IQWiG Reports – Commission No. V20-04

Relationship between volume of services and quality of treatment outcome for transcatheter aortic valve implantation (TAVI)[1]

Extract

[1] Translation of Chapters 1 to 7 of the rapid report V20-04 *Zusammenhang zwischen Leistungsmenge und Qualität des Behandlungsergebnisses bei der Durchführung von kathetergestützten Aortenklappenimplantationen* (Version 1.0; Status: 30 June 2021 [German original], 13 September 2021 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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This report was prepared without involvement of external experts. The report underwent an external review.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Appendix D of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External review of the rapid report

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IQWiG thanks the external reviewer for his collaboration in the project.

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Key statement

Research question

The aims of this investigation are to

- present and assess the relationship between volume and quality of treatment outcome in the performance of transcatheter aortic valve implantation (TAVI) (research question 1),
- present studies which investigate the effects of a minimum number of cases introduced into the healthcare system on the quality of treatment outcome in TAVI (research question 2).

As supplementary information, the interventional procedures included in and excluded from the studies considered relevant are described in detail.

Conclusion

Eight retrospective observational studies were included in the investigation for research question 1 (present and assess the relationship between volume and quality of treatment outcome in TAVI).

In summary, the results for research question 1 were the following: All 8 studies on research question 1 provided usable data on at least 1 outcome. All studies had a low informative value of results.

For the outcomes of all-cause mortality and inpatient mortality, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher-volume hospitals. On the operator level, this correlation was found only for the outcome of inpatient mortality.

For the outcomes of bleeding, ventilation > 48 hours, and hospital readmission, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher-volume hospitals. Due to a lack of usable data, this relationship was not established on the operator level for these outcomes.

For the outcome of length of hospital stay, it was not possible to derive any consistent (monotonic decreasing) relationship between hospital volume and quality of treatment outcome. The relationship between operator volume and quality of treatment outcome was not investigated in this regard.

For the abort-of-TAVI component of the outcome of conversion to surgery / abort of TAVI, a correlation between hospital volume and quality of treatment outcome was found in favour of higher volume. No usable data were available for the conversion-to-surgery component; therefore, no conclusion can be drawn on it. This relationship was not investigated on the operator level.

The composite outcomes were disregarded when assessing the relationship between hospital or operator volume. For the individual components of these outcomes, results were available and presented in the report.

For all other outcomes, no correlation was found between hospital or operator volume and quality of treatment outcome, or no usable data were available. This relationship was not investigated on the level of the combined hospital-operator volume for any of the outcomes mentioned in the report.

No pertinent studies were found regarding research question 2 (present studies which investigate the extent to which the quality of treatment outcome is impacted by minimum numbers of cases introduced in the healthcare system for TAVI).

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List of abbreviations

Abbreviation	Meaning
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ND	no data
OR	odds ratio
RR	relative risk
SGB	Sozialgesetzbuch (Social Code Book)
TAVI	transcatheter aortic valve implantation
TAVR	transcatheter aortic valve replacement
TVT	transcatheter valve therapy

1 Background

Relationship between volume of services and quality of treatment outcome

As early as in 1979, Luft et al. examined the relationship between volume of services (hereinafter "volume") and quality of treatment outcome for 12 surgical procedures of different levels of complexity [1]. Their investigations showed that, for complex surgical procedures, there is a correlation between hospital volume and quality of treatment outcome. In the following years, various studies showed a similar correlation for many medical services in different healthcare systems, with volume being investigated per hospital and per physician [2-5].

The legal mandate of the Federal Joint Committee (G-BA) regarding minimum volume rules [6] is based upon the idea that there is a concrete connection between the probability of treatment success and the experience of the parties principally involved in rendering the service [6]. As part of quality assurance of registered hospitals, the G-BA therefore defines a catalogue of plannable services for which the quality of the treatment outcomes is dependent on the volume provided. This dependency is to be assessed on the basis of appropriate studies [7]. In December 2003, the G-BA for the first time set minimum volumes which are binding in Germany in accordance with §137a (3), Sentence 1, No. 2 Social Code Book V.

These minimum volume rules are binding for hospitals registered in accordance with §108 SGB V and specify in which cases a hospital may render the services for which minimum volumes have been set forth [8]. Hospitals may render the services in question only if the hospital owner annually declares vis-a-vis the state associations of the statutory health insurers that the specified minimum volume will be met in the next year as well [8]. However, some exceptions apply. For instance, minimum volumes generally do not apply in case of emergency. In addition, state authorities responsible for hospital planning can define exceptions for services where the implementation of minimum volume rules may jeopardize state-wide service provision to the population.

Currently, no annual minimum volume has been specified for transcatheter aortic valve implantation (TAVI) [8].

TAVI

In TAVI, a diseased heart valve is replaced either via a peripheral vascular access, e.g. through the femoral artery, or less commonly via the apex of the heart (transapically). The replacement heart valve is mounted on a stent and collapsed, advanced to the aortic valve, and positioned on the diseased aortic valve, which is then expanded [9,10].

TAVI is indicated in patients with severe aortic valve stenosis, particularly older patients at moderate to high surgical risk for whom valve replacement by open-heart surgery would be associated with a high risk [11]. Typically, aortic valve stenosis requires an interventional or surgical procedure if the valve area is below 1 cm^2 [12].

In Europe and the United States, aortic valve stenosis is among the most common valvular heart diseases [13]. This defect may be either congenital or acquired, and 3 forms are distinguished: supravalvular, valvular, and subvalvular. Since rheumatic fever and the resulting defect have become rare, calcific aortic stenosis has now gained in relevance, particularly in advanced age, representing about 40% of valve disorders [12,13]. A typical symptom is facial paleness despite normally perfused mucous membranes [14]. Further symptoms at higher degrees of stenosis include diminished exercise performance, rapid fatigue, dyspnoea, angina pectoris attacks, dizziness, and syncope [9,12].

Between 2007 and 2013, the number of TAVI procedures performed in Germany increased from 144 to 9147, while the volume of open-heart aortic valve replacement surgeries decreased [15]. In 2017, nearly 18 000 TAVI procedures and over 9000 open-heart aortic valve replacements were performed in Germany [16]. One year later, over 21 000 aortic valves were replaced interventionally and more than 8400 via open heart surgery [17].

2 Research question

The aims of this investigation are to

- present and assess the relationship between volume and quality of treatment outcome in the performance of TAVI (research question 1),
- present studies which investigate the effects of a minimum number of cases introduced into the healthcare system on the quality of treatment outcome in TAVI (research question 2).

As supplementary information, the interventional procedures included in and excluded from the studies considered relevant are described in detail.

3 Course of the project

3.1 Project timeline

On 15 October 2020, the G-BA commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) with a systematic literature search and evaluation of the evidence on the volume-outcome relationship for TAVI.

On the basis of the project outline, a rapid report was generated and additionally subjected to an external review. This report was sent to the G-BA and published 4 weeks later on the IQWiG website.

3.2 Changes over the course of the project

In Chapter 4, the name used for the third analysis level for volume was changed: “per hospital-operator combination” was replaced by “per combined hospital-operator volume”.

In Section 4.1.3, the outcome of inpatient mortality was replaced by perioperative mortality.

In Section 4.1.9, cross-references were removed, except for (see Section 4.1.2) and (see Section 4.1.5), and notes on the reasons for inclusion were added in the table rows.

In Section 4.1.10, the sentence

- “In accordance with IQWiG General Methods [21], for inclusion criteria I1 (population) and I2 (use of a minimum number of cases; comparator intervention with respect to the study’s comparator group or volume) as well as I8 (transferability), it sufficed if at least 80% of included patients fulfilled these criteria.”

  was replaced by

- “For inclusion criteria I1 (population) and I2 (use of a minimum number of cases; comparator intervention with respect to the study’s comparator group or volume) as well as I8 (transferability), it sufficed if at least 80% of included patients fulfilled these criteria.”

4 Methods

4.1 Criteria for study inclusion in the investigation

4.1.1 Population

The assessment included studies with patients who underwent TAVI.

4.1.2 Volume of services

Volume is defined as the number of TAVI procedures performed per hospital, per operator, or per hospital-operator combination within a defined time period.

4.1.3 Outcomes

For the investigation, the following outcomes were examined:

- Mortality, such as
  - overall survival
  - perioperative mortality
- Morbidity, such as
  - adverse effects of therapy, such as
    - stroke
    - myocardial infarction
    - life-threatening bleeding
    - acute renal failure
    - complications at the vascular access site
    - annular rupture
    - paravalvular aortic regurgitation
- Health-related quality of life, including activities of daily living and dependence on help from others
- Length of hospital stay

If usable data were found on other outcomes or validated quality indicators, they were permitted to be included as well.

4.1.4 Study types

Observational studies (e.g. cohort studies or case control studies) or controlled interventional studies were suitable for answering the research questions.

For controlled interventional studies, the intervention to be examined was the specification of a minimum number of cases. Possible comparator groups were groups with a different or no specified volume.

4.1.5 Adjustment

In TAVI, the outcome is materially influenced by individual risk factors such as the underlying disease, type of procedure, comorbidities, and complication management. Further indication-specific risk factors are also possible.

Therefore, control of relevant confounders (risk adjustment) was a prerequisite for study inclusion. Control was assumed to exist if the study analysis involved suitable statistical methods to adjust for relevant confounders in an effort to address the problem of potential structural inequalities (unfair comparisons) between hospitals or treatment providers (operators, nurses, etc.) with high and low volume.

Likewise, cluster effects (e.g. greater similarity of outcomes in patients within the same hospital versus patients from different hospitals due to hospital-specific characteristics) must have been taken into consideration by means of adequate statistical methods.

4.1.6 Study duration

There were no restrictions regarding the study duration.

4.1.7 Publication period

In departure from the G-BA's commission, the investigation was limited to studies with a publication date of January 2013 or later because searches performed in preparation of the project revealed that studies could be expected from that year forward.

4.1.8 Transferability

To ensure the transferability of study results to the German healthcare system, studies from European countries as well as the United States, Canada, Australia, and New Zealand were eligible for inclusion.

For international studies, at least 80% of the data had to come from the above countries.

4.1.9 Tabular presentation of the criteria for study inclusion

The table below lists the criteria which had to be met by studies included in the assessment.

Table 1: Overview of inclusion and exclusion criteria for studies

Inclusion criteria	
I1	Patients who underwent TAVI
I2	Investigation of the relationship between volume and quality of the treatment outcome (see Section 4.1.2) or Comparison of the use of a minimum number of cases with the use of a different or no minimum number of cases
I3	Outcomes: ▪ Mortality: overall survival, perioperative mortality ▪ Morbidity: adverse effects of therapy such as stroke, myocardial infarction, life-threatening bleeding, acute renal failure, complications at the vascular access site, annular rupture, paravalvular aortic regurgitation ▪ Health-related quality of life, including activities of daily living and dependence on help from others ▪ Length of hospital stay
I4	Observational studies or controlled interventional studies
I5	Adjustment, i.e. adequate control of confounders and consideration of cluster effects (see Section 4.1.5)
I6	Publication date of January 2013 or later
I7	Full publication available[a]
I8	Transferability to the German healthcare system, i.e. studies from European countries as well as the United States, Canada, Australia, and New Zealand were eligible for inclusion.
Exclusion criterion	
E1	Multiple publications without relevant additional information

a. In this context, a study report in accordance with ICH E3 [18] or a report about the study which met the criteria of the TREND statement [19] or the STROBE statement [20] and allowed an assessment of the study was considered a full publication so long as the information on both the study methods and study results provided in these documents was not confidential.

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TAVI: transcatheter aortic valve implantation; TREND: Transparent Reporting of Evaluations with Nonrandomized Designs

4.1.10 Inclusion of studies which do not fully meet the above criteria

For inclusion criteria I1 (population) and I2 (use of a minimum number of cases; comparator intervention with respect to the study's comparator group; volume) as well as I8 (transferability), it sufficed if at least 80% of included patients fulfilled these criteria. For such studies, subgroup analyses, if any, on patients who fulfilled the inclusion criteria were used. Studies in which fewer than 80% of patients fulfilled inclusion criteria I1, I2, and I8 were included only if subgroup analyses were available for patients who did fulfil the inclusion criteria.

4.2 Information retrieval

4.2.1 Focused information retrieval to search for systematic reviews

In parallel to the preparation of the project outline, a search for systematic reviews was conducted in the MEDLINE database (which includes the Cochrane Database of Systematic Reviews) and the HTA database as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

The search was not restricted to a publication date. The search strategies for the search in bibliographic databases are found in Appendix A. The search was conducted on 28 October 2020.

The selection was performed by 1 person and then reviewed by a 2nd person. Any discrepancies were resolved by discussion between them.

It was ascertained whether at least 1 high quality, current systematic review existed whose information retrieval was a suitable basis for the assessment.

For this purpose, the quality of information retrieval of these systematic reviews was assessed. If at least 1 high-quality and current overview was found, the underlying studies or documents were checked by 1 person for their relevance to the present assessment, and the result was reviewed by a 2nd person. IQWiG used neither any evaluations of the included studies nor the data extraction.

The final decision as to which systematic reviews to include for the assessment was taken after completing the project outline on the basis of the criteria set down therein.

4.2.2 Comprehensive information retrieval from primary studies

For the comprehensive information retrieval, a systematic search was conducted for relevant studies or documents.

In cases where at least 1 systematic review was usable as a basis for the information retrieval (see Section 4.2.1), the systematic review was used for the information retrieval from primary studies for the time period covered by the review. The information retrieval was complemented by a systematic search for relevant studies or documents for the time period not covered by the review.

The following primary and further information sources as well as search techniques were considered:

Primary information sources

- Bibliographic databases
  - MEDLINE
  - Embase
  - Cochrane Central Register of Controlled Trials

Further information sources and search techniques

- Use of further search techniques
  - Screening of reference lists of systematic reviews found (see Section 4.2.1)
- Requests to authors

4.2.3 Selection of relevant studies

Selection of relevant studies or documents from the results of the bibliographic search

In a first step, the titles and, if available, abstracts of the hits retrieved in the bibliographic databases were screened for potential relevance in terms of the inclusion criteria (see able 1). In a second step, any documents considered potentially relevant were checked for relevance based on their full texts. Both steps were performed by 2 persons independently of each other. Any discrepancies were resolved by discussion between them.

Selection of relevant studies or documents from further information sources

Search results from the additionally considered information sources were screened for studies by 1 reviewer. The studies found were then checked for relevance. The entire process was then checked by a 2nd person. Any discrepancies in either of the listed selection steps were resolved by discussion between the 2 reviewers.

4.3 Information synthesis and analysis

4.3.1 Presentation of the individual studies

All information needed for the investigation was extracted from the documents regarding the included studies and entered into standardized tables. Any discrepancies found in connection with the comparison of information from different documents or from multiple data points within the same document, provided such discrepancies had the potential of considerably influencing the interpretation of results, are presented in the results section of the report.

Results were typically omitted from the investigation whenever they were based on fewer than 70% of the patients to be included in the analysis, that is, whenever more than 30% of patients were excluded from analysis.

Results were also omitted from the investigation whenever the percentage of patients excluded from analysis differed by more than 15% between groups.

Whenever the studies' authors used several statistical models and justified their choice of a preferred model for their underlying data, the statistical model preferred by the authors was used, provided the model fulfilled the conditions defined in Section 4.1.5. Whenever several models were appropriate for the underlying data, the simpler model was used, taking into account Section 4.1.5.

Since categorical analysis is associated with a loss of information (e.g. the linearity assumption may be violated within the individual categories) and might deliver less reliable results than continuous analysis [21], results of continuous modelling were preferred over results from categorical modelling and included in the report, provided that potential non-linear relationships were adequately taken into account in continuous modelling. However, if the studies presented results exclusively for categorical analysis or only the results from categorical analysis were usable, the summary assessment relied on categorical analyses.

4.3.2 Assessment of the informative value of results from observational studies

The informative value of the results from the included observational studies was assessed on the basis of quality criteria developed especially for studies assessing volume-outcome relationships [21-24]. In terms of the informative value of results, the assessment considered the way the risk adjustment was performed, i.e. the risk factors taken into account and the sources used (administrative databases, clinical databases, medical records). Likewise, the quality of the statistical models used to examine any correlation between volume and outcome was assessed; said quality depends on the form in which the volume attribute was entered into the analysis (continuous versus categorical data), on the consideration of cluster effects (see Section 4.1.5), and on the examination of model quality [25]. The completeness of reporting (e.g. description of analysed data and reporting of point estimates, confidence intervals, and p-values) was likewise considered an aspect impacting the informative value of results. Based on the entirety of these quality criteria, the observational studies were categorized by quality into those with high versus low informative value of results.

4.3.3 Assessment of the risk of bias regarding the results of controlled interventional studies

The risk of bias regarding the results of the included controlled interventional studies was assessed in accordance with the General Methods [26].

4.3.4 Summary assessment of information

The results on the outcomes reported in the studies were comparatively described in the report.

Where possible, beyond the comparison of results from the individual studies, suitable metaanalytical methods were used [26]. A final summary assessment of the information was performed in any case. Where possible, results reported on subgroups (e.g. intervention-specific analyses) were presented separately and summarized.

5 Results

5.1 Information retrieval

5.1.1 Focused information retrieval to search for systematic reviews

Among the 2 identified systematic reviews (see Section 9.1 of the full report), no systematic review was rated as current and of high quality and taken into consideration for the purposes of identifying primary studies.

5.1.2 Comprehensive information retrieval

5.1.2.1 Primary information sources

5.1.2.1.1 Bibliographic databases

Figure 1 shows the results of the systematic literature search in the bibliographic databases and the study selection in accordance with the criteria for study inclusion. The search strategies for the search in bibliographic databases are found in Appendix A. The most recent search was conducted on 14 December 2020.

The references of the hits screened at full-text level but excluded are found in Section 9.2 of the full report, with the respective reason for exclusion.

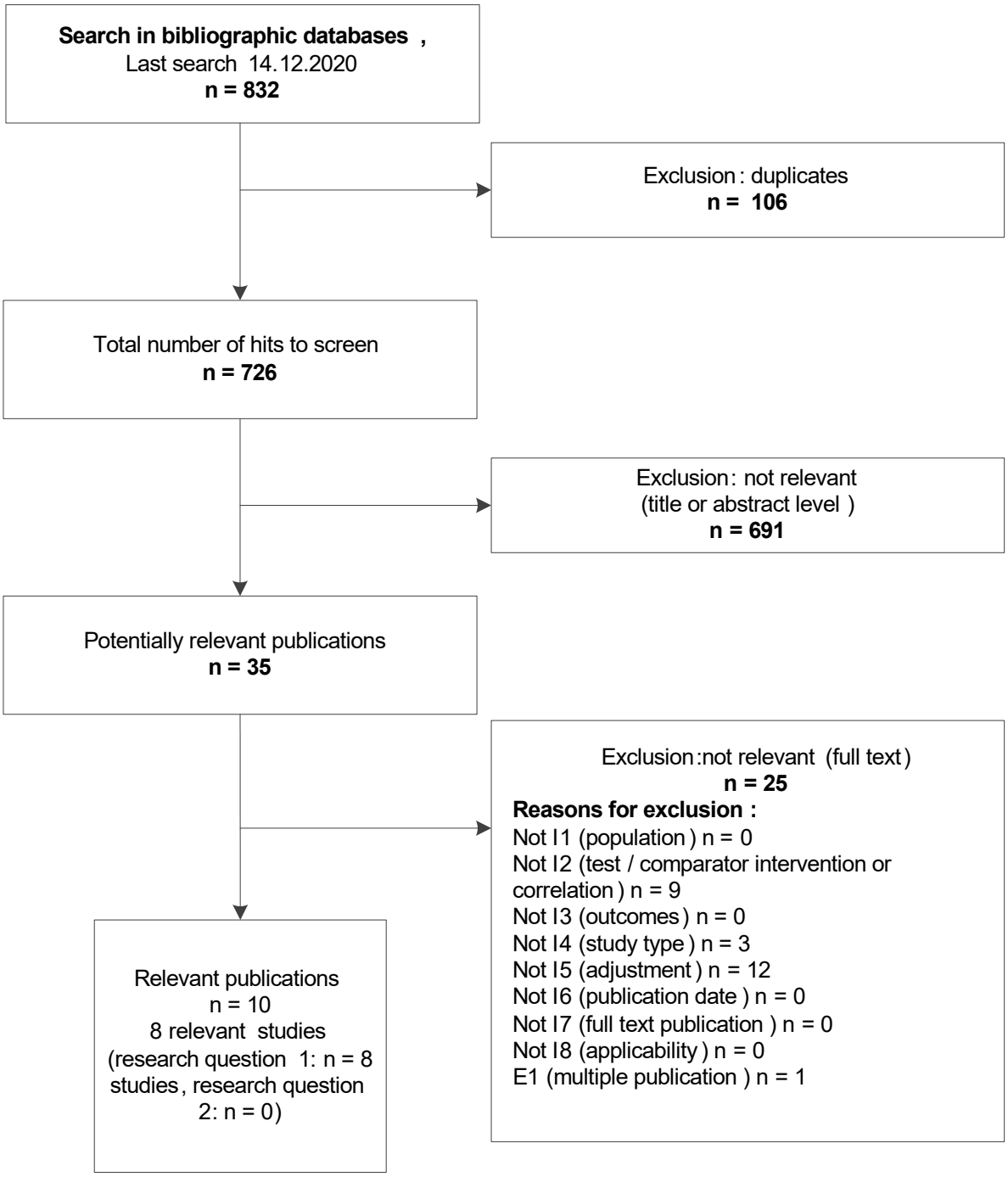

Figure 1: Result of the bibliographic search and study selection

5.1.2.2 Further information sources and search techniques

Relevant studies or documents found through further information sources and search techniques are presented below unless they had already been found through primary information sources.

5.1.2.3 Use of further search techniques

As part of the focused information retrieval, 2 systematic reviews were found – the corresponding references are provided in Section 9.1 of the full report. The lists of references of these systematic reviews were screened.

No relevant studies or documents not already identified in other search steps were found.

5.1.2.4 Requests to authors

No requests to authors to obtain additional information on relevant studies were necessary since such information was not expected to have a relevant impact on the assessment.

5.1.3 Resulting study pool

Through the various search steps, a total of 9 relevant studies (11 publications) were found for research question 1 (see also Table 2). No pertinent studies were found to answer research question 2.

Table 2: Study pool for research question 1

Study	Full publication (in professional journals)
Ando 2018	Yes [27]
Kaier 2018[a]	Yes [28-30]
Khera 2017	Yes [31]
Mao 2018	Yes [32]
Rymer 2019	Yes [33]
Salemi 2019	Yes [34]
Vemulapalli 2019	Yes [35]
Verma 2017	Yes [36]

a. The reference “Kaier 2018 study” is used to collectively refer to the publications by Kaier 2018, Oettinger 2020, and Nimptsch 2017 because the Kaier 2018 and Nimptsch 2017 publications are largely based on identical data. The Oettinger 2020 publication supplements the Kaier 2018 publication by an analysis of the years 2015 and 2016.

5.2 Characteristics of the studies included in the assessment

The characteristics of the studies included for research question 1 are presented in Table 3 and summarized below.

Table 3: Characteristics of the studies included for research question 1 (multipage table)

Study / study design[a] (data source)	Recruitment country / follow-up period[b] / study objective	Inclusion and exclusion criteria	Intervention	Total number of units	Volume definition / number of hospitals per volume category
Ando 2018 Retrospective cohort study (HCUP-NIS)	USA / 2011–30/09/2015 / investigation of the relationship between hospital volume and inpatient mortality or failure to rescue or complications overall	Inclusion criteria: ▪ Patients with severe aortic stenosis who underwent TAVI ▪ Age ≥ 50 years Exclusion criteria: ▪ Patients with aortic insufficiency	TAVI Access: ND ICD-9-CM code: ▪ 35.05	48 886	Categories for annual hospital volume: ▪ Low volume (1st quintile): ≤ 30 ▪ Moderate volume (2nd, 3rd, and 4th quintiles): 31–130 ▪ High volume (5th quintile): > 130[c] Number of hospitals: ND
Kaier 2018[d] Retrospective observational study (DRG statistics)	Germany / 2008–2016 / investigation of the relationship between hospital volume and inpatient mortality, stroke, bleeding, length of hospital stay, pacemaker implantation, and ventilator therapy > 48 hours[e]	Inclusion criteria: ▪ Patients who underwent TAVI ▪ OPS codes: ▫ 5-35a.0 ▫ 5-35a.00 ▫ 5-35a.01 ▫ 5-35a.02	TAVI Access: ▪ transfemoral ▪ other	2008–2016 total (Oettinger 2020): 73 466	Categories for annual hospital volume: Kaier 2018: ▪ Low volume: < 50 ▪ Moderate volume: 50–99 ▪ High volume: ≥ 100

Table 3: Characteristics of the studies included for research question 1 (multipage table)

Study / study design[a] (data source)	Recruitment country / follow-up period[b] / study objective	Inclusion and exclusion criteria	Intervention	Total number of units	Volume definition / number of hospitals per volume category
Kaier 2018[d] Retrospective observational study (DRG statistics) (continued)		Exclusion criteria: ▪ Patients with aortic regurgitation or additional simultaneous cardiac procedure or simultaneous PCI Inclusion criteria (Nimptsch 2017): ▪ Patients who underwent TAVR ▪ Age ≥ 20 years ▪ OPS code 535a0 Exclusion criteria: ND	TAVI Access: ▪ transfemoral ▪ other	2008–2014 (Kaier 2018): 43 996 2015–2016 (Oettinger 2020): 29 470 2009–2014 (Nimptsch 2017): 50 765[f]	Kaier 2018 (continued) Number of hospitals: ▪ Total: 113 ▪ Oettinger 2020: ▪ Low volume: < 50 ▪ High volume: ≥ 50 Number of hospitals: ND Nimptsch 2017: Hospitals were categorized into quintiles based on total volume within the 6-year observation period: Median and IQR are reported for the number of TAVR procedures performed annually per hospital: ▪ Very low volume (1st quintile): 31 (12–50), 48 hospitals ▪ Low volume (2nd quintile): 98 (69–123), 1 hospitals ▪ Moderate volume (3rd quintile): 141 (99–161), 12 hospitals ▪ High volume (4th quintile): 169 (142–228), 9 hospitals ▪ Very high volume (5th quintile): 286 (233–328), 6 hospitals

Table 3: Characteristics of the studies included for research question 1 (multipage table)

Study / study design[a] (data source)	Recruitment country / follow-up period[b] / study objective	Inclusion and exclusion criteria	Intervention	Total number of units	Volume definition / number of hospitals per volume category
Khera 2017 Retrospective observational study (Nationwide Readmissions Database)	USA / 2014 / investigation of the relationship between hospital volume and hospital readmission within 30 days	▪ Inclusion criteria: ▪ Patients who underwent TAVR in 2014 Exclusion criteria: ▪ Patients whose post-TAVR discharge was in 12/2014 and for whom no follow-up data were available ▪ Patients who died during the hospital stay ▪ Hospitals which performed < 5 TAVR in the 1st quarter ▪ Patients who had repeat TAVR within 30 days[g]	TAVR ICD-9-CM code: ▪ 35.05 ▪ 35.06	16 252	Categories for annual hospital volume: ▪ Low volume: < 50 ▪ Moderate volume: ≥ 50 < 100 ▪ High volume: ≥ 100 Number of hospitals: ▪ Total: 129
Mao 2018 Retrospective observational study (Medicare data)	USA / 1/10/2011–31/12/2015 / investigation of the relationship between hospital volume and all-cause mortality or 30-day mortality, stroke (as part of a composite outcome), hospital readmission within 30 days	Inclusion criteria: ▪ Patients who underwent TAVR between 10/2011 and 12/2015 Exclusion criteria: ▪ Patients who were discharged from hospital in 12/2015 (at the end of the study period) were not included in the analysis of the 30-day outcomes. ▪ Hospitals in which only 1 or 2 TAVR were performed within a 5-year period ▪ Isolated procedures (TAVR) from a hospital's early years, at least 1 year apart	TAVR ICD-9-CM codes: ▪ 35.05 ▪ 35.06 ICD-10-CM codes: ▪ 02RF37Z/H ▪ 02RF38Z/H ▪ 02RF3JZ/H ▪ 02RF3KZ/H	60 538	Categories for annual hospital volume 1 / 2 / 3 / 4 (median)[h,i]: ▪ Low volume: < 35 / < 52 / < 84 / < 137 ▪ High volume: ≥ 35 / ≥ 52 / ≥ 84 / ≥ 137 Number of hospitals: ▪ Total: 438

Table 3: Characteristics of the studies included for research question 1 (multipage table)

Study / study design[a] (data source)	Recruitment country / follow-up period[b] / study objective	Inclusion and exclusion criteria	Intervention	Total number of units	Volume definition / number of hospitals per volume category
Rymer 2019 Retrospective observational study (TVT Registry data)	USA/ 11/11/2011--30/06/2017 / investigation of the relationship between hospital volume and the outcomes (aborted TAVR)	Inclusion criteria: ▪ > 18 years ▪ Elective TAVR ▪ First TAVR Exclusion criteria: ▪ Emergency or urgent TAVR ▪ Patients with information missing about potential TAVR abortion ▪ Patients with information missing about possible inpatient adverse events	TAVR[j] Procedure codes: ND	106 169	Categories for annual hospital volume from 11/2011 up to the respective intervention in question[k]: ▪ Low volume: 1–99 ▪ Moderate volume: 100–299 ▪ High volume: 300–599 ▪ Very high volume: > 600[l] Number of hospitals: ▪ Total: 524
Salemi 2019 Retrospective observational study (New York State Department of Health Statewide Planning and Research Cooperative System)	USA / 01/2012–12/2016 / investigation of the relationship between physician volume and a composite outcome (inpatient mortality, stroke, acute myocardial infarction) as well as the individual outcomes of inpatient mortality, stroke, acute myocardial infarction[m]	Inclusion criteria: ▪ Elective and nonelective transfemoral TAVR in New York State Exclusion criteria: ▪ Procedures missing data on medical licence ▪ Procedures for whom the operator could not be identified	Transfemoral TAVR International Classification of Diseases-Ninth Revision: ▪ 35.05 International Classification of Diseases-Tenth Revision: ▪ 02RF37Z ▪ 02RF38Z ▪ 02RF3JZ ▪ 02RF3KZ ▪ X2RF332	All TAVR: 8771 Elective TAVR: 5916	Categories for annual hospital volume: ▪ Low volume: < 83 ▪ Moderate volume: 83–196 ▪ High volume: ≥ 197 Categories for annual operator volume: ▪ Low volume: 1–23 ▪ Moderate volume: 24–79 ▪ High volume: ≥ 80 Number of hospitals: ▪ Total: 30 ▪ For elective TAVR: 27 Number of operators ▪ Total: 207 ▪ For elective TAVR: 169

Table 3: Characteristics of the studies included for research question 1 (multipage table)

Study / study design[a] (data source)	Recruitment country / follow-up period[b] / study objective	Inclusion and exclusion criteria	Intervention	Total number of units	Volume definition / number of hospitals per volume category
Vemulapalli 2019 Retrospective observational study (TVT Registry data)	USA / 1/01/2015–31/12/2017 / investigation of the relationship between hospital or operator volume and 30-day mortality, composite complication outcome (stroke, paravalvular leak, vascular complications, severe bleeding, kidney injury)	Inclusion criteria: ▪ All TAVR in patients with severe symptomatic aortic stenosis and moderate or high surgical risk Exclusion criteria: ND	Transfemoral TAVR Procedure codes: ND	96 256 TAVI 554 hospitals 2935 operators	Categories for annual hospital volume: ▪ Low volume (1st quartile): 5–36, 140 hospitals ▪ Moderate volume (2nd quartile): 37–54, 138 hospitals ▪ High volume (3rd quartile): 55–85, 137 hospitals ▪ Very high volume (4th quartile): 86–371, 139 hospitals Categories for annual operator volume (median): ▪ Low volume (1st quartile): 11 ▪ Moderate volume (2nd quartile): ND ▪ High volume (3rd quartile): ND ▪ Very high volume (4th quartile): 70
Verma 2017 Retrospective observational study (Banner Health data)	USA / 01/2014–06/2015 / investigation of the relationship between hospital volume and the composite outcome of all-cause mortality, new post-TAVR dialysis, post-TAVR permanent pacemaker, hospital readmission within 30 days[n]	Inclusion criteria: Patients who underwent TAVR with a Sapien-XT valve (Edwards Lifesciences, Irvine, CA) due to severe, symptomatic aortic stenosis Exclusion criteria: ▪ Patients with an off-label indication ▪ Patients with missing data	TAVR[o] Procedure codes: ND	181	Categories for annual hospital volume: ▪ Low volume: < 40; 1 hospital ▪ Moderate volume: 40–75; 1 hospital ▪ High volume: > 75; 1 hospital

Table 3: Characteristics of the studies included for research question 1 (multipage table)

Study / study design[a] (data source)	Recruitment country / follow-up period[b] / study objective	Inclusion and exclusion criteria	Intervention	Total number of units	Volume definition / number of hospitals per volume category

a. If a study, e.g. secondary data analysis or registry study, specified a data source, it is entered here.
b. In secondary data analyses or registry studies, for instance, the follow-up duration is the data collection period.
c. There is a discrepancy in the text versus Table 1 of the publication regarding the limit of the high-volume category: ≥ 130 versus > 130.
d. Since Oettinger 2020 and Kaier 2018 are based on identical data for the period 2008 through 2014, the present report includes Oettinger 2020 results for the period 2015 through 2016 only. The data pool of Nimptsch 2017 largely overlaps that of Kaier 2018; the investigation period of Kaier 2018 and Oettinger 2020 fully covers the investigation period of Nimptsch 2017.
e. Not all outcomes were investigated for the entire 2008–2016 period.
f. The numbers of patients included in the respective analyses are discrepant due to differences both in the length of the investigation period and in the inclusion criteria for the analyses by Kaier 2018 / Oettinger 2020 versus Nimptsch 2017.
g. "For patients who underwent repeat TAVR within 30 days (n = 4), the second discharge record was considered a readmission…"
h. "For the year periods being investigated, a hospital was determined to be high volume if the numbers of TAVR procedures it performed during these years were above the median (year 1 median, 35; year 2 median, 52; year 3 median, 84; and year 4 median, 137) for most of the time. For example, for analysis of procedures performed within 1 year after initiating TAVR programs, hospitals performing 35 TAVRs or more that year were considered to have a high TAVR volume. For analysis of procedures performed within 2 years after initiation of a TAVR program, hospitals performing 35 TAVRs or more in year 1 and 52 TAVRs or more in year 2 were considered to have a high TAVR volume. For analysis of the entire 4-year period, hospitals performing TAVR procedures above the median for at least 3 years were considered to have a high TAVR volume."
i. In the Mao 2018 study, there are discrepancies in the reporting of volume limits: > 35 and ≥ 35, > 52 and ≥ 52, > 84 and ≥ 84, > 137 and ≥ 137.
j. Rymer 2019 lists the valve models and valve sizes in Table 4 and the central figure of the publication.
k. "Total TAVR volume was defined as cumulative institutional TAVR volume since November 2011. Total TAVR volume accounted for the procedural volume from November 2011 until the procedure itself and did not account for procedures performed in the future."
l. The hospital volume categories are cited this way in Rymer 2019.
m. The authors of the Salemi 2019 study stated that due to a low event rate, they did not present myocardial infarctions separately, as planned.
o. Verma 2017 additionally investigated the outcome of stroke, which is not listed in the study objective.
p. Verma 2017 lists the access and valve sizes in Table 2, for instance.

ACC: American College of Cardiology; CA: California; CM: clinical modification; DRG: diagnosis-related group; HCUP-NIS: Healthcare Cost and Utilization Project – National Inpatients Sample; ICD: International Statistical Classification of Diseases and Related Health Problems; IQR: interquartile range; ND: no data; OPS: Operation and procedure code; PCI: percutaneous coronary intervention; PCS: Procedure Coding System; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement; TVT: transcatheter valve therapy; USA: United States of America

5.2.1 Study design and data source

The 8 included studies were retrospective observational studies. Rymer 2019 and Vemulapalli 2019 employed data from the Transcatheter Valve Therapy (TVT) registry[2]. Ando 2018 used the databases of the Healthcare Cost and Utilization Project (National [Nationwide] Inpatient Sample, State Inpatient Database)[3]. Khera 2019 is based on data from the Nationwide Readmissions Database. Mao 2018 used administrative data from the U.S. Centers for Medicare[4] and Medicaid Services. Salemi 2019 employed data from the New York State Department of Health Statewide Planing and Research Cooperative System. Verma 2017 used data from Banner Health[5]. Finally, the Kaier 2018 study, including the publications Oettinger 2020 and Nimptsch 2017, used billing data from German hospitals (diagnosis-related group [DRG] statistics) for the investigations.

5.2.2 Recruitment country, follow-up period, and study objective

Seven of the 8 studies (Ando 2018, Khera 2017, Mao 2018, Rymer 2019, Salemi 2019, Vemulapalli 2019, and Verma 2017) were conducted in the United States, while the Kaier 2018 study, including the Oettinger 2020 and Nimptsch 2017 publications, was conducted in Germany.

The follow-up duration of the studies varied from 1 year (Khera 2017) to 9 years (Oettinger 2020 publication of the Kaier 2018 study).

Six of 8 studies investigated the relationship between volume and mortality or survival rates (Ando 2018, Kaier 2018, including the Oettinger 2020 and Nimptsch 2017 publications, Mao 2018, Salemi 2019, Vemulapalli 2019, and Verma 2017). Ando 2018 analysed the relationship between volume and adverse effects of therapy, including failure to rescue and complications overall. Four studies investigated the relationship between volume and stroke (Kaier 2018, including the Oettinger 2020 publication, Salemi 2019, Vemulapalli 2019, and Verma 2017). The Kaier 2018 study, including the Oettinger 2020 publication, and Vemulapalli 2019 additionally analysed bleeding. Vemulapalli 2019 scrutinized the relationship between volume and vascular complications. Verma 2017 investigated the relationship between volume and postinterventional renal failure. Like Verma 2017, the Oettinger 2020 publication of the Kaier 2018 study investigated the relationship between volume and implantation of a (permanent) pacemaker. The Kaier 2018 study analysed the relationship between hospital volume and the administration of more than 48 hours of postinterventional ventilation [28]. Alongside investigating the outcomes of mortality and adverse effects of therapy, some studies also looked at effects on other outcomes: Kaier 2018

[2] The Transcatheter Valve Therapy Registry is an initiative of the Society of Thoracic Surgeons and the American College of Cardiology.

[3]The database of the Healthcare Cost and Utilization Project (National [Nationwide] Inpatient Sample, State Inpatient Database) comprises comprehensive information on inpatient care.

[4] Medicare is the U.S. national insurance system which covers older people (65 years and older), people with disabilities, and people with dialysis-dependent kidney failure.

[5] Banner Health is a large US hospital group.

and Khera 2017 investigated the postinterventional length of stay, for instance. In addition, Khera 2017, Mao 2018, and Verma 2017 analysed the need for inpatient readmission. Rymer 2019 and Vemulapalli 2019 also studied the relationship between volume and aborted TAVI. One study (Vemulapalli 2019) investigated the relationship between volume and conversion from TAVI to open-heart surgery. Finally, Mao 2018, Salemi 2019, Vemulapalli 2019, and Verma 2017 analysed a composite outcome. None of the studies investigated the relationship between volume and the outcome of health-related quality of life.

5.2.3 Main inclusion criteria of the studies

Three of the 8 studies (Ando 2018, the Nimptsch 2017 publication of the Kaier 2018 study, and Rymer 2019) reported specific age groups as inclusion criteria for the study population. They ranged from > 18 years to ≥ 50 years.

Three studies (Ando 2018, Vemulapalli 2019, and Verma 2017) specified the valvular disease, e.g. severe symptomatic aortic stenosis, to be treated with the interventional therapy.

5.2.4 Information provided on the interventional therapy

Two of 8 studies (Ando 2018 and Khera 2017) specified the procedure as TAVI, without providing any further details. Rymer 2019 and Verma 2017 reported the valve models used. The Oettinger 2019 publication of the Kaier 2018 study discussed different TAVI access routes. Salemi 2019 and Vemulapalli 2019 limited their investigations to TAVI performed via transfemoral access. Finally, 2 U.S. studies (Mao 2018 and Salemi 2019) reported detailed procedural codes in accordance with ICD-9-CM or ICD-10-CM.

5.2.5 Volume definition

In 6 of the 8 included studies (Ando 2018, Kaier 2018, including the Oettinger 2020 publication, Khera 2017, Salemi 2019, Vemulapalli 2019, and Verma 2017), volume was defined as the number of TAVI procedures performed annually per hospital. Two studies additionally defined volume per operator and year (Salemi 2019 and Vemulapalli 2019). The Mao 2018 study determined volume for the 4-year investigation period and initially calculated median volumes for each year. For the first year, hospitals exceeding this median were categorized as high-volume hospitals. For the second year of the study, hospitals exceeding the respective median volume in both years of the investigation were deemed high volume. To qualify as a high-volume hospital for the 4-year study period, hospitals had to exceed the respective median volume in at least 3 years. One further study (Rymer 2019) calculated hospital volume for the period from study start to the specific procedure. In 1 publication of the Kaier 2018 study, hospital volume was categorized based on the total volume in the 6-year follow-up period [30].

In the Mao 2018 study, hospital volume was dichotomized, and the median per study year was reported for the 4-year study period (see above). Four studies (Ando 2018, Khera 2017, Salemi 2019, and Verma 2017) used 3 categories/terciles (high, moderate, and low volume) for

the number of performed procedures per hospital and/or operator, providing specific thresholds, ranges, or the median procedure volume. Ando 2018 initially formed quintiles for hospital volume and then combined quintiles 2 to 4 to form the middle category. Two studies (Rymer 2019 and Vemulapalli 2019) formed 4 categories with similar patient numbers/quartiles (very high, high, moderate, and low volume) for the number of performed TAVI procedures per hospital, and they reported ranges for each.

The 3 publications for the Kaier 2018 study differed in the way they categorized the number of performed TAVI procedures per hospital: The Kaier 2018 publication used 3 categories for hospital volume, reporting 2 thresholds and 1 range. In the Oettinger 2020 publication of the Kaier 2018 study, hospital volume was categorized as low versus high volume, and thresholds were specified. The Nimptsch 2017 publication, in contrast, categorized hospital volume by quintiles as very high, high, moderate, low, or very low. It reported medians and interquartile ranges (IQR). The Kaier 2018 study analysed hospital volume both categorically [28,29] and continuously [30]. The present report uses the results of the continuous analysis [30].

5.2.6 Data on the study population

The key characteristics of the study populations for research question 1 are presented in Table 21 of Appendix B of the full report and summarized below.

The 8 included studies investigated different volumes of patients undergoing TAVI. These volumes ranged from 181 (Vermi 2017) to 106 169 (Rymer 2019). All studies discussed the patient age distribution at least to some degree. In one publication on the Kaier 2018 study, the age group was listed only as an inclusion criterion [30]. The sex ratios of the study populations were reported by all studies except for 1 publication of the Kaier 2018 study [30].

Five of the 8 studies (Ando 2018, Khera 2017, Salemi 2019, Vemulapalli 2019, and Verma 2017) provided information on the underlying illness, aortic stenosis. Three of 8 studies (Kaier 2018, including the Nimptsch 2017 publication, Mao 2018, and Rymer 2019) specified only the procedure, transcatheter aortic valve implantation. All 8 studies additionally reported comorbidities of analysed patients; only the Nimptsch 2017 publication of the Kaier 2018 study did not provide any information on this.

5.3 Assessment of the informative value of results

Table 4 presents the informative value of results. Cluster effects were adequately taken into account in all 8 included studies.

The most important rating criteria were high quality of data, adequate patient flow, adequate consideration of cluster effects, sufficient risk adjustment, adequate handling of missing data, and adequate reporting of relevant aspects. For each of the 8 studies, the informative value of results was rated as low. This was particularly due to data being either of low quality or incomplete, lack of information on patient flow, non-consideration of relevant risk factors, and unclear information on the handling of missing data.

In 3 studies (Kaier 2018, including the Oettinger 2020 and Nimptsch 2017 publications, Salemi 2019, and Vemulapalli 2019), the authors conducted both categorical and continuous volume analyses. The other 5 studies (Ando 2018, Khera 2017, Mao 2018, Rymer 2019, and Verma 2017) reported only categorical volume analysis.

Two of 8 studies (Kaier 2018, including the Oettinger 2020 and Nimptsch 2017 publications, as well as Rymer 2019) adjusted for risk factors only on the patient level. Three further studies (Ando 2018, Khera 2017, and Mao 2018) adjusted for factors on both the patient and the hospital levels. Salemi 2019 adjusted for factors on the patient, hospital, and operator levels. Vemulapalli 2019 adjusted for factors on the patient and operator levels. The Verma study reported adjusting for risk factors but mentioned only patient-level factors, not factors on the hospital or operator level.

One of 8 included studies (the Nimptsch 2017 publication of the Kaier 2018 study) reported information on a check of model quality, and none of the studies stated whether the applied statistical models had been validated (see Table 4). The authors of 3 studies (Khera 2017, Rymer 2019, and Vemulapalli 2019) discussed how missing data was handled.

Table 5 and Table 6 show an overview of the relevant risk factors taken into account in the studies on the level of patients, operators, and hospitals.

On the patient level, this primarily involved the factors of age, sex, ancestry, and comorbidities. Few studies adjusted for the underlying illness (Kaier 2018, including the Oettinger 2020 and Nimptsch 2017 publications) or for the urgency of the procedure (Mao 2018 and Vemulapalli 2019). Salemi 2019, the only study to adjust for factors other than operator volume, additionally took into account the amount of time for which the respective operator has been performing TAVI. The operator's medical speciality was not taken into account by Salemi 2019. The Vemulapalli 2019 analysis included only operator volume. On the hospital level, Ando 2018, Khera 2017, and Mao 2018 took into account the factors of volume, academic status, number of hospital beds, hospital geographic region, year of study publication, and, e.g. the volume of open-heart aortic valve replacements.

Table 4: Informative value of results

Study	High quality of individual data[a]	Adequate patient flow	Volume analysis	Plausible procedure for determining the volume thresholds	Suitable model class	Adequate procedure for considering cluster effects	Adequate risk adjustment[a]	Adequate handling of missing data	Information on a check of model quality	Model validation	Information on point estimate, including precision	Adequate reporting of relevant aspects	Further aspects	Informative value of results
Ando 2018	Unclear	Unclear	Categorical	Yes	Yes	Yes	No[b]	Unclear	No	Unclear	In part	Yes	None	Low
Kaier 2018	Yes	Unclear	▪ Continuous[d] ▪ Categorical	Yes	Yes	Yes	No[b,c]	Unclear	Yes[e]	Unclear	Yes	Yes	None	Low
Khera 2017	Unclear	Yes	Categorical	Yes	Yes	Yes	No[b]	Yes	No	Unclear	Yes	Yes	None	Low
Mao 2018	No	Unclear	Categorical	Yes	Yes	Yes	No[b]	Unclear	No	Unclear	In part	Yes	None	Low
Rymer 2019	Unclear	Yes	Categorical	Unclear	Yes	Yes	No[b,c]	Yes	No	Unclear	Yes	Yes	None	Low
Salemi 2019	Unclear	Yes	▪ Continuous ▪ Categorical	Yes	Yes	Yes	Yes	Unclear	No	Unclear	In part	Yes	None	Low
Vemulapalli 2019	Unclear	Yes	▪ Continuous ▪ Categorical	Yes	Yes	Yes	No[c]	Yes	No	Unclear	Yes	Yes	None	Low
Verma 2017	Unclear	Yes	Categorical	Yes	Yes	Yes	Unclear	Unclear	No	Unclear	Yes	No	None	Low

a. "Yes" or "no" was stated only if unambiguous information was available for the specific study.
b. No risk adjustment on the operator level.
c. No risk adjustment on the hospital level.
d. Continuous analysis available only for 1 outcome.
e. Data for checking the model are available only for Nimptsch 2017.

Table 5: Patient-level risk factors considered in the adjustment

Study	Risk adjustment level													
	Patient													
	Underlying disease	Age	Sex	Ancestry	Place of residence / region	Socioeconomic status	Type of insurance	Comorbidities	Severity of disease	Length of hospital stay	Type of vascular access	Year of surgery	Urgency of intervention	STS PROM score
Ando 2018	-	X	X	X	-	X	X	X	-	-	-	-	-	-
Kaier 2018	X	X	X	-	-	-	-	X	X	-	X[a]	X	-	-
Khera 2017	-	X	X	-	-	X	X	X	-	X	X	-	-	-
Mao 2018	-	X	X	X	-	-	-	X	-	-	X	-	X	-
Rymer 2019	-	X	X	X	-	-	-	X	X	-	-	-	-	-
Salemi 2019	-	X	X	X	-	-	X	X	X	-	-	-	-	-
Vemulapalli 2019	-	X	X	X	-	-	-	X	X	-	-	X	X	-
Verma 2017[b]	-	X	X	-	-	-	-	X	X	-	X	-	-	X

a. Not all analyses adjusted for this independent variable.
b. It is unclear for which independent variables an adjustment was performed. The authors reported only that they made an adjustment.
X. Factor adjusted for in study analysis.
-. The studies do not report any data on this factor.
PROM: predicted risk of mortality; STS: Society of Thoracic Surgeons

Table 6: Operator-level and hospital-level risk factors considered in the adjustment

Study	Risk adjustment level												
	Operator				Hospital								
	Volume[a]	Operator specialization	Experience with TAVI	Sex	Academic status	Number of hospital beds	Number of examined nurses per bed	Hospital legal form (for-profit vs. not-for-profit)	Rural vs. urban hospital	Geographic region	Volume[a]	Volume of other procedures, e.g. SAVR	Publication year
Ando 2018	-	-	-	-	X	-	-	-	X	-	-	-	X
Kaier 2018	-	-	-	-	-	-	-	-	-	-	-	-	-
Khera 2017	-	-	-	-	X	X	-	-	-	-	-	-	-
Mao 2018	-	-	-	-	X	-	-	-	-	X	-	X	-
Rymer 2019	-	-	-	-	-	-	-	-	-	-	-	-	-
Salemi 2019	X	-	X	-	-	-	-	-	-	-	X	-	-
Vemulapalli 2019	X	-	-	-	-	-	-	-	-	-	-	-	-
Verma 2017[b]	-	-	-	-	-	-	-	-	-	-	-	-	-

a. In principle, all analyses included volume as an essential factor; in the studies marked, the adjustment was made specifically for hospital volume and operator volume.
b. The authors reported having performed an adjustment but failed to list the independent variables which were included in the final model.
X. Factor adjusted for in study analysis.
-. The studies do not report any data on this factor.
SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation

5.4 Overview of outcomes relevant for the assessment

All included studies, that is, Ando 2018, Kaier 2018, including the Oettinger 2020 and Nimptsch 2017 publications, Khera 2017, Mao 2018, Rymer 2019, Salemi 2019, Vemulapalli 2019, and Verma 2017, provided usable data for at least 1 outcome.

It was therefore possible to extract data on relevant outcomes from these studies. Table 7 presents an overview of the available data on relevant outcomes from the included studies.

For the outcome category of mortality, 6 of the 8 included studies reported results on the relationship between volume and quality of treatment outcome. One study (Verma 2017) provided no usable results. On the outcome of all-cause mortality, 1 of 6 studies (Mao 2018) provided usable results. Four of the 6 studies (Ando 2018, Kaier 2018, including the Oettinger 2020 and Nimptsch 2017 publications, Salemi 2019 as well as Vemulapalli 2019) provided results on the outcome of inpatient mortality.

For the outcome category of morbidity, 5 of the 8 included studies reported results; 2 studies (Vemulapalli 2019 and Verma 2017) provided no usable results for at least some outcomes of this category. For the outcome of adverse effects of therapy, including failure to rescue and complications overall, 1 study (Ando 2018) reported results on the components of failure to rescue and complications. The two components of the outcome were evaluated together in the present report (see Section 5.5.2.1).

The included studies investigated further outcomes of the morbidity outcome category: For instance, the Verma 2017 study analysed the outcome of dialysis-dependent renal failure (postinterventional) but did not report any usable data. Four studies (Kaier 2018, including the Oettinger 2020 publication, Salemi 2019, Vemulapalli 2019, and Verma 2017) analysed the outcome of stroke. The Vemulapalli 2019 and Verma 2017 studies did not provide any usable data on this topic.

The outcome of bleeding was investigated by 2 studies (Kaier 2018, including the Oettinger 2020 publication, and Vemulapalli 2019); all studies were usable for assessing the relationship between volume and treatment quality. Vemulapalli 2019 analysed the outcome of vascular complications including leaks and myocardial infarctions, but it provided no usable data.

Two of 5 studies (the Oettinger 2020 publication of the Kaier 2018 study as well as Verma 2017) investigated the outcome of pacemaker implantation. Only the Oettinger 2020 publication of the Kaier 2018 study provided usable data. Furthermore, the Kaier 2018 study looked at the outcome of ventilation > 48 hours [28].

The included studies provided no data on the outcome of health-related quality of life, including activities of daily living and dependence on help from others.

Two of the 8 studies (Kaier 2018 and Khera 2017) investigated the outcome of length of hospital stay. However, the Khera 2017 study did not provide any usable data. For the outcome of hospital readmission, 2 of 3 studies (Khera 2017 and Mao 2018) reported usable results. Verma 2017, in contrast, did not provide any usable data on this outcome.

Two studies investigated the outcomes of conversion to surgery (Vemulapalli 2019) and abort of TAVI (Rymer 2019). However, Vemulapalli 2019 did not provide any usable data. The two outcomes were evaluated together in the present report (see Section 5.5.5.2).

Four of 8 studies (Mao 2018, Salemi 2019, Vemulapalli 2019, and Verma 2017) investigated a composite outcome. Except for Vemulapalli 2019 (morbidity only), these studies combined outcomes from the mortality and morbidity categories. All 4 studies provided usable results.

Table 7: Matrix of relevant outcomes

Study	Outcomes														
	Mortality		Morbidity							Health-related quality of life	Length of hospital stay	Other outcomes			
	All-cause mortality	Inpatient mortality	Adverse effects of therapy including failure to rescue and complications overall	Dialysis-dependent renal failure	Stroke	Bleeding	Vascular complications including leaks and myocardial infarctions	Pacemaker implantation	Ventilation > 48 hours			Hospital readmission	Conversion to surgery[a,b]	Aborted TAVI[b]	Composite outcomes
Ando 2018	-	●	●	-	-	-	-	-	-	-	-	-	-	-	-
Kaier 2018	-	●	-	-	●	●	-	●	●	-	●	-	-	-	-
Khera 2017	-	-	-	-	-	-	-	-	-	-	○	●	-	-	-
Mao 2018	●	-	-	-	-	-	-	-	-	-	-	●	-	-	●
Rymer 2019	-	-	-	-	-	-	-	-	-	-	-	-	-	●	-
Salemi 2019	-	●	-	-	●	-	-	-	-	-	-	-	-	-	●
Vemulapalli 2019	-	●	-	-	○	●	○	-	-	-	-	-	○	-	●
Verma 2017[c]	○	-	-	○	○	-	-	○	-	-	-	○	-	-	●

●. Data were reported and were usable.
○. Data were reported but were not usable for the investigation.
-. No data were reported (no further information), or the outcome was not surveyed.
a. Switch of the interventional approach to open-heart surgery.
b. The 2 outcomes "conversion to surgery" and "aborted TAVI" are analysed together below.
c. "The primary endpoint was a composite of mortality, dialysis-dependent renal failure, cerebrovascular accident, need for new permanent pacemaker and readmission within 30 days."
TAVI: transcatheter aortic valve implantation

5.5 Results on relevant outcomes

5.5.1 Mortality

5.5.1.1 Results on the outcome of all-cause mortality

Two of 8 included studies (Mao 2018 and Verma 2017) reported results on the outcome of all-cause mortality (see Table 8). All studies had a low informative value of results. The Verma 2017 study did not provide any usable data on this topic.

Results on the hospital level

For the outcome of all-cause mortality, Mao 2018 reported a statistically significant difference in favour of higher-volume hospitals.

In the Mao 2018 study, annual hospital volume was categorized into low and high based on the medians of the respective annual volumes and the combined medians for a 4-year period (see Section 5.2.5). The comparison of low-volume hospitals (reference category) versus high-volume hospitals over a 4-year period with regard to 2-year mortality after TAVR showed a statistically significant difference in favour of higher-volume hospitals (hazard ratio [HR]: 0.89; 95% confidence interval [CI]: [0.84; 0.95]; p-value: no data [ND]). In the above comparison, the same relationship was established as early as 30 days post intervention (HR: 0.83; 95% CI: [0.74; 0.93]; p-value: ND) and 1 year post intervention (HR: 0.87; 95% CI: [0.81; 0.94]; p-value: ND).

Results on the operator level

For the outcome of all-cause mortality, the relationship between volume and quality of treatment outcome was not investigated on the operator level.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary for the outcome of all-cause mortality

In summary, for the outcome of all-cause mortality, a correlation between hospital volume and quality of treatment outcome in favour of higher-volume hospitals was derived based on 1 study of low informative value of results. The relationship between operator volume or the combined hospital-operator volume and this outcome was not investigated.

Table 8: Results – all-cause mortality (multipage table)

Study	Outcome definition	N	Volume specification	All-cause mortality, raw n (%)	Adjusted hazard ratio [95% CI]; p-value
Mao 2018	Overall survival		Categories for annual hospital volume 1 / 2 / 3 / 4 (median)[a,b]:	Estimated risk (%):	
			Procedures across all years:		
	After 30 days	30 584	Low volume: < 137 or < median in a further year	1715 (5.6)	Reference category
		27 753	High volume: ≥ 137 and ≥ median (35 / 52 / 84) in at least 2 further consecutive years	1281 (4.6)	0.83 [0.74; 0.93]; ND
	After 1 year	11 098			
		ND	Low volume: < 137 or < median in a further year	20.8	Reference category
		ND	High volume: ≥ 137 and ≥ median (35 / 52 / 84) in at least 2 further consecutive years	18.8	0.87 [0.81; 0.94]; ND
	After 2 years	24 751			
		ND	Low volume: < 137 or < median in a further year	32.5	Reference category
		ND	High volume: ≥ 137 and ≥ median (35 / 52 / 84) in at least 2 further consecutive years	30.5	0.89 [0.84; 0.95]; ND
			Procedures in the 1st year:		
	After 30 days	5385	Low volume: < 35	369 (6.9)	Reference category
		5577	High volume: ≥ 35	375 (6.7)	0.93 [0.77; 1.12]; ND
	After 1 year	11 098			
		ND	Low volume: < 35	23.6	Reference category
		ND	High volume: ≥ 35	23.7	0.93 [0.84; 1.03]; ND

Table 8: Results – all-cause mortality (multipage table)

Study	Outcome definition	N	Volume specification	All-cause mortality, raw n (%)	Adjusted hazard ratio [95% CI]; p-value
Mao 2018 (continued)	Overall survival (continued)		Categories for annual hospital volume 1 / 2 / 3 / 4 (median)[a,b] (continued):		
			Procedures in the 1st year (continued):		
	After 2 years	24 751			
		ND	Low volume: < 35	35.1	Reference category
		ND	High volume: ≥ 35	35.3	0.94 [0.87; 1.03]; ND
			Procedures in the 2nd year:		
	After 30 days	21 089	Low volume: < 35 or < 52	1332 (6.3)	Reference category
		3353	High volume: ≥ 35 and ≥ 52	169 (5.0)	0.82 [0.67; 0.99]; ND
	After 1 year	11 098			
		ND	Low volume: < 35 or < 52	22.4	Reference category
		ND	High volume: ≥ 35 and ≥ 52	19.1	0.85 [0.78; 0.92]; ND
	After 2 years	24 751			
		ND	Low volume: < 35 or < 52	34.0	Reference category
		ND	High volume: ≥ 35 and ≥ 52	31.1	0.88 [0.83; 0.93]; ND
Verma 2017	All-cause mortality after 30 days	181	Annual hospital volume:		No usable data
		21	Low volume: < 40	2 (9.5)	
		62	Moderate volume: 40–75	3 (4.8)	
		98	High volume: > 75	6 (6.1)	

a. "For the year periods being investigated, a hospital was determined to be high volume if the numbers of TAVR procedures it performed during these years were above the median (year 1 median, 35; year 2 median, 52; year 3 median, 84; and year 4 median, 137) for most of the time. For example, for analysis of procedures performed within 1 year after initiating TAVR programs, hospitals performing 35 TAVRs or more that year were considered to have a high TAVR volume. For analysis of procedures performed within 2 years after initiation of a TAVR program, hospitals performing 35 TAVRs or more in year 1 and 52 TAVRs or more in year 2 were considered to have a high TAVR volume. For analysis of the entire 4-year period, hospitals performing TAVR procedures above the median for at least 3 years were considered to have a high TAVR volume."

b. In the Mao 2018 study, there are discrepancies in the reporting of volume limits: > 35 and ≥ 35, > 52 and ≥ 52, > 84 and ≥ 84, > 137 and ≥ 137.

CI: confidence interval; N: number of included patients; n: number of patients with an event; ND: no data; TAVR: transcatheter aortic valve replacement

5.5.1.2 Results on the outcome of inpatient mortality

Four of the 8 included studies (Ando 2018, Kaier 2018, including the Oettinger 2020 and Nimptsch 2017 publications, Salemi 2019 as well as Vemulapalli 2019) reported usable results on the outcome of inpatient mortality (see Table 9). All studies had a low informative value of results.

Results on the hospital level

For inpatient mortality, the studies Ando 2018, Kaier 2018, including the Oettinger 2020 and Nimptsch 2017 publications, as well as Vemulapalli 2019 showed statistically significant differences in favour of high-volume hospitals.

Ando 2018 compared low-volume hospitals (reference category) with moderate-volume and high-volume hospitals (relative risk [RR]: 0.81; 95% CI: [0.68; 0.95]; p = 0.006; RR: 0.67; 95% CI: [0.54; 0.85]; p < 0.001). Each comparison revealed a statistically significant difference in favour of higher-volume hospitals.

The Kaier 2018 study is associated with 3 individual publications based on analyses of the German DRG data on TAVIs. The Oettinger 2020 publication supplemented the Kaier 2016 publication, which reported results for the period 2008 through 2014, by including results for 2015 through 2016. These two publications used identical inclusion criteria. The Nimptsch 2017 publication presented results for the period 2009 through 2014; its inclusion criteria differ slightly from Kaier 2018 and Oettinger 2020. For instance, the Kaier 2018 study conducted a continuous analysis of hospital volume for the years 2009 through 2014 [30]. This analysis showed a statistically significant reduction in the risk of inpatient mortality whenever the volume increased by 50 cases per year (odds ratio [OR]: 0.92; 95% CI: [0.89; 0.94]; p < 0.05). A volume increase by at least 157 cases annually (95% CI: [142; 171]) therefore prevents 1 death per 133 patients undergoing TAVI (95% CI: [101; 193]). The categorical analyses provided in the Kaier 2018 and Oettinger 2020 publications corroborate this result.

Vemulapalli 2019 conducted a continuous analysis of hospital volume for the outcome of inpatient mortality in patients treated via transfemoral access. For this outcome, the analysis showed a statistically significant result in favour of higher-volume hospitals (relative reduction of mortality between a hospital volume of 27 and 143: 19.45%; 95% CI: [8.63; 30.26]; p-value [for adj. association] = 0.009). A categorical analysis was conducted for patients who were treated via nontransfemoral access. For the outcome of inpatient mortality, Vemulapalli 2019 compared each low, moderate, and high-volume hospital with very high-volume hospitals (reference category). A statistically significant result was found only for the comparisons of the reference category with low-volume hospitals (OR: 1.65; 95% CI: [1.20; 2.27]; p-value: ND) and moderate-volume hospitals (OR: 1.37; 95% CI: [1.10; 1.70]; p-value: ND), each in favour of higher-volume hospitals.

Results on the operator level

Salemi 2019 compared hospitals performing low volumes of TAVI (reference category) with moderate-volume and high-volume hospitals. No statistically significant difference was found for the outcome of inpatient mortality; this result does not contradict the results of Vemulapalli 2019, however, since the ORs for the moderate and high-volume categories in Salemi 2019 are smaller than their reference value and decrease across volume categories. While this difference is not statistically significant, the Vemulapalli 2019 results discussed below do reach significance.

Vemulapalli 2019 continuously analysed operator volume for the outcome of inpatient mortality in patients treated via transfemoral access. For this outcome, the analysis showed a statistically significant result in favour of higher-volume operators (relative reduction of mortality between an operator volume of 11 and 70: 24.25 %; 95% CI: [10.40; 38.10]; p-value [for adj. association] = 0.009).

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of inpatient mortality

In summary, on the basis of 3 studies with low informative value of results, a correlation between hospital volume and quality of treatment outcome in favour of higher-volume hospitals was derived for the outcome of inpatient mortality. For the same outcome, 2 studies with low informative value of results allowed deriving a correlation between operator volume and quality of treatment outcome in favour of high operator volume. This outcome was not investigated on the level of the combined hospital-operator volume.

Table 9: Results – inpatient mortality (multipage table)

Study	Outcome definition	N	Volume specification	Mortality, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Ando 2018	Inpatient mortality	48 886	Annual hospital volume:		relative risk [95% CI]; p-value:
		10 407	Low volume: ≤ 30	445[b] (4.28)	Reference category
		28 811	Moderate volume: 31–130	925[b] (3.21)	0.81 [0.68; 0.95]; 0.006[d]
		9668	High volume: < 130[a]	229[b] (2.37) p = 0.006[c]	0.67 [0.54; 0.85]; < 0.001[d]
Kaier 2018[e]	Inpatient mortality				
			Nimptsch 2017		
			Median annual hospital volume (IQR):		
2009–2014		50 765	Very low volume (1st quintile): 31 (12–50)		Continuous analysis:
			Low volume (2nd quintile): 98 (69–123)		volume increase by 50 cases annually: 0.92[f] [0.89, 0.94][f]; < 0.05[f]
			Moderate volume (3rd quintile): 141 (99–161)		An increase in annual volume by at least 157 [142; 171] cases prevents 1 death per 133 [101; 193] patients undergoing TAVI
			High volume (4th quintile): 169 (142–228)		
			Very high volume (5th quintile): 286 (233–328)		
			Kaier 2018		
2008-2014		43 996	Annual hospital volume:	2532[b] (5.76)[b]	
		6451[b]	Low volume: < 50	506[b] (7.84)[b]	Reference category
		9360[b]	Moderate volume: 50–99	662[b] (7.07)[b]	0.989 [0.437; 2.241]; 0.98
		28 185[b]	High volume: ≥ 100	1364[b] (4.84)[b]	0.668 [0.506; 0.882]; 0.004
2008		613	Low volume: < 50	62[b] (10.11)	ND
		236	Moderate volume: 50–99	22[b] (9.32)	
		273	High volume: ≥ 100	18[b] (6.59)	

Table 9: Results – inpatient mortality (multipage table)

Study	Outcome definition	N	Volume specification	Mortality, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[e](continued)	Inpatient mortality (continued)				
			Kaier 2018 (continued)		
2009		1234	Low volume: < 50	121[b] (9.81)	ND
		658	Moderate volume: 50–99	55[b] (8.36)	
		707	High volume: ≥ 100	43[b] (6.08)	
			Annual hospital volume:		
2010		1155	Low volume: < 50	104[b] (9.00)	ND
		1875	Moderate volume: 50–99	152[b] (8.11)	
		1776	High volume: ≥ 100	109[b] (6.14)	
2011		1107	Low volume: < 50	85[b] (7.68)	ND
		1957	Moderate volume: 50–99	157[b] (8.02)	
		3459	High volume: ≥ 100	203[b] (5.87)	
2012		960	Low volume: < 50	59[b] (6.15)	ND
		1569	Moderate volume: 50–99	111[b] (7.07)	
		5711	High volume: ≥ 100	287[b] (5.03)	
2013		765	Low volume: < 50	42[b] (5.49)	ND
		1930	Moderate volume: 50–99	113[b] (5.85)	
		6452	High volume: ≥ 100	341[b] (5.29)	
2014		617	Low volume: < 50	33[b] (5.34)	ND
		1135	Moderate volume: 50–99	52[b] (4.58)	
		9807	High volume: ≥ 100	363[b] (3.70)	

Table 9: Results – inpatient mortality (multipage table)

Study	Outcome definition	N	Volume specification	Mortality, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[e] (continued)	Inpatient mortality (continued)				
			Oettinger 2020		
2008–2016		Total: 73 467			
2015–2016		29 470			
		587	Low volume: < 50	31[b] (5.28)[b]	Reference category
		28 883	High volume: ≥ 50	868[b] (3.01)[b]	0.62 [0.43; 0.90]; 0.012
			Annual hospital volume:		
2015		13 703[b]			ND
		382	Low volume: < 50	23[b] (6.02)	
		13 321	High volume: ≥ 50	470[b] (3.53)	
2016		15 767[b]			ND
		205	Low volume: < 50	8[b] (3.90)	
		15 562	High volume: ≥ 50	398[b] (2.56)	
			Nimptsch 2017		
2009–2014	**Inpatient mortality:** Death before hospital discharge	50 765		Observed relative frequency (%), 95% CI:	Adjusted relative frequency (%), 95% CI:
			Median annual hospital volume (IQR):		
		9915	Very low volume (1st quintile): 31 (12–50)	7.7 [ND]	7.6 [7.1; 8.2]
		10 009	Low volume (2nd quintile): 98 (69–123)	ND	ND
		9926	Moderate volume (3rd quintile): 141 (99–161)	ND	ND
		9935	High volume (4th quintile): 169 (142–228)	ND	ND

Table 9: Results – inpatient mortality (multipage table)

Study	Outcome definition	N	Volume specification	Mortality, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[e] (continued)					
			Nimptsch 2017 (continued)		
		10 980	Very high volume (5th quintile): 286 (233-328)	5.1 [ND]	5.2 [4.8; 5.7]
Salemi 2019	Inpatient mortality	All TAVI:	Annual operator volume:		
		2914	Low volume: < 24	ND	ND
		2922	Moderate volume: 24–79	ND	ND
		2935	High volume: ≥ 80	ND	ND
		Elective TAVI:			
		1973	Low volume: < 24	53 (2.7)	Reference category
		1860	Moderate volume: 24-79	32 (1.7)	0.69 [0.42; 1.13]; ND
		2083	High volume: ≥ 80	30 (1.4)	0.59 [0.32; 1.08]; ND
Vemulapalli 2019	Death within 30 days	Transfemoral approach–	Annual hospital volume, range:		**Continuous analysis** Relative reduction in mortality between a hospital volume of 27 and 143: 19.45% [8.63; 30.26], p-value (adjusted association) 0.009
		96 256		1643 (1.7)	
		6827	Low volume (1st quartile): 5-36	139 (2.0)	
		13 753	Moderate volume (2nd quartile): 37-54	265 (1.9)	
		22 799	High volume (3rd quartile): 55-85	400 (1.8)	
		52 877	Very high volume (4th quartile): 86-371	839 (1.6)	
		Nontransfemoral approach	Annual hospital volume, median (IQR):		
		8644		ND	
		ND	Low volume (1st quartile): 1 (0-2)	ND	1.65 [1.20; 2.27]; ND

Table 9: Results – inpatient mortality (multipage table)

Study	Outcome definition	N	Volume specification	Mortality, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Vemulapalli 2019 (continued)	30-day mortality (continued)	Transfemoral access	Annual operator volume (median):		
		ND	Moderate volume (2nd quartile): 3 (1–5)	ND	1.37 [1.10; 1.70]; ND
		ND	High volume (3rd quartile): 5 (3–8)	ND	1.19 [0.94; 1.49]; ND
		ND	Very high volume (4th quartile): 11 (7–16)	ND	Reference category
		Transfemoral access	Annual operator volume (median):		**Continuous analysis**
		ND	Low volume (1st quartile): 11	ND	Relative reduction in mortality between an operator volume of 11 and 70: 24.25 % [10.40; 38.10], p-value (adjusted association) = 0.009
		ND	Moderate volume (2nd quartile): ND	ND	
		ND	High volume (3rd quartile): ND	ND	
		ND	Very high volume (4th quartile): 70	ND	

a. There is a discrepancy in the text versus Table 1 of the publication regarding the limit of the high-volume category: ≥ 130 versus > 130.
b. IQWiG calculations.
c. p-value from chi square test.
d. "Statistical significance of the mortality rates and FTR rate differences between the hospital volume categories was determined in the contrast of the regression coefficients from the Poisson regression model. Subsequently, pairwise comparison was conducted with Bonferroni correction for multiple comparisons."
e. Since Oettinger 2020 and Kaier 2018 are based on identical data for the period 2008 through 2014, the present report uses Oettinger 2020 results for the period 2015 through 2016 only. The data pool of Nimptsch 2017 largely overlaps that of Kaier 2018; the investigation period of Kaier 2018 and Oettinger 2020 fully covers the investigation period of Nimptsch 2017.
f. Read off a graph (Figure 2).

CI: confidence interval; FTR: failure to rescue; IQR: interquartile range; N: number of included patients; n: number of patients with an event; ND: no data; TAVI: transcatheter aortic valve implantation

5.5.2 Morbidity

5.5.2.1 Adverse effects of therapy including failure to rescue and complications overall

One of the 8 included studies provided usable results on the outcome of adverse effects of therapy including failure to rescue and complications overall (see Table 10) [27]. The study has a low informative value of results.

Results on the hospital level

Ando 2018 showed no statistically significant difference for either component of the outcome of adverse effects of therapy including failure to rescue and complications overall.

Results on the operator level

For the outcome of adverse effects of therapy including failure to rescue and complications overall, the relationship between volume and quality of treatment outcome was not investigated on the operator level.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of adverse effects of therapy including failure to rescue and complications overall

In summary, on the basis of 1 study with low informative value of results, no correlation between hospital volume and quality of treatment outcome was found for the outcome of adverse effects of therapy including failure to rescue and complications overall. The relationship between operator volume or the combined hospital-operator volume and this outcome was not investigated.

Table 10: Results – Adverse effects of therapy including failure to rescue and complications overall

Study	Outcome definition	N	Volume specification	Complications overall, raw n (%); p-value	Adjusted rate [95% CI]; p-value
Ando 2018	**Failure to rescue:** Inpatient mortality after at least one severe complication	10 849[c]	Annual hospital volume:		
		ND	Low volume: ≤ 30	ND (13.59)	8.24 [3.39; 20.03]
		ND	Moderate volume: 31–130	ND (12.88)	8.20 [3.45; 19.52]
		ND	High volume: < 130[a]	ND (8.87); 0.084	6.12 [2.37; 15.81]; 0.291
	Complications overall	48 886	Annual hospital volume:		
		10 407	Low volume: ≤ 30	2576[b] (24.75)	27.04 [ND]
		28 811	Moderate volume: 31–130	6249[b] (21.69)	23.70 [ND]
		9668	High volume: < 130[a]	2023[b] (20.92); 0.058	23.13 [ND]; 0.063

a. There is a discrepancy in the text versus Table 1 of the publication regarding the limit of the high-volume category: ≥ 130 versus > 130.
b. IQWiG calculations.
c. Since only patients with severe complications after TAVI were included, it remains unclear how many patients were analysed in the individual volume categories for this outcome.
CI: confidence interval; N: number of included patients; n: number of patients with an event; ND: no data; TAVI: transcatheter aortic valve implantation

5.5.2.2 Dialysis-dependent renal failure

One of 8 included studies (Verma 2017) considered the outcome of dialysis-dependent renal failure on the hospital level (see Table 11). The study has a low informative value of results and provides no usable data.

Results on the hospital level

Verma 2017 reported only raw event rates; therefore, no conclusion can be drawn on the relationship between hospital volume and quality of treatment outcome.

Results on the operator level

For the outcome of dialysis-dependent renal failure, the relationship between volume and quality of treatment outcome was not investigated on the operator level.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of dialysis-dependent renal failure

In summary, on the basis of 1 study without usable data, it was not possible to draw any conclusions on the relationship between hospital or operator volume and quality of the treatment outcome for the outcome of dialysis-dependent renal failure. This outcome was not investigated on the level of the combined hospital-operator volume.

Table 11: Results – Dialysis-dependent renal failure

Study	Outcome definition	N	Volume specification	Dialysis dependence after TAVR, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Verma 2017	Dialysis dependence after TAVR	181	Annual hospital volume:		No usable data
		21	Low volume: < 40	4 (19.1)	
		62	Moderate volume: 40–75	5 (8.1)	
		98	High volume: > 75	12 (12.2)	
CI: confidence interval; N: number of included patients; n: number of patients with an event; TAVR: transcatheter aortic valve replacement					

5.5.2.3 Stroke

Four of the 8 included studies (Kaier 2018, including the Oettinger 2020 publication, Salemi 2019, Vemulapalli 2019, and Verma 2017) reported results on the outcome of stroke (see Table 12). All studies had a low informative value of results. Vemulapalli 2019 and Verma 2017 did not provide any usable data.

Results on the hospital level

The Kaier 2018 study showed no statistically significant difference for the outcome of stroke.

Results on the operator level

Salemi 2019 investigated the outcome of stroke on the operator level for the subpopulation of patients with elective TAVI. It showed no statistically significant difference.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of stroke

In summary, on the basis of 1 study with low informative value of results, no correlation between hospital volume and quality of treatment outcome was derived for the outcome of stroke. Furthermore, on the basis of 1 study with low informative value of results, no correlation between operator volume and quality of treatment outcome was derived for this outcome. This outcome was not investigated on the level of the combined hospital-operator volume.

Table 12: Results – Stroke (multipage table)

Study	Outcome definition	N	Volume specification	Stroke, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[a]	Stroke				
			Kaier 2018		
			Annual hospital volume:		
2008–2014		43 996		1086[b] (2.47)[b]	
		6451[b]	Low volume: < 50	174[b] (2.70)[b]	Reference category
		9360[b]	Moderate volume: 50–99	229[b] (2.45)[b]	0.929 [0.339; 2.547]; 0.886
		28185[b]	High volume: ≥ 100	683[b] (2.42)[b]	0.969 [0.398; 2.363]; 0.945
2008		613	Low volume: < 50	20[b] (3.26)	ND
		236	Moderate volume: 50–99	5[b] (2.12)	
		273	High volume: ≥ 100	7[b] (2.56)	
2009		1234	Low volume: < 50	44[b] (3.57)	
		658	Moderate volume: 50–99	22[b] (3.34)	
		707	High volume: ≥ 100	15[b] (2.12)	
2010		1155	Low volume: < 50	29[b] (2.51)	
		1875	Moderate volume: 50–99	48[b] (2.56)	
		1776	High volume: ≥ 100	39[b] (2.20)	
2011		1107	Low volume: < 50	26[b] (2.35)	
		1957	Moderate volume: 50–99	46[b] (2.35)	
		3459	High volume: ≥ 100	104[b] (3.01)	
2012		960	Low volume: < 50	22[b] (2.29)	
		1569	Moderate volume: 50–99	38[b] (2.42)	
		5711	High volume: ≥ 100	120[b] (2.10)	
2013		765	Low volume: < 50	16[b] (2.09)	
		1930	Moderate volume: 50–99	45[b] (2.33)	
		6452	High volume: ≥ 100	174[b] (2.70)	

Table 12: Results – Stroke (multipage table)

Study	Outcome definition	N	Volume specification	Stroke, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[a] (continued)	Stroke (continued)		Annual hospital volume:		
2014		617	Low volume: < 50	17[b] (2.75)	
		1135	Moderate volume: 50–99	25[b] (2.20)	
		9807	High volume: ≥ 100	224[b] (2.28)	
			Oettinger 2020		
			Annual hospital volume:		
2008-2016		73 467		1763 [b,c] (2.40)	ND
		7039	Low volume: < 50	186[b] (2.64)	
		66 428	High volume: ≥ 50	1574[b] (2.37)	
2015-2016		29 470		676[b] (2.29)[b]	
		587	Low volume: < 50	12[b] (2.04)[b]	Reference category
		28 883	High volume: ≥ 50	664[b] (2.30)[b]	1.32 [0.74; 2.34]; 0.346
2015		Total: 13 703[a]		336[b] (2.45)[b]	ND
		382	Low volume: < 50	11[b] (2.88)	
		13 321	High volume: ≥ 50	325[b] (2.44)	
2016		Total: 15 767[a]		341[b,d] (2.16)[b]	ND
		205	Low volume: < 50	1[b] (0.49)	
		15 562	High volume: ≥ 50	339[b] (2.18)	

Table 12: Results – Stroke (multipage table)

Study	Outcome definition	N	Volume specification	Stroke, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Salemi 2019	Stroke		Annual operator volume:		
		All TAVI:			
		2914	Low volume: < 24	ND	ND
		2922	Moderate volume: 24–79	ND	ND
		2935	High volume: ≥ 80	ND	ND
		Elective TAVI:	Annual operator volume:		
		1973	Low volume: < 24	29 (1.5)	Reference category
		1860	Moderate volume: 24–79	37 (2.0)	1.11 [0.63; 1.95]; ND
		2083	High volume: ≥ 80	28 (1.3)	0.62 [0.30; 1.30]; ND
Vemulapalli 2019	Stroke		Annual hospital volume:		No usable data
		96 256		2093 (2.2)	
		6827	Low volume (1st quartile): 5–36	153 (2.2)	
		13 753	Intermediate volume (2nd quartile): 37-54	303 (2.2)	
		22 799	High volume (3rd quartile): 55–85	524 (2.3)	
		52 877	Very high volume (4th quartile): 86–371	1113 (2.1)	
			Annual operator volume:		
		ND	Low volume (1st quartile): Mean: 11	ND	
		ND	Moderate volume (2nd quartile): ND	ND	
		ND	High volume (3rd quartile): ND	ND	
		ND	Very high volume (4th quartile): Mean: 70	ND	
Verma 2017	Cerebrovascular event / transient ischaemic attack following TAVR	181	Annual hospital volume:		No usable data
		21	Low volume: < 40	1 (4.8)	
		62	Moderate volume: 40–75	2 (3.2)	
		98	High volume: > 75	2 (2.0)	

Table 12: Results – Stroke (multipage table)

Study	Outcome definition	N	Volume specification	Stroke, raw n (%)	Adjusted odds ratio [95% CI]; p-value
a. Since Oettinger 2020 and Kaier 2018 are based on identical data for the period 2008 through 2014, the present report includes Oettinger 2020 results for the period 2015 through 2016 only. The data pool of Nimptsch 2017 largely overlaps that of Kaier 2018; the investigation period of Kaier 2018 and Oettinger 2020 fully covers the investigation period of Nimptsch 2017. b. IQWiG calculations. c. Discrepancy by 3 cases. d. Discrepancy by 1 case. CI: confidence interval; N: number of included patients; n: number of patients with an event; ND: no data; TAVI: transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement					

5.5.2.4 Bleeding

Two of the 8 included studies (Kaier 2018, including the Oettinger 2020 publication, and Vemulapalli 2019) reported results on the outcome of bleeding (see Table 13). All studies had a low informative value of results.

Results on the hospital level

For the outcome of bleeding, Kaier 2018 and Vemulapalli 2019 demonstrated statistically significant differences in favour of high-volume hospitals.

For the period 2008 through 2014, Kaier 2018 compared low-volume hospitals (reference category) with moderate-volume and high-volume hospitals (OR: 0.485; 95% CI: [0.291; 0.811]; p-value = 0.006) [28]. For the outcome of bleeding, this resulted in a statistically significant difference in favour of higher-volume hospitals for the 2008 through 2014 period. In the Oettinger 2020 publication of the Kaier 2018 study, low-volume hospitals (reference category) were compared with high-volume hospitals for the 2015 through 2016 period. No statistically significant difference was shown.

For the outcome of severe or life-threatening bleeding, Vemulapalli 2019 compared low-volume, moderate-volume, and high-volume hospitals each with very high-volume hospitals (reference category) (OR: 1.25; 95% CI: [1.08; 1.45]; p-value: ND); the difference between low-volume and very high-volume hospitals was the only one to be statistically significant, but a trend in favour of higher volumes was identifiable across all comparisons. This means that the ORs for the volume categories compared with the reference value (very high volume) increase from one volume category to the next, but the 95% CIs include the indifference value.

Results on the operator level

For the outcome of bleeding, the relationship between volume and quality of treatment outcome was not investigated.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of bleeding

In summary, on the basis of 2 studies with low informative value of results, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher-volume hospitals for the outcome of bleeding. The relationship between operator volume or the combined hospital-operator volume and this outcome was not investigated.

Table 13: Results – Bleeding (multipage table)

Study	Outcome definition	N	Volume specification	Bleeding, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[a]	**Bleeding**: Need for transfusion of ≥ 5 units of red blood cell concentrates		Kaier 2018		
			Annual hospital volume:		
2008–2014		6451[b]	Low volume: < 50	696[b] (10.79)[b]	Reference category
		9360[b]	Moderate volume: 50–99	815[b] (8.71)[b]	0.806 [0.506; 1.286]; 0.366
		28185[b]	High volume: ≥ 100	1664[b] (5.90)[b]	0.485 [0.291; 0.811]; 0.006
		43 996		3175[b] (7.22)[b]	
2008		613	Low volume: < 50	88[b] (14.36)	ND
		236	Moderate volume: 50–99	27[b] (11.44)	
		273	High volume: ≥ 100	20[b] (7.33)	
2009		1234	Low volume: < 50	175[b] (14.18)	ND
		658	Moderate volume: 50–99	74[b] (11.25)	
		707	High volume: ≥ 100	51[b] (7.21)	
2010		1155	Low volume: < 50	140[b] (12.12)	ND
		1875	Moderate volume: 50–99	214[b] (11.41)	
		1776	High volume: ≥ 100	111[b] (6.25)	
2011		1107	Low volume: < 50	104[b] (9.39)	ND
		1957	Moderate volume: 50–99	177[b] (9.04)	
		3459	High volume: ≥ 100	322[b] (9.31)	
2012		960	Low volume: < 50	81[b] (8.44)	ND
		1569	Moderate volume: 50–99	132[b] (8.41)	
		5711	High volume: ≥ 100	360[b] (6.30)	
2013		765	Low volume: < 50	71[b] (9.28)	ND
		1930	Moderate volume: 50–99	126[b] (6.53)	
		6452	High volume: ≥ 100	386[b] (5.98)	
2014		617	Low volume: < 50	37[b] (5.99)	ND
		1135	Moderate volume: 50–99	65[b] (5.73)	

Table 13: Results – Bleeding (multipage table)

Study	Outcome definition	N	Volume specification	Bleeding, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[e] (continued)	Bleeding (continued)				
			Kaier 2018 (continued)		
			Annual hospital volume:		
2014		9807	High volume: ≥ 100	414[b] (4.22)	
			Oettinger 2020		
2008–2016	**Bleeding**: Need for transfusion of ≥ 5 units of red blood cell concentrates	73 467		4202 [b,c] (5.72)	ND
		7039	Low volume: < 50	719[b] (10.21)	
		66 428	High volume: ≥ 50	3487[b] (5.25)	
2015–2016		29 470			
		587	Low volume: < 50	23[b] (3.92)[b]	Reference category
		28 883	High volume: ≥ 50	1007[b] (3.49)[b]	0.90 [0.59; 1.37]; 0.633
2015		13 703[e]		539[b] (3.93)	ND
		382	Low volume: < 50	14[b] (3.66)	
		13 321	High volume: ≥ 50	525[b] (3.94)	
2016		15 767[e]		490[b] (3.11)	ND
		205	Low volume: < 50	9[b] (4.39)	
		15 562	High volume: ≥ 50	482[b] (3.10)	

Table 13: Results – Bleeding (multipage table)

Study	Outcome definition	N	Volume specification	Bleeding, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Vemulapalli 2019	**Bleeding:**		Annual hospital volume, range:		
	severe bleeding	96 256		3796 (4.0)	ND
		6827	Low volume (1st quartile): 5–36	330 (4.9)	
			Moderate volume (2nd quartile): 37–54	571 (4.2)	
			High volume (3rd quartile): 55–85	941 (4.2)	
	Bleeding:		Annual hospital volume, range:		
	severe bleeding (continued)		Very high volume (4th quartile): 86-371	1954 (3.8)	
	Life-threatening bleeding	96 256		2024 (2.1)	ND
		6827	Low volume (1st quartile): 5–36	179 (2.6)	
		13 753	Moderate volume (2nd quartile): 37–54	323 (2.4)	
		22 799	High volume (3rd quartile): 55–85	502 (2.2)	
		52 877	Very high volume (4th quartile): 86–371	1020 (2.0)	
	Severe or life-threatening bleeding	96 256		5727 (5.9)	
		6827	Low volume (1st quartile): 5–36	514 (7.5)	1.25 [1.08; 1.45]; ND
		13 753	Moderate volume (2nd quartile): 37–54	903 (6.6)	1.12 [0.98; 1.28]; ND
		22 799	High volume (3rd quartile): 55–85	1400 (6.1)	1.06 [0.94; 1.21]; ND
		52 877	Very high volume (4th quartile): 86–371	2910 (5.5)	Reference category

a. Since Oettinger 2020 and Kaier 2018 are based on identical data for the period 2008 through 2014, the present report includes Oettinger 2020 results for the period 2015 through 2016 only. The data pool of Nimptsch 2017 largely overlaps that of Kaier 2018; the investigation period of Kaier 2018 and Oettinger 2020 fully covers the investigation period of Nimptsch 2017.
b. IQWiG calculations.
c. Rounding error.
CI: confidence interval; N: number of included patients; n: number of patients with an event; ND: no data

5.5.2.5 Vascular complications including leaks and myocardial infarctions

One of the 8 included studies (Vemulapalli 2019) reported results on the outcome of vascular complications including leaks and myocardial infarctions (see Table 14). In clinical routine, these complications are evaluated separately. In this report, however, they were combined because the component of myocardial infarction was not analysed separately by any of the included studies (also see footnote on Salemi 2019 in Table 3). The study had a low informative value of results. Vemulapalli 2019 provided no usable data for this outcome; therefore, no conclusion can be drawn on the relationship between volume and quality of treatment outcome.

Table 14: Results – Vascular complications including leaks and myocardial infarctions

Study	Outcome definition	N	Volume specification	Vascular complications, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Vemulapalli 2019	**Vascular complications:**		Annual hospital volume:		No usable data
	Moderate and severe paravalvular leaks	96 256		2630 (2.7)	
		6827	Low volume (1st quartile): 5–36	169 (2.5)	
		13 753	Moderate volume (2nd quartile): 37–54	340 (2.5)	
		22 799	High volume (3rd quartile): 55–85	639 (2.8)	
		52 877	Very high volume: 86–371	1482 (2.8)	
	Vascular access site complications requiring treatment	96 256		3945 (4.1)	
		6827	Low volume (1st quartile): 5–36	272 (4.0)	
		13 753	Moderate volume (2nd quartile): 37–54	533 (3.9)	
		22 799	High volume (3rd quartile): 55–85	992 (4.4)	
		52 877	Very high volume: 86–371	2148 (4.1)	
CI: confidence interval; N: number of included patients; n: number of patients with an event; ND: no data					

5.5.2.6 Pacemaker implantation

Two of the 8 included studies (Oettinger 2018 publication of the Kaier 2018 study as well as Verma 2017) reported results on the outcome of pacemaker implantation (see Table 15). All studies had a low informative value of results. Verma 2017 did not provide any usable data.

Results on the hospital level

The Oettinger 2020 publication of the Kaier 2018 study showed no statistically significant difference for the outcome of pacemaker implantation.

Results on the operator level

For the outcome of pacemaker implantation, the relationship between volume and quality of treatment outcome was not investigated on the operator level.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of pacemaker implantation

In summary, on the basis of 1 study with low informative value of results, no correlation between hospital volume and quality of treatment outcome was derived for the outcome of pacemaker implantation. The relationship between operator volume or the combined hospital-operator volume and this outcome was not investigated.

Table 15: Results – Pacemaker implantation

Study	Outcome definition	N	Volume specification	Pacemaker implantation after TAVI, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[a]	Pacemaker implantation	29 470			
			Oettinger 2020		
			Annual hospital volume:		
2015–2016		587	Low volume: < 50	101[b] (17.21)[b]	Reference category
		28 883	High volume: ≥ 50	4131[b] (14.30)[b]	0.82 [0.63; 1.07]; 0.142[c]
2015		13 703[b]		2046[b] (14.93)	ND
		382	Low volume: < 50	73[b] (19.11)	
		13 321	High volume: ≥ 50	1973[b] (14.81)	
2016		15 767[b]		2185[b] (13.86)	ND
		205	Low volume: < 50	28[b] (13.66)	
		15 562	High volume: ≥ 50	2158[b] (13.87)	
Verma 2017	Pacemaker implantation following TAVR	181	Annual hospital volume:		No usable data
		21	Low volume: < 40	4 (19.1)	
		62	Moderate volume: 40–75	9 (14.5)	
		98	High volume: > 75	13 (13.3)	

a. Since Oettinger 2020 and Kaier 2018 are based on identical data for the period 2008 through 2014, the present report includes Oettinger 2020 results for the period 2015 through 2016 only. The data pool of Nimptsch 2017 largely overlaps that of Kaier 2018; the investigation period of Kaier 2018 and Oettinger 2020 fully covers the investigation period of Nimptsch 2017.
b. IQWiG calculations.
c. This OR is based on the comparison of high-volume hospitals versus low-volume hospitals in the period 2015 through 2016.
CI: confidence interval; N: number of included patients; n: number of patients with an event; ND: no data; OR: odds ratio; TAVI: transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement

5.5.2.7 Ventilation > 48 hours

One of the 8 included studies (Kaier 2018) reported results on the outcome of ventilation > 48 hours (see Table 16) [28]. The study had a low informative value of results.

Results on the hospital level

Kaier 2018 demonstrated a statistically significant difference in favour of higher-volume hospitals for the outcome of ventilation > 48 hours.

For the period 2008 through 2014, the Kaier 2018 study compared low-volume hospitals (reference category) with moderate-volume and high-volume hospitals [28]. No statistically significant difference was shown for the comparison of low-volume versus moderate-volume hospitals. However, for the comparison of low-volume versus high-volume hospitals, a statistically significant difference in favour of higher-volume hospitals was shown for the outcome of ventilation > 48 hours (OR: 0.492; 95% CI: [0.263; 0.918]; $p < 0.026$).

Results on the operator level

For the outcome of ventilation > 48 hours, the relationship between volume and quality of treatment outcome was not investigated on the operator level.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of ventilation > 48 hours

In summary, on the basis of 1 study with low informative value of results, a correlation between hospital volume and quality of treatment outcome in favour of higher-volume hospitals was derived for the outcome of ventilation > 48 hours. The relationship between operator volume or the combined hospital-operator volume and this outcome was not investigated.

Table 16: Results – Ventilation > 48 hours (multipage table)

Study	Outcome definition	N	Volume specification	Ventilation > 48 hours, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[a]	Ventilation > 48 hours	43 996		2578[b] (5.86)[b]	
				Kaier 2018	
			Annual hospital volume:		
2008–2014		6451[a]	Low volume: < 50	528[b] (8.18)[b]	Reference category
		9360[a]	Moderate volume: 50–99	611[b] (6.53)[b]	0.716 [0.400; 1.283]; 0.262
		28 185[a]	High volume: ≥ 100	1439[b] (5.11)[b]	0.492 [0.263; 0.918]; 0.026
2008		613	Low volume: < 50	60[b] (9.79)	
		236	Moderate volume: 50–99	16[b] (6.78)	
		273	High volume: ≥ 100	13[b] (4.76)	
2009		1234	Low volume: < 50	117[b] (9.48)	
		658	Moderate volume: 50–99	47[b] (7.14)	
		707	High volume: ≥ 100	52[b] (7.36)	
2010		1155	Low volume: < 50	101[b] (8.74)	
		1875	Moderate volume: 50–99	163[b] (8.69)	
		1776	High volume: ≥ 100	89[b] (5.01)	
2011		1107	Low volume: < 50	89[b] (8.04)	
		1957	Moderate volume: 50–99	162[b] (8.28)	
		3459	High volume: ≥ 100	252[b] (7.29)	
2012		960	Low volume: < 50	70[b] (7.29)	
		1569	Moderate volume: 50–99	86[b] (5.48)	
		5711	High volume: ≥ 100	308[b] (5.39)	

Table 16: Results – Ventilation > 48 hours (multipage table)

Study	Outcome definition	N	Volume specification	Ventilation > 48 hours, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Kaier 2018[a] (continued)	Ventilation > 48 hours (continued)				
				Kaier 2018	
			Annual hospital volume:		
2013		765	Low volume: < 50	53[b] (6.93)	
		1930	Moderate volume: 50–99	88[b] (4.56	
		6452	High volume: ≥ 100	341[b] (5.29)	
2014		617	Low volume: < 50	38[b] (6.15)	
		1135	Moderate volume: 50–99	49[b] (4.32)	
		9807	High volume: ≥ 100	384[b] (3.92)	

a. Since Oettinger 2020 and Kaier 2018 are based on identical data for the period 2008 through 2014, the present report includes Oettinger 2020 results for the period 2015 through 2016 only. The data pool of Nimptsch 2017 largely overlaps that of Kaier 2018; the investigation period of Kaier 2018 and Oettinger 2020 fully covers the investigation period of Nimptsch 2017.
b. IQWiG calculations.
CI: confidence interval; N: number of included patients; n: number of patients with an event

5.5.3 Results on the outcome of health-related quality of life, including activities of daily living and dependence on help from others

The included studies did not report any data on the outcome of health-related quality of life.

5.5.4 Length of hospital stay

Two of the 8 included studies (Kaier 2018 and Khera 2017) reported results on the outcome of length of hospital stay (see Table 17). All studies had a low informative value of results. The Khera 2017 study did not provide any usable data.

Results on the hospital level

For the period 2008 through 2014, the Kaier 2018 study compared low-volume hospitals with moderate-volume and high-volume hospitals regarding the outcome length of hospital stay [28]. The presented coefficients did not yield a consistent direction regarding the change in length of hospital stay. For the comparison of low-volume versus moderate-volume hospitals, a statistically significant difference to the disadvantage of moderate-volume hospitals was shown. In contrast, for the same outcome, the comparison of low-volume versus high-volume hospitals showed a statistically significant difference in favour of higher-volume hospitals.

Results on the operator level

For the outcome of length of hospital stay, the relationship between volume and quality of treatment outcome was not investigated on the operator level.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of length of hospital stay

In summary, on the basis of 1 study of low informative value of results, no consistent (monotonically decreasing) relationship between hospital volume and quality of treatment outcome was found for the outcome of length of hospital stay when comparing low-volume hospitals with moderate-volume and high-volume hospitals. The relationship between operator volume or the combined hospital-operator volume and this outcome was not investigated.

Table 17: Results – Length of hospital stay (multipage table)

Study	Outcome definition	N	Volume specification	Length of hospital stay in days, raw mean (SD)	Regression coefficient [95 % CI]; p-value
Kaier 2018[a]	Length of hospital stay				
			Kaier 2018		
			Annual hospital volume:		
		43 996		ND	
2008–2014		6451[b]	Low volume: < 50	ND	0
		9360[b]	Moderate volume: 50–99	ND	2.959 [1.133; 4.786]; 0.001
		28 185[b]	High volume: ≥ 100	ND	−4.148 [−5.574; −2.721]; < 0.001
2008		613	Low volume: < 50	19.2 (ND)	
		236	Moderate volume: 50–99	21.8 (ND)	
		273	High volume: ≥ 100	14.7 (ND)	
2009		1234	Low volume: < 50	21.6 (ND)	
		658	Moderate volume: 50–99	18.5 (ND)	
		707	High volume: ≥ 100	18.0 (ND)	
2010		1155	Low volume: < 50	21.0 (ND)	
		1875	Moderate volume: 50–99	19.1 (ND)	
		1776	High volume: ≥ 100	17.0 (ND)	
2011		1107	Low volume: < 50	20.0 (ND)	
		1957	Moderate volume: 50–99	19.3 (ND)	
		3459	High volume: ≥ 100	17.3 (ND)	
2012		960	Low volume: < 50	18.7 (ND)	
		1569	Moderate volume: 50–99	18.9 (ND)	
		5711	High volume: ≥ 100	16.7 (ND)	

Table 17: Results – Length of hospital stay (multipage table)

Study	Outcome definition	N	Volume specification	Length of hospital stay in days, raw mean (SD)	Regression coefficient [95 % CI]; p-value
Kaier 2018 (continued)[a]	Length of hospital stay (continued)				
			Kaier 2018 (continued)		
			Annual hospital volume:		
2013		765	Low volume: < 50	20.2 (ND)	
		1930	Moderate volume: 50–99	18.2 (ND)	
		6452	High volume: ≥ 100	16.3 (ND)	
2014		617	Low volume: < 50	19.9 (ND)	
		1135	Moderate volume: 50–99	18.3 (ND)	
		9807	High volume: ≥ 100	15.3 (ND)	
Khera 2017	Length of hospital stay	16 252	Annual hospital volume:		No usable data
		663	▪ Low volume: < 50	5.5 (5.0)	
		3067	▪ Moderate volume: ≥ 50 < 100	5.9 (7.5)	
		12 522	High volume: ≥ 100	6.0 (5.8)	
				p = 0.74	

a. Since Oettinger 2020 and Kaier 2018 are based on identical data for the period 2008 through 2014, the present report includes Oettinger 2020 results for the period 2015 through 2016 only. The data pool of Nimptsch 2017 largely overlaps that of Kaier 2018; the investigation period of Kaier 2018 and Oettinger 2020 fully covers the investigation period of Nimptsch 2017.
b. IQWiG calculations.

CI: confidence interval; N: number of included patients; n: number of patients with an event; ND: no data; SD: standard deviation

5.5.5 Results on further outcomes

5.5.5.1 Hospital readmission

Three of the 8 included studies (Khera 2017, Mao 2018, and Verma 2017) reported results on the outcome of hospital readmission (see Table 18). All studies had a low informative value of results. Verma 2017 did not provide any usable data.

Results on the hospital level

The Kaier 2017 and Mao 2018 studies demonstrated statistically significant differences in favour of higher-volume hospitals for the outcome of hospital readmission (within 30 days after a procedure).

Khera 2017 compared low-volume hospitals (reference category) with moderate-volume and high-volume hospitals. The latter difference was statistically significant in favour of higher-volume hospitals (OR: 0.75; 95% CI: [0.60; 0.92]; p-value = 0.007). The comparison of moderate-volume versus high-volume hospitals resulted in a statistically significant difference in favour of higher-volume hospitals (OR: 0.76; 95% CI: [0.68; 0.85]; p-value: ND).

Mao 2018 compared low-volume hospitals (reference category) with high-volume hospitals (OR: 0.91; 95% CI: [0.84; 0.98]; p-value: ND). The difference was statistically significant in favour of higher-volume hospitals.

Results on the operator level

For the outcome of hospital readmission, the relationship between volume and quality of treatment outcome was not investigated on the operator level.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of hospital readmission

In summary, on the basis of 2 studies with low informative value of results, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher-volume hospitals for the outcome of hospital readmission. The relationship between operator volume or the combined hospital-operator volume and this outcome was not investigated.

Table 18: Results – Hospital readmission (multipage table)

Study	Outcome definition	N	Volume specification	Hospital readmission, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Khera 2017	Hospital readmission within 30 days after the procedure	16 252	Annual hospital volume:	2668[a] (16.4)	
		663	Low volume: < 50	129 (19.5)	Reference category
		3067	Moderate volume: ≥ 50 to < 100	582 (19.0)	0.98 [0.78; 1.23]; n.s.
		12 522	High volume: ≥ 100	1957 (15.6)	0.75 [0.60; 0.92]; 0.007
		3067	Moderate volume: ≥ 50 to < 100	582 (19.0)	Reference category
		12 522	High volume: ≥ 100	1957 (15.6)	0.76 [0.68; 0.85]; ND
				Days to readmission, median (IQR): 9 (5–17)	
Mao 2018	Hospital readmission within 30 days after the procedure		Annual hospital volume[b,c]:		
			Procedures across all years:		
		30 584	Low volume: < 137 or < median in a further year	7175 (23.5)	Reference category
		27 753	High volume: ≥ 137 and ≥ median (35 / 52 / 83) in at least 2 further consecutive years	5912 (21.3)	0.91 [0.84; 0.98]; ND
			Procedures in the 1st year:		
		5383	Low volume: < 35	1376 (25.6)	Reference category
		5577	High volume: ≥ 35	1505 (26.9)	1.04 [0.93; 1.17]; ND
			Procedures in the 2nd year:		
		21089	Low volume: < 35 or < 52	5293 (25.1)	Reference category
		3353	High volume: ≥ 35 and ≥ 52	845 (25.2)	0.99 [0.88; 1.13]; ND
Verma 2017	Hospital readmission within 30 days after the procedure, any cause	181	Annual hospital volume:		No usable data
		21	Low volume: < 40	10 (47.6)	
		62	Moderate volume: 40–75	20 (32.3)	
		98	High volume: > 75	9 (9.2)	
	Hospital readmission within 30 days after the procedure, cardiac cause	21	Low volume: < 40	9 (42.9)	
		62	Moderate volume: 40–75	16 (25.8)	
		98	High volume: > 75	6 (6.12)	

Table 18: Results – Hospital readmission (multipage table)

Study	Outcome definition	N	Volume specification	Hospital readmission, raw n (%)	Adjusted odds ratio [95% CI]; p-value

a. IQWiG calculations.
b. "For the year periods being investigated, a hospital was determined to be high volume if the numbers of TAVR procedures it performed during these years were above the median (year 1 median, 35; year 2 median, 52; year 3 median, 84; and year 4 median, 137) for most of the time. For example, for analysis of procedures performed within 1 year after initiating TAVR programs, hospitals performing 35 TAVRs or more that year were considered to have a high TAVR volume. For analysis of procedures performed within 2 years after initiation of a TAVR program, hospitals performing 35 TAVRs or more in year 1 and 52 TAVRs or more in year 2 were considered to have a high TAVR volume. For analysis of the entire 4-year period, hospitals performing TAVR procedures above the median for at least 3 years were considered to have a high TAVR volume."
c. In the Mao 2018 study, there are discrepancies in the reporting of volume limits: > 35 and ≥ 35, > 52 and ≥ 52, > 84 and ≥ 84, > 137 and ≥ 137.

CI: confidence interval; IQR: interquartile range; N: number of included patients; n: number of patients with an event; ND: no data; n.s.: not significant; TAVR: transcatheter aortic valve replacement

5.5.5.2 Conversion to surgery / abort of TAVI

Two of the 8 included studies (Rymer 2019 and Vemulapalli 2019) reported results on the outcome of conversion to surgery / abort of TAVI (see Table 19). All studies had a low informative value of results. Vemulapalli 2019 provided no usable data; therefore, no conclusion can be drawn on the relationship between volume and the "conversion to surgery" component of this outcome.

Results on the hospital level

Rymer 2019 demonstrated a statistically significant difference in favour of higher-volume hospitals for the abort-of-TAVI component.

In Rymer 2019, very-high-volume hospitals (reference category) were compared with low-volume, moderate-volume, and high-volume hospitals for the period 2011 through 2017 (OR: 2.12; 95% CI: [1.45; 3.12]; OR: 1.87; 95% CI: [1.37; 2.54]; OR: 1.69; 95% CI: [1.22; 2.33]; p-value < 0.01). For each comparison, the difference was statistically significant in favour of higher-volume hospitals. Further, no statistically significant difference was found for the period 2015 through 2017 in a subgroup analysis of patients who were treated exclusively via transfemoral access.

Results on the operator level

For the outcome of conversion to surgery / abort of TAVI, the relationship between volume and quality of treatment outcome was not investigated on the operator level.

Results on the level of the combined hospital-operator volume

For this outcome, the relationship between volume and quality of treatment outcome was not investigated on the level of the combined hospital-operator volume.

Summary on the outcome of conversion to surgery / aborted TAVI

In summary, on the basis of 1 study with low informative value of results, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher-volume hospitals for the abort-of-TAVI component of the outcome: conversion to surgery / abort of TAVI. The relationship between operator volume or the combined hospital-operator volume and this outcome was not investigated.

Table 19: Results – Conversion to surgery / aborted TAVI (multipage table)

Study	Outcome definition	N	Volume specification	Conversion to open-heart surgery / aborted TAVR, raw n (%)	Adjusted odds ratio [95% CI]; p-value
Rymer 2019	Aborted TAVI	106 169	Hospital volume from 11/2011 up to the intervention in question[a]:		
2011–2017		Total		1150 (1.1)	
		ND	Low volume: 1–99	ND	2.12 [1.45; 3.12]; ND
		ND	Moderate volume: 100–299	ND	1.87; [1.37; 2.54]; ND
		ND	High volume: 300–599	ND	1.69; [1.22; 2.33]; ND
		ND	Very high volume: > 600[b]	ND	Reference category
					P < 0.01[c]
2015–2017		Only patients with a transfemoral access			
		85 986		410 (0.5)	
			Low volume: 1–99	ND	1.16 [0.74; 1.81]; ND
			Moderate volume: 100–299	ND	1.18 [0.83; 1.69]; ND
			High volume: 300–599	ND	1.09 [0.77; 1.55]; ND
			Very high volume: > 600[b]		Reference category p-value: 0.82
Vemulapalli 2019	Conversion to open-heart surgery		Annual hospital volume, range:		No usable data
		96 256		466 (0.5)	
		6827	Low volume (1st quartile): 5–36	44 (0.6)	
		13 753	Moderate volume (2nd quartile): 37–54	75 (0.5)	
		22 799	High volume (3rd quartile): 55–85	125 (0.5)	
		52 877	Very high volume (4th quartile): 86–371	222 (0.4)	
	Aborted TAVI	96 256		431 (0.4)	
		6827	Low volume (1st quartile): 5–36	43 (0.6)	
		13 753	Moderate volume (2nd quartile): 37–54	76 (0.6)	
		22 799	High volume (3rd quartile): 55–85	89 (0.4)	
		52 877	Very high volume (4th quartile): 86–371	223 (0.4)	

Table 19: Results – Conversion to surgery / aborted TAVI (multipage table)

Study	Outcome definition	N	Volume specification	Conversion to open-heart surgery / aborted TAVR, raw n (%)	Adjusted odds ratio [95% CI]; p-value
a. "Total TAVR volume was defined as cumulative institutional TAVR volume since November 2011. Total TAVR volume accounted for the procedural volume from November 2011 until the procedure itself and did not account for procedures performed in the future." b. The hospital volume categories were cited this way in the Rymer 2019 publication. c. p-value for the influence of the volume variable in the model. CI: confidence interval; N: number of included patients; n: number of patients with an event; ND: no data; TAVI: transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement					

5.5.5.3 Composite outcomes

Four of the 8 included studies (Mao 2018, Salemi 2019, Vemulapalli 2019, and Verma 2017) reported usable results on the composite outcomes. All studies had a low informative value of results.

Except for Vemulapalli 2019, the above 4 studies analysed outcomes from the outcome categories of mortality and morbidity jointly. Vemulapalli 2019 combined only the outcomes of the morbidity category. In general, the studies' outcome definitions were heterogeneous.

Since separate results from multiple studies were available for the components of the composite outcomes, e.g. stroke, the results of these outcomes were disregarded when assessing the relationship between hospital or operator volume and treatment quality.

5.5.6 Metaanalyses

No metaanalytical summary of results was generated for any of the reported outcomes because the studies had very heterogeneous volume categories and used different adjustment factors in their analyses.

5.6 Overall evaluation of results

A total of 8 studies were found to have investigated the relationship between hospital or operator volume and quality of treatment outcome in TAVI (research question 1). The relationship between volume and quality of treatment outcome was not investigated on the combined hospital-operator level for any of the outcomes listed below. All studies provided exclusively results of low informative value.

For research question 2, no studies of meaningful interpretive value were found. Therefore, it was not possible to draw a conclusion on any effects of minimum case numbers introduced for TAVI on the quality of treatment outcome.

For the outcome of all-cause mortality, based on 1 study, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher-volume hospitals. The relationship between operator volume and this outcome was not investigated.

For the outcome of inpatient mortality, based on 3 studies, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher volume. Furthermore, on the basis of 2 studies, a correlation between operator volume and quality of treatment outcome was derived in favour of higher volume.

Studies with results on various outcomes were found for the outcome category of morbidity as well. For the outcome of adverse effects of therapy including failure to rescue and complications overall, based on 1 study, no correlation between hospital volume and quality of treatment outcome was found. The relationship between operator volume and quality of treatment outcome was not investigated.

For the outcome of dialysis-dependent renal failure, it was not possible to draw any conclusions on the relationship between hospital or operator volume and quality of treatment outcome on the basis of 1 study without usable data.

For the outcome of stroke, based on 1 study, no correlation between hospital volume and quality of treatment outcome was found. Furthermore, on the basis of 1 study, no correlation between operator volume and quality of treatment outcome was derived.

For the outcome of bleeding, based on 2 studies, a correlation between hospital volume and quality of treatment outcome was found in favour of higher volume. The relationship between operator volume and quality of treatment outcome was not investigated.

For the outcome of vascular complications including leaks and myocardial infarctions, no usable data were available, and no conclusion can be drawn on the relationship between hospital volume and quality of treatment outcome. The relationship between operator volume and quality of treatment outcome was not investigated.

For the outcome of pacemaker implantation, based on 1 study, no correlation between hospital volume and quality of treatment outcome was found. The relationship between operator volume and quality of treatment outcome was not investigated.

For the outcome of ventilation > 48 hours, based on 1 study, a correlation between hospital volume and quality of treatment outcome was found in favour of higher volume. The relationship between operator volume and quality of treatment outcome was not investigated.

No studies were available on the outcome of health-related quality of life, including activities of daily living and dependence on help from others. Therefore, no conclusion can be drawn on the relationship between hospital or operator volume and quality of treatment outcome.

On the basis of 1 study, no consistent (monotonic decreasing) relationship between hospital volume and quality of treatment outcome was found for the outcome of length of hospital stay when comparing low-volume hospitals with moderate-volume or high-volume hospitals. The relationship between operator volume and quality of treatment outcome was not investigated.

For the outcome of hospital readmission, based on 2 studies, a correlation between hospital volume and quality of treatment outcome was found in favour of higher volume. The relationship between operator volume and quality of treatment outcome was not investigated.

For the abort-of-TAVI component of the outcome of conversion to surgery / aborted TAVI, based on 1 study, a correlation between hospital volume and quality of treatment outcome was found in favour of higher volumes. No usable data were available for the conversion to surgery component; therefore, no conclusion can be drawn in this regard. Further, the relationship between operator volume and quality of treatment outcome was not investigated.

Due to the presentation of the individual components, the composite outcomes reported in 4 studies were disregarded when assessing the relationship between hospital volume or operator volume and quality of treatment outcome.

Table 20 below summarizes the results of the included studies on the relevant outcomes.

Table 20: Overview of the observed results for the outcomes and any volume-outcome correlation

Study	Outcomes													
	Mortality		Morbidity							Health-related quality of life	Length of hospital stay	Other outcomes		
	All-cause mortality	Inpatient mortality	Adverse effects of therapy including failure to rescue and complications overall	Dialysis-dependent renal failure	Stroke	Bleeding	Vascular complications including leaks and myocardial infarctions	Pacemaker implantation	Ventilation > 48 hours			Hospital readmission	Conversion to surgery[a] / aborted TAVI	Composite outcomes
	Hospital level													
Results of post-TAVI outcomes when comparing very high or high volume versus low volume	(↑)	(↑)	(↔)	-	(↔)	(↑)	-	(↔)	(↑)	-	(↑↓)	(↑)	(↑)	(*)
	Operator level:													
Results of post-TAVI outcomes when comparing very high or high volume versus low volume	-	(↑)	-	-	(↔)	-	-	-	-	-	-	-	-	(*)
	Level of the hospital-operator volume combination													
Results of post-TAVI outcomes when comparing very high or high volume versus low volume	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(↑) Based largely on 1 or more studies with low informative value of results showing statistically significant differences in outcome in favour of higher-volume hospitals and/or operators. Studies with results which are not statistically significant point in the same direction or do not call the association into question.
(↔) Studies of low informative value of results showed no statistically significant differences in favour of higher-volume operators and/or hospitals.
(↑↓) Based on 1 study of low informative value of results, no consistent direction of difference is found (monotonic decreasing).
- The included studies did not report any (usable) data.
(*) Not used for the assessment of the relationship between hospital or operator volume and quality of treatment outcome.
a. Switch of the interventional approach to open heart surgery.
TAVI: transcatheter aortic valve implantation

6 Discussion

For transcatheter aortic valve implantation, this report derived a correlation between hospital volume and quality of treatment outcome regarding various outcomes in favour of higher volume (research question 1). On the operator level, a correlation between volume and treatment quality in favour of higher volume was shown only for the outcome of inpatient mortality (research question 1).

As was the case in the previously published reports on the relationship between volume and treatment quality [37-44], no pertinent studies investigating the effects of a specific minimum number of cases introduced into the healthcare system were found to answer research question 2 of the report.

All studies constituted analyses of routine and/or registry data. Consequently, the studies were categorized as retrospective observational studies. This is further complicated by the fact that some of the data used for deriving relationships between volume and quality of treatment outcome stem from a single study. Further, all studies included in the report were rated as having a low informative value of results, particularly due to incomplete adjustments for hospital and operator risk factors. This is not surprising since routine data usually do not provide the information needed for these adjustments [45,46]. Hence, the result for the outcome of length of hospital stay in the Kaier 2018 study, for instance, might be due to a lack of adjustment on the hospital and operator levels [28]. After all, the STROBE statement stipulates that all outcomes of an observational study be defined [20]. However, such definitions are lacking in some of the studies included in the report. For instance, 3 studies fail to define a follow-up observation period, e.g. 30 days after TAVI, for the outcome of inpatient mortality [27,28,34]. This can cause considerable bias in the results for this outcome.

As was the case in prior reports [39,42], the publications included in this report formed volume categories in differing ways or analysed volume as a continuous variable, creating a heterogeneous picture. For hospital or operator volume, for instance, the included studies formed 2, 3 or more categories, each with different thresholds. As a result, the same threshold might correspond to high volume in one study and very high volume in another, or one study's high volume might exceed another study's very high volume.

The 3 German publications included in the report were aggregated into 1 study because the investigations' underlying data (German DRG data, almost identical time period and same OPS code) were largely identical. The Oettinger 2020 publication supplements the investigation period of the Kaier 2018 publication by the years 2015 and 2016. Even so, the Kaier 2018, Oettinger 2020, and Nimptsch 2017 publications used different hospital volume categories [28-30].

The study authors used different analysis methods for the investigations. As discussed in the information synthesis and analysis section, this report preferred continuous analyses over categorical ones where both were available for the same study. The data of the Kaier 2018 and

Nimptsch 2017 studies were about 87% identical (see above). Consideration was given to whether to exclude the Nimptsch 2017 publication with the shorter investigation period as a duplicate publication. However, the Nimptsch 2017 publication provides a continuous analysis for the outcome of inpatient mortality, while the Kaier 2018 publication offers only a categorical analysis of this outcome. Hence, the Nimptsch 2017 publication was not excluded, and the outcome of inpatient mortality was analysed largely based on its results [30].

As per the commission, the interventions investigated in the studies were presented in the appendix of the full report. Two of the 8 studies provided no information whatsoever on operation and procedure keys [33,35]. These two studies also failed to identify the TAVI access paths.

As was the case for the previously published reports on the relationship between volume and treatment quality [37-44], no study investigating health-related quality of life with regard to hospital or operator volume was found for this report. This apparent empirical gap is remarkable in light of the mean age and expected morbidity of patients who require TAVI.

In the present report, 7 of 8 studies are from the United States [27,31-36]. The authors of the Vemulapalli 2019 study presented a diagram of 30-day mortality versus inpatient mortality (Figure 2A in [35]). The figure showed that the results for 30-day mortality exhibit greater spread in low-volume hospitals than in higher-volume hospitals. The extent to which it is possible to derive any evidence supporting a minimum number of cases suitable for Germany from these types of results remains questionable. Although clinical standards in Germany and the USA are very similar, the care structures in the two countries differ fundamentally, for instance in terms of the system’s organization and financing, the number of patients requiring treatment, and the home-to-hospital distance [47].

The G-BA has not yet specified a minimum case number for TAVI [8]. The consensus paper of the German Cardiac Society and the German Society for Thoracic and Cardiovascular Surgery, published in 2020, specifies minimum volumes for TAVI (hospitals: 50 annually; operators: 25 annually) in the context of certification [48]. If the Vemulapalli 2019 [35] results were assumed to be transferable to Germany, 30-day mortality results would be expected to exhibit a large spread at an annual volume of 50 per hospital [48].

7 Conclusion

Eight retrospective observational studies were included in the investigation for research question 1 (present and assess the relationship between volume and quality of treatment outcome in TAVI).

In summary, the results for research question 1 were the following: All 8 studies on research question 1 provided usable data on at least 1 outcome. All studies had a low informative value of results.

For the outcomes of all-cause mortality and inpatient mortality, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher-volume hospitals. On the operator level, this correlation was found only for the outcome of inpatient mortality.

For the outcomes of bleeding, ventilation > 48 hours, and hospital readmission, a correlation between hospital volume and quality of treatment outcome was derived in favour of higher-volume hospitals. Due to a lack of usable data, this relationship was not established on the operator level for these outcomes.

For the outcome of length of hospital stay, it was not possible to derive any consistent (monotonic decreasing) relationship between hospital volume and quality of treatment outcome. The relationship between operator volume and quality of treatment outcome was not investigated in this regard.

For the abort-of-TAVI component of the outcome of conversion to surgery / abort of TAVI, a correlation between hospital volume and quality of treatment outcome was found in favour of higher volume. No usable data were available for the conversion-to-surgery component; therefore, no conclusion can be drawn on it. This relationship was not investigated on the operator level.

The composite outcomes were disregarded when assessing the relationship between hospital or operator volume. For the individual components of these outcomes, results were available and presented in the report.

For all other outcomes, no correlation was found between hospital or operator volume and quality of treatment outcome, or no usable data were available. This relationship was not investigated on the level of the combined hospital-operator volume for any of the outcomes mentioned in the report.

No pertinent studies were found regarding research question 2 (present studies which investigate the extent to which the quality of treatment outcome is impacted by minimum numbers of cases introduced in the healthcare system for TAVI).

8 References for English extract

Please see full rapid report for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects/v20-04.

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to October 27, 2020

The following filters were adopted:

- Systematic review: Wong [49] – High specificity strategy

#	Searches
1	Transcatheter Aortic Valve Replacement/
2	(transcatheter aortic valve replacement* or transcatheter aortic valve implantation* or TAVI).ti,ab.
3	((transapical or transventricular or percutaneous or transcatheter*) adj3 (valve* or prosthe* or bioprosthe*)).ab,ti.
4	or/1-3
5	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
6	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
7	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
8	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
9	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
10	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
11	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
12	or/5-11
13	cochrane database of systematic reviews.jn.
14	(search or MEDLINE or systematic review).tw.
15	meta analysis.pt.
16	or/13-15
17	and/4,12,16
18	17 not (exp animals/ not humans.sh.)
19	18 and (english or german).lg.

2. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	(transapical or transventricular or percutaneous or transcatheter* OR TAVI) AND ((minimum* OR hospital*) AND volume*)

Search for primary literature

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to December Week 1 2020
- Ovid MEDLINE(R) Daily Update December 09, 2020

#	**Searches**
1	Transcatheter Aortic Valve Replacement/
2	(transcatheter* adj1 aortic adj1 valve* adj1 (implant* or replacement*)).ab,ti.
3	(TAVI or TAVR).ab,ti.
4	or/1-3
5	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
6	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
7	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
8	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
9	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
10	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
11	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
12	or/5-11
13	and/4,12
14	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
15	hi.fs. or case report.mp.
16	or/14-15
17	13 not 16
18	..l/ 17 yr=2013-Current

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to December 11, 2020
- Ovid MEDLINE(R) Epub Ahead of Print December 11, 2020

#	**Searches**
1	(transcatheter* adj1 aortic adj1 valve* adj1 (implant* or replacement*)).ab,ti.
2	(TAVI or TAVR).ab,ti.
3	or/1-2
4	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
5	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
6	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
7	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
8	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
9	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
10	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
11	or/4-10
12	and/3,11
13	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
14	hi.fs. or case report.mp.
15	or/13-14
16	12 not 15
17	..l/ 16 yr=2013-Current

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 December 10

#	**Searches**
1	Transcatheter aortic valve implantation/
2	(transcatheter* adj1 aortic adj1 valve* adj1 (implant* or replacement*)).ab,ti.
3	(TAVI or TAVR).ab,ti.
4	or/1-3
5	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
6	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
7	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
8	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
9	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
10	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
11	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
12	or/5-11
13	and/4,12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (Conference Abstract or Conference Review or Editorial).pt.
17	..l/ 16 yr=2013-Current

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 12 of 12, December 2020

#	**Searches**
#1	[mh ^"Transcatheter Aortic Valve Replacement"]
#2	(transcatheter* NEAR/1 aortic NEAR/1 valve* NEAR/1 (implant* or replacement*)):ti,ab
#3	(TAVI or TAVR):ti,ab
#4	#1 or #2 or #3
#5	((minim* or high* or low or patient or outcome* or importance*) NEAR/3 (volume* or caseload)):ti,ab
#6	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) NEAR/2 (factor* or effect*)):ti,ab
#7	((hospital* or center* or centre* or unit*) NEAR/5 (type or level or small* or size)):ti,ab
#8	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) NEAR/2 (volume* or caseload* or experience* or characteristic* or performance*)):ti,ab
#9	((improve* NEAR/2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)):ti,ab
#10	((surgeon* or surgical* or physician* or provider* or specialist*) NEAR/3 outcome*):ti,ab
#11	(referral* NEAR/3 (selective* or volume* or rate*)):ti,ab
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11
#13	#4 and #12
#14	#13 not (*clinicaltrial*gov* or *who*trialsearch* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so with Publication Year from 2013 to present, in Trials