresolved. Currently, sizing in BAV includes three different techniques: an annular sizing, a supra-annular sizing, or a balloon sizing. Several trials proposed various BAV classifications in order to define anatomical differences, predict complications, and identify orifice area/patient aortic annulus area ratio. The most commonly used BAV classification was established by Sievers and Schmidtke, who used the number of raphes to distinguish three major anatomical types: type 0 (no raphe), type 1 (one raphe), and type 2 (two raphes), followed by two additional characteristics, including spatial position of raphes and functional status of the valve (16). Recently, the Bicuspid Aortic Valve Anatomy and Relationship with Devices (BAVARD) program used the annular-based sizing and intercommissural distance (ICD) to predict sealing, position, and size of the device, potentially avoiding excessive oversizing and its consequences (17). The objective of this program was to identify the sizing ratios used for TAVI in BAV, assess the prostheses' geometry after implantation and compare the results with the TAV patients. Tchetche et al. retrospectively analyzed 101 patients with BAV with available pre- and post-TAVI multidetector computed tomography and compared them with 88 TAV patients (17). The authors concluded that annular-based sizing in BAV was valid in selecting the TAVI device size while supra-annular sizing could be used in cases when the mean annular diameter is larger than the ICD (17). In addition, Petronio et al. proposed another novel approach called Calcium Algorithm Sizing for bicuspid Evaluation with Raphe (CASPER) (18). The algorithm focuses on the combination of three major anatomical features: raphe length with respect to annulus diameter, calcium burden, and calcium localization in relation to raphe. However, this method was validated in a relatively small patient cohort and further trials with larger population of patients with BAV and different morphological varieties are needed.

Annular sizing remains the major treatment approach in most patients with BAV, yet some BAV anatomies may require sizing at the supra-annular level. Because of the unequal-sized leaflets and reduced number of commissures, the orifice in BAV is usually smaller, more asymmetrical, and less circular than in TAV. As a result, the leaflets do not open in the same way during TAVI and conventional

annular sizing may result in over-sizing at the level of the leaflets, leading to more asymmetry and increased risk of trauma related to calcification in the aortic valvular complex (1).
Blackman et al. recently published guidelines for sizing and positioning the balloon-expandable Edwards SAPIEN 3/Ultra transcatheter heart valve (THV) in BAV (1). The consensus describes the following anatomical factors that influence sizing optimization in patients with BAV:

1) *Calcification of the raphe.* Severe raphe calcification reduces valve expansion or may cause malpositioning of the transcatheter heart valve (THV), leading to potential undersizing relative to the aortic annulus
2) *Calcification of the cusps.* In case of an extreme calcification of the cusps, relative undersizing should be considered as anchoring in the supra-annular space is enhanced.
3) *Configuration of the aortic valve.* Relative undersizing may also be considered in patients with a tapered, as opposed to tubular or flared, valve configuration, i.e., where the supra-annular space is smaller.
4) *Large annuli.* A large annular area (above the upper limit of the SAPIEN 3 sizing chart) is often the case in patients with BAV and sizing to the supra-annular space should be considered.

Considering these anatomical variables, the circle technique has been suggested in cases of sizing optimization at the supra-annular level (1). This method includes a projection of an ellipse circle, which is one size smaller than the annulus size, in addition to the circle that is equivalent to the conventional sizing method. The technique is particularly helpful for visually identifying anatomic features, such as excessive calcified raphe, bulky leaflets, or eccentric calcifications in the aortic valvular complex, and preventing major vascular complications. Further advantages of the circle method include the indication of the sealing zone at the commissures, visual reassurance of the size and position, treatment of patients with large annuli, and its easy reproduction. However, as there are no strict thresholds on the sizing of the valve, physicians have to match the circle to the patient's BAV anatomy. The SAPIEN 3 THV has previously shown a good index of circularity, even in BAV (17). Therefore, projecting a circle through the aortic complex is the ideal approach for sizing as well as the positioning of the device. There is, however, limited data validation for the circle approach in patients with BAV.

In view of this, this project aims to validate the circle method for sizing and positioning of the device by evaluating the 30-day and 3-month outcomes of all consecutive patients with BAV undergoing TAVI.

## 2.2 RISKS AND BENEFITS

### 2.2.1 Risks and Benefits - Statement on medical justifiability

This project is non-interventional. Therefore, additional risks and direct benefits for individual patients do not apply.

The project is conducted under the direction of qualified physicians. All participating investigators and sites are screened and qualified. They must be experienced in conducting clinical research and have adequate personnel to assure compliance to the study protocol.

# 3 PROJECT DESIGN & OBJECTIVES

## 3.1 PROJECT DESIGN

This is a non-interventional, retrospective, multicenter, international project. A minimum of 40 patients in Germany and Poland will be enrolled in the project by contributing sites during the enrollment period.

## 3.2 PROJECT OBJECTIVES

### 3.2.1 Primary Objective

The primary objective of this project is to validate the circle method for sizing and positioning of the SAPIEN 3 THV in patients with BAV. In particular we aim to assess whether patients with BAV that received a SAPIEN 3 / Ultra THV suffered from fewer complications if valve size was *identical* to the one determined using the circle method compared to a situation where circle method derived valve size is *different* from the actually implanted valve.
We will use circles to simulate the SAPIEN 3 THV at 0, 3, 6, and 9 mm in 3mensio above and below the coronary arteries.

### 3.2.2 Secondary Objective

The secondary objective of this project is to develop general recommendations on how to size the valve using the circle method.

### 3.2.3 Exploratory Endpoints

Complications:

- Death
- Stroke
- ParaValvular Leakage (PVL)
- Pacemaker implantations
- Coronary occlusion
- Sinus sequestration
- Valve malposition ( Valve embolization / valve migration / other)
- Fistula to right ventricular outflow tract (RVOT)
- Annulus rupture

## 3.3 TIMELINES

- Document preparation: Q1/early Q2 2022
- IRB/IEC approvals per site: from Q2/2022 ongoing
- Recruitment period: 6 months
- Follow-up: 30 days, 3 months

## 3.4 PROJECT TERMINATION

The project ends after the last patient completes the observational period, all outstanding data queries are resolved, and all sites are closed. Participating sites will be notified in writing of the project completion.

# 4 PARTICIPATING SITES

## 4.1 PARTICIPATING SITES

The project aims to collect data in three medical centers in Germany, Poland and the United Kingdom. A mean of 20 patients will be enrolled per site during a period of 6 months.

Site selection is based on the site's prior experience and patient availability.

## 4.2 INFORMATION FOR SITE PERSONNEL

Site project contributors and support staff will be required to make themselves familiar with the requirements of the Project Protocol and the completion of electronic Case Report Forms (eCRF). In case of questions, the sites should contact:

IPPMed - Institute for Pharmacology and Preventive Medicine
Marie Zielinski (Project Manager)
Tel.: +49 4471 8503326
Email: marie.zielinski@ippmed.de

## 4.3 FEASIBILITY

The participating centers are departments of large academic, public or private hospitals. All centers have electronic medical records containing procedural perioperative data. All centers provide major surgery projects. Each center will have more than 20 eligible patients per year. This leads to an average number of at least 40 eligible patients who will be enrolled during the recruitment period in all centers. Therefore, including 40 patients into the project is realistic and feasible (expecting that about 60% of patients will give informed consent). All centers have experience in performing clinical research with patient-centered outcomes and guarantee feasibility of recruitment.

# 5 PARTICIPATING PATIENTS

## 5.1 PATIENT POPULATION

A minimum of 60 patients in total (mean 20 per site) with BAV having TAVI surgery.

### 5.1.1 Inclusion Criteria:

1. Patients undergoing transcatheter aortic valve implantation (TAVI) with SAPIEN 3 / Ultra THV valve prosthesis
2. TAVI performed
3. 3mensio evaluation of Computed Tomography (CT) data

### 5.1.2 Exclusion criteria:

1. Surgical Aortic Valve Replacement
2. Pregnancy at the time of TAVI

# 6 DOCUMENTATION

## 6.1 STANDARD EXAMINATIONS

The clinical outcome data collected and entered should be based on the site standards of care for aortic valve replacement. The collected data include medical history, physical assessments, safety parameters, ECG, laboratory results, and transthoracic / transesophageal echocardiography.

# 7 DATA MANAGEMENT

## 7.1 DATA CAPTURING

The data will be captured by an electronic case report form (eCRF). Participating sites / investigators will receive a confidential login and password to access the site, which is secured.

Study patients will undergo routinely 3D cardiac imaging prior TAVI. A central imaging core lab will be established to independently review and analyze the CTs taken. There will be no study-specific CT manual, all images shall be taken according to the site's clinical routine. Instructions for uploading the images to the core lab will be provided to investigators.

## 7.2 DATA PROTECTION

The personal data of patients will solely remain at the center, where they were treated. Data will only be entered into the eCRF if informed consent was given in writing by the patient. Only pseudonymized data will be stored in the eCRF database.

For each patient entered into the database, the system generates a project-ID. This ID is composed of the center code and a consecutive patient number by each center.

Pseudonymized data will be accessible to:

- the participating center
- IPPMed or its authorized representatives in the event of monitoring (source data verification)
- where required, aggregated and pseudonymized adverse event data will also be sent to the competent national authority and, where required, to the ethics committees involved

The clinical data of the project will only be published or presented using anonymized, aggregated patient data. The pseudonymized data will be stored in the database for a period of 10 years and then will be anonymized.

## 7.3 DATA MANAGEMENT SYSTEM

The eCRF database is provided by Software for Trials Europe (Berlin, Germany). It is stored on a dedicated server under the supervision of IPPMed in a professional hosting environment at Hetzner AG (Nürnberg, Germany).

### 7.4 DATA COLLECTION SCHEDULE

| | Baseline | Intervention | Discharge | 30 days | 3/12 months |
|---|---|---|---|---|---|
| Demographics | x | | | | |
| Comorbidities* | x | | | | |
| Electrocardiogram (ECG) | x | | x | x | x |
| Echocardiogram (TTE) | x | | x | x | x |
| Echo Core Lab | x | | | | |
| Risk Scores** | x | | | x | x |
| Procedural Data*** | | x | | | |
| Discharge Details | | | x | | |
| Complications | | x | x | x | x |
| Death Form | | | x | x | x |

* Includes cardiovascular & cerebrovascular comorbidities, prior cardiac interventions and bicuspid valve disease

** Includes EuroSCORE II, STS and Frailty

*** Includes procedural and device-related information (delivery, success)

### 7.5 MONITORING

No monitoring visit is planned.

## 8 STATISTICAL ANALYSIS

### 8.1 SAMPLE SIZE DETERMINATION

Each site will recruit an average of 20 patients according to availability. A sample size of at least 60 patients in total is aimed for.

### 8.2 DESCRIPTIVE ANALYSIS

Statistical analysis will be performed for the total study population. Continuous variables will be presented as mean ± SD or as median with interquartile range, and categorical variables (e.g. gender) will be reported as frequencies and percentages. The Kolmogorov-Smirnov test will be used to test for normal distribution. For comparisons, Chi-Square or Fisher exact test will be used for categorical variables, and Student's t-test or Mann-Whitney U for continuous variables.

All statistical analyses will be performed using IBM SPSS Statistics version 29 (IBM, Armonk, New York) or R Core Team (https://www.R-project.org/).

## 9 ETHICAL AND REGULATORY CONSIDERATIONS

### 9.1 DECLARATION OF HELSINKI

The project will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later versions. Specific country regulations will be complied with.

### 9.2 GOOD CLINICAL PRACTICE

The project will be conducted in accordance with the European Medical Device Regulation (Regulation (EU) 2017/745 of 5 April 2017) and ISO 14155:2011.

### 9.3 PATIENT INFORMED CONSENT

It is the responsibility of the investigator to provide each patient with full and adequate verbal and written information regarding the objectives of the project before inclusion in the project. Besides, the patient will be informed that there are no potential risks (due to the non-interventional, retrospective character of the project) and no guaranteed benefits as a result of participation in this project. The participation in the project is completely voluntary and the patient will not be paid to take part in the registry. The CRO will provide the patient information and informed consent template / data protection statement for the registry. The patient consent will be given by signing the patient informed consent form.

It is the responsibility of the investigator to obtain a signed informed consent from all patients enrolled in the registry. The retrospective patients will give their written approval prior to the data entry into the eCRF system (unless otherwise agreed by the local IRB/IEC). If the patient refuses to sign the informed consent, patient data will not be collected.

Consent may be withdrawn by the patient at any time, without giving reasons and without leading to disadvantages with regard to further medical care. If the patient withdraws from the registry, any (data) material already obtained will be destroyed.

### 9.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

Each site is responsible for adhering to the rules and regulations of its institution, ethics committee, and local and national authorities regarding releasing patient data.

IPPMed will provide the protocol (in English) to the investigators who should get in touch with their local ethics committee and seek approval. Ethics approval has to be obtained by the time of first patient inclusion. If ethical approval is denied, sites will not able to participate in the project.

### 9.5 DATA PROTECTION AND PATIENT CONFIDENTIALITY

IPPMed is dedicated to maintaining the confidentiality and privacy of patients whose data are enrolled in the project. Passwords are issued to appropriate personnel to ensure confidentiality and protection of the database by allowing variable levels of access to the computer system. All project documents will only identify the patient by a patient project identification number assigned by the CRO.

### 9.6 PUBLICATION POLICY

In case of a publication, authors will base their authorship on the published ICMJE criteria (19). The order of authors will be determined based on their role, their contribution to the manuscript development and their patient numbers contributed to the project.

Clinical sites have the right, consistent with academic standards, to publish their individual results independent from this project. The site agrees to share any proposed submission for publication with the CRO prior to submission.

## 10 FUNDER AND CONFLICT OF INTEREST INFORMATION

The registry is funded by an investigator initiated grant from Edwards Lifesciences (Pernerova 697/35, Prague 8- Karlin, 18600, Prague, Czech Republic). The funding body will not contribute to the collection, analysis or interpretation of the collected data. IPPMed has received research funding, and honoraria for consultancy from Edwards Lifesciences. Some of the investigators have received proctoring fees from Edwards Lifesciences and other medical devices manufacturers in the the past.

### 10.1 GENERAL LIABILITY

The project device is commercially available and has insurance coverage for the country specific requirements for commercial device liability.

## 11 REFERENCES


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