Endovascular implantation of a transcatheter tricuspid valve replacement for tricuspid valve insufficiency

Addendum to Project H23-03 (§137h assessment)[1]

ADDENDUM (§137H ASSESSMENT)

Project: H24-03 Version: 1.0 Status: 11 Sep 2024 DOI: 10.60584/H24-03_en

[1] Translation of the addendum H24-03 *Endovaskuläre Implantation eines Transkatheter-Trikuspidalklappenersatzes bei Trikuspidalklappeninsuffizienz - Addendum zum Projekt H23-03* (Version 1.0; Status: 11 September 2024). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Endovascular implantation of a transcatheter tricuspid valve replacement for tricuspid valve insufficiency

Commissioning agency

Federal Joint Committee

Commission awarded on

31 July 2024

Internal Project No.

H24-03

DOI-URL

https://doi.org/10.60584/H24-03_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Endovascular implantation of a transcatheter tricuspid valve replacement for tricuspid valve insufficiency; (§137h assessment) [online]. 2024 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/H24-03_en.

Keywords

Heart Valve Prosthesis Implantation, Tricuspid Valve Insufficiency, Endovascular Procedures, Device Approval, Risk Assessment, Benefit Assessment

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List of abbreviations

Abbreviation	Meaning
6MWT	6-minute walk test
AE	adverse event
CEC	Clinical Events Committee
EQ-5D-5L VAS	European Quality of Life Questionnaire 5 Dimensions 5 Levels visual analogue scale
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KCCQ	Kansas City Cardiomyopathy Questionnaire
MAE	major adverse event
MCS	Mental Component Summary
MID	minimal important difference
MVARC	Mitral Valve Academic Research Consortium
NYHA	New York Heart Association
OMT	optimized medical therapy
PCS	Physical Component Summary
RCT	randomized controlled trial
RH	requesting hospital
RVAD	right ventricular assist device
SAE	serious adverse event
SF-36	Short Form-36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SSED	Summary of Safety and Effectiveness Data

1 Background

On 31 July 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment of project H23-03 ("Endovascular implantation of a transcatheter tricuspid valve replacement for tricuspid valve insufficiency") [1]. The commission specifically includes an assessment of the harmfulness of the method in question, taking into account all study data submitted, including the TRISCEND study report, which is now available in its entirety for the assessment, including appendices. In addition, the conclusions in the assessment, which is conducted in accordance with §137h of the German Social Code Book (SGB) V, on the benefit and ineffectiveness of the method were reviewed.

2 Assessment

2.1 Evidence in report H23-03 (assessment in accordance with §137h SGB V)

In report H23-03 (assessment in accordance with §137h SGB V), it was concluded that no conclusions could be drawn from the data submitted regarding the benefit or ineffectiveness of endovascular implantation of a transcatheter tricuspid valve replacement in patients with tricuspid valve insufficiency, as no comparative data were available.

During the supplementary review of the case series with regard to harmfulness, in the documents on the single-arm TRISCEND study - the study with the largest number of patients analysed to date (N 56) and, as far as can be ascertained, the only study submitted with systematic recording of adverse events (AEs) - relevant discrepancies were shown between the results in the publication of the interim analysis [2] on the one hand and the excerpt from the study report [3], which was classified as highly confidential at the time, on the other. Due to the above-mentioned discrepancies, the usable documents on the TRISCEND study that were not marked as highly confidential did not constitute a sufficiently reliable source for the assessment of harmfulness. An adequate assessment of harmfulness was not possible on the basis of these data. For this reason, the key points of a testing study were not addressed.

The documents required for the assessment of harmfulness relating to the TRISCEND study were submitted to IQWiG as non-highly confidential documents in the course of the G-BA's commissioning of this addendum. In addition, further documents were submitted to IQWiG for assessment.

2.2 Characterization and assessment of the additional documents available for assessment

The documents provided comprise a total of 5 documents. These are described below:

- An excerpt from the TRISCEND study report is available (without version date, data cut-off date 20 October 2020, based on the date of implantation) [3], which was submitted by the requesting hospital (RH) as a highly confidential document as part of the initial assessment of the method in accordance with §137h SGB V. The high confidentiality of this document has since been lifted. This document essentially contains information on all AEs, including serious AEs (SAEs), for 56 analysed patients up to 30 days after implantation.
- In the study report (version 16 March 2023, data cut-off 27 October 2022, based on the date of implantation) [4] and the accompanying appendices [5-10] to the TRISCEND study, relevant and comprehensive results are reported on (S)AEs and mortality for a period of up to 2 years after implantation for a subpopulation of 192 patients. These results are used for the supplementary review of the harmfulness of the method.

- The publication Kodali 2022 [2] reports the 30-day results of a subpopulation (N = 56) of the TRISCEND study. This publication was already submitted for the previous assessment H23-03 and is described there in Section 2.3.2 [1]. The subpopulation described therein corresponds to the subpopulation of the above-mentioned excerpt from the study report, and the same data cut-offs appear to have been selected.
- The publication Kodali 2023 [11] reports the 1-year results of a subpopulation (N= 176) of the TRISCEND study. A patient-based analysis of the SAEs is not presented. Only the rate of major adverse events (MAEs), a combined outcome of certain AEs, is reported. There is no relevant information in it that goes beyond the above-mentioned study report.
- The document "Summary of Safety and Effectiveness Data (SSED)" [12] from the Food and Drug Administration (FDA) contains technical aspects as well as preclinical and clinical study results. Among other things, it includes an interim analysis of a subpopulation from another study, namely the currently ongoing RCT TRISCEND II, including overall mortality for a period of up to 18 months after implantation. This RCT was already described in the previous assessment H23-03 in Section 2.3.2, but no results had been submitted for the initial assessment. The additional data from this RCT that have now been submitted were reviewed to determine whether they provide additional insights into the benefit, harmfulness, or ineffectiveness of the method.

In a revised version of the submission form [13] (status: 16 July 2024) that was handed in, in the context of incidents/adverse events it is stated in Section IIIA.3 that both the study report and the SSED are no longer classified as highly confidential. No further changes have been made to the content of the submission form. All information in this addendum refers to the current version of the submission form.

The SSED now provides data on the method from an RCT, the highest level of evidence, for the first time. These results are being examined to determine the extent to which they provide insights into the benefit, ineffectiveness, or harmfulness of the method. In addition, the additional data submitted on the TRISCEND case series are being reviewed with regard to harmfulness. The complete study report and the associated appendices (version 16 March 2023, data cut-off 27 October 2022) are primarily used for this purpose, as these documents report results with the longest follow-up period (up to 2 years after implantation). In addition, a much more comprehensive and detailed presentation of data on SAEs and mortality is available than in the previous documents.

2.3 Relevant results

2.3.1 TRISCEND study

Comparison between excerpt from the study report and publication

The discrepancy mentioned in report H23-03, which was noted during the assessment of harmfulness, specifically referred to a discrepancy in the number of deaths reported between the Kodali 2022 publication and the excerpt from the study report (data cut-off date 20 October 2020), which was still classified as highly confidential at that time. Both the Kodali 2022 publication and the excerpt from the study report describe 2 deaths among the 56 patients analysed within a period of 30 days after implantation. However, the excerpt from the study report describes 2 additional patients in narrative form who also died within 30 days of implantation and, according to the study report, had not yet been adjudicated by the Clinical Events Committee (CEC) at that time. These 2 additional deaths are not mentioned in the Kodali 2022 publication. Based on the patient IDs in the study report excerpt, it can be seen that these 2 patients were not part of the analysed cohort (N = 56). This can be explained by the selected data cut-off date, which is such that these 2 patients are not included in the analysis because the implantation took place on the day of the data cut-off or 7 days later. The documents do not indicate how the cut-off date was determined. The study protocol [14] also does not describe any interim analyses.

In addition, the excerpt from the study report contained much more detailed information on AEs than the Kodali 2022 publication. Of particular relevance was a patient-based list of all AEs that occurred, including a classification of the possible causal relationship of the event to the medical device and the procedure, as well as a classification into serious and non-serious AEs. Although no discrepancies were found in this regard with the Kodali 2022 publication, which only reported the rate of MAEs, this information provided a much more comprehensive picture of the potential risks of the method (see also the following section on the results from the current version of the study report). However, due to the highly confidential nature of the excerpt from the study report, the discrepancy regarding the reported deaths and the detailed information on AEs could not be explained at the time of writing H23-03. With the complete, current, and non-highly confidential study report now available, it is possible to assess harmfulness.

Results from the current version of the study report

The complete study report presented reflects the data as of 27 October 2022. At that time, a subpopulation of 192 patients was included, of whom 186 received a transcatheter tricuspid valve replacement using the medical device under assessment. 176 patients completed the follow-up after 30 days; 142 patients after 6 months, 118 patients after 1 year, and 31 patients after 2 years. Recruitment had not yet been completed at some of the study centres at this point in time. According to the study report, up to 200 patients are to be recruited.

Table 1 shows the key findings on mortality and SAEs for the period up to 2 years after implantation from the study report, which are relevant for assessing harmfulness.

Table 1: Results on mortality and serious adverse events from the TRISCEND study (period up to 2 years after implantation)

	Patients with events		
	N	**n**	**%**
Mortality			
Total	192	25[a]	13.0
Procedure/device-related[b]	192	9[c]	4.7[c]
Of which definitely procedure/device-related	192	6[c]	3.1[c]
Not procedure/device-related[b]	192	15[c]	7.8[c]
SAE			
Total	192	130	67.7
Exclusively procedure/device-related[b]	192	49[c]	25.5[c]
Of which definitely procedure/device-related	192	29[c]	15.1[c]
Exclusively non-procedure/device-related[b]	192	53[c]	27.6[c]
Both procedure/device-related *and* non-procedure/device-related[b]	192	28[c]	14.6[c]
Of which definitely procedure/device-related	192	20[c]	10.4[c]

a. Includes 1 death that had not yet been adjudicated by the CEC at the time of data cut-off on 27 October 2022, and 2 deaths that occurred more than 2 years after implantation.
b. Procedure- and/or device-related events that were classified as possibly, probably, or definitely procedure- and/or device-related.
c. Calculated by IQWiG.

CEC: Clinical Events Committee; IQWiG: Institute for Quality and Efficiency in Health Care; n: number of patients with events; N: number of patients analysed; SAE: serious adverse event

Of the 24 deaths adjudicated by the CEC, 18 were classified as cardiovascular (75.0%). The most common cause of death was heart failure with biventricular dysfunction in a total of 7 patients.

The majority of patients (130 out of 192, 67.7%) suffered at least one SAE. A total of 77 out of 192 (40.1%) included patients were affected by at least 1 procedure- and/or device-related SAE (classified as possibly, probably or related) to the procedure or device), including 49 (25.5%) with a definite device- and/or procedure-related AE. Heart failure was the most common SAE, affecting a total of 36 of the 192 (18.8%) patients included. Among the procedure- and device-related SAEs, cardiac arrhythmias were the most common. These affected a total of 24 (patients with procedure-related AEs) and 17 (patients with device-related AEs) of the 192 patients included (12.5% and 8.9%, respectively). A total of 5 patients experienced tricuspid valve dislocation ("device dislocation"), mostly shortly after the

procedure. In one patient, the implanted tricuspid valve detached completely ("device dislodgement").

After the data cut-off date of the study report, there were 6 further deaths in the period from 27 October 2022 to 15 March 2023 ("clinical study report date"). This results in an overall mortality rate of 16.1% (31 out of 192 patients included) as of 15 March 2023.

2.3.2 TRISCEND II study

The TRISCEND II study had already been described in assessment H23-03 as a study for which no results were yet available (H23-03, Section 2.3.2). The following section describes the key findings of the interim analyses of the TRISCEND II study (NCT04482062) presented in the SSED that are relevant for assessing the benefit, ineffectiveness, or harmfulness of the method. As this study was proposed by the RH as a testing study, a detailed characterization and commentary on this study is also provided in Chapter 4.

The SSED contains an interim analysis of the results for the individual components of the combined primary outcome of the TRISCEND II study. This is assessed after 12 months and consists of 7 components:

1) All-cause mortality,
2) Implantation of a right ventricular assist device (RVAD) or heart transplantation,
3) Tricuspid valve surgery or percutaneous tricuspid intervention,
4) Annualized rate of heart failure hospitalizations,
5) Improvement in health-related quality of life (according to the total score of the Kansas City Cardiomyopathy Questionnaire [KCCQ]),
6) Improvement in New York Heart Association (NYHA) functional class, and
7) Improvement in the 6-minute walk test (6MWT).

There are restrictions for 2 of the 7 components (improvement in NYHA functional class and improvement in health-related quality of life according to the KCCQ total score). These components cannot be used for the assessment of benefit (see Section 4.2).

According to the information in the SSED, 259 patients have so far been randomized to the intervention group and 133 patients to the control group of the TRISCEND II study. 220 (84.9%) patients in the intervention group and 98 (73.7%) patients in the control group completed the 1-year follow-up by 15 December 2023.

The SSED only presents the available results of the interim analysis outcomes in a descriptive manner, without specifying effect sizes.

For the outcomes of total mortality, tricuspid valve surgery or percutaneous tricuspid intervention (period up to 18 months after implantation) and hospitalization due to heart failure (period up to 1 year after implantation), transcatheter tricuspid valve replacement showed numerically better results compared with optimized medical therapy (OMT). Neither group underwent RVAD implantation or heart transplantation.

For the outcome of physical performance, results for the 6MWT (response criterion: improvement in walking distance by at least 30 metres) were available for a period of 1 year after implantation. This also showed a numerical advantage for the intervention.

In addition, results from a further interim analysis of 150 randomized patients for a period of 6 months after implantation in the SSED were reported. The results for the outcome of health-related quality of life, collected using the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the Short Form-36 Health Survey (SF-36), European Quality of Life Questionnaire 5 Dimensions 5 Levels visual analogue scale (EQ-5D-5L VAS), and the KCCQ also showed a numerical advantage for the intervention.

In addition, there is a presentation of MAEs after 30 days (see details in Section 4.1), but only for the intervention group. Instead of a group comparison, these were compared with a performance target. This is considered insufficient to adequately assess the potential harm of the intervention. Results on SAEs were also only reported as an event-based analysis of device- or procedure-related SAEs at the time up to 6 months after implantation. However, there is no complete patient-based analysis, in particular of the overall rate of SAEs in a group comparison.

Without information on the frequency of SAEs in both groups, these results are insufficient for a final conclusion on the balance of benefit and harm. In addition, these are only interim analyses. In particular for the outcome of health-related quality of life, only descriptive data from 150 of the planned 400 patients are available.

2.4 Comment and consequences for the assessment

The patients examined in the TRISCEND and TRISCEND II studies are those with severe tricuspid valve regurgitation who are symptomatic despite guideline-based drug therapy and who, according to current guidelines, are scheduled for tricuspid valve surgery but are not suitable for surgical procedures (repair or valve replacement) due to the decision of the heart team or the surgical risk and/or for whom a transcatheter tricuspid valve repair procedure is not suitable for anatomical reasons (such as excessive coaptation gap or significant leaflet tethering).

Comparative data are generally required to assess the harmfulness of a method. Single-arm studies such as the TRISCEND study are generally not sufficiently informative to provide proof

of harmfulness due to the lack of comparison, and their usability is therefore limited. In individual cases, however, the results of such studies may indicate harmfulness, for example, based on the observed frequency and severity of complications that can be clearly attributed to the intervention.

Although the TRISCEND study shows that both the overall rate of patients with at least one SAE (67.7%) and the rate of patients affected by at least one procedure- and/or device-related SAE (40.1%) is high, but this does not seem to be reflected in an increased overall mortality rate (13%). When interpreting these findings, it should be taken into account that this is a group of seriously ill patients and therefore a high morbidity and mortality rate is to be expected. The mortality rate reported in the literature reviewed cursorily for a population with isolated severe tricuspid valve insufficiency over a period of approximately 2 years is around 20% [15,16]. The available results from the interim analyses of the TRISCEND II study do not contradict these observations.

The results on mortality and SAEs from the TRISCEND study presented in Section 2.3.1 do not, when viewed in conjunction with the documents evaluated in report H23-03, indicate that the method is harmful.

The results presented for the RCT TRISCEND II from the SSED did provide additional insights for the assessment in accordance with §137h SGB V. However, due to the lack of information on the frequency of SAEs in both groups, these results are not sufficient for a final conclusion on the balance of benefit and harm. In addition, these are only interim analyses, and, in particular for the outcome of health-related quality of life, only descriptive data from 150 of the total of 400 patients to be included are available to date.

Overall, the submitted documents therefore do not allow any conclusions to be drawn about the benefit, harmfulness, or ineffectiveness of the method.

3 Conclusion

An overall review of all documents submitted for the §137h assessment of endovascular implantation of a transcatheter tricuspid valve replacement in patients with tricuspid valve insufficiency has still not revealed any benefit or ineffectiveness. In particular, the complete study report of the TRISCEND study now enables an assessment of harmfulness to be made; no such harmfulness could be identified.

4 Key points of a testing study

Since the overall review of the documents submitted for the method reveals neither benefit nor ineffectiveness nor harmfulness, the testing study proposed by the RH is presented and commented on below.

4.1 Proposal for a possible testing study contained in the submission form

In the sections provided for this purpose, the submission form [13] contains information on the ongoing TRISCEND II study, which the RH proposes as a testing study. In addition, the study protocol [17] and the SSED [12] were submitted.

The information contained in the submission form, the study protocol, and the SSED for the ongoing TRISCEND II study is summarized below.

Study objective

The submission form (Section IVA.1, p. 140) states that the study objective is to investigate whether minimally invasive, percutaneous implantation of a transcatheter tricuspid valve replacement in combination with OMT (intervention group) is superior to OMT alone (control group) in the treatment of patients with at least severe tricuspid valve regurgitation in terms of the occurrence of the hierarchy of combined outcomes (see Section "Study type and outcomes" below) in the 1-year follow-up.

Study population

According to the study protocol (Section 6.1), the study population comprises adult patients with severe tricuspid valve regurgitation who are classified by their local heart team as candidates for endovascular implantation of a transcatheter tricuspid valve replacement.

The study population is described in the submission form (Section IVA.2, p. 142ff) using the inclusion and exclusion criteria. Essentially, adult patients who, despite OMT, have clinical signs of tricuspid valve regurgitation, symptoms due to tricuspid valve regurgitation, or a history of hospitalization for heart failure due to tricuspid valve regurgitation are included. Patients must be receiving OMT that includes stable doses of oral diuretics at the time of assessment of tricuspid valve regurgitation, unless there is a known documented intolerance. Tricuspid valve regurgitation is classified as at least severe based on a transthoracic echocardiogram. In addition, patients are deemed suitable for endovascular valve replacement according to the assessment of the local heart team.

The submission form lists 37 exclusion criteria. Key exclusion criteria include severely impaired left and/or right heart function (e.g., severe aortic, mitral, and/or pulmonary valve stenosis and/or regurgitation), clinically relevant untreated coronary artery disease requiring revascularization, evidence of acute coronary syndrome or recent myocardial infarction within

the last 30 days, inability to walk at least 100 metres (6MWT), and concomitant disease(s) that, in the opinion of the investigating physician, limit life expectancy to up to 12 months.

Intervention and control intervention

In the submission form (Section IVA.3, p. 144f.), the tricuspid valve replacement system with OMT is designated as the test intervention and OMT alone as the control intervention.

Study type and outcomes

In the submission form (Sections IVA.5, p. 153ff and IVA.7, p. 157f.), the RH describes the TRISCEND II study as a prospective, global, multicentre, randomized, controlled pivotal clinical study with a study duration of 8 years. Up to 400 patients are to be randomized in a 2:1 ratio to the intervention group or control group at up to 90 study centres worldwide, hereinafter referred to as the randomized cohort. According to the study protocol (Section 8.18), patients in the control group may be re-evaluated after 2 years for endovascular implantation of a transcatheter tricuspid valve replacement (crossover). Patients in the control group may also undergo surgical tricuspid valve treatment or percutaneous transcatheter intervention, which is considered treatment failure (study protocol, Section 4.1.3). Data analysis is blinded (Section IVA.5, p. 153f.).

In addition to the randomized cohort, 2 further cohorts are described in the study protocol (Sections 5.1.1 and 5.1.3): If patients are deemed unsuitable for the randomized cohort based on certain exclusion criteria (e.g., poor right ventricular heart function), treatment with the requested method is still possible in the registry cohort, a parallel single-arm registry, after assessment by the Central Screening Committee. The registry cohort is expected to include up to 150 patients. With the exception of the randomization procedure, these patients will undergo the same schedule of examinations (study protocol, p. 57) as the patients in the randomized cohort. The aim is to collect additional data on the results of the requested method in the treatment of tricuspid valve regurgitation.

The roll-in cohort will include up to 3 successful roll-in patients per centre (up to a total of 270 patients). These patients must meet the inclusion and exclusion criteria for the randomized cohort or registry cohort. For study centres in Germany, roll-in patients must meet the criteria for the randomized cohort. The aim is to gain experience in the application of the requested method before randomizing patients at each study centre.

The primary outcome specified in the submission form (Section IVA.4, p. 147) is a hierarchically combined outcome. This is assessed after 12 months and consists of 7 components:

1) Overall mortality,
2) Implantation of an RVAD or heart transplantation,

3) Tricuspid valve surgery or percutaneous tricuspid intervention,
4) Annualized frequency of heart failure hospitalizations,
5) Improvement in health-related quality of life (according to the KCCQ total score),
6) Improvement in NYHA functional class, and
7) Improvement in 6MWT.

According to the RH, this composite outcome ranks its components according to clinical significance and includes components that assess safety as well as clinical and functional outcomes.

In addition, the RH specifies secondary outcomes. A 5-point scale (mild, moderate, severe, massive, torrential) is used to assess the reduction in TI severity (echocardiographic outcome) in patients in the intervention group, measured before and after implantation at baseline and at discharge [18]. The patient-relevant secondary outcomes according to the study protocol are collected after 12 months and then once a year for 5 years. They include, among other things, total mortality, heart failure hospitalizations, non-elective tricuspid valve reintervention (percutaneous or surgical), permanent RVAD implantation or heart transplantation, and the need for abdominal paracentesis. As a safety outcome in the intervention group, the RH cites a composite outcome (consisting of MAEs) that is collected at 30 days. According to the study protocol (Sections 4.1.2 and 11.1.1.3), this is defined as the occurrence of at least one of the following 10 events: Cardiovascular mortality, myocardial infarction, stroke, new need for renal replacement therapy, major bleeding (fatal, life-threatening, extensive, or major bleeding as defined by the Mitral Valve Academic Research Consortium [MVARC]), non-elective percutaneous or surgical tricuspid valve reintervention, major complications at the access site or vascular complications, major cardiac structural complications due to access-related problems, device-related pulmonary embolism, and arrhythmia and conduction disturbance requiring permanent pacing. The proportion of patients with MAE should only be collected for the intervention group and evaluated against a pre-specified performance target of 70%. If the proportion of patients with MAE after 30 days is below 70%, this will be considered a study success.

Although the study protocol states that AEs and SAEs will be recorded separately throughout the study (Section 10.1), there is no description of how they are to be analysed. Information on the planned statistical analysis is only provided for individual events and specific time points in the description of the primary safety and efficacy outcome and in the description of the clinical outcomes. In addition, the study protocol mentions other outcomes, such as laboratory parameters (Section 4.5.3) and economic parameters (Section 4.5.4).

Sample size calculation

According to the submission form (Section IVA.7, p. 157), the primary hierarchically combined outcome will be analysed after 12 months using the Finkelstein-Schoenfeld method. The RH has described detailed assumptions for the sample size calculation and the individual components. In summary, with a sample size of 400 patients, a power of approximately 81% is expected for demonstrating superiority.

Further aspects

In addition, the RH (Section IVA.6, p. 155ff and Section IVA.8, p. 159) also provides information on investigator qualifications and selection criteria, training on study initiation visits, training on the product and procedure, monitoring, data management, Data Safety Monitoring Board, Clinical Events Committee, Central Screening Committee, central laboratory for echocardiographic imaging, central laboratory for quality of life, and study costs.

4.2 Comment and consequences for a testing study

In the following, the key points of the ongoing TRISCEND II study are commented on and it is explained that, based on the results of the TRISCEND II study, it appears fundamentally possible to evaluate the benefit of the requested method in addition to continued guideline-based drug therapy in comparison to the continued use of guideline-based drug therapy alone. A testing study is therefore not considered necessary.

Study objective

The chosen study objective is comprehensible and reasonable.

Study population

These are patients with severe tricuspid valve regurgitation who remain symptomatic despite guideline-based drug therapy and who are classified by the local heart team as candidates for endovascular implantation of a transcatheter tricuspid valve replacement. However, there is no explicit statement that these patients are not suitable for a conventional surgical procedure (repair or valve replacement) and/or that they are not suitable for a tricuspid valve repair procedure for anatomical reasons (such as excessive coaptation gap or significant leaflet tethering). According to the submitted study protocol, patients in the control group may also undergo surgical tricuspid valve treatment or percutaneous transcatheter intervention, which is considered treatment failure. This could mean that at least some of the patients in the TRISCEND II study do not correspond to the therapeutic indication of the present research question. However, the information also allows for the interpretation that these cases involve emergency procedures and that the risk assessment has changed, for example, due to a significant deterioration in a patient's condition. Whether this interpretation applies to the TRISCEND II study is unclear based on the available documents.

Even if information is missing or not explicitly described, based on an overall review of the inclusion and exclusion criteria of the TRISCEND II study and taking into account the submitted CE certificate [19] and the instructions for use [20], it cannot currently be assumed that the therapeutic indication differs significantly between the TRISCEND II study and the present research question.

Intervention and control intervention

Endovascular implantation of a transcatheter tricuspid valve replacement in addition to continued guideline-based drug therapy as an intervention and the sole continuation of guideline-based drug therapy as a control intervention are reasonable and understandable. The control intervention corresponds to the current standard of care.

Study type

The chosen study design of an RCT with a follow-up period of up to 5 years is comprehensible and reasonable. However, a randomized comparison will not be available for the entire duration of the study, as patients in the control group can be re-evaluated for endovascular implantation of a transcatheter tricuspid valve replacement after 2 years (crossover). The duration of the randomized comparison of 2 years appears sufficient to assess the possible long-term advantages and disadvantages of the study intervention.

The study protocol does not describe the generation of the randomization sequence and the concealment of group allocation. However, both must be carried out adequately so that the benefit of this method can be evaluated with a sufficient level of certainty for subsequent guidance decisions. Blinded data analysis alone is plausible in view of the intervention and control intervention. However, the lack of blinding of patients and treating staff may influence the risk of bias and the certainty of results.

The 37 exclusion criteria for the randomized cohort, each of which is understandable in itself, could, in their overall effect, lead to a relevant selection of the patient group and thus limit the external validity of the results of the randomized cohort. In order to assess the external validity of the study, it would be desirable to include an overview of the up to 150 patients who were still eligible for treatment with the requested method (the registry cohort) in the subsequent analysis and presentation of the study results, specifying the exclusion criteria. The roll-in cohort of up to 270 patients aims to enable each study centre to gain experience in the use of the requested method prior to randomization. A systematic examination of this cohort with regard to a learning curve therefore seems appropriate.

Outcomes

Primary outcome

The primary outcome of the TRISCEND II study is a hierarchically combined outcome according to the Finkelstein-Schoenfeld method, which is analysed after 12 months and consists of 7 components. Combined outcomes can be used to assess the benefit, which requires, among other things, that all components be relevant to the patient [21]. The 7 components - total mortality, implantation of an RVAD or heart transplantation, tricuspid valve surgery or percutaneous tricuspid intervention, annualized frequency of heart failure hospitalizations, improvement in health-related quality of life according to the KCCQ total score, improvement in functional class according to NYHA, and improvement in the 6MWT - are generally considered to be patient-relevant. The hierarchy of the components is understandable.

According to the study protocol, a difference of at least 30 metres is considered an improvement for the 6MWT component. The submission form describes the response criterion in terms of an individual minimum important difference (MID) with reference to 2 publications: [22,23]. A cursory review of these sources revealed no reasons to question the plausibility of the MID mentioned. For the component "improvement in the 6MWT", an analysis with a response criterion of at least 30 metres appears appropriate for the present therapeutic indication in the context of a benefit assessment in view of the 6-minute walking distance measured at baseline (approximately 240 metres) [12].

There are restrictions for 2 components. For the health-related quality of life component according to the KCCQ total score, a difference of at least 10 points is considered an improvement according to the study protocol. As explained in IQWiG's General Methods 7.0 [21], a response criterion should be prespecified to correspond to at least 15% of the scale range of an instrument in order to reliably reflect a change that is noticeable to patients. For the analysis of the KCCQ total score results, this corresponds to a response threshold of 15 points, as the scale ranges from 0 to 100. Therefore, an analysis with a response threshold of at least 10 points cannot be used for a benefit assessment.

For an adequate assessment of benefit, it is necessary, among other things, that outcome operationalizations reliably and directly reflect concrete changes in health status [21]. However, this requirement is not met for the change in NYHA class due to the non-standardized survey methodology [24]. Therefore, the component "improvement in functional class according to NYHA" cannot be used for a benefit assessment.

In summary, the primary outcome as described in the study protocol cannot be used for a subsequent benefit assessment. Separate analyses of the individual components are necessary. The extent to which this is planned cannot be clearly determined from the study protocol. The definition of overall mortality and heart failure hospitalizations (components of

the primary outcome) as secondary outcomes indicates that at least these components will be presented separately. Furthermore, the SSED contains an interim analysis of the individual components of the primary outcome [12] (see Section 2.3). It can therefore be assumed that the components of the primary outcome will also be presented separately in a later publication.

Secondary outcomes

Most of the secondary outcomes are patient-relevant, such as myocardial infarction, stroke, or major bleeding as defined by MVARC. In contrast, the reduction in tricuspid valve regurgitation severity (echocardiographic outcome) is not considered patient-relevant, as the scale used [18] is based on the physiological parameters of the width or area of the vena contracta and the opening area of the regurgitation.

For the comparison of the treatment groups with regard to some outcomes, such as the secondary outcomes myocardial infarction, stroke, or severe bleeding, as well as for some components of the primary outcome (implantation of an RVAD or heart transplantation, tricuspid valve surgery or percutaneous tricuspid intervention, annualized frequency of heart failure hospitalizations), the study protocol does not specify which statistical method should be used. Similarly, it does not specify how the AEs will be presented at 12 months. Therefore, based on the available documents, it is not possible to conclusively clarify the extent to which these analyses can be used for a benefit assessment or are sufficient. The presentation of MAEs after 30 days exclusively for the intervention group and the comparison with a performance target (instead of a group comparison) is considered insufficient to adequately assess the potential harm of the intervention. In order to adequately assess the potential harm of this method, it is particularly necessary to present complete, usable analyses of the SAEs in a group comparison.

Sample size calculation

The presentation of the sample size calculation is comprehensible.

Even if the primary outcome cannot be used for a later benefit assessment, 5 of the 7 components and the patient-relevant secondary outcomes are fundamentally suitable for demonstrating a possible advantage of the test intervention compared to the control intervention.

Other aspects

There are no comments on the other aspects.

5 Prospects of success for a testing study

The prospects of success for the TRISCEND II study, which is fundamentally suitable for demonstrating benefit, can be assessed as very good overall. Descriptive results from an interim analysis of a subpopulation are already available in the SSED [12]. According to the study registry entry (last updated on 16 January 2024), 7 study centres from Germany are participating [25].

If the TRISCEND II study is completed as planned, it will provide a large RCT that is expected to yield informative results for evaluating the benefit of the method in relation to the research question at hand.

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