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**The relationship between preoperative frailty and outcomes  
following Transcatheter Aortic Valve Implantation (TAVI):  
*a systematic review and meta-analysis***

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## Abstract

**Aims:** Transcatheter aortic valve implantation (TAVI) is an increasingly common intervention for patients with aortic stenosis deemed high-risk for major cardiac surgery, but identifying those who will benefit can be challenging. Frailty reflects physiological reserve and may be a useful prognostic marker in this population. We performed a systematic review and meta-analysis of the association between frailty and outcomes after TAVI.

**Methods and Results:** Five databases were searched between January 2000 and May 2015. From 2,623 articles screened, 54 were assessed for eligibility. Ten cohort studies (n=4,592) met the inclusion criteria of reporting a measure of frailty with early ( $\leq 30$  days) or late ( $>30$  days) mortality and procedural complications following TAVI as defined by the Vascular Academic Research Consortium (VARC).

Frailty was associated with increased early mortality in four studies (n=1,900) (HR 2.35, 95% CI 1.78-3.09,  $p < 0.001$ ), and increased late mortality in seven studies (n=3159) (HR 1.63, 95% CI 1.34-1.97,  $p < 0.001$ ). Objective frailty tools identified an even higher risk group for late mortality (HR 2.63, 95% CI 1.87-3.70,  $p < 0.001$ ). Frail individuals undergoing TAVI have a mortality rate of 34 deaths per 100 patient years, compared to 19 deaths per 100 patient years in non-frail patients. There was limited reporting of VARC procedural outcomes in relation to frailty, preventing meta-analysis.

**Conclusions:** Frailty assessment in an already vulnerable TAVI population identifies individuals at even greater risk of poor outcomes. Use of objective frailty tools may inform patient selection, but this requires further assessment in large prospective registries.

**Keywords:** TAVI, frailty, aortic stenosis, prognosis, risk factors, ageing

## Introduction

Aortic stenosis is the most common valvular disease in the Western World, affecting 1 in 8 individuals over the age of 75 years. The incidence of functionally important disease is rising in line with the ageing population, providing challenges for conventional valve replacement surgery.<sup>1</sup> Patients over 80 years old undergoing elective cardiac surgery have more operative complications and a 10 percent mortality rate at 30 days; therefore decisions around intervention in older patients are complex.<sup>2</sup> Transcatheter Aortic Valve Implantation (TAVI) has become a widespread and viable alternative for patients considered high-risk for conventional surgery. Population modelling suggests in excess of 91,000 people fall into this category across North America each year.<sup>1</sup> The Society of Thoracic Surgeons (STS)<sup>3</sup> and EuroSCORE<sup>4</sup> tools are often used to guide treatment based on the predicted risk of poor outcomes, but these scoring systems have not been designed or formally tested in TAVI populations. The application of such scores in elderly patients suitable for conventional surgery has also been questioned.<sup>5,6</sup> Many believe that a holistic approach through frailty assessment may improve the decision making process.

Frailty is a multimodal concept describing loss of strength, endurance and physiological reserve across multiple systems that increases vulnerability for developing dependency or death.<sup>7</sup> It becomes more common with age, but is a very distinct concept of biological rather than chronological years; indeed the majority of individuals over 85 years old are not frail. Common models focus on the development of a phenotype or the gradual accumulation of deficits over time, but there is no clear consensus on the best form of measurement.<sup>7-9</sup> Within non-cardiac surgical cohorts, frailty is predictive of mortality, post-operative complications and institutionalisation.<sup>10-13</sup> It is plausible that such measures applied to high-risk patients undergoing TAVI may improve the discrimination of current risk

assessment tools for important patient outcomes. In this systematic review, we evaluate the effect of pre-operative frailty on important patient outcomes after TAVI.

## **Methods**

### ***Search Strategy***

We conducted a systematic literature review of Medline, EMBASE and CINAHL databases between 1<sup>st</sup> January 2000 and 1<sup>st</sup> June 2015 using the key search terms of frailty (and its synonyms) and TAVI (and its synonyms) (Supplementary Appendix). Reference and forward citation searching via the Web of Science (Thomson Reuters) was performed on papers meeting the criteria for inclusion. Hand-searching using the primary search terms was performed within the three most commonly identified journals from the initial search. This was repeated using the Google Scholar search engine.

### ***Eligibility criteria***

We included any primary peer-reviewed paper where a measure of frailty was defined by the authors prior to TAVI, and where this was related to at least one of the predefined post-TAVI outcomes. No other assessments were adjudicated to represent frailty unless stipulated as a determinant of frailty by the authors of a study. No restrictions were placed on the age of study participants, specific vascular route or operator technique by which TAVI was performed. Results in all languages were considered, using translation services where required to adjudicate eligibility.

The primary outcome was all-cause mortality after TAVI, either reported in the short ( $\leq 30$  days) or long term ( $> 30$  days). Secondary outcomes comprised procedural complications as defined by the Valve Academic Research Consortium (VARC) standardized

endpoint definitions. These include cardiovascular mortality, myocardial infarction, major stroke, bleeding, acute kidney injury requiring dialysis and numerous other vascular complications.<sup>14</sup> Any measures of functional capacity or patient independence after TAVI were sought as secondary outcomes where the relationship to a pre-TAVI frailty measure was presented. Review articles and non-peer reviewed material (such as conference proceedings and poster abstracts) were excluded.

### ***Data extraction***

All extracted abstracts and full-text articles meeting the inclusion criteria were assessed between three researchers (AA, AV and CH), such that two people independently reviewed each submission. Disagreements were resolved by consensus including the third reviewer. For each study meeting the inclusion criteria, a standardised data extraction form was developed to record study design, TAVI population demographics, assessed risk of the population (STS and EuroSCORE), specific frailty measure, length to follow-up and any data related to the primary and/or secondary outcomes. Where the relationship between frailty and outcome was qualitatively but not quantitatively expressed, primary authors were contacted in an attempt to gain additional primary data. Where the same study appeared to be reported across more than one article, only the most complete submission was included, with the aim of maximising the volume of frailty data included.

### ***Quality and bias assessment***

No validated quality assessment tool has been widely established to assess observational studies that are not designed to directly compare two groups. The Newcastle-Ottawa Scale was used to provide a structured assessment of sample selection (4 points), comparability (2

points) and outcomes (3 points).<sup>15</sup> This gives a maximum score of 9 points. Studies were independently assessed by two reviewers and disagreement resolved by consensus:  $\geq 7$  points considered high quality for frailty reporting,  $< 7$  moderate or low quality. Publication bias was assessed in the primary endpoint with the greatest number of studies by creating a funnel plot and using Egger's regression test.<sup>16</sup> We then corrected for asymmetry using the trim and fill method to determine an adjusted effect size.<sup>17</sup>

### ***Data synthesis and analysis***

All included studies were observational cohorts with respect to frailty. Meta-analysis was performed when at least three studies reported a comparable endpoint to generate a meta-estimate. Given the wide number of frailty tools available, significant heterogeneity was expected across the studies and therefore a random-effects model (maximum likelihood approach) was chosen to calculate summary effect estimates.<sup>18</sup> Statistical analysis was performed using the *metafor* statistical package within R version 3.1.3 (<http://www.r-project.org>) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA). A value of  $p < 0.05$  was considered statistically significant.

## **Results**

### ***Search results and patient characteristics***

We identified 2,623 abstracts from our initial search, resulting in 54 articles for full-text review to assess eligibility. Ten studies from Europe and North America met the full inclusion criteria (Figure 1). These comprised 4,592 patients undergoing TAVI in whom a frailty measure was made prior to surgery. The mean age was 80 to 86 years, 34% to 53% of participants were men, and the STS-predicted 30-day mortality rates where available were

between 6.3% and 16.6%. In those studies detailing the access route chosen for TAVI, the femoral approach was the most common, although this ranged from 47% to 100% of cases. The proportion of TAVI patients identified as frail varied greatly across the included studies, from 5% to 83% (Table 1).

### **Definitions of frailty**

Frailty was identified by authors as either *subjective* (four studies) or *objective* (six studies). Subjective frailty was based on the judgement of a clinical team without reporting use of a specific tool. Objective frailty was determined by use of a tool specifically with the purpose of defining frailty, such as activity of daily living assessments, comprehensive geriatric assessment and frailty indices. With the exception of one small study of 30 patients by Kamga *et al*<sup>19</sup>, frailty data was available as a dichotomised variable when related to outcomes, even where it had been measured on a continuous scale.

### **Frailty and mortality**

Four studies (n=1,900) reported frailty (using objective measures) and early ( $\leq 30$  days) mortality after TAVI (Table 2 and Figure 2), identifying greater than doubling of the risk of early death amongst patients identified as frail (HR 2.35, 95% CI 1.78-3.09,  $p < 0.001$ ). All papers reported unadjusted univariate analyses for the association between frailty and mortality. There was no significant heterogeneity between studies ( $I^2 = 0\%$ ,  $p = 0.33$ ).

Seven studies (n=3,159) quantified the relationship between frailty and late mortality  $> 30$  days after TAVI, with every study completing at least one year of follow-up (Table 3 and Figure 2). All reported an increased risk of death amongst frail patients, with an overall effect size of HR 1.63 (95% CI 1.34-1.97,  $p < 0.001$ ). The was only marginally increased by



restricting analysis to studies undertaking adjustment for potential confounders (5 studies, HR 1.85, 95% CI 1.34-2.55,  $p < 0.001$ ) or including only studies of higher quality for frailty reporting (4 studies, HR 1.79, 95% CI 1.28-2.50,  $p < 0.001$ ). There was moderate heterogeneity ( $I^2 = 66\%$ ,  $p = 0.01$ ), which was reduced by performing a sensitivity analysis by the type of frailty measure used (Figure 3 and Supplementary Figure 1). The mortality risk for frail patients was greater amongst those studies using an objective measure (HR 2.63, 95% CI 1.87-3.70,  $p < 0.001$ ) rather than subjective assessment (HR 1.42, 95% CI 1.28-1.59,  $p < 0.001$ ).

Five studies provided the absolute number of deaths by frailty status allowing combined incidence estimations. This calculation totalled 3629 TAVI patients (24.6% frail) followed for the equivalent of 2717 patient years. Amongst those with frailty, 34 deaths/100 patient years were observed, against 19 deaths/100 patient years in non-frail individuals (Table 4). Two studies could not be included in the meta-analysis due to frailty being reported as a continuous variable (Kamga *et al*<sup>19</sup>), or because only a composite end point of MACCE (major adverse cardiovascular or cerebrovascular event) rather than all-cause mortality was reported (Ewe *et al*<sup>20</sup>). However, both studies did report significant associations of frailty with poorer outcomes including late mortality.

### ***Frailty and VARC outcomes***

There was wide variation in the reporting of secondary outcomes across the included studies, with only three studies reporting comparable outcomes in relation to frailty. Meta-analysis of these endpoints was therefore not possible. VARC outcome measures  $\leq 30$  days after TAVI were reported in relation to frailty status in only two of the included studies, totalling 544 patients (Table 2). Both used objective tools, and reported increased effect

estimates for the risk of major bleeding and renal failure requiring dialysis in frail patients, but only the latter complication reached significance in the paper by Puls *et al* (OR 2.23, 95% CI 1.12-4.47,  $p=0.02$ ). Both studies reported no increase in the risk of stroke amongst frail individuals after TAVI.

### **Quality and risk of bias**

Six studies met our frailty-defined criteria for high quality (Newcastle-Ottawa scale score  $\geq 7$ ) and four were considered moderate or low in quality (Supplementary Table S1). No study scored maximum points. All those considered of lower quality did not include adjustment for potential confounders of the relationship between frailty and outcomes. Publication bias was observed amongst the seven studies reporting late mortality (Egger's test for asymmetry  $p=0.02$ ). Adjustment by the trim and fill method (see Supplementary Figure S2 funnel plot) had no effect on the size estimate, which remained statistically significant (HR 1.59, 95% CI 1.33-1.90,  $p<0.001$  vs HR 1.63, 95% CI 1.34-1.97,  $p<0.001$  before adjustment).

### **Discussion**

In this systematic review and meta-analysis we explored the relationship between pre-procedure frailty and outcomes after TAVI in 10 studies from Europe and North America comprising 4,592 patients. We have made several important observations. First, the measurement of frailty detects a population at double the risk of both early and late mortality after TAVI. Second, using objective measures of frailty appears to identify an even more vulnerable group than 'end-of-the-bed' subjective assessment. However, it is worth acknowledging that such subjective frailty assessment still provides important discrimination

of risk within a population already considered at 'high-risk' for conventional surgery. Third, VARC complication rates in relation to frailty status are not well reported, with only very limited data to suggest increased risk of dialysis requirement and bleeding risk in frail patients. However, these observations were not suitable for meta-analysis and are subject to competing risk bias from the increased early mortality observed amongst those with frailty.

A recent review by Puri *et al* has emphasised the potential value of frailty assessment in TAVI candidates.<sup>21</sup> Through the process of systematic review and meta-analysis, we have further clarified the growing body of research in this area and have numerically quantified the mortality risk of frailty identified by both objective and subjective measures. Established methods for determining those most likely to benefit from TAVI over medical management or conventional surgical aortic valve replacement are lacking. The PARTNER randomised controlled trial of high-risk severe aortic stenosis patients, demonstrated improved survival with TAVI, but 43% of patients had still died within 2 years of intervention compared to 68% with standard medical care. The stroke rate of 13.8% in the TAVI cohort was also more than double that of medically managed patients,<sup>22-25</sup> although rates are falling as procedural techniques improve.<sup>26</sup> TAVI as an intervention may therefore have population level survival benefits over medical management, but the severe aortic stenosis population is heterogeneous and individual risk is likely to vary greatly.

Mortality prediction using traditional risk assessment tools such as the STS mortality score and logistic EuroSCORE was commonly reported amongst the reviewed papers. It is possible to directly compare these figures to observed early ( $\leq 30$  days) mortality in six of the included studies (Supplementary Table S2). This comparison highlights the poor correlation of predictive scores with actual outcomes in this population, which is perhaps unsurprising given these tools were developed in younger cohorts excluding TAVI. Others have also

identified the weakness of existing risk scores.<sup>5,6</sup> It is noteworthy that these predictive algorithms only provide prognostic estimates for early surgical outcomes, which may not be the most important endpoint after TAVI. In such complex older patients approaching the end of life, quality of life after intervention may be more important than survival or avoidance of procedural complications. A systematic review by Kim *et al* of function and quality of life after TAVI reported mixed patient outcomes, with improvements in physical function amongst survivors not matched by changes in psychological and general health measures.<sup>27</sup>

Frailty has gained traction within surgical and cardiovascular literature as a potential metric for the currently unmeasured risk of older patients undergoing complex interventions.<sup>10-13</sup> Whilst this may be seen as positive for the holistic care of older patients, there is wide variation in definitions and measurement. In this review, the six studies that sought to objectively measure frailty each used different tools, varying from functional scales to composite scores including nutrition, cognition and mobility. In the absence of trial data with randomisation based upon frailty, it is not possible to infer which elements of these measures will carry the most prognostic weight. However, it is notable that all the tools used included some estimation of participation in activities of daily living. It is possible that such measures are particularly sensitive to procedural risk in severe aortic stenosis populations, as impairments may reflect established heart failure at the time of consideration for TAVI.

There remains no consensus on the optimum approach to frailty assessment. The majority of studies included in this review considered frailty as a dichotomised variable for the purpose of outcome analysis. This reflects the phenotypic model of frailty and is perhaps attractive as a simple clinical concept.<sup>8</sup> However, forcing a continuous variable into a binary form limits the consideration of a 'pre-frail' status, and may be open to criticism for the

potentially arbitrary nature of the threshold used to define frailty. Dichotomous phenotypic frailty assessment may also suffer from saturation amongst the highest risk populations and therefore provide limited discrimination compared to an index of deficits.<sup>28</sup> A formal Frailty Index, such as that first described by Rockwood *et al*<sup>29</sup>, may better reflect the accumulation of markers of frailty over time. Three of the included studies do present some outcome data per unit change in the chosen frailty index, but given the differences in the structure of these scales meta-estimation of a combined effect size was not possible or logical.

Although the included studies comprise 4,592 patients undergoing TAVI, there are even larger published population registries in America, the United Kingdom, France, Germany, Italy and Belgium. Unfortunately, there is currently no systematic measurement of frailty within any of these cohorts of consecutive patients.<sup>30-34</sup> It is likely that these registries will be used to produce future TAVI-specific surgical risk assessment tools similar to STS and EuroSCORE, and therefore inclusion of frailty measurement would provide a valuable opportunity to test effectiveness in large populations.

### **Limitations**

Several limitations of our review should be considered. First, there are no studies randomised by frailty status, and so it is likely that patient selection in the observational cohort studies included in our meta-analysis was already influenced by underlying and unmeasured frailty. This is inevitable given the nature of TAVI as a treatment reserved for high-risk aortic stenosis patients requiring valve replacement. Whilst this selection bias may limit interpretation of frailty measurement in a broader aortic stenosis population, the results are representative of real-world TAVI cohorts. Studies evaluating frailty and

outcomes in patients referred for TAVI, but in whom the procedure was felt too high risk by their multidisciplinary team, would be informative but to our knowledge, no such studies have been reported. Second, we have only included studies where frailty was defined by the researchers. It is possible that other data exist including similar measurements without specific use of the term frailty. However, such studies would be less likely to report outcomes directly related to these measures without acknowledging the concept of frailty. Third, the meta-estimate for early mortality is based on a small number of studies, without adjustment for potential confounders. We were limited by the infrequent reporting of standardised VARC complications in relation to frailty status and these interpretations are open to competing risk bias. Therefore, whilst the observations of the effect of frailty on early outcomes are important, further work is required in this area. It is in this light that the addition of objective frailty measures to ongoing large TAVI registries would be helpful.

### **Conclusions**

We demonstrate that frailty is associated with poorer early and late outcomes in TAVI patients. Objective frailty tools identify an even more vulnerable population at greater than double the late mortality risk of non-frail patients. There is currently a lack of consistency in frailty measures and clarity in reporting against standardised early VARC outcomes. Given the ongoing uncertainty in appropriate patient selection for TAVI, randomised controlled trials should consider including patients based on an objective assessment of frailty status.

### **Supplementary Data**

This section includes the Medline electronic search strategy, individual study quality (risk of bias) assessment, sensitivity meta-analyses for late mortality after TAVI, a comparison of predicted against observed early mortality, and a funnel plot for publication bias.

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**Disclosures**

Conflict of interest: none declared

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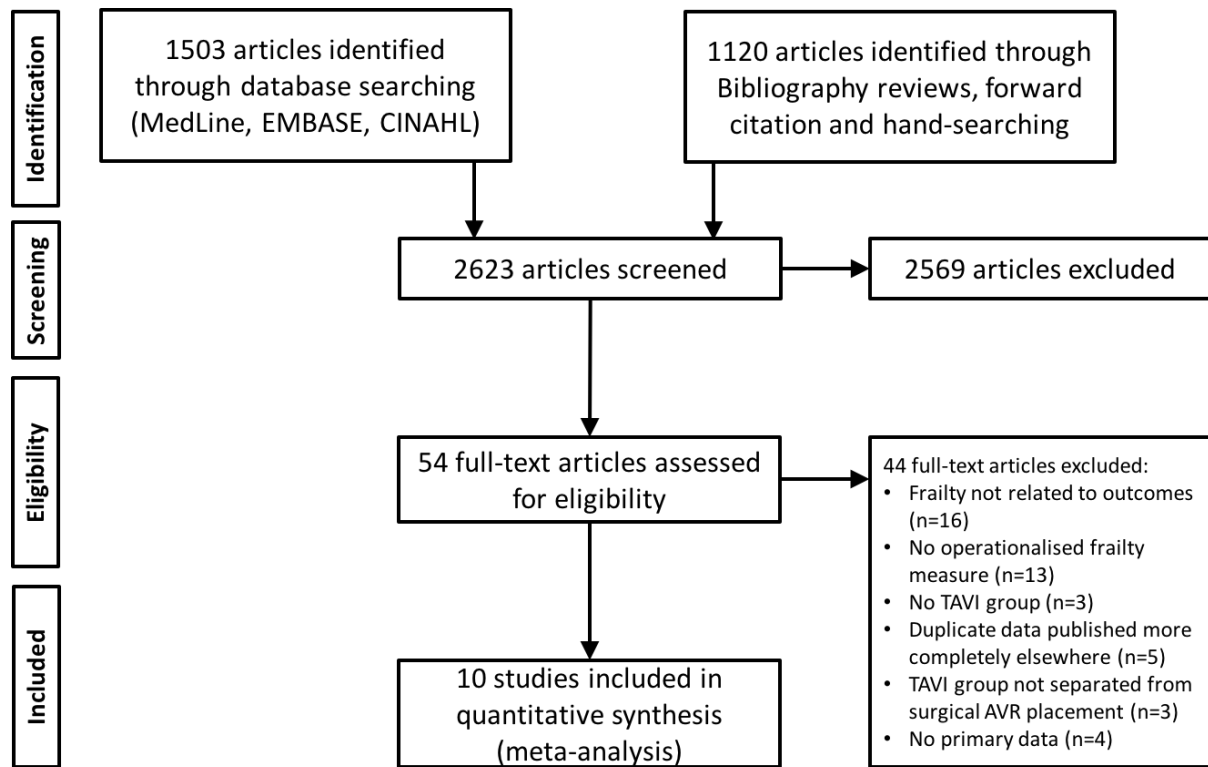
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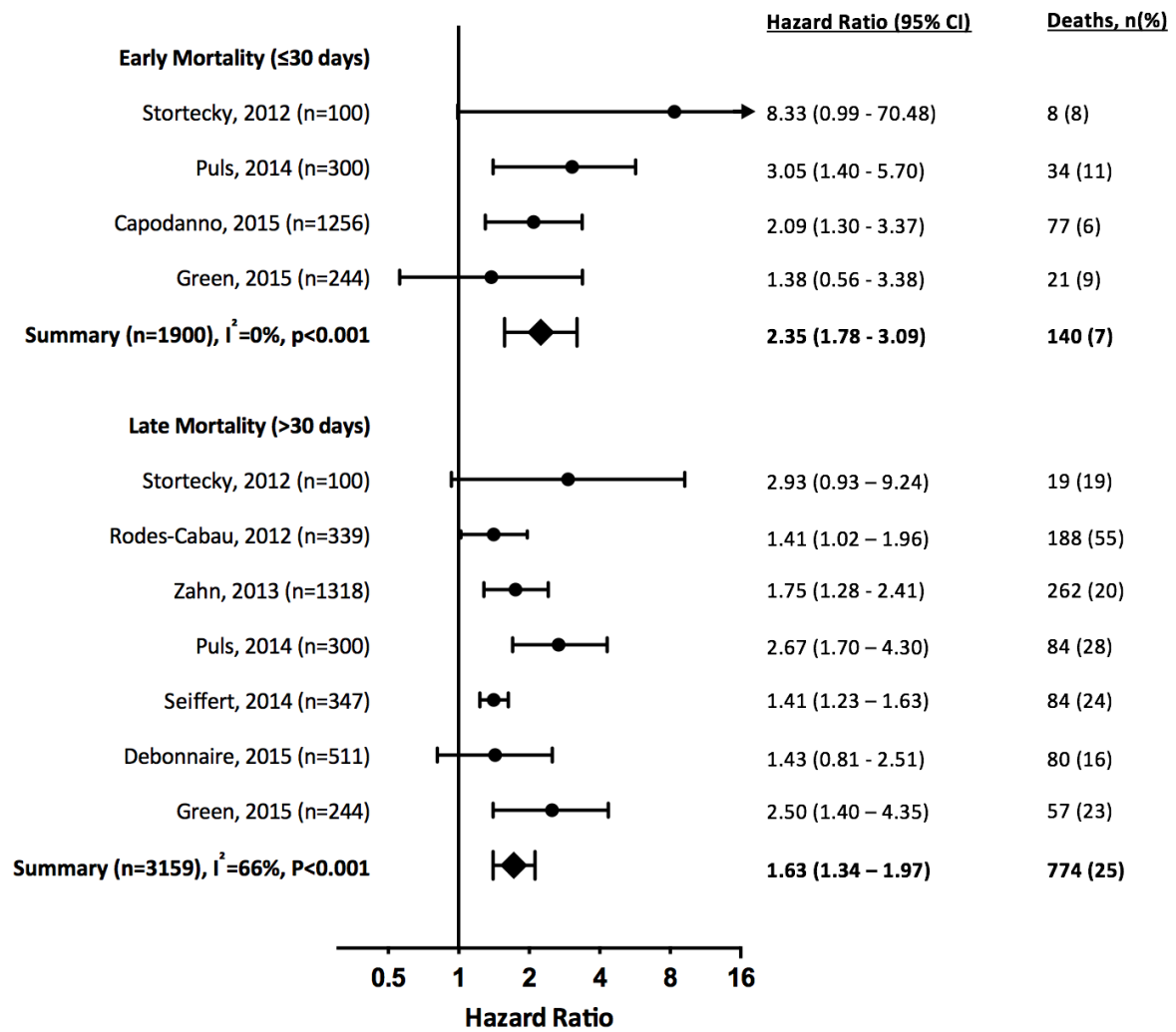
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**Figure 1:** Flow diagram of reviewed studies

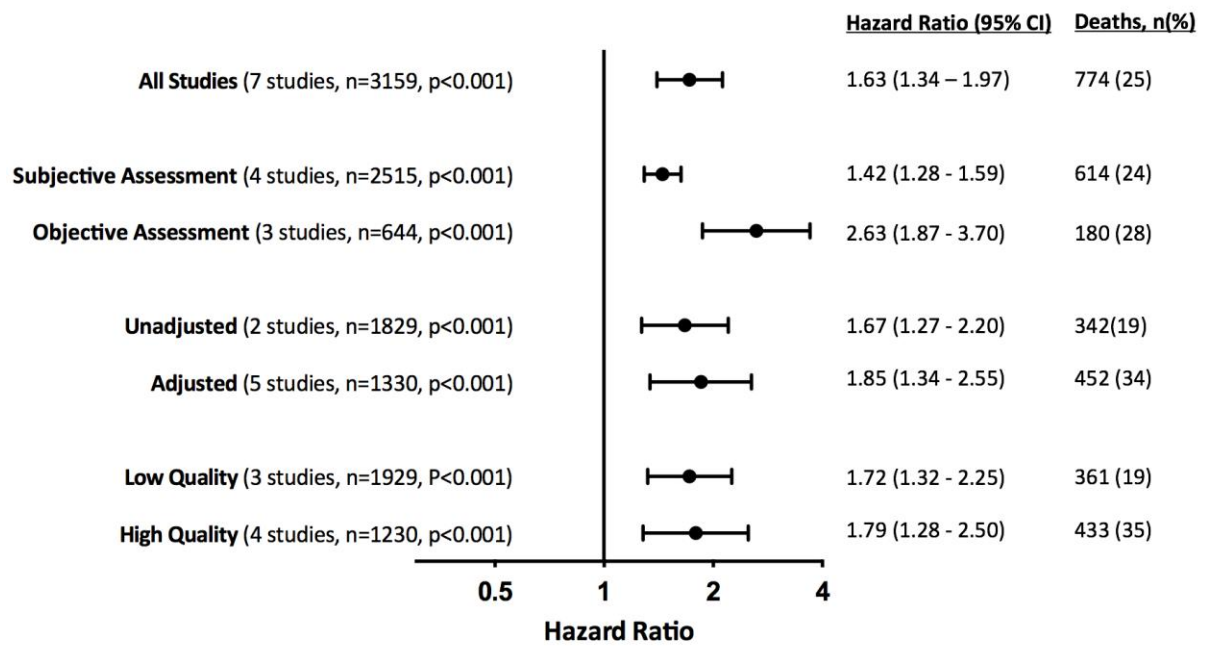




**Figure 2:** Risk of early ( $\leq 30$  days after TAVI) and late ( $>30$  days) mortality in studies suitable for meta-analysis ordered by date of publication. Summary meta-estimate calculations based on random effects model analysis.



**Figure 3:** Risk of late (>30 days after TAVI) mortality amongst frail patients. Summary meta-estimates presented grouped by type of frailty assessment used (subjective vs objective), adjustment for confounders (unadjusted vs adjusted) and study quality with regard to frailty reporting (high vs low). All summary meta-estimate calculations based on random effects model analysis. Individual study level data is presented in Supplementary Figure S1.



**Table 1: Contextual details of included studies**

Author, year	Country	Definition of frailty	n	Mean age (years)	Male gender (%)	Proportion frail (%)	TAVI access route	30-day mortality (%)	1-year mortality (%)
Ewe, 2010 <sup>20</sup>	Netherlands/Italy	Fried criteria based on gait speed, grip strength, weight loss, physical activity and exhaustion	147	80	43	32.7	Femoral 11%, apical 49%	6.8	15.0
Stortecky, 2012 <sup>35</sup>	Switzerland	Frailty Index based upon geriatric assessment of cognition, nutrition, timed get-up-and-go, ADLs and disability. Scored 0-7 with $\geq 3$ considered frail	100	84	40	49	Femoral 55%, apical 14%, subclavian 1%	8.0	19.0
Rodes-Cabau, 2012 <sup>36</sup>	Canada	Subjective assessment of multidisciplinary team	339	81	45	25.1	Femoral 48%, apical 52%	10.6	-
Kamga, 2013 <sup>19</sup>	Belgium	ISAR score (self-reported functional dependence, recent hospitalisation, impaired memory, difficulties with vision and polypharmacy)  SHERPA score (age, ADLs, cognitive decline, falls and self-perceived health)	30	86	53	ISAR: 83.3% moderate or high risk  SHERPA: 73.3% moderate or high risk	Femoral 100%	-	26.7

Zahn, 2013 <sup>37</sup>	Germany	Presumed subjective assessment (limited detail)	1318	82	42	17.7	Femoral 8%, apical 9%, subclavian 2%, aortic 1%	-	19.9
Puls, 2014 <sup>38</sup>	Germany	Katz Index of ADLs (score <6 frail)	300	82	34	48	Femoral 7%, apical 53%	11.3	28
Seiffert, 2014 <sup>39</sup>	Germany	Subjective assessment guided by CHSA Clinical Frailty Scale <sup>29</sup> score ≥6	347*	81	52	4.6	-	-	24.2
Capodanno, 2014 <sup>40</sup>	Italy	Geriatric Status Scale based upon ADLs, cognition, continence and mobility. Scored 0-3 with ≥2 labelled frail	1256†	82	42	24.4	-	6.1	-
Debonnaire, 2015 <sup>41</sup>	Netherlands/ Italy	Presumed subjective assessment	511	82	38	19.2	Femoral 22%, apical 48%	5.7	15.7
Green, 2015 <sup>42</sup>	USA	Frailty score composed of serum albumin, grip strength, gait speed and ADLs. Scored between 0-12 with ≥6 considered frail	244	86	52	45.1	Femoral 49%, others presumed apical	8.6	23.5

Abbreviations: ADLs = activities of daily living. Observed mortality data refer to the whole study population including frail and non-frail individuals.

\*Only the Bonn subgroup that received frailty assessment considered from this multicentre study

†Only the development cohort of this study included. The validation data set does not contain frailty related outcome data.

**Table 2: Early ( $\leq 30$  days) outcomes related to frailty in included studies**

Author, year	Outcome(s) related to frailty	Adjustment	Effect estimate*	Lower 95% CI	Upper 95% CI	p-value
Stortecky, 2012 <sup>35</sup>	30 day MACCE	Nil	4.78	0.96	23.77	0.05
	30 day MAACE (per unit increase in frailty index)	Nil	1.66	1.14	2.44	0.01
	30 day all cause mortality	Nil	8.33	0.99	70.48	0.03
	30 day all cause mortality (per unit increase in frailty index)	Nil	2.18	1.32	3.61	0.002
Puls, 2014 <sup>38</sup>	All cause mortality	Nil	3.05	1.4	5.7	0.003
	Procedural myocardial infarction	Nil	1.08	0.15	7.59	0.94
	Procedural major stroke	Nil	0.98	0.41	2.33	0.95
	Procedural TIA	Nil	1.08	0.07	17.16	0.95
	Life-threatening or disabling bleeding	Nil	0.86	0.45	1.62	0.63
	Major bleeding	Nil	2.17	0.84	5.62	0.11
	Minor bleeding	Nil	1.50	1.05	2.16	0.03
	Renal failure requiring dialysis	Nil	2.01	1.09	3.70	0.02
	Capodanno, 2014 <sup>40</sup>	All cause mortality	Nil	2.09	1.30	3.37

Green, 2015 <sup>42</sup>	All cause mortality	Nil	1.34	0.59	3.04	0.48
	Cardiovascular mortality	Nil	1.22	0.47	3.14	0.68
	Major stroke	Nil	0.61	0.06	6.63	0.68
	Major bleeding	Nil	1.74	0.69	4.42	0.24
	Major vascular complications	Nil	1.42	0.49	4.11	0.52
	Permanent pacemaker insertion	Nil	1.02	0.46	2.26	0.97
	Renal failure requiring dialysis	Nil	1.57	0.60	4.07	0.36

\*Where not presented directly by authors, relative risk ratios calculated from 2 by 2 tables for those with and without frailty.

Abbreviations: MAACE = major adverse cardiovascular and cerebral events.

**Table 3: Late ( $\geq 30$  days) outcomes related to frailty in included studies**

Author, year	Outcome(s) related to frailty	Adjustment	Effect estimate*	Lower 95% CI	Upper 95% CI	p-value
Ewe, 2010 <sup>20</sup>	MACCE defined as composite of death, nonfatal stroke, heart failure or nonfatal myocardial infarction (mean follow-up 9.1 months)	Logistic EuroSCORE, peripheral vascular disease, previous CABG, baseline LVEF	4.20	2.00	8.84	<0.001
Stortecky, 2012 <sup>35</sup>	1 year MACCE	Nil	4.89	1.64	14.6	0.003
	1 year MACCE	STS score	4.17	1.37	12.72	0.01
	1 year MACCE	Logistic EuroSCORE	4.48	1.48	13.53	0.01
	1 year MACCE (per unit increase in frailty index)	Nil	1.80	1.33	2.45	<0.001
	1 year all cause mortality	Nil	3.68	1.21	11.19	0.02
	1 year all cause mortality	STS score	2.93	0.93	9.24	0.07
	1 year all cause mortality	Logistic EuroSCORE	3.29	1.06	10.15	0.04
	1 year all cause mortality (per unit increase in frailty index)	Nil	1.80	1.31	2.47	<0.001
Rodes-Cabau, 2012 <sup>36</sup>	All cause mortality (mean follow-up 42 $\pm$ 15 months)	Atrial fibrillation, cerebrovascular disease, COPD, eGFR, pulmonary hypertension	1.41	1.02	1.96	0.034
	Late all-cause mortality (excluding mortality within 30 days of TAVI)	Age, atrial fibrillation, COPD, eGFR	1.52	1.07	2.17	0.021

Kamga, 2013 <sup>19</sup>	1 year all cause mortality (per 1 unit increase in SHERPA score)	Unclear but likely gender, BMI, pulmonary hypertension, diabetes	2.74	1.39	5.39	0.004
Zahn, 2013 <sup>37</sup>	1 year mortality	Nil	1.50	1.19	1.89	<0.001
Puls, 2014 <sup>38</sup>	All cause mortality (median follow up 537 days)	Age and sex	2.67	1.7	4.3	<0.0001
Seiffert, 2014 <sup>39</sup>	1 year mortality	Age and sex	1.41	1.23	1.63	<0.001
Debonnaire, 2015 <sup>41</sup>	1 year mortality	Nil	1.29	0.80	2.06	0.29
Green, 2015 <sup>42</sup>	1 year all cause mortality (frailty dichotomised)	Nil	2.18	1.27	3.75	0.005
	1 year all cause mortality (frailty dichotomised)	Stepwise inclusion of variables† with entry/stay criteria of 0.1/0.1 and a maximum of one covariate for every 10 events.	2.5	1.40	4.35	0.002
	1 year all cause mortality (per unit increase in frailty score)	Nil	1.12	1.02	1.22	0.01
	Poor outcome (death or poor quality of life‡) at 6 months	Stepwise inclusion of variables† as above	2.21	1.09	4.46	0.03
	Poor outcome (death or poor quality of life‡) at 1 year	Stepwise inclusion of variables† as above	2.40	1.14	5.05	0.02

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Abbreviations: MACCE = major adverse cardiovascular and cerebral events; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; BMI = body mass index; TIA = transient ischaemic attack; STS = Society of Thoracic Surgeons.



\*Where not presented directly by authors, relative risk ratios calculated from 2 by 2 tables for those with and without frailty.

†Candidate variables: age, sex, body mass index, access route, STS score, diabetes, hypertension, angina, heart failure, New York Heart Association class IV, coronary artery disease, previous coronary angioplasty, previous CABG, cerebrovascular disease, peripheral vascular disease, previous balloon aortic valvuloplasty, permanent pacemaker, renal disease, liver disease, chronic pulmonary disease, aortic valve mean gradient, ejection fraction, moderate or severe mitral regurgitation.

‡ Poor quality of life defined as Kansas City Cardiomyopathy Questionnaire Overall Summary score < 45, or a decrease of  $\geq 10$  points on serial testing before and after TAVI.

**Table 4: Comparisons of mortality in frail and non-frail patients after TAVI**

Author, year	Zahn 2013 <sup>37</sup>	Puls 2014 <sup>38</sup>	Capodanno 2014 <sup>40</sup>	Debonnair 2015 <sup>41</sup>	Green 2015 <sup>42</sup>	Overall
Frail (n)	233	144	306	98	110	891
Frail deaths (n)	70	80	30	20	36	236
Non-frail (n)	1085	156	950	413	134	2738
Non-frail deaths (n)	217	37	47	60	21	382
Follow-up period	Mean 12.9 months	Median 537 days	30 days	1 year (censored)	1 year (censored)	-
Frail years of follow- up	250	212	25	98	110	695
Non-frail years of follow-up	1166	230	78	413	134	2021
Death rate/100 frail patient years	28	38	120	20	33	<b>34</b>
Death rate/100 non- frail patient years	19	16	60	15	16	<b>19</b>