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Comparative Survival after Trans-apical, Direct Aortic, and Subclavian Transcatheter Aortic Valve Implantation

Data from the UK TAVI Registry

Running title: Comparative Survival after non-femoral TAVI

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Abstract

Many patients have ilio-femoral vessel anatomy unsuitable for conventional trans-femoral (TF) trans-catheter aortic valve implantation (TAVI). Safe and practical alternatives to the TF approach are therefore needed. This study compared outcomes of alternative non-femoral routes, trans-apical (TA), direct aortic (DA) and subclavian (SC), with standard femoral access. In this retrospective study, data from 3,962 patients in the UK TAVI registry were analysed. All patients who received TAVI via a femoral, subclavian, transapical or direct aortic approach were eligible for inclusion. The primary outcome measure was survival up to two years. Median Logistic EuroSCORE was similar for SC, DA, and TA, but significantly lower in the TF cohort (22.1% vs 20.3% vs 21.2% vs 17.0% respectively, p<0.0001). Estimated one-year survival was similar for TF (84.6±0.7%) and SC (80.5±3%, p=0.27), but significantly worse for TA (74.7±1.6%, p<0.001) and DA (75.2±3.3%, p<0.001). A Cox proportional hazard model was used to analyse survival up to 2-years. Survival in the SC group was not significantly different to the TF group (HR 1.22, 95% CI 0.88-1.70, p=0.24). In contrast, survival in the TA (HR 1.74, 95% CI 1.43-2.11;p<0.001) and DA (HR 1.55, 95% CI 1.13-2.14; p<0.01) cohorts was significantly reduced compared to TF. In conclusion, trans-apical and direct aortic TAVI were associated with similar survival, both significantly worse than with the trans-femoral route. In contrast, subclavian access was not significantly different to trans-femoral, and may represent the safest non-femoral access route for TAVI.

Key words TAVI - femoral - non-femoral access routes – survival

Introduction

Trans-catheter Aortic Valve Implantation (TAVI) has expanded rapidly as an alternative to surgical aortic valve replacement (SAVR), with well over 250,000 patients treated worldwide since 2002, and trial data extending into high, intermediate, and even low-risk operable patients.[1] The trans-femoral (TF) approach is generally accepted as the default access route for TAVI. However, small vessel caliber and peripheral vascular disease preclude TF access in a significant cohort of patients.[2] In the most recent trial investigating the new Edwards Sapien III valve, 36% of patients required non-femoral access.[3] With the miniaturization in TAVI delivery systems, including the 14Fr CoreValve Evolut R®, it is commonly estimated, that 10-15% of patients will still have unsuitable femoral access. Clinicians need to understand the relative outcomes of alternative non-femoral access routes to guide optimal treatment of these patients. Trans-apical (TA), subclavian/axillary (SC) and most recently direct aortic (DA) access have developed as the principal alternatives to TF.[4-6] While femoral access is routinely gained percutaneously by the operator, all non-femoral access routes mandate a surgical cut-down to either the apex of the heart, subclavian artery or to the ascending aorta via a right sided mini-thoracotomy or central sternotomy.[7-9] Previous studies have reported worse outcomes, including reduced survival, after non-femoral TAVI. However, very few data exist comparing the different non-femoral access routes. The aim of this study was to compare morbidity and mortality associated with different non-femoral access routes following TAVI.

Methods

The UK TAVI registry is a large prospectively collected database that includes 100% of patients undergoing TAVI in any of the 33 centres performing TAVI procedures in

the U.K. Detailed information about the design of the database was published previously.[2] It includes 3980 patients who underwent TAVI between January 2007 and December 2012. All centres use the same database as recommended by the National Institute for Cardiovascular Outcomes Research (NICOR). Data are collected at each hospital, electronically encrypted, and transferred online to the National Central Cardiac Audit database. This algorithm allows for linkage to the National Health Service Central Register, with all-cause mortality tracked for patients in England and Wales by unique National Health Service number up to July 2013.

Data collected include patient demographics, indications for TAVI, procedural characteristics, and adverse outcomes including complications up to the time of hospital discharge. Survival was monitored long-term.

The primary outcome measure was long-term survival up to July 2013. Secondary outcome measures were procedural and in-hospital complications (including stroke, major vascular complications, bleeding, tamponade, pacemaker implantation, and renal replacement therapy), in-hospital, 30-day and 1 year mortality.

Statistical analyses were performed using SPSS 20.0 (IBM Corporation, 1 New Orchard Road Armonk, New York 10504-1722, United States) and Stata 12.1 (StataCorp LP 4905 Lakeway Drive College Station, Texas 77845 USA). Continuous variables are presented as the median and inter-quartile range (IQR) (25–75 percentile). The χ^2 and Kruskal-Wallis test were used as appropriate. For survival analysis, a Kaplan-Meier curve was computed and a log rank p-value was calculated. A Cox proportional hazard model was applied for the primary outcome measure, corrected for EuroScore, valve type, presence and severity of coronary artery disease, access route, heart rhythm, occurrence of post-procedural aortic regurgitation as assessed by echocardiography and year of implantation. Co-variates

that were already incorporated into the EuroScore (NYHA and CCS class, age, gender, critical pre-operative state, recent myocardial infarct, kidney failure, diabetes, extracardiac arteriopathy, previous cardiac surgery, chronic lung disease, LV function, pulmonary hypertension) were not included as separate co-variates into the Cox proportional hazard model. A sensitivity analysis was performed to confirm that survival with SC access was not significantly different to a TF approach. Patients were matched 1:4 for the variables LogEuroScore, BMI, previous cardiac surgery, valve type, extracardiac arteriopathy and year of implant) and then a conditional logistic regression analysis was performed. A two-sided p-value of <0.05 was considered significant.

This study complies with the Declaration of Helsinki. The data were collected as part of a mandatory U.K. national cardiac audit and all patient identifiable fields were removed prior to analysis. The National Institute for Cardiovascular Outcomes Research, which includes the UK TAVI Registry, has support under section 251 of the National Health Service Act 2006. Ethical approval was not required under research governance arrangements for the analyses.

Results

In total, 3980 patients were registered in the UK TAVI database. Three patients who underwent TAVI via a carotid approach and 15 patients with missing information on access route were excluded. Finally, 2828 patients who underwent TAVI via TF, 761 patients with TA, 185 patients with DA, and 188 patients with SC access were included. **Table 1** summarises baseline characteristics among the study groups.

In-hospital mortality was lowest in the TF group (3.7%, n=105, p<0.0001 vs pooled non-TF). Amongst the non-femoral access groups only the SC route (4.3% n=8, p=0.69) was not significantly different to TF, whilst TA (9.5%, n=72, p<0.0001) and DA (7.6%, n=14, p<0.02) were associated with higher mortality.In-hospital morbidity is summarised in **Table 2**.

An unadjusted Kaplan-Meier survival chart is shown in Figure 1. There was no difference in survival between TA (1-year estimator 74.7±1.6% p<0.0001) and DA (1-year estimator 75.2±3.3%) approaches, both of which were associated with significantly lower long-term survival than TF (1-year estimator: 84.6±0.7%, p<0.0001). In contrast, unadjusted survival of the SC cohort was not significantly different to TF (1-year estimator 80.5±3% p=0.27).

In total, 3323 patients were included in the Cox proportional hazard model. Detailed results are shown in **Table 3**. As the SC route was the only non-femoral access route which was not significantly different to TF on the Cox regression analysis, we confirmed this finding further using a *propensity matched* population, and a conditional logistic regression analysis which demonstrated a non-inferiority of the SC route, if compared to the TF access (p=0.86).

Discussion

This is the largest study to compare survival among non-femoral TAVI access routes in a real-world setting, using a large dataset retrieved from the UK TAVI registry. Trans-apical and direct aortic approaches were associated with almost identical survival, both significantly lower than after trans-femoral TAVI. Subclavian access

was the only non-femoral approach for which survival was not significantly different to TF, and may represent the safest non-femoral access route for TAVI.

Despite progressive reduction in caliber of TAVI deliver systems, from initial 24Fr Sapien and 25Fr first generation CoreValve, to the 14-18 Fr expandable e-sheath, 18Fr CoreValve, and 14Fr Evolut R systems available today, a significant proportion of patients remain, in whom small and/or diseased vessels preclude a trans-femoral approach. For these patients an alternative access route is required. In the current study non-femoral access was employed in 23.4% of patients in year 2012, even with the availability of the expandable sheath by Edwards and the 18Fr CoreValve. In treating such patients, clinicians need to understand the relative outcomes from alternative non-femoral approaches in order to guide optimal treatment.

Trans-apical access with the Edwards SAPIEN valve was the first non-femoral approach utilized for patients with unsuitable ilio-femoral vessels.[7] However, most studies have demonstrated worse outcomes, including increased short- and long-term mortality, with a TA approach. In the FRANCE-2 registry of 3,195 TAVI cases, mortality was higher with TA patients compared to TF at 30 days (13.9% vs.8.5%) and 1 year (32.3% vs. 21.7%).[10] In the PARTNER trial mortality at 30 days according to actual treatment was 8.7% for TA vs. 3.7% TF, and at 1 year 29.1% vs. 21.3%.[11] However, since most centers adopt a TF-first approach, and since those undergoing TA access invariably have a worse risk profile, it is unclear to what extent worse outcomes relate to the patient rather than the procedure itself. More favorable results have also been reported by single centers performing high-volume TA TAVI, raising the possibility of a more significant learning curve or volume/outcome relationship with the trans-apical approach.[12]

The present study found a TA approach to be associated with increased short-term as well as long-term mortality. In common with the FRANCE-2 data, TA access was independently associated with reduced survival after multivariable analysis. While precise factors behind the worse outcomes seen with TA remain uncertain, we found that renal replacement therapy, a known predictor of increased mortality, was more frequently required with TA. Previous studies have also shown higher levels of cardiac biomarker release after TA TAVI, less improvement in left ventricular ejection fraction, and apical wall motion abnormalities and scarring on cardiac MRI which might be a source of arrhythmia and adverse late events .[13, 14]

Given the invasive nature and uncertain outcomes of the TA route, direct access to the ascending aorta has emerged as an alternative non-femoral access route. The DA approach has the advantages of obviating separation of the pleura. Hence, this access route may reduce post-operative pain and potentially respiratory complications. Potentially, this access route avoids injury to the left ventricular myocardium and it is indeed a highly familiar procedure for cardiac surgeons. As a consequence, its use has expanded rapidly with both the Edwards SAPIEN and Medtronic CoreValve systems.

To our knowledge, the present study reports the largest series of DA cases published so far, and is the first study to compare DA and TA approaches. We found no difference in both early and late mortality between DA and TA, with Kaplan-Meier survival curves almost superimposed. After multivariable analysis both DA and TA were independent predictors of reduced survival. While it is impossible to fully correct for differences in the DA and TA cohorts, *a priori* risk profiles including Logistic EuroSCORE appear similar, while the proximity of the unadjusted survival curves is striking.

In contrast to TA and DA, both short and long-term survival in patients undergoing TAVI via a subclavian approach were not significantly different to the TF route, including after multivariable analysis. While the SC Kaplan-Meier survival curve was nearly superimposed on the TF curve up to 6 months, the survival graphs diverged thereafter. It is likely that late survival relates more to patient co-morbidities than the TAVI procedure, and the increased *a priori* risk of the subclavian cohort, reflected by the higher Logistic EuroSCORE, may therefore explain the late separation of the survival curves. Our findings are consistent with Italian registry data in which there was no difference between survival after subclavian and trans-femoral TAVI in a propensity-matched analysis.[15] The recently published US CoreValve High-Risk study also reported a numerically lower 30-day mortality with subclavian (8.6%, n=70) than with DA access (13.6%, n=80).[16] The explanation for the favorable outcome of SC in comparison to DA/TA remains uncertain. The surgical subclavian cut-down is less invasive than DA and TA access, leaving the chest cavity untouched. The requirement for and duration of general anaesthesia, ventilation, and ICU stay might also be less. That the recovery process might be more favorable with SC is supported by our finding that the median hospital stay was one day less than with TA and DA approaches. The main downside of SC in the present study was the high rate of post-procedural pacemaker implantation related to the predominant use of CoreValve for the subclavian approach.[17] However, it is reassuring, that pacemaker implantation after TAVI did not affect long-term survival in a previous series.[18]

The main limitation of the present study is, that the patient population was relatively heterogeneous with significant differences in baseline characteristics between different access routes. It was noticeable, however, that Logistic EuroSCORE was very similar in the 3 non-femoral groups. Although we adjusted for these differences

in a Cox proportional hazard and a propensity match analysis, unmeasured confounders may always limit the conclusions that can be drawn from observational studies. Furthermore, some valve systems are specific to certain non-femoral techniques (Edwards SAPIEN to TA, Medtronic Corevalve to SC), and many UK centres have concentrated on one valve system and one alternative access technique rather than attempting multiple techniques infrequently. Data from the present study were collected mainly with 1st and 2nd generation valves. With the advent of the latest valve generation (e.g. Medtronic Evolute and Edwards SAPIEN 3) a further miniaturization of delivery systems was achieved, and the TF approach will probably become feasible for >85% of TAVI candidates. Cause of death data were unavailable; hence, we were unable to determine whether differences in survival related to cardiovascular or non-cardiovascular mortality. Finally, individual data on operator experience was not available, but the multivariable model was adjusted for the year of TAVI.[19]

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Disclosures

Georg M Fröhlich: none declared

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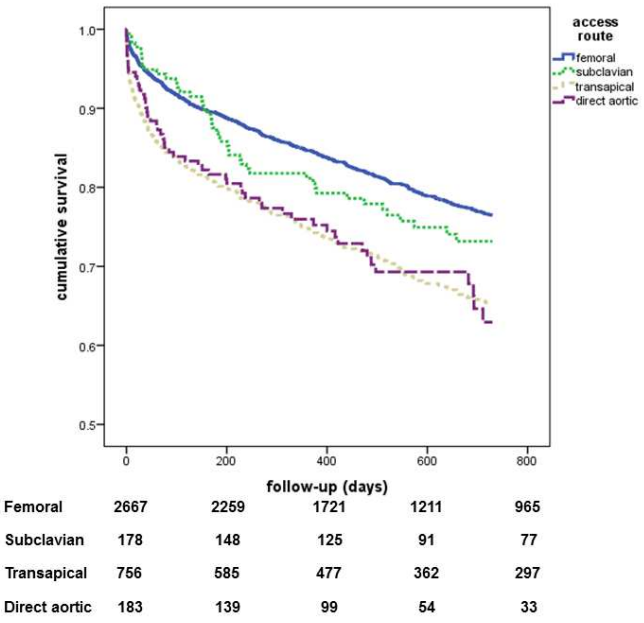
Legend to Figure

Figure 1. Kaplan-Meier curve (unadjusted) to compare survival with femoral versus non-femoral access routes (p<0.001)

Figure 1.



Variable	subclavian (n=188)	transapical (=761)	direct aortic (n=185)	femoral (n=2828)	p-value
age (years)	83 (78-86)	82 (77-86)	84 (77-88)	83 (77-87)	0.18
male	123 (65%)	425 (56%)	90 (49%)	1451 (51%)	<0.0001

logistic EuroScore	22 (14-34)	20 (14-31)	21.2 (15-33)	17 (11-26)	<0.0001*
body-mass-index (kg/m2)	26 (23-29)	26 (23-29)	25 (23-29)	26 (23-30)	0.005*
creatinine	108 (86-136)	104 (86-132)	100 (81-136)	101 (82-130)	0.03*
diabetes	45 (23%)	167 (22%)	39 (21%)	629 (23%)	0.8
smoker					<0.0001*
ex-smoker	109 (61%)	395 (54%)	106 (59%)	1334 (50%)	
current smoker	9 (5.0%)	25 (3.0%)	10 (6.0%)	56 (2.1%)	
atrial fibrillation	32 (17%)	163 (22%)	30 (16%)	591 (21%)	0.01
neurological disease	35 (19%)	127 (17%)	28 (15%)	409 (15%)	0.42
previous MI	52 (28%)	166 (22%)	43 (23%)	622 (22%)	0.08†
previous PCI	45 (24%)	154 (20%)	33 (18%)	606 (21%)	0.52
previous cardiac surgery	63 (33%)	324 (42%)	44 (24%)	830 (29%)	<0.0001
coronary artery disease	94 (51%)	406 (55%)	88 (48%)	1155 (42%)	<0.0001
left ventricular ejection fraction (LVEF)					0.3
>50%	99 (53%)	466 (62%)	105 (57%)	1714 (61%)	
30-49%	68 (36%)	229 (30%)	60 (32%)	818 (29%)	
<30%	19 (10%)	57 (8%)	20 (11%)	272 (10%)	
aortic gradient (mmHg)	75 (60-98)	74 (61-90)	76 (63-94)	75 (61-92)	0.17
aortic valve area (cm2)	0.7 (0.5-0.8)	0.64 (0.5-0.8)	0.60 (0.5-0.8)	0.65 (0.5-0.8)	0.19
aortic annulus (mm)	23 (21-25)	22 (21-24)	23 (21-24)	23.0 (21-24)	<0.0001
pulmonary hypertension	28 (15%)	70 (10%)	28 (15%)	401 (15%)	0.007*
chronic lung disease	52 (28%)	200 (27%)	71 (39%)	738 (27%)	0.01
Procedural characteristics local anaesthesia	5 (3.0%)	15 (2.0%)	2 (1.0%)	501 (18%)	<0.0001
Procedural characteristics					<0.0001
CoreValve	186 (99%)	3 (0.4%)	67 (36%)	1626 (58%)	
Edwards	2 (1.0%)	753 (99)	118 (64)	1161 (41%)	
valve-in-valve procedure	3 (2.0%)	44 (6.0%)	5 (3.0%)	97 (3.4%)	0.1
valve size (mm)	29 (26-29)	26 (23-26)	26 (23-29)	26 (26-29)	<0.0001
aortic regurgitation post implant					
moderate to severe	15 (8.0%)	21 (4.0%)	8 (5.0%)	214 (8.0%)	<0.0001

Table 1. Baseline characteristics

*non-significant among non-femoral access routes †p=0.03 among non-femoral access routes

Variable	**subclavian (n=188)**	**transapical (=761)**	**direct aortic (n=185)**	**femoral (n=2828)**	**p-value**

in-hospital death	8 (4.3%)	72 (9.5%)	14 (7.6%)	105 (3.7%)	<0.0001
30-day mortality	5 (2.9%)	80 (11%)	15 (8.4%)	121(4.7%)	<0.0001
12-months mortality	33 (20%)	187 (27%)	42 (29%)	388 (18%)	<0.0001
stroke in hospital	6 (3.0%)	23 (3.0%)	1 (1.0%)	58 (2.1%)	0.12
TIA in hospital	3 (2.0%)	4 (1.0%)	0	16 (0.6%)	0.22
tamponade	4 (2.0%)	4 (1.0%)	1 (1.0%)	22 (0.8%)	0.07
major vascular complication	4 (2.0%)	3 (0.4%)	6 (3.0%)	98 (3.5%)	<0.0001
need for vascular surgery	3 (2.0%)	7 (1.0%)	3 (2.0%)	63 (2.3%)	0.59
emergency valve in valve procedure	7 (4.0%)	7 (1.0%)	2 (1.0%)	77 (2.7%)	0.01
need for haemofiltration	7 (4.0%)	54 (7.0%)	19 (10%)	71 (2.5%)	<0.0001
GI bleeding	2 (1.0%)	15 (2.0%)	0	21 (0.8%)	0.01
Pacemaker implantation post TAVI	43 (23%)	37 (5.0%)	13 (7.0%)	363 (13%)	<0.0001
hospital stay (days)	7.0 (5.0-10.0)	8.0 (5.0-15.0)	8.0 (5.0-16.0)	5.5 (4.0-8.0)	<0.0001
follow-up (days)	609 (312-994)	567 (225-1056)	421(202-680)	544 (283-929)	<0.0001

Table 2. Outcomes

Variable	Hazard ratio	95% CI	p-value
logistic EuroScore	1.02	1.01-1.02	<0.001
year of implant 2012 vs. 2007	0.39	0.25-0.61	<0.001
subclavian vs. femoral access	1.22	0.88-1.70	0.241
trans-apical vs. femoral access	1.74	1.43-2.11	<0.001
direct aortic vs. femoral access	1.55	1.13-2.14	0.007
CoreValve vs. Edwards	1.00	0.83-1.20	1.0
atrial fibrillation vs. sinus rhythm	1.32	1.12-1.55	0.001
no/mild AR vs. moderate/severe AR	1.82	1.48-2.24	<0.001
1-vessel disease vs. no CAD	1.15	1.0-1.38	0.13
2-vessel disease vs. no CAD	1.13	0.90-1.42	0.29

3-vessel disease vs. no CAD	1.03	0.83-1.27	0.82

Table 3. Cox proportional hazard model