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ORIGINAL ARTICLE

Factors That Prevent Progression to Transcatheter Aortic Valve Implantation (TAVI)

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Background Transcatheter aortic valve implantation (TAVI) is increasingly used for intermediate- and high-risk patients with severe symptomatic aortic stenosis (AS). However, safe undertaking of the procedure may be precluded by various anatomic factors. This study sought to identify prevalence of factors that prevent progression to TAVI.

Methods TAVI candidates with severe AS undergoing workup coronary angiography and iliac vessel angiography (±cardiac-gated CT) were identified and factors precluding TAVI were reviewed retrospectively from a single-centre cardiac database over a 10-year period.

Results 197 patients were included; mean age was 81.5 ± 6.5 years (±SD); 46.2% were male. 26.9% of TAVI candidates could not proceed to femoral access TAVI due to various factors including unsuitable peripheral vasculature (13.2%), untreated coronary artery disease (CAD) deemed high risk for TAVI (8.1%), unfavourable aortic characteristics (4.1%), and low-lying coronary ostia (1.5%). Factors associated with unsuitable femoral vasculature included female gender ($p < 0.01$) and any CAD ($p = 0.03$). Factors associated with the presence of unrevascularised CAD included male gender ($p < 0.01$), estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 ($p = 0.02$), history of CAD ($p < 0.01$), while prior percutaneous coronary intervention (PCI) or bypass surgery were protective (both $p < 0.01$). Rates of progression to TAVI have increased over the last 10 years ($p < 0.01$) from 58.3% prior to 2012 to 83.7% in 2016 and 2017, while incidence of unsuitable peripheral vasculature preventing TAVI ($p = 0.01$) and CAD deemed unsuitable for TAVI ($p = 0.04$) have both decreased.

Conclusions Non-progression to TAVI among higher risk patients with severe AS has become less common over the last 10 years with improvements in operator experience, lower profile devices, and wider ranges of valve sizes.

Keywords Transcatheter aortic valve implantation • Coronary artery disease • Femoral access • Aortic stenosis

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Introduction

Aortic stenosis (AS) is the most common valvular pathology in the elderly population and the preferred treatment has undergone major changes over the last 10 years with the development of transcatheter aortic valve implantation (TAVI) [1–3]. TAVI is now an accepted treatment for severe AS in high-risk surgical patients [2,3], and a reasonable alternative to surgical aortic valve replacement (SAVR) in intermediate-surgical risk patients [4] following demonstration of non-inferiority in the Placement of Aortic Transcatheter Valves (PARTNER II) and Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trials [5,6]. As indications expand to lower risk patients, TAVI procedural numbers are expected to increase [7], and with this, factors that may preclude patients from safely undergoing this procedure, become of increasing importance. Femoral arterial approach is the preferred access route for TAVI placement [8,9], however in the presence of diseased or narrowed vessels, alternate approaches (subclavian, direct aortic or apical) are required, which have increased periprocedural adverse events, prolonged recovery, and higher mortality [8–10]. Alternatively, the patient may require referral for SAVR. Similarly, incidental coronary artery disease (CAD) is present in up to three-quarters of patients with severe AS [11], and may increase mortality following TAVI, with severe disease potentially limiting patient suitability to proceed [12]. Aortic annulus size or orientation and low-lying coronary ostia at risk of occlusion during TAVI deployment also require careful assessment and may preclude the ability to safely perform the procedure. The aim of this retrospective cohort study is to identify the prevalence of factors that may prevent progression to TAVI in a real-world environment, as well as risk factors and subsequent management among a cohort of potential candidates with severe AS.

Materials and Methods

All consecutive patients with severe AS referred for consideration for TAVI who underwent preparatory peripheral and coronary angiography, with or without cardiac-gated computed tomography (CT), between August 2008 and February 2017 at the Alfred Hospital, a large tertiary centre in Melbourne, Australia were identified from the hospital cardiac database. Following screening angiography, patients are reviewed by the hospital 'Heart Team' (a multidisciplinary team of interventional cardiologists, non-interventional cardiologists and cardiothoracic surgeons) to decide on final suitability for TAVI, considering co-morbidities, Society of Thoracic Surgery Predicted Risk of Mortality (STS-PROM) score, frailty indices and the results of TAVI workup.

A detailed review of the hospital electronic medical records, coronary and iliofemoral angiography reports, and cardiac-gated CT reports was performed to identify patient demographics, subsequent management, and reasons for progression or non-progression to TAVI. Severe AS was defined as either valve area $<1.0\ cm^2$, dimensionless performance index (DPI) <0.25, or mean gradient >40 mmHg in the setting of normal left ventricular (LV) function on transthoracic echocardiography. Low-gradient severe AS was confirmed by dobutamine echocardiography if appropriate.

Native CAD was defined as $\geq 50\%$ stenosis (or the presence of a stent or prior coronary artery bypass graft [CABG]) in one or more native vessels on coronary angiography. Significant CAD was defined as $\geq 50\%$ stenosis in at least one native coronary artery or $\geq 50\%$ stenosis in a bypass graft in the absence of a patent previous stent or bypass graft supplying the same territory. Peripheral vasculature was considered to have precluded femoral access TAVI if vessels were assessed as unsuitable in angiographic reports or if 'Heart Team' decision cited unsuitable peripheral vessels as the main reason for not progressing to TAVI.

Valve types available at our institution during the study period include valves using 18 Fr delivery sheaths requiring a minimum femoral vessel diameter of 6 mm (CoreValve, Medtronic Inc., Minneapolis, MN, USA, available since August 2008; Edwards Sapien XT, Edwards Lifesciences Corporation, Irvine, CA, USA, available since July 2013; and St Jude Portico, St Jude Medical, Minneapolis, MN, USA, available since July 2015), as well as more recently 14 Fr and 16 Fr delivery sheaths requiring a minimum femoral vessel diameter of 5 mm and 5.5 mm, respectively (Medtronic Evolut R, Medtronic Inc., available since January 2015 and Edwards Sapien 3, Edwards Lifesciences Corporation, available since June 2015). Over the study period 284 TAVI procedures were performed at our institution, with 70 TAVIs performed in 2016, and more than 90 procedures in 2017.

Patients excluded from the study included: 1) patients considered unsuitable for TAVI due to frailty, comorbidities, patient preference, or death prior to procedure; 2) patients who had their TAVI workup by referring doctors at other hospitals; 3) patients being considered for TAVI for AS occurring in the context of a prior bioprosthetic SAVR. Trial patients from the CoreValve Trial, Edwards Solace Trial, Medtronic Forward Evolut R Trial, Portico 1 Trial, and Portico IDE Trial were included in the study, and made up 58% of the patients proceeding to TAVI. The project was approved by the Alfred Hospital Research and Ethics Committee.

Statistical Analysis

Statistical analysis was performed using Stata version 14.2 for Macintosh (Stata Corp LP, College Station, TX, USA). Baseline characteristics are presented as frequencies and percentages for categorical variables, and mean $\pm$ SD for continuous variables. Factors associated with unsuitable iliofemoral vasculature and presence of significant CAD were assessed using multivariate logistic regression. Comparison between continuous variables in anatomical characteristics between men and women uses unpaired t-test and comparison between left and right uses paired t-test. All calculated p-values were two-sided and p-values of <0.05 were considered statistically significant.

Results

There were 271 patients in total who underwent TAVI workup screening angiography across the study period, 74 of these patients were excluded due to alternate reasons for not proceeding to TAVI (including frailty or comorbidities – 50.0%, loss-to-follow-up – 16.2%, patient preference – 9.4%, low surgical risk favouring surgical AVR – 6.8%, resectable lung malignancy during surgical aortic valve replacement [AVR] – 5.4%, death – 5.4%, or other reasons – 6.8%), while 197 patients were included in the study. Baseline characteristics are presented in Table 1. Mean age was 81.5 ± 6.5 years and 46.2% were male. Overall, 76.1% progressed to TAVI, 73.1% via femoral approach, and 3.0% via non-femoral approach (Figure 1).

Femoral Access

Unsuitable iliofemoral vasculature prevented progression to femoral access TAVI in 13.2% of the cohort: 10.2% were unsuitable due to narrow iliofemoral vessels with associated calcification, atheroma, or tortuosity; while 3.0% were unsuitable due to narrow diameter alone (Figure 1). Mean minimum luminal diameter by angiography of iliofemoral vessels that precluded progression to TAVI was 4.3 ± 1.6 mm. Cardiac-gated CT measurements of femoral vessels were available for 58.2% of the cohort and are presented in Table 2.

Among the 13.2% with unsuitable iliofemoral vessels, aortic stenosis was managed medically in 2.0%, with balloon aortic valvuloplasty with or without PCI in 3.0%, with SAVR with or without CABG in 5.1%, or via non-femoral approach TAVI in 3.0% (including left subclavian in 0.5%; and direct aortic approach via mini-thoracotomy in 2.5%) (Figure 1). In patients with available subclavian CT measurements, only two patients out of 55 (3.6%) had at least one subclavian with a diameter >6 mm in the presence of bilaterally narrow femoral vessels (both left and right ≤6 mm), which may have allowed access in the presence of unsuitable femoral vessels. No peripheral interventions were performed to iliofemoral vessels to allow femoral access for TAVI.

In multivariate analysis factors associated with unsuitable iliofemoral vessels for femoral access TAVI included female gender (odds ratio [OR] 7.4, 95% confidence interval [CI] 2.3-23.5, $p < 0.01$), and any CAD (OR 12.4, 95% CI 1.2-123.0, $p < 0.01$), while diabetes was protective (OR 0.24, 95% CI 0.1-1.0, $p = 0.05$) (Table 3). Unsuitable iliofemoral vessels that precluded TAVI predicted both presence ($p = 0.02$) and severity ($p = 0.04$) of native CAD, but not the presence of significant CAD ($p = 0.26$) in the whole cohort after adjustment for age and gender.

Coronary Artery Disease

Among the cohort, 31.0% had a prior history of CAD, 8.1% had prior PCI, and 14.2% had prior CABG, while 69.0% had no history of CAD (Table 1). Coronary angiography screening identified incidental significant CAD during TAVI workup in 27.4% of patients (or 39.7% of the 136 patients with no prior history of CAD) (Table 1). Significant CAD that may potentially require intervention at the time of TAVI consideration, defined as at least one unrevascularised coronary artery or graft with ≥50% stenosis, was present in 45.2% of patients (Table 1). At least one unrevascularised coronary artery or graft with a stenosis ≥70% was present in 31.5%. In multivariate analysis, factors associated with the presence of significant CAD at time of TAVI workup included a history of CAD (OR 18.3, 95% CI 3.4-98.3, $p < 0.01$), eGFR < 30 mL/

Table 1 Characteristics of patients with severe AS being assessed for TAVI.

	All patients N = 197
Demographic	
Age (years), mean ± SD	81.5 ± 6.5
Male, n(%)	91 (46.2)
BMI (kg/m^2), mean ± SD (n = 173)	27.6 ± 5.2
Comorbidities	
Hypertension, n(%)	151 (76.7)
Hypercholesterolaemia, n(%)	111 (56.4)
Smoking, n(%)	65 (33.0)
Diabetes, n(%)	49 (24.9)
eGFR < 30, n(%)	12 (6.1)
Active malignancy, n(%)	11 (5.6)
COPD, n(%)	34 (17.3)
Stroke, n(%)	29 (14.7)
Presence of Coronary Artery Disease	
Prior history coronary disease, n(%)	61 (31.0)
Prior PCI, n(%)	16 (8.1)
Prior CABG, n(%)	28 (14.2)
Incidental coronary disease[1], n(%)	54 (27.4)
1 Vessel n(%)	36 (18.3)
2 Vessels, n(%)	13 (6.6)
3 Vessels, n(%)	5 (2.5)
Left main, n(%)	0 (0)
Significant coronary disease[2]	
≥50% Stenosis: Any Vessel, n(%)	89 (45.2)
≥70% Stenosis: 1 Vessel n(%)	49 (24.9)
2 Vessels, n(%)	9 (4.6)
3 Vessels, n(%)	4 (2.0)
Coronary artery severity[3], mean(±SD)	1.1 ± 1.2

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

[1]Incidental coronary disease defined as ≥1 coronary artery stenosis in a patient with no prior history of coronary disease.

[2]Significant coronary disease defined as the presence of ≥1 coronary artery or bypass graft with a stenosis of ≥50% (in the absence of a patent previous stent or bypass graft); vessels with unrevascularised stenosis of ≥70% also included in table.

[3]Coronary artery severity defined as number of vessels with a stenosis of ≥50% (1, 2 or 3), with a left main coronary stenosis ≥50% designated a score of 4.

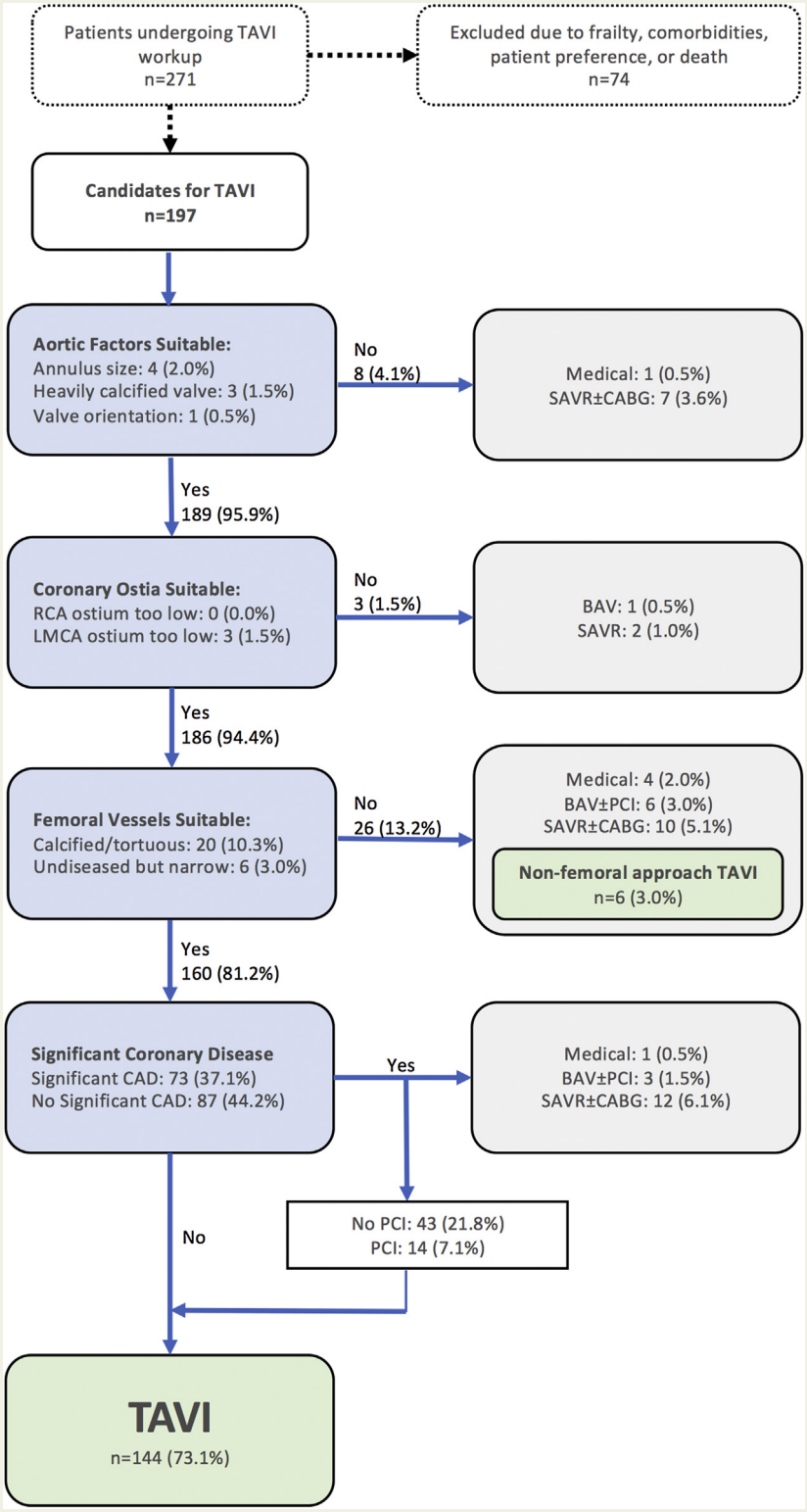

Figure 1 Progression to TAVI in severe AS: Flow chart demonstrating prevalence of factors that can prevent progression to TAVI among a cohort of patients with severe AS being assessed for suitability to proceed.
Abbreviations: CAD, coronary artery disease; medical, medical management for AS ± CAD; BAV, balloon aortic valvuloplasty; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; CABG, coronary artery bypass graft surgery.

Table 2 Cardiac-gated CT measures in patients being assessed for TAVI.

	All patients	Females	Males	P-value
Femoral Vessels	*n = 107*	*n = 51*	*n = 56*	
Left MLD (mm), mean ± SD	7.7 ± 1.7	7.1 ± 1.5	8.2 ± 1.6	<0.01
≤6 mm (18F Catheter), n(%)	22 (20.6)	15 (29.4)	7 (12.5)	
≤5 mm (14F Catheter), n(%)	8 (7.5)	6 (11.8)	2 (3.6)	
≤4 mm (10F Catheter), n(%)	2 (1.9)	1 (2.0)	1 (1.8)	
Right MLD (mm), mean ± SD	7.7 ± 1.7	7.1 ± 1.2	8.3 ± 1.9	<0.01
≤6 mm (18F Catheter), n(%)	23 (21.5)	14 (27.5)	9 (16.1)	
≤5 mm (14F Catheter), n(%)	8 (7.5)	4 (7.8)	4 (7.1)	
≤4 mm (10F Catheter), n(%)	2 (1.9)	1 (2.0)	1 (1.8)	
Subclavian Vessels	*n = 55*	*n = 24*	*n = 31*	
Left MLD (mm), mean ± SD	7.2 ± 1.5	6.7 ± 1.5	7.7 ± 1.3	0.01
≤6 mm (18F Catheter), n(%)	17 (30.9)	11 (45.8)	6 (19.4)	
≤5 mm (14F Catheter), n(%)	4 (7.3)	4 (16.7)	0 (0.0)	
≤4 mm (10F Catheter), n(%)	1 (1.8)	1 (4.2)	0 (0.0)	
	n = 49	*n = 23*	*n = 26*	
Right MLD (mm), mean ± SD	7.5 ± 1.9	6.8 ± 1.9	8.1 ± 1.7	0.01
≤6 mm (18F Catheter), n(%)	11 (22.5)	7 (30.4)	4 (15.4)	
≤5 mm (14F Catheter), n(%)	4 (8.2)	3 (13.0)	1 (3.9)	
≤4 mm (10F Catheter), n(%)	1 (2.0)	1 (4.4)	0 (0.0)	
Coronary Ostia Height Above Annulus	*n = 108*	*n = 51*	*n = 57*	
Left main (mm), mean ± SD	15.5 ± 2.9	14.6 ± 2.8	16.3 ± 2.7	<0.01
Height ≤12 mm, n(%)	14 (13.0)	9 (17.7)	5 (8.8)	
Height ≤10 mm, n(%)	4 (3.7)	4 (7.8)	0 (0.0)	
Right Coronary (mm), mean ± SD	17.0 ± 3.1	15.7 ± 2.7	18.1 ± 2.9	<0.01
Height ≤12 mm, n(%)	7 (6.5)	6 (11.8)	1 (1.8)	
Height ≤10 mm, n(%)	1 (0.9)	1 (2.0)	0 (0.0)	
Aortic Annulus	*n = 101*	*n = 58*	*n = 61*	
Aortic annulus area (mm^2), mean ± SD	490.5 ± 89.5	447.2 ± 67.7	531.4 ± 88.9	<0.01

Coronary ostia recommended to be >10–12 mm above annulus to avoid complication of ostia occlusion during TAVI procedure.
Analysis uses two-sample t-test for continuous variables to compare between genders.
Abbreviations: MLD, minimum luminal diameter; TAVI, transcatheter aortic valve implantation; CT, computed tomographic.

min/1.73 m^2 (OR 6.4, 95% CI 1.4-28.1, p = 0.02), and male gender (OR 3.4, 95% CI 1.6-7.0, p < 0.01) (Table 4). Prior PCI (OR 0.07, 95%CI 0.0-0.5, p = 0.01), prior CABG (OR 0.07, 95% CI 0.0-0.4, p < 0.01) and hypercholesterolaemia (possibly due to the use of statins) (OR 0.32, 95% CI 0.2-0.7, p < 0.01) were less likely to have significant CAD at time of TAVI workup.

Of the 89 patients with significant CAD, 16 patients were precluded from TAVI for other reasons not related to CAD, while 16 did not proceed to TAVI due to CAD alone (8.1%) and instead were managed either medically (0.5%), with balloon aortic valvuloplasty with or without PCI (1.5%), or with SAVR with or without CABG (6.1%) (Figure 1). The remaining 57 patients with significant CAD proceeded to TAVI following 'Heart Team' decision for either PCI in selected patients with a stenosis of ≥70% (24.6%) or no PCI (75.4%) prior. Among patients with significant CAD, those proceeding to PCI had a mean stenosis in the stented vessel of 85.0 ± 9.0%, while non-stented patients had a mean stenosis of 70.5 ± 22.8% in the most severely affected vessel, p = 0.01.

Coronary Ostium Height

Low left-main coronary ostium height (<10 mm above the annulus) precluded TAVI in three patients (1.5%) with patients proceeding to either balloon aortic valvuloplasty (one patient), or SAVR (two patients) (Table 1, Figure 1). Right coronary ostium height did not preclude TAVI in the cohort. In patients with available cardiac-gated CT (54.8% of the cohort), mean left coronary ostium height was 15.5 ± 2.9 mm (14.6 ± 2.8 mm in females, 16.3 ± 2.7 mm in males, p < 0.01), while right coronary ostium height was significantly higher (p < 0.01) at 17.0 ± 3.1 mm (15.7 ± 2.7 mm in females, 18.1 ± 2.9 mm in males, p < 0.01) (Table 2).

Table 3 Risk factors for unsuitable iliofemoral vessels in patients being assessed for TAVI.

	Iliofemoral Vessels Unsuitable for TAVI		
	No	Yes	
	N = *171*	N = *26*	P-value*
Demographic			
Age, mean ±SD	81.5 ± 6.3	81.6 ± 7.4	0.67
Female, n(%)	**86 (50.3)**	**20 (76.9)**	**<0.01**
BMI, mean ± SD (n = 173)	27.8 ± 5.3	26.0 ± 4.8	0.08
Comorbidities			
Hypertension, n(%)	129 (75.4)	22 (84.6)	0.22
Hypercholesterolaemia, n(%)	100 (58.5)	11 (42.3)	0.18
Smoking, n(%)	54 (31.6)	11 (42.3)	0.14
Diabetes, n(%)	**46 (26.9)**	**3 (11.5)**	**0.05**
eGFR < 30, n(%)	11 (6.4)	1 (3.9)	0.33
Active malignancy, n(%)	11 (6.4)	0 (0.0)	N/A
COPD,n(%)	29 (17.0)	5 (19.2)	0.36
Stroke, n(%)	25 (14.6)	4 (15.4)	0.75
Presence of Coronary Artery Disease			
Any coronary disease, n(%)	**93 (54.4)**	**19 (73.1)**	**0.03**
Significant coronary disease[1], n(%)	76 (44.4)	14 (53.9)	0.21
Prior history coronary disease, n(%)	51 (29.8)	10 (38.5)	0.49
Prior PCI, n(%)	13 (7.6)	3 (11.5)	0.87
Prior CABG, n(%)	23 (13.5)	5 (19.2)	0.90
Coronary artery severity[2], mean ± SD	1.0 ± 1.2	1.5 ± 1.4	0.11
Vascular Factors precluding TAVI			
Aortic factors unsuitable, n(%)	7 (4.1)	1 (3.9)	0.64
Coronary ostium unsuitable, n(%)	3 (1.8)	0 (0.0)	N/A

Abbreviations: TAVI, transcatheter aortic valve implantation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary; BMI, body mass index disease.

*Multivariate logistic regression including all variables. However, BMI and coronary artery severity score performed in separate analyses as BMI data not available for all patients and coronary artery severity score and any coronary disease were judged too similar; note – prior PCI and prior CABG both *negative* predictors of active coronary disease in multivariate analysis (after adjustment for prior history of coronary disease).

[1]Significant coronary disease defined as the presence of ≥1 coronary artery or bypass graft with a stenosis of ≥50% (in the absence of a patent previous stent or bypass graft supplying the same territory).

[2]Coronary artery severity defined as number of vessels with a stenosis of ≥50% (1, 2 or 3), with a left main coronary stenosis ≥50% designated a score of 4.

Aortic Factors

Unsuitable aortic annulus size prevented progression to TAVI in four patients (2.0%) – two patients too small, two patients too large; while unsuitable aortic valve orientation prevented progression in one patient (0.5%) with all five patients proceeding to SAVR (Figure 1). All cases of annulus size or orientation preventing progression to TAVI occurred prior to 2015 when there was a more limited range of valve sizes. A heavily calcified aortic valve at risk of annular rupture or coronary ostia occlusion prevented TAVI in three patients (1.5%), with two patients proceeding to SAVR while one patient was medically managed (Figure 1).

Temporal Changes

Progression to TAVI increased over the study period ($p < 0.01$), with 58.3% of patients proceeding prior to 2012 versus 83.7% proceeding in 2016 and 2017 (Figure 2). Prevalence of peripheral vessels preventing progression to femoral access TAVI has changed across the last 10 years ($p = 0.01$) with changes in availability of different delivery catheter sizes (19.4% unsuitable prior to 2012 vs 4.1% unsuitable in 2016 and 2017) (Figure 2). There were no temporal changes in left ($p = 0.15$) or right ($p = 0.33$) femoral vasculature diameters across the study period, nor overall proportion of narrow vessels with a diameter ≤6 mm ($p = 0.10$).

Prevalence of CAD deemed more appropriate for an alternate approach by the 'Heart Team' and thus preventing TAVI reduced over the period from 16.7% prior to 2012 to 4.1% in 2016 and 2017 ($p = 0.04$), despite rates of significant CAD remaining stable across the period ($p = 0.67$) (Figure 2). Prevalence of unsuitable aortic factors did not change across the period ($p = 0.70$) (Figure 2). There were no significant

Table 4 Risk factors for significant coronary disease in patients being assessed for TAVI.

	Significant Coronary Disease[1]		
	No	Yes	
	N = *108*	N = *89*	P-value*
Demographic			
Age, mean ±SD	81.7 ± 6.2	81.3 ± 6.8	0.35
Male, n(%)	**39 (36.1)**	**52 (58.4)**	**<0.01**
BMI, mean ± SD (n = 173)	27.7 ± 5.0	27.5 ± 5.6	0.77
Comorbidities			
Hypertension, n(%)	86 (79.6)	65 (73.0)	0.67
Hypercholesterolaemia, n(%)	**70 (64.8)**	**41 (46.1)**	**<0.01**
Smoking, n(%)	34 (31.5)	31 (34.8)	0.76
Diabetes, n(%)	28 (25.9)	21 (23.6)	0.75
eGFR < 30, n(%)	**3 (2.8)**	**9 (10.1)**	**0.02**
Active malignancy, n(%)	7 (6.5)	4 (4.5)	0.07
COPD,n(%)	18 (16.7)	16 (18.0)	0.92
Stroke, n(%)	14 (13.0)	15 (16.9)	0.90
Prior history coronary disease, n(%)	**26 (24.1)**	**35 (39.3)**	**<0.01**
Prior PCI[2], n(%)	**8 (7.4)**	**8 (9.0)**	**0.01**[2]
Prior CABG[2], n(%)	**16 (14.8)**	**12 (13.5)**	**<0.01**[2]
Vascular Factors precluding TAVI			
Iliofemoral vessels unsuitable, n(%)	13 (12.0)	13 (14.6)	0.41
Aortic factors unsuitable, n(%)	7 (6.5)	1 (1.1)	0.12
Coronary ostium unsuitable, n(%)	1 (0.9)	2 (2.3)	0.23

Abbreviations: TAVI, transcatheter aortic valve implantation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary; BMI, body mass index disease.

*Multivariate logistic regression including all variables. However, BMI and coronary artery severity score performed in separate analyses as BMI data not available for all patients and coronary artery severity score and significant coronary disease were judged too similar.

[1]Significant coronary disease defined as the presence of ≥1 coronary artery or bypass graft with a stenosis of ≥50% (in the absence of a patent previous stent or bypass graft supplying the same territory).

[2]Note – prior PCI and prior CABG both negative predictors of significant coronary disease in multivariate analysis (given adjustment for prior history of coronary disease).

temporal changes in baseline characteristics across the study period including age, gender, or comorbidities.

Discussion

Among our cohort, 73.1% of referred candidates proceeded to femoral access TAVI in a real-world environment. Previous trial cohorts have found rates of progression to TAVI from 19-46% among referred candidates, mainly related to not meeting trial criteria [1,13–15], however, among these cohorts, some patients were excluded due to frailty, other comorbidities, and death prior to procedure – these were excluded from our study. Our study demonstrates a relatively low rate of non-progression among TAVI candidates undergoing TAVI workup (83.7% in 2016 and 2017), with significant improvements over the last 10 years.

Femoral approach is the preferred access strategy for TAVI, with multiple studies demonstrating improved outcomes compared to non-femoral approaches [8–10]. However, peripheral artery disease is estimated to be present in 24.5% of patients undergoing femoral access TAVI and in 47.9% of those undergoing non-femoral access TAVI, and is associated with higher rates of bleeding and mortality [16]. In our cohort, 96% of patients who proceeded to TAVI by any approach, used femoral access. There are limited data available on rates of non-progression to TAVI in non-trial patients due to unsuitable femoral access where other access points were deemed unsuitable (13.2% in the current study, of which only 3.0% could proceed to non-femoral access). Novel approaches to treat patients with narrow peripheral vessels have included performing sheath-less TAVI procedures [17], and the use of peripheral angioplasty in calcified or narrowed vessels immediately prior to TAVI [18]. Factors associated with unsuitable femoral access included female gender and coronary disease, which is somewhat intuitive, however the protective association for diabetes is less understandable and may be related to chance given the large number of baseline variables assessed.

Current TAVI sheath sizes range from 14-19 Fr (4.67-6.33 mm) and developments in smaller sheath sizes and technique have clearly improved ability to navigate narrow femoral vessels as shown by the significant reduction in patients unable to proceed to TAVI due to unsuitable peripheral vasculature over the study period, with no change in patient vessel diameters. Further reduction in sheath diameter will likely diminish the impact of narrow peripheral vasculature on ability to proceed to femoral access TAVI, as well as reduce mortality related to vascular complications [19]. Access via the transaortic or subclavian approach remains an alternative to the transfemoral approach, and although these approaches were considered among our cohort for patients with unsuitable vasculature, the worsened trial outcomes for these patients were taken into account during the decision process [8–10]. Similarly, diseased subclavian arteries may coexist with diseased femoral arteries limiting this access route in unsuitable femoral access patients (we found only 3.6% of patients had narrow femoral arteries with accessible subclavian arteries). Therefore, among the reducing number of patients with unsuitable femoral access there were few patients (3%) who proceeded to non-femoral access TAVI, with only 2.5% using transaortic access, 0.5% using subclavian access, and no patients using transapical access. Nonetheless, these access points remain viable alternatives.

In the current study, incidental CAD was present in 27.4% of patients and 31.0% had a known history of CAD (total

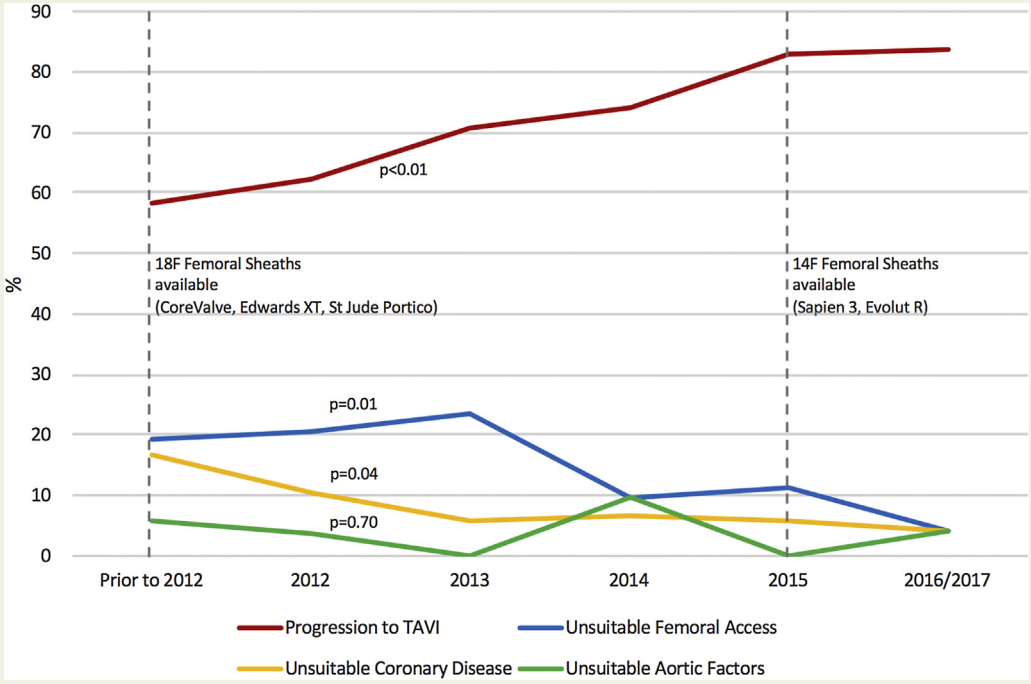

Figure 2 Temporal changes in progression to TAVI: Percentage of TAVI candidates with severe AS able to proceed to TAVI by year, compared against prevalence of procedural factors preventing progression to TAVI by year, including unsuitable femoral access, coronary disease judged more suitable for an alternate approach by the hospital 'Heart Team', and unsuitable aortic factors (including low-lying coronary ostia); p-value reflects whether significant change in prevalence across the period. Dotted lines indicate when 18F (6 mm diameter) and 14F (5 mm diameter) sheath sizes became available and their relation to acceptable iliofemoral vessel access for transcatheter aortic valve implantation (TAVI).

58.4%). Previous studies have reported rates of CAD at 49-76% among TAVI patients [11,20]. In SAVR, multiple studies have demonstrated that untreated CAD increases postoperative mortality, making CABG for concomitant CAD at time of SAVR the standard of care [21,22]. However, there are mixed data assessing the effect of CAD on outcomes following TAVI, with early studies suggesting an increase in mortality [20], while others have shown no difference [11,23]. Concerningly, a recent systematic review and meta-analysis demonstrated increased vascular complications and 30-day mortality among patients undergoing TAVI and PCI during the same procedure compared to TAVI alone [24]. The current approach to concomitant unrevascularised CAD in TAVI patients is controversial with the treatment approach determined by individual centres on a patient by patient basis. The current study demonstrates that most patients with unrevascularised CAD, who are not precluded for another reason, proceed to TAVI without intervention (21.8% no PCI vs. 7.1% PCI vs. 8.1% SAVR or did not proceed).

Other factors demonstrated to affect progression to TAVI in our cohort included coronary ostium height above the annulus (1.5%), due to concerns regarding coronary ostial occlusion, which is estimated to complicate 0.7% of TAVI procedures [27], occurring more frequently in the left coronary ostium (88% in one review) [25]. Given that ostial occlusion can be a catastrophic complication, coronary ostium height remains an important consideration, however low coronary ostium (<10 mm above annulus) had minimal overall impact on the total cohort, only affecting three patients. The left coronary ostium appears to be more prone to occlusion compared to the right coronary, likely related to a significantly lower height. It is worth noting that coronary ostia height needs to be interpreted in the context of Sinus of Valsalva diameter, as low-lying ostia in the presence of a large Sinus of Valsalva relative to the annulus may not necessarily pose a significant risk of ostial occlusion. Emergent PCI for occluded coronary ostia is technically feasible, however has been associated with increased mortality [26].

Aortic annulus rupture has been estimated to occur in around 1% of balloon-expandable TAVI procedures but is rare with the use of self-expanding valves [19,27]. Risk factors include a small aortic valve annulus, calcification and annular oversizing ≥20%, with mortality reported at up to 50% [27]. To reduce occurrence of this complication, heavily calcified valves and annulus size were previously identified as factors that, in some situations (1.5% and 2.0% respectively in our cohort), preclude patients from progression to TAVI. However, no patient was prevented from progressing to TAVI for this reason since 2014 in our study, highlighting that patients are no longer excluded for this reason alone given the availability of self-expanding valves and a wider range of valve sizes, which are now able to treat a greater range of aortic annulus size.

Limitations of this study include its retrospective cohort design at a single metropolitan centre. Trial patients made up over half the patients proceeding to TAVI, and more recent trials (Portico 1, Portico IDE, and Medtronic Forward) had more liberal criteria for accessing vessel diameter and aortic annulus size. This mostly reflects improvements in valve sizes and delivery systems rather than being due to a change in study criteria alone. Patients that did not proceed to TAVI due to frailty, comorbidities or death prior to procedure were unable to be accurately captured with the study design given that many of these patients likely did not proceed to angiographic workup screening, and therefore were excluded from the current study. It is worth noting that, in some instances, relative adverse anatomical factors in the presence of frailty or comorbidities may be enough to recommend balloon aortic valvuloplasty (BAV) only or medical management. The impact of these relative contraindications in the presence of frailty is not captured by this study, which attempts to focus on anatomical factors alone. Furthermore, factors such as frailty and comorbidities may become the more significant problem as improvements in delivery design reduce the impact of anatomical factors preventing progression to TAVI as demonstrated by our study. Despite the above, the paper is felt to provide valuable insight into factors that may prevent progression to TAVI at any TAVI centre, and highlights the need to identify ways to address these factors.

Conclusions

Rates of non-progression to TAVI among higher risk patients with severe symptomatic AS are now relatively low and have reduced over the last 10 years. Significant factors that may prevent progression to TAVI include unsuitable iliofemoral vasculature, concomitant unrevascularised CAD, and unfavourable aortic anatomy including coronary ostial height. Iliofemoral vasculature and unfavourable aortic anatomy can likely be navigated with improvements in TAVI delivery and design, while the approach to unrevascularised CAD requires large-scale randomised control trials (RCTs) to identify a therapeutic approach that provides the best outcome.

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