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Frailty in patients undergoing transcatheter aortic valve implantation: a protocol for a systematic review

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ABSTRACT

Introduction Aortic stenosis is a significant cause of morbidity and mortality in older patients. The advent of transcatheter aortic valve implantation (TAVI) offers an alternative to surgical aortic valve replacement for patients with severe symptomatic aortic stenosis who are at high or intermediate risk of adverse events. Existing evidence highlights the importance of frailty as a predictor of poor outcomes post-TAVI. The objective of this study is to review the operationalisation of frailty instruments for TAVI recipients and determine clinical outcomes and the change in quality of life in frail patients undergoing TAVI.

Methods and analysis Methods are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 checklist. We will search relevant databases to identify published, completed but unpublished and ongoing studies. We will include studies of patients with aortic stenosis, diagnosed as frail and who underwent a TAVI procedure that report mortality, clinical outcomes or health-related quality of life. Retrospective or prospective cohort studies, randomised controlled trials and non-randomised controlled trials will be eligible for inclusion. Two researchers will independently screen articles for inclusion, with disagreements resolved by a third reviewer. One researcher will extract data with audit by a second researcher. The risk of bias in studies will be evaluated using the Quality in Prognosis Studies tool. Meta-analysis of mortality, survival curve and the change in quality of life will be performed if appropriate. Subgroup analysis, sensitivity analysis and meta-regression will be performed if necessary.

Ethics and dissemination Due to the nature of this study, no ethical issues are foreseen. We will disseminate the results of our systematic review through a peer-reviewed journal.

Trial registration number CRD42018090597.

Strengths and limitations of this study

- This review is anticipated to be the first to determine the frequency of adverse outcomes and pool the survival after transcatheter aortic valve implantation in frail patients.
- The strengths of this review are the comprehensive literature search strategy and inclusion of frail patients from randomised controlled trials and observational studies.
- This review will exclude studies in which dimensions of frailty were assessed without reference to the goal of frailty measurement.

INTRODUCTION

Research on the benefits of transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve replacement (SAVR) and medical management is ongoing; however, it has been recognised that some patient populations fail to benefit from TAVI.[1] With increasing economic and clinical implications of TAVI, better understanding of how patient factors impact survival, functionality, complications and quality of life remains a priority.[2]

Patients referred for TAVI typically have advanced age and multiple comorbidities, and the prevalence of frailty can be as high as 63%.[3 4] Frailty is defined as a syndrome of impaired physiological reserve and increased vulnerability to stressors.[5] When exposed to stressors, such as chronic illness and surgery, frail patients are prone to adverse events, procedural complications, prolonged recovery, functional decline and mortality.[6] Although multiple studies have shown the value of frailty in predicting patient outcomes after TAVI, there is still a lack of consensus on the best way to assess frailty in clinical practice, with no single standard method of measuring frailty.[1 3] Without a clear consensus on frailty assessment practices, further review of frailty instruments and clinical outcomes of TAVI recipients becomes more important.[1]

This study aims to review the operationalisation of frailty instruments for TAVI recipients and to determine the mortality, clinical outcomes and change in quality of life in frail patients undergoing TAVI. The specific review questions will include: (1) how is frailty measured in patients undergoing TAVI?,

(2) what is the frequency of adverse clinical outcomes, including death, acute myocardial infraction, stroke, renal failure, pacemaker implantation, major bleeding, vascular complication, aortic regurgitation, readmission and re-intervention after TAVI in frail patients with aortic stenosis? and (3) how does quality of life change after TAVI in frail patients with aortic stenosis?

METHODS AND ANALYSIS

The methods of this systematic review are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols 2015 checklist.[7]

Eligibility criteria

Participants

We will include patients with aortic stenosis, diagnosed as frail, who underwent a TAVI procedure. The mean age of the study population will be restricted to 65 years and older. Since the focus of this review is on frailty rather than baseline surgical risk, we will not use baseline surgical risk as an exclusion criterion. We anticipate that the majority of studies will include patients at high or intermediate surgical risk.

We will include frail patients whose status had been assessed and measured using one of the following approaches: (A) comprehensive geriatric assessment linked to a frailty index, such as the Rockwood Frailty Index, (B) a multidimensional frailty index such as the Fried Frailty Index, (C) a single-item measure of frailty such as gait speed and (D) clinical judgement without the use of specific frailty assessment tools.[8–11] We will consider assessments that are directly measured or self-reported. Since new frailty indices are continually being developed, we will include studies using frailty measures that we have not anticipated.

Some methods of frailty assessment do not have a defined 'frailty threshold'. Studies will be excluded if mean frailty scores are reported without dichotomising the study population into frail and non-frail groups, or if frailty cut-off points were defined by the study sample (ie, percentile or median). If different studies use the same frailty measure but use a different cut-off for frailty, we will report frailty using the criteria defined by each individual study.[12] If a study reports separately on a 'pre-frail' group, we will exclude these data from the frail group.

We will only include studies that intended to measure frailty, even if the method of frailty assessment has been newly developed. If studies do not specify the method of frailty measurement, we will search the original protocol or cited references for the method used to measure frailty. Studies will be excluded if a method of frailty assessment is not referenced. We will not consider studies that used either comorbidity or disability alone as a marker of frailty, since these are related but distinct factors[13]; however we will consider studies where comorbidity or disability are measured as part of a multidimensional frailty assessment. Studies will be excluded if baseline frailty status is measured after the TAVI procedure or if the study is specifically focused on dimensions of frailty such as cognition, nutritional status, mood or mental health symptoms with no reference to the goal of frailty measurement. If multiple studies originating from the same patient population are found, we will include relevant data from all studies. If multiple frailty measurements were used in one study, we will extract all data, but we will incorporate study data into data synthesis once, using the more established, more commonly used frailty measure.

Intervention

We will include all forms of TAVI, regardless of procedural approach, types of valves and type of anaesthesia. We will exclude single cohort studies that investigated the effects of interventions such as improved health services and rehabilitation programmes on patients undergoing TAVI.

Outcome measures

The primary outcome will be mortality. Secondary outcomes will be clinical outcomes and health-related quality of life. Both utility-based and psychometric measures of quality of life will be included. A complete list of outcome measures is summarised in table 1. We will add additional outcomes to the list, if outcomes we have not anticipated are found in the literature.

Types of study

This review will include any study reporting mortality, clinical outcomes or quality of life in patients meeting frailty criteria. We will include studies describing non-comparative cohorts of patients undergoing TAVI who have been diagnosed with frailty and studies describing comparative cohorts of frail and non-frail patients undergoing TAVI in which outcomes are reported separately for frail patients. In studies of comparative cohorts, only data in the frail cohorts will be extracted. Studies with a sample size of fewer than 20 frail patients will be excluded. We will include data from randomised controlled trials (RCTs) in which patients were randomised to TAVI or SAVR, if outcomes are reported separately by treatment and frailty status.

Information sources

A systematic search strategy will be employed to identify published, unpublished and ongoing studies. We will search the online databases Medline, Embase, PsycINFO, Cochrane Library, Web of Science and ClinicalTrials.gov for articles published in 2006 or later. A search of conference abstracts will be performed on relevant conferences held in the last 3 years. In the search strategy, the publication language will not be limited as study authors have the ability to read articles published in multiple languages. We will also search the reference lists of articles and relevant reviews identified in the search for any additional studies. Search strategies for each database will be reported and a PRISMA flow diagram presented.[14]

Table 1 Data extraction template

Publication details	First author
	Year of publication
	Name of the journal
Study characteristics	Study design of the original study.
	Length of follow-up.
	Rates of loss to follow-up.
	Sample size of the frail group.
	Proportion frail.
Participant characteristics	Mean age of patients.
	Percentage female.
	Measures of surgical risk, including the Society of Thoracic Surgery (STS) risk score or the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (mean score or proportion of patients in each category).
	Measures of heart function including atrial fibrillation, left ventricular ejection fraction and New York Heart Association classification (mean score or proportion of patients in each category).
	Prior coronary artery bypass grafting.
	Prior myocardial infarction.
	Prior percutaneous coronary intervention.
	Prior stroke or transient ischaemic attack.
	Approach of TAVI procedure.
	Other baseline clinical measures.
	Baseline quality of life measures.
Frailty assessment details	Measure of frailty.
	Frail cut-off/definition used.
	Type of frailty assessment.
	Dimensions included in the frailty measure (ie, comorbidity, disability, cognition, nutrition and physical function).
Outcomes of interest	Death.
	Myocardial infarction.
	Stroke.
	Bleeding complications.
	Acute kidney injury.
	Vascular complications.
	Conduction disturbances.
	New pacemaker implantation.
	Repeat coronary or valvular intervention.
	Neurocognitive dysfunction.
	Delirium.
	Length of ventilation.
	Length of hospitalisation.
	Readmission.
	Postprocedure frailty.
	Postprocedure quality of life measures (mean scores and change from baseline).

TAVI, transcatheter aortic valve implantation.

Search strategy

The specific search strategies for each database will be developed by an information specialist with experience conducting systematic reviews. The research team will provide input and feedback into the development of the strategy. A draft search strategy for Embase is

Table 2 Search strategy for Embase

#	Searches
1	frailty/
2	frail elderly/
3	geriatric assessment/
4	frailty.mp.
5	or/1–4
6	geriatric patient/
7	very elderly/
8	aged/
9	aged hospital patient/
10	geriatrician/
11	*geriatrics/
12	(aged or aging or older or elderly or senior* or geriatric or centenarian or nonagenarian or octogenarian or septuagenarian or sexagenarian).mp.
13	or/6–12
14	exhaustion/
15	limited mobility/
16	“timed up and go test” /
17	exp walk test/
18	walking speed/
19	gait/
20	physical activity/
21	Performance Oriented Mobility Assessment/
22	grip strength/
23	hand strength/
24	muscle strength/
25	daily life activity/
26	exp “activity of daily living assessment”/
27	exp ADL disability/
28	exp disability/
29	exp functional status assessment/
30	exp neuropsychological test/
31	mental function assessment/
32	cognition assessment/
33	exp cognition/
34	exp cognitive defect/
35	memory assessment/
36	nutritional assessment/
37	((exhaustion or fatigue* or tired* or mobility or gait or walk* or stand or balance or bath* or dress* or toilet* or continence or feeding or cognition or memory or mental or disability or NYHA or Karnofsky or CSHA or functional* or Katz or Fried or Rockwood or frailty or nutrition*) adj7 (assess* or phenotype* or eval* or test* or exam* or instrument* or index or indices or scale* or score* or tool* or declin* or dependenc* or impair*)).mp.
38	(chair adj2 (rise or stand)).mp.
39	((grip* or grasp* or hand* or musc*) adj2 strength).mp.
40	weight loss.mp.
41	or/14–40
42	13 and 41
43	5 or 42
44	((transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillary or trans-axillary or transarterial* or trans-arterial* or subclavian* or sub-clavian* or transcatheter* or trans-catheter* or transcutaneous* or trans-cutaneous* or per-cutaneous* or percutaneous* or transcaval* or trans-caval* or “direct aortic” or tavi or tavr or pavi or pavr or sapien or cribier or revalv* or lotus or “direct flow” or jenavalve or portico or engager or evolut) adj3 aortic valv*).mp.
45	transcatheter aortic valve implantation/
46	or/44–45
47	43 and 46
48	limit 46 to yr=“2006 -Current”

given in table 2. This strategy will be adapted for other databases.

Data management

We will use Covidence systematic review software to manage data (Veritas Health Innovation, Melbourne, Australia). The title and abstract of all articles identified in the search will be uploaded to Covidence for abstract screening. Full-text articles will be uploaded for further screening, and reasons for exclusion will be noted at the full-text review stage. All included articles will be allocated a unique study ID code to track articles throughout the data screening and extraction process. Data extraction and quality appraisal will be managed in Microsoft Excel (2018).

Selection process

Two reviewers will independently review all abstracts identified in the initial search, and studies meeting the inclusion criteria will be included for full-text retrieval. Full-text review of articles will be performed independently by two reviewers. Disagreements will be resolved by a third reviewer.

Data collection process

We plan to use a standardised data collection form. Data will be extracted by one reviewer and independently audited by another reviewer. Disagreements will be resolved by obtaining consensus between the two reviewers or consultation with a third reviewer when necessary. We will attempt to contact study authors to obtain missing

data. Reasons for missing data and how each study dealt with missing data will be recorded.

Data items

The data collection form will include the list of fields given in table 1. If any information is not reported, this will be recorded in the corresponding field. If two or more studies present Kaplan-Meier curves with time to death, we will collect these data. If the numbers are not directly available, we will digitise the curves to retrieve patient level time to event data.[15]

Risk of bias in individual studies

Two reviewers will independently assess the risk of bias in individual studies using the Quality in Prognosis Studies (QUIPS) tool, which rates the studies as 'high risk', 'moderate risk' or 'low risk' of bias in the following domains: study population, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting.[16] For our research purpose, we will not consider the study confounding and model development strategy sections of the tool as we anticipate they will not apply to the types of studies we will include.

Data synthesis

We will categorise clinical outcomes and report the frequency at each time point in tabular form. We will group results reported at similar times into prespecified periods of interest. For example, results reported at 4 weeks and 8 weeks may be grouped with results at 6 weeks. For continuous outcomes we will report the mean value and standard deviation (SD).

Primary outcomes

For all studies, we will abstract the number of deaths and the median follow-up time and calculate the mortality rate per 100 person-years. We will pool mortality from multiple studies and model the death rate using a meta-analysis based on the Poisson distribution.[17] For studies reporting mortality, we will perform a meta-analysis of the odds of death at 30 days and 12 months, respectively. A single pooled Kaplan-Meier curve of time to death will be reproduced and presented by reconstructing the time to death data from individual studies.[15]

Clinical outcomes

For time-to-event outcomes, if studies present Kaplan-Meier curves with time to myocardial infarction, stroke, bleeding complications, acute kidney injury, vascular complications, conduction disturbances, new pacemaker implantation, repeat coronary or valvular intervention, neurocognitive dysfunction, delirium and readmission, we will use the same methods described above to collect the information on numbers at risk and total number of events, and then create a single pooled Kaplan-Meier curve for each clinical outcome. If studies do not report time to event data, we will extract the number of events and the median follow-up time to calculate the event rate per 100-person years. Event rates from multiple studies will be pooled using a meta-analysis based on the Poisson distribution. For postprocedure length of hospitalisation, we will pool data from multiple studies using a meta-analysis of the mean length of hospitalisation.

Quality of life measures

When two or more studies report mean quality of life using the same measures at baseline and the same follow-up time point, we will pool mean scores to analyse changes in quality of life. We will calculate the mean change in quality of life along with the SD, from baseline (T_1) to the follow-up time point (T_2). When two or more studies report mean quality of life at baseline and the same follow-up time point but using different overall measures, we will calculate standardised change scores for each study using the formula $\frac{Qol\ T2 - Qol\ T1}{\sqrt{\left[(N1-1)*(SD\ Qol\ T2)^2+(N2-1)*(SD\ Qol\ T1)^2\right]/(N1+N2-2)}}$.[18] We will report the standardised change scores for each time point and pool the standardised change scores from each study using a random effects model. If studies measure quality of life using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), and report the mean mental component score (MCS) and the mean physical component score (PCS) separately, we will pool MCS and PCS.

Assessment of heterogeneity

For each meta-analysis, we will consider the studies included to identify and characterise potential sources of heterogeneity. Differences across studies in the patient population (eg, mean age, percentage female and comorbidity) may be potential sources of heterogeneity in study estimates. We will calculate the I-squared statistic to estimate the percentage of total variation across studies due to heterogeneity. Heterogeneity will be considered substantial if the I-squared value is greater than 50%.[19]

Subgroup analyses

We plan to perform the following subgroup analyses; however, the analysis will only be performed if we obtain sufficient data for the proposed groups. Studies will be grouped on the basis of: (1) surgical risk of the population (inoperable vs high risk vs intermediate risk), (2) approach (transfemoral vs non-transfemoral), (3) type of frailty measure (multidimensional assessment vs single item assessment, objective measures vs clinical judgement, and established frailty measures vs newly developed tools) and (4) types of studies (observational studies vs RCTs).

Sensitivity analyses

We will perform sensitivity analyses to test if the findings are robust. If studies have a wide range of quality, we will exclude low-quality studies from sensitivity analysis. We may also perform sensitivity analysis restricting meta-analysis to frequently used, established frailty instruments only.

Meta-regression

Meta-regression will be performed to further investigate the potential sources of clinical heterogeneity and to

determine the influence of mean age, frailty (continuous variable) and quality of life measurements on outcomes if we obtain sufficient data.[20] The *metareg* function (STATA V.14.0) will be used to undertake meta-regression with log-risk estimates, and the standard error will be determined from 95% CIs for the log-risk estimates.

Quality of Evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to conduct an evaluation of the body of work represented by the included studies.

Patient and public involvement statement

Due to the nature of the study, patients are not involved in this project.

DISCUSSION

Frailty is increasingly being recognised as an important prognostic indicator to predict poor outcomes in patients undergoing TAVI procedures. Green *et al* analysed data from the Placement of AoRtic TraNscathetER Valves (PARTNER) Trial and found that frailty was associated with increased mortality and a higher risk of poor outcome 1 year after TAVI.[2] Further to this, Zajarias *et al* evaluated patients in the PARTNER II randomised trial and demonstrated higher 30-day and 1-year mortality in frail patients.[21] However, since most studies have focused on improving surgical risk prediction, more research centred on patient outcomes and quality of life are needed.[22]

While frailty has been identified as an important concept, there is a lack of consensus in the literature on how it should be assessed and that makes the field of study challenging. In this regard, Dent *et al* reviewed the definitions and quality of more than a dozen frailty measurements used in research and clinical practice.[8] In a systematic review, Kim *et al* identified 13 frailty instruments and evaluated their ability to predict negative outcomes for a range of cardiac surgical procedures, including TAVI.[22] The Frailty in Older Adults Undergoing Aortic Valve Replacement (FRAILTY-AVR) study found that within the same cohort of TAVI patients assessed with seven different frailty tools, the prevalence of frailty ranged from 35% to 74% depending on the frailty tool.[23] With this review, we aim to summarise the frailty methods being used in TAVI patients, describe the dimensions of frailty being assessed in each study and synthesise prognostic information. Our goal is to help move the field of frailty measurement in TAVI towards greater consensus.

Our review has several strengths. We will perform a comprehensive literature search to identify both published and unpublished studies; our search will include RCTs and observational studies, as well as references from previous reviews. Furthermore, two reviewers will independently use the QUIPS tool to assess the risk of bias, and we will use GRADE to evaluate the body of work represented by the included studies. To the best of our knowledge, this will be the first review to investigate the frequency of adverse outcomes and to pool estimates of survival after TAVI in frail patients from multiple studies.

Our study also has some limitations. While many frailty assessments are similar, different methods of frailty assessment cannot be assumed to be interchangeable.[24 25] Although we will perform subgroup analysis by type of frailty measure to account for these differences, the pooled results may be subject to heterogeneity. In addition, while we will perform subgroup analysis by type of frailty assessment, we do not anticipate being able to adjust for dimensions of frailty in our analysis. Our study will characterise prognosis for frail patients undergoing TAVI, and we will not compare prognosis to other groups of patients or treatments. While this provides a focused synthesis, interpretation of the results will occur in the context of previously conducted systematic reviews of TAVI and will be somewhat subjective. We expect to encounter studies that applied multiple frailty instruments in the same patient group, and in this situation, we will only extract data from one frailty instrument, and this may introduce selection bias. Finally, some studies may define an intermediate 'pre-frail' state. Though less vulnerable than the frail group, prefrail patients are at higher risk than robust patients for experiencing adverse outcomes.[26 27] We may not find sufficient data to synthesise outcomes for this important subgroup.

With increased uptake of TAVI, the goal of our study to better understand how frailty impacts survival, functionality, complications and quality of life is of great clinical importance.[2] Clinical practice guidelines recommend assessing frailty as one component of risk when considering heart valve procedures for patients.[28] The literature describes a number of different frailty measures capable of improving risk prediction in TAVI patients, suggesting that frailty assessment will help identify patients most likely to benefit from TAVI.[1] Preprocedural frailty assessment can help identify potentially modifiable factors that may improve outcomes for frail patients.[29] Research into the impact of preoperative interventions to improve outcomes for frail patients are ongoing, but preliminary studies have demonstrated positive impacts on surgical outcomes of frail people.[30 31]

We believe the results of this review will inform clinicians, patients and healthcare administrators of the best available evidence about the impact of frailty in patients undergoing TAVI. We also expect that our findings will fill certain gaps, as well as trigger further research to enhance clinical decision making with a focus on patient-important outcomes.

Ethics and dissemination

Due to the nature of the study, there are no ethical concerns and informed consent will not be required. We will disseminate the results of our systematic review through a peer-reviewed journal.

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Contributors All authors proposed and designed the purpose, review questions and methods of this systematic review. Searching strategy was developed by JeM, and revised by ZL, ED and AJ-B. ZL drafted the manuscript. All coauthors have contributed to the revision of manuscript.

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