BMJ Open

Rockwood Clinical Frailty Scale as a predictor of adverse outcomes among older adults undergoing aortic valve replacement: a protocol for a systematic review

Tadhg Prendiville [ID],[1] Aoife Leahy,[1] Laura Quinlan,[1] Anastasia Saleh,[1] Elaine Shanahan,[1] Ahmed Gabr,[1] Catherine Peters,[1] Ivan Casserly,[2] Margaret O'Connor,[1] Rose Galvin[3]

[1]Department of Ageing and Therapeutics, University Hospital Limerick, Dooradoyle, Limerick, Ireland
[2]Department of Cardiology, Mater Misericordiae University Hospital, Dublin, Ireland
[3]School of Allied Health, Faculty of Education and Health Sciences, Ageing Research Centre, Health Research Institute, University of Limerick, Limerick, Ireland

Correspondence to
Dr Tadhg Prendiville;
tadhg.prendiville@ucdconnect.ie

ABSTRACT

Introduction Frailty is associated with adverse outcomes relating to cardiac procedures. It has been proposed that frailty scoring should be included in the preoperative assessment of patients undergoing aortic valve replacement. We aim to examine the Rockwood Clinical Frailty Scale (CFS), as a predictor of adverse outcomes following aortic valve replacement.

Methods and analysis Prospective and retrospective cohort studies and randomised controlled trials assessing both the preoperative frailty status (as per the CFS) and incidence of adverse outcomes among older adults undergoing either surgical aortic valve replacement or transcatheter aortic valve replacement will be included. Adverse outcomes will include mortality and periprocedural complications, as well as a composite of 30-day complications. A search will be conducted from 2005 to present using a prespecified search strategy. Studies will be screened for inclusion by two reviewers, with methodological quality assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Relative risk ratios with 95% CIs will be generated for each outcome of interest, comparing frail with non-frail groups. Data will be plotted on forest plots where applicable. The quality of the evidence will be determined using the Grading of Recommendations, Assessment, Development and Evaluation tool.

Ethics and dissemination Ethical approval is not required for this study as no primary data will be collected. We will publish the review in a peer-reviewed journal on completion.

PROSPERO registration number CRD42020213757.

INTRODUCTION

Surgical (SAVR) or transcatheter aortic valve replacement (TAVR) remains the mainstay of treatment for severe aortic stenosis, with the latter originally developed to facilitate intervention in the older, more frail and higher risk population.[1] TAVR has more recently been shown to be equivalent to SAVR in the

Strengths and limitations of this study

► This study will synthesise the totality of evidence with respect to the association of Clinical Frailty Scale-defined frailty with adverse outcomes after surgical and transcatheter aortic valve replacement in older people and inform evidence-based practice on the utility of such an instrument.

► The review will employ rigorous methods to identify, select, appraise and synthesise the findings, adhering to standardised reporting guidelines to standardise the conduct and reporting of the review.

► Limitations of the review may include a low number of suitable studies, low-quality evidence of included studies and heterogeneity in the conduct and reporting of study outcomes and duration of follow-up.

intermediate and low-risk groups,[2 3] leading to its wider use as a valve replacement strategy, particularly in older people.[4–6]

Frailty is common in older people and is associated with poorer outcomes following either TAVR or open cardiac surgery.[7 8] It is characterised by decreased physiological reserve, making an individual vulnerable to increased dependency and/or mortality when exposed to a stressor.[9] The prevalence of frailty is expected to increase as life expectancy continues to rise.[10 11]

The Rockwood Clinical Frailty Scale (CFS),[12] first described in 2005, is a semi-quantitative tool used to estimate an individual's degree of frailty on a scale of 1 (very fit) to 9 (terminally ill). Patients who score a 5 or higher are considered frail. The main advantage of the CFS is its ease of application, as a score can be derived through a brief interview with a patient or family member without the need for further objective data such as grip

strength or gait speed. Interobserver variability has been reported however,[13] which may affect the applicability of the scale, particularly among non-geriatricians.

It has been recommended that a measure of frailty be included in the preoperative risk assessment of older patients undergoing aortic valve replacement.[14] We aim to examine the data on the association of frailty (as defined by the CFS) with adverse outcomes following either TAVR or SAVR.

METHODS
Study design
We will conduct a systematic review to identify research studies which reported the incidence of adverse outcomes following either SAVR or TAVR, in which patients had their frailty status measured preoperatively using the CFS. Our study will use the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy principles and will reference the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standardised reporting guidelines.[15]

Search identification
Using a predefined search strategy, a systematic search will be conducted using the MEDLINE (Ovid), PubMed, CINAHL, Scopus, Embase, PsycINFO, Science Direct, Academic Search Complete, WHOLIS by Virtual Health Library, Web of Science and Cochrane Library databases. Studies published after 2005 (when the CFS was first published) will be included. There will be no language restriction. Search results will be imported into Endnote and duplicates removed. All abstracts will be screened independently by two reviewers (TP and LQ/MOC) regarding suitability for inclusion, with disputes resolved by a third independent reviewer (RG).

A sample search strategy for PubMed is included in the online supplemental data 1.

Eligibility criteria
Studies will be selected for inclusion if they examine the incidence of adverse outcomes following SAVR or TAVR in older adults and include a preoperative frailty assessment using the CFS. Both the 7-item and 9-item CFS will be examined, with a score of >4 indicating a frail patient.[12] Prospective and retrospective cohort studies and randomised controlled trials will be included. Our population of interest will be patients greater than 65 years of age undergoing these interventions.

Primary and secondary outcomes
The primary outcome for this study will be 12-month mortality post-aortic valve replacement. Data on a number of secondary outcomes (as defined by the Valve Academic Research Consortium) will be collected,[16] as well as rates of functional decline or rehospitalisation and length of stay in hospital or the intensive care unit (ICU).

All secondary outcomes are listed in the online supplemental data 2.

Meta-analysis will be undertaken where data are available on a similar outcome across two or more studies. Data relating to TAVR and SAVR will be reported separately.

Study quality
The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool will be used to assess the methodological quality of included studies by examining the risk of bias as well as the generalisability of the studies to our population of interest.[17] Each primary/secondary outcome will be taken as a 'reference standard' and will be reported separately, while the CFS will be taken as the index test—in practice we will use this to ensure that rates of adverse outcomes were not interpreted prior to application of the CFS. Each paper will be independently assessed by two reviewers (TP and AS). Disagreements regarding study quality will be resolved by discussion with a third reviewer (CP). The Grading of Recommendations, Assessment, Development and Evaluation tool will be used to determine the strength of the body of evidence collected.

Data extraction
Data extraction will be completed independently by two separate authors (TP and AL). A data extraction form will be used to compile relevant data. Data will be extracted including authors and year of publication, country, population studied, sample size, baseline demographics, baseline CFS Score, characteristics of the person scoring the CFS (research, cardiology or geriatric clinician), valve procedure undertaken, reported outcomes and length of follow-up. Relevant authors will be contacted if additional data are required.

Statistical analysis
Stata V.12 and Review Manager V.5.4.1 will be used to analyse data. Relative risk ratios with 95% CIs will be calculated for each dichotomous outcome of interest (comparing frail with non-frail patient groups). Continuous variables will be presented as mean±SD or median with IQR (for non-parametric data) and compared using independent sample T-testing (parametric data) or Mann Whitney U testing (non-parametric data).

Data on similar outcomes across two or more studies will be presented on forest plots. Meta-analysis will be undertaken where applicable.

Data statement
Dataset will be made available from the Open Science Framework repository, doi: 10.17605/OSF.IO/7HPVE.

Patient and public involvement
The writing of this review protocol did not include input from patients or the general public. The outcomes we are looking to measure were determined from clinical observation of older adults and the AVR (ie, SAVR/TAVR) process. The dissemination of our review will include

patient and public involvement. The Ageing Research Centre at the University of Limerick has established a stakeholder group of older adults to support patient and public involvement and input in study designs from the outset. We will engage with this group, who will provide important input to inform the discussion around our review findings.

Ethics and dissemination

No primary data are to be collected for this review, so ethical approval is not required. We will aim to publish our study in a peer-reviewed journal on completion.

DISCUSSION

This systematic review aims to examine the totality of evidence regarding the strength of association of frailty (as measured by the CFS) with adverse outcomes after aortic valve replacement among hospitalised older adults.

The incorporation of TAVR has expanded the treatment of aortic valve disease in a frail older cohort where surgery would not otherwise have been considered,[1] though contemporary data show increasing usage in the intermediate and lower risk populations.[4 18] The risks of TAVR are outlined in the literature, with overall 30-day mortality rates of 2.3%, 5.4% and 4.2% according to recent data from the US, French and German registries, respectively.[4 6 19] Furthermore, data from the UK suggest that approximately 40% of patients undergoing TAVR are frail, while in the USA at least 60% of patients had at least one marker of frailty noted. Both of these cohorts demonstrated increased mortality following the procedure.[20 21] Other frailty-associated factors, such as low body mass index or age greater than 90 years, have also been associated with poorer outcomes.[22 23]

Current widely used risk scores for aortic valve procedures include the Society of Thoracic Surgeons (STS) risk score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE),[24 25] both of which were developed in the SAVR population. These appear to correlate poorly with mortality following TAVR,[26 27] giving rise to the development of newer, more specific TAVR risk scores.[28–30] Neither the STS Score nor the EuroSCORE include an objective measurement of frailty though assessing frailty has the potential to improve their predictive performance, particularly in older adults. There is a lack of consensus on how frailty is best measured.[31] Frailty tools specific to TAVR such as the Essential Frailty Toolset (EFT) have been developed in recent years and have shown statistical significance in predicting mortality.

The role of frailty scores is twofold—not only to predict which patients are at high risk of complications but also in which patients the procedure may be clinically futile (despite being technically successful). Both the CFS and EFT were consistently predictive of mortality and futility for older patients with severe frailty undergoing TAVR.[31]

The CFS is a commonly used and well-validated measure of frailty, taking into account a patient's level of mobility and ability to perform activities of daily living.[32–35] A key advantage of the CFS is obviating the need for an independent dedicated mobility and cognitive assessment to inform test scoring. Other scores such as the Geriatric Assessment Frailty Score by Skaar *et al* are labour intensive, requiring a mini-mental state exam (MMSE), weight, height, Hospital Anxiety and Depression Scale Score, Charlson Comorbidity Index and Nottingham Activities of Daily Living Scale Score to be calculated.[36] Therefore, it would be difficult to translate this process from research into clinical practice on a wider scale. The EFT involves a cognitive assessment using the MMSE or mini-Cog and a prespecified mobility assessment along with laboratory testing.

While the CFS was initially designed for geriatricians as a means of summarising the findings of a comprehensive geriatric assessment,[12] due to its relative brevity of application it may be more accessible to other non-geriatric trained clinicians as a means of assessing frailty.[37] Better understanding of the influence of the background expertise of the rating clinician (eg, cardiology or geriatric trained) will inform on the validity of the CFS. Significant inter-rater variability in the application of the CFS was reported by Surkan *et al* across intensive care and geriatric medicine specialists, although the score remained prognostically significant.[13] In contrast, other studies have reported good inter-rater agreement: one comparing trained research assistants with geriatric experts[34] and another comparing primary care physicians, community nurses, internal medicine doctors and intensivists.[38]

Understanding the ability of the CFS to predict outcomes following aortic valve replacement will inform clinical practice.

ORCID iD
Tadhg Prendiville http://orcid.org/0000-0003-1036-9859

REFERENCES

1 Leon MB, Smith CR, Mack M, *et al*. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
2 Leon MB, Smith CR, Mack MJ, *et al*. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–20.
3 Mack MJ, Leon MB, Thourani VH, *et al*. Transcatheter aortic-valve replacement with a Balloon-Expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–705.
4 Carroll JD, Mack MJ, Vemulapalli S, *et al*. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol* 2020;76:2492–516.
5 Ludman PF. Uk TAVI registry. *Heart* 2019;105:s2–5.
6 Auffret V, Lefevre T, Van Belle E, *et al*. Temporal trends in transcatheter aortic valve replacement in France: FRANCE 2 to FRANCE TAVI. *J Am Coll Cardiol* 2017;70:42–55.
7 Sepehri A, Beggs T, Hassan A, *et al*. The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg* 2014;148:3110–7.
8 Anand A, Harley C, Visvanathan A, *et al*. The relationship between preoperative frailty and outcomes following transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes* 2017;3:123–32.
9 Morley JE, Vellas B, van Kan GA, *et al*. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013;14:392–7.
10 Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–56.
11 Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. *Nature* 2008;451:716–9.
12 Rockwood K, Song X, MacKnight C, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95.
13 Surkan M, Rajabali N, Bagshaw SM, *et al*. Interrater reliability of the clinical frailty scale by Geriatrician and intensivist in patients admitted to the intensive care unit. *Can Geriatr J* 2020;23:223–9.
14 Kim DH, Kim CA, Placide S, *et al*. Preoperative frailty assessment and outcomes at 6 months or later in older adults undergoing cardiac surgical procedures: a systematic review. *Ann Intern Med* 2016;165:650–60.
15 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
16 Kappetein AP, Head SJ, Généreux P, *et al*. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg* 2012;42:S45–60.
17 Whiting PF, Rutjes AWS, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
18 Eggebrecht H, Mehta RH. Transcatheter aortic valve implantation (TAVI) in Germany 2008-2014: on its way to standard therapy for aortic valve stenosis in the elderly? *EuroIntervention* 2016;11:1029–33.
19 Husser O, Fujita B, Hengstenberg C, *et al*. Conscious Sedation Versus General Anesthesia in Transcatheter Aortic Valve Replacement: The German Aortic Valve Registry. *JACC Cardiovasc Interv* 2018;11:567–78.
20 Martin GP, Sperrin M, Ludman PF, *et al*. Do frailty measures improve prediction of mortality and morbidity following transcatheter aortic valve implantation? an analysis of the UK TAVI registry. *BMJ Open* 2018;8:e022543.
21 Kiani S, Stebbins A, Thourani VH, *et al*. The Effect and Relationship of Frailty Indices on Survival After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2020;13:219–31.
22 Voigtländer L, Twerenbold R, Schäfer U, *et al*. Prognostic impact of underweight (Body Mass Index <20 kg/m^2) in patients with severe aortic valve stenosis undergoing transcatheter aortic valve implantation or surgical aortic valve replacement (from the German Aortic Valve Registry [GARY]). *Am J Cardiol* 2020;129:79–86.
23 Blumenstein J, Möllmann H, Bleiziffer S, *et al*. Transcatheter aortic valve implantation in nonagenarians: insights from the German aortic valve registry (GARY). *Clin Res Cardiol* 2020;109:1099–106.
24 Nashef SAM, Roques F, Sharples LD, *et al*. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;41:734–45.
25 O'Brien SM, Shahian DM, Filardo G, *et al*. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. *Ann Thorac Surg* 2009;88:S23–42.
26 Silva LS, Caramori PRA, Nunes Filho ACB, *et al*. Performance of surgical risk scores to predict mortality after transcatheter aortic valve implantation. *Arq Bras Cardiol* 2015;105:241–7.
27 D'Ascenzo F, Ballocca F, Moretti C, *et al*. Inaccuracy of available surgical risk scores to predict outcomes after transcatheter aortic valve replacement. *J Cardiovasc Med* 2013;14:894–8.
28 Edwards FH, Cohen DJ, O'Brien SM, *et al*. Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. *JAMA Cardiol* 2016;1:46–52.
29 Iung B, Laouénan C, Himbert D, *et al*. Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. *Heart* 2014;100:1016–23.
30 Capodanno D, Barbanti M, Tamburino C, *et al*. A simple risk tool (the OBSERVANT score) for prediction of 30-day mortality after transcatheter aortic valve replacement. *Am J Cardiol* 2014;113:1851–8.
31 Afilalo J, Lauck S, Kim DH, *et al*. Frailty in older adults undergoing aortic valve replacement: the frailty-avr study. *J Am Coll Cardiol* 2017;70:689–700.
32 Basic D, Shanley C. Frailty in an older inpatient population: using the clinical frailty scale to predict patient outcomes. *J Aging Health* 2015;27:670–85.
33 Stille K, Temmel N, Hepp J, *et al*. Validation of the clinical frailty scale for retrospective use in acute care. *Eur Geriatr Med* 2020;11:1009-1015.
34 Kaeppeli T, Rueegg M, Dreher-Hummel T, *et al*. Validation of the clinical frailty scale for prediction of Thirty-Day mortality in the emergency department. *Ann Emerg Med* 2020;76:291–300.
35 Shears M, Takaoka A, Rochwerg B, *et al*. Assessing frailty in the intensive care unit: a reliability and validity study. *J Crit Care* 2018;45:197–203.
36 Skaar E, Eide LSP, Norekvål TM, *et al*. A novel geriatric assessment frailty score predicts 2-year mortality after transcatheter aortic valve implantation. *Eur Heart J Qual Care Clin Outcomes* 2019;5:153–60.
37 Elliott A, Phelps K, Regen E, *et al*. Identifying frailty in the emergency department-feasibility study. *Age Ageing* 2017;46:840–5.
38 Nissen SK, Fournaise A, Lauridsen JT, *et al*. Cross-sectoral inter-rater reliability of the clinical frailty scale - a Danish translation and validation study. *BMC Geriatr* 2020;20:443.