Activity and outcomes for aortic valve implantations performed in England and Wales since the introduction of transcatheter aortic valve implantation

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INTRODUCTION

Aortic stenosis is the most common valvular heart disease and patients with severe aortic stenosis who develop symptoms have a poor prognosis. Aortic valve replacement (AVR) for aortic stenosis is established as a Class I indication for patients with severe aortic stenosis who are symptomatic or those with impairment of left ventricular function in the absence of symptoms [1]. The number of AVRs performed in the UK increased significantly between 2004 and 2009, with good overall procedural mortality rates and survival [2]. However, a significant number of patients with severe aortic stenosis have previously been deemed to be at excessively high risk for AVR. Transcatheter aortic valve implantation (TAVI) was introduced as a less invasive alternative to AVR for those patients deemed to be...
at excessively high risk of morbidity or mortality following AVR. The first TAVI was performed in man in 2002 [3], and the first patient underwent TAVI in the UK in 2007. There has been widespread adoption of TAVI worldwide. A comprehensive registry, compatible with the National Adult Cardiac Surgery Audit (NACSA), has been established in the UK allowing data on all patients undergoing TAVI to be collected. The outcomes from this registry have previously been published [4].

The objective of this study was to analyse all aortic valve implantation activity across England and Wales in the TAVI era. Specifically, we have investigated: (i) trends in AVR activity since the introduction of TAVI; (ii) trends in TAVI activity over the period of the study; (iii) differences in characteristics between patients undergoing AVR and TAVI; (iv) contemporary outcomes of AVR and TAVI (procedural mortality, postoperative length of hospital stay and post-discharge survival).

MATERIALS AND METHODS

Data extraction and preprocessing

Prospectively collected data for all AVRs performed in England and Wales between 1 January 2006 and 31 December 2012 were extracted from The National Institute for Cardiovascular Outcomes Research (NICOR) NACSA registry (version 4.1.2) on 14 January 2014. Data from 2006 were included to provide information on AVRs performed in the year preceding the first UK TAVI but were excluded from the risk profile and outcome analyses. Reproducible computing algorithms were applied to the database [5]. The data are returned regularly to each unit for local validation.

Prospectively collected data for all TAVI procedures performed in England and Wales between 1 January 2007 and 31 December 2012 were extracted from the NICOR national TAVI registry (version 3.9) on 13 October 2013. All centres that perform TAVI submit data to the UK TAVI registry and data are verified and validated with submitting centres [4].

Study variables

Details of the NICOR NACSA and TAVI registries and variable definitions used for the study are available at http://www.ucl.ac.uk/nicor/audits/adultcardiacsurgery/datasets and http://www.ucl.ac.uk/nicor/audits/tavi/dataset. Procedures were classified as: (i) isolated AVR; (ii) AVR + coronary artery bypass graft (CABG) surgery; (iii) AVR + other surgery or (iv) TAVI. A breakdown of the surgical procedures included in the AVR + other surgery is given in Supplementary Material, Table S1. All TAVI approaches were included. An algorithm was written to index the procedures chronologically within and between admission spells for each patient. Only the first indexed procedure in each admission spell was retained for analysis. The logistic EuroSCORE was calculated for each record [6].

Outcome variables

The outcomes for this study were (i) in-hospital mortality, defined as death due to any cause during admission to the base hospital for the procedure; (ii) 30-day mortality, defined as death due to any cause within 30 days of the procedure; (iii) survival from all-cause mortality and (iv) postoperative length of stay (PLOS). Any patient who died in hospital on the day of surgery was recorded as having a survival time/PLOS of 0.5 days. If the PLOS was <4 days for AVR, then this was considered to be implausible and the PLOS data were treated as missing. Follow-up status until the point of discharge was collected by the clinical registries. Post-discharge survival status was determined through linkage of patient NHS numbers with the Data Linkage Extract Service at the NHS Information Centre as of July 2013 for AVR patients and March 2014 for TAVI patients.

Statistical analysis

Continuous data are summarized as mean [standard deviation (SD)] or median [interquartile range (IQR)]. Dichotomous and categorical data are summarized as number (percentage). Missing data for binary or categorical patient characteristic variables were imputed with the modal value, with missing data for continuous variables imputed with the median value. Outcomes and patient characteristic data were summarized for procedures performed on or after 1 January 2007. A case-complete analysis was performed excluding records with missing mortality data. Outcome data were not compared between procedure groups using statistical hypothesis testing due to known confounding by indication for treatment. Statistical comparisons are made within procedure groups with the Mann–Whitney U-test (continuous variables between two independent groups), and a chi-squared test for trend in proportions (over time).

Kernel density estimation is used to calculate smoothed histogram plots for patient age at procedure and logistic EuroSCORE. Boxplots are used to summarize the logistic EuroSCORE distributions by each procedure and year. Survival curves were calculated using the Kaplan–Meier estimator for each procedure group. For patients who had a reintervention during a separate admission spell within the study period, records were treated and analysed independently. To evaluate the impact of TAVI on the volume and in-hospital mortality of AVR (±CABG) in different surgical risk groups, logistic EuroSCORE groups based on quintiles of risk from 2006 were defined and applied to data from 2007–2012. All data cleaning and analyses were performed using the R statistical computing software version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Exploratory graphical analyses were performed using the ggplot2 package (version 0.9.3.1) [7].

RESULTS

Data extraction and volume

Over the study period there were 67 857 procedures performed representing 67 149 unique patients across 37 hospitals. A total of 77 records were within-admission re-do aortic valve surgery or TAVI, and these records were excluded from all future reporting with only the initial procedure retained. As shown in Fig. 1, the number of TAVIs performed has risen year-on-year from 66 in 2007 (0.8% of all procedures) to 1186 in 2012 (10.9% of all procedures). The total number of AVRs performed has also risen from 8019 in 2006 to 9654 in 2012. After excluding AVR data from 2006, a total of 59 761 records remain for reporting of risk profiles and outcomes: 24 335 isolated AVR, 18 387 AVR + CABG, 13 282 AVR + other surgery and 3757 TAVI.
Patient and operative characteristics

Patient characteristics and operative data (Table 1) showed large differences between procedural groups. Patients were older in the TAVI group [mean 81.3 years (SD 7.6)] than all the AVR procedural groups. The mean logistic EuroSCORE of 21.9% of the TAVI group was higher than all AVR procedural groups with the mean logistic EuroSCORE for the isolated AVR group 7.9%. The proportion of women (46.9%) and the incidence of previous cardiac surgery (33.1%) were higher in the TAVI group than all the AVR groups. Age and logistic EuroSCORE distributions for the procedural groups are shown in Fig. 2.

In-hospital and 30-day mortality

There were 86 (0.1%) records with missing in-hospital mortality status, which were excluded from reporting of in-hospital mortality: 70 for TAVI and 16 across the AVR groups. The in-hospital mortality rates were 6.1% (226/3687) for TAVI, 2.1% (511/24 330) for isolated AVR, 4.2% (769/18 381) for AVR + CABG and 8.2% for AVR + other (1090/13 277). In-hospital mortality rates by calendar year significantly reduced over the study period for all procedural groups as shown in Fig. 3: TAVI 15.2 to 5.3% (P = 0.004); isolated AVR 2.4 to 1.9% (P = 0.033); AVR + CABG 4.4 to 3.9% (P = 0.043); AVR + other surgery 10.5 to 6.4% (P < 0.001). The 30-day mortality rates were 6.2% for TAVI, 2.1% for isolated AVR, 3.9% for AVR + CABG and 7.7% for AVR + other surgery.

Survival

For procedures performed during 2007 and later, survival could not be tracked after discharge from hospital for a total of 1146 (2.0%) and 92 (2.4%) patients in the AVR and TAVI registries respectively. In all but 16 patients, we were able to track them until discharge, at which point they were censored. The 16 patients who could not be tracked at all were excluded from the survival analysis. Median follow-up times for the TAVI and AVR groups were 2.1 (range 0.0 to 7.1) and 3.0 (range 0.0 to 6.6) years, respectively. There were 10 753 mortalities in total, 1352 for TAVI, 3092 for isolated AVR, 3559 for AVR + CABG and 2750 for AVR + other surgery.

The 1- and 5-year survival rates following TAVI were 81.7 and 46.1%, respectively (Fig. 4). For AVR, the 1- and 5-year survival rates were, respectively, 94.4 and 82.6% for isolated AVR, 90.4 and 74.6% for AVR + CABG and 86.4 and 74.5% for AVR + other surgery. The Kaplan–Meier estimates of 1-year survival for TAVI have increased from 63.3% in 2007 to 84.5% in 2012, as shown in Fig. 5. Small improvements in absolute survival rates have also been observed in all AVR groups.

Postoperative length of stay

For procedures performed during 2007 and later, there were 450 (0.8%) records with missing PLOS: 46 for TAVI and 404 for AVR. These records were excluded from the PLOS analysis. Although
the PLOS distribution curves for isolated AVR and TAVI are different, as shown in Fig. 6, the average PLOS was the same (median 7 days; IQR 5 days for isolated AVR and median 7 days; IQR 6 days for TAVI). The median PLOS reduced from 8 (IQR 8) days in 2007 to 6 (IQR 5) days in 2012 for the TAVI group. There was a reduction of 1 day between 2007 and 2008 in the isolated AVR group that was maintained for the study. The median (IQR) PLOS for AVR + CABG and AVR + other surgery were 9 (8) and 10 (9) days, respectively, with no changes in PLOS distribution over time.

Impact of transcatheter aortic valve implantation on aortic valve replacement

Following the introduction of TAVI, the absolute volume of isolated AVR and AVR + CABG rose from 6635 in 2007 to 7307 in 2012. The distribution of logistic EuroSCORE has remained stable over the study period for all AVR groups (Supplementary Material, Fig. S1). The mean logistic EuroSCORE has decreased non-significantly from 25.5% in 2007 to 21.9% in 2012 in the TAVI group (P = 0.103). There were 6172 isolated AVRs and AVR + CABG procedures performed during 2006 with the logistic EuroSCORE thresholds defined as follows: ≤2.76% (Q1: lowest risk group); >2.76% and ≤4.53% (Q2); >4.53% and ≤7.05% (Q3); >7.05% and ≤11.7% (Q4); >11.7% (Q5: highest risk group). Increases were initially observed in all risk groups; however, annual volumes in Q1 and Q2 have decreased since 2008 (Fig. 7). There has been an ongoing increase in volume in the highest risk AVR groups. A trend of decreasing in-hospital mortality was observed in each risk group except the lowest risk group. The absolute change was greatest in the highest risk group (Q5), decreasing from 9.4% in 2006 to 6.3% in 2012.

DISCUSSION

TAVI has significantly changed the management of patients with aortic stenosis. Since the first TAVI was performed in the UK, there has been an increase in the proportion of aortic valve implantations performed as TAVIs from under 1% in 2007 to over 10% in 2012. The volume of AVRs over the study period has also increased. The most noticeable increase in AVR volume has been for high-risk patients despite the introduction of TAVI. TAVI patients have a higher incidence of risk factors than patients undergoing AVR.
Figure 2: Distributions of patient age and logistic EuroSCORE for procedural groups. TAVI: transcatheter aortic valve implantation; AVR: aortic valve replacement; CABG: coronary artery bypass graft.

Figure 3: In-hospital mortality rates by procedural group. TAVI: transcatheter aortic valve implantation; AVR: aortic valve replacement; CABG: coronary artery bypass graft.
There has been a significant decrease in in-hospital mortality over time for all procedural groups with the greatest absolute decrease observed in the TAVI group. There has also been a significant improvement in 1-year mortality following TAVI. The median PLOS after TAVI was the same as for isolated AVR and shorter than for AVR + CABG or AVR + other surgery.

Clinical registry data report ‘real world’ data, but treatment comparisons based on these data are potentially biased by confounding by indication. A statistical comparison of outcomes between procedural groups by regression adjustment or propensity-score matching analysis has therefore not been performed. This is because there are a number of confounding factors such as patient frailty that feed into decision-making for allocation of patients to AVR or TAVI, which are not included in the datasets. We have used the logistic EuroSCORE to provide an indication of procedural risk. As this risk model was developed for cardiac surgery prior to the
introduction of TAVI, it is unlikely to accurately represent the risk profiles of the patients in this study and was merely used to classify surgical AVR groups [8, 9].

Randomized studies of TAVI and AVR include the PARTNER trial and the Core Valve US Pivotal High Risk Study. PARTNER trial Cohort A recruited patients with severe AS deemed to be high risk for AVR and randomized patients to either TAVI or AVR with no significant difference in mortality rates out to 2 years [10, 11]. PARTNER trial cohort B compared TAVI to medical management in patients deemed too high risk for AVR and found that TAVI significantly decreased the rate of mortality at 2 years but was associated with a higher rate of stroke in the first 30 days [12, 13]. The CoreValve High Risk Study included patients with severe AS with a high risk of mortality within 30 days [14]. A statistically significantly improved survival rate at 1 year was observed in the TAVI group with a similar rate of cardiovascular or cerebrovascular events at 30 days or discharge.

In addition to the UK registry data presented here, several other TAVI registries have been established [15], including the SOURCE registry (Edwards LifeSciences SAPIEN™) and the ADVANCE registry (Medtronic CoreValve™) [16, 17]. At the 1-year follow-up, all-cause mortality rates were reported as 23.9% (1038 enrolled patients) and 17.9% (1015 enrolled patients), respectively. The FRANCE 2 registry has reported on all TAVIs performed in France between January 2010 and October 2011 with a 1-year mortality rate of 24.0% [18]. AVR registry data from 108 687 isolated AVRs performed between 1997 and 2006 in the USA also demonstrated that morbidity and mortality have reduced over time despite increases in patient age and overall risk profile [19]. The German Aortic Valve registry has reported both TAVI and AVR data [20]. A total of 13 680 patients were enrolled during 2011, of whom 28.3% underwent TAVI, compared with the 9.2% in the UK during the same year [21]. The mean age and predicted risk of patients undergoing isolated AVR were similar to this study; however, contribution to this registry is voluntary.

Propensity-score matched studies comparing AVR and TAVI have been published. No statistically significant differences between AVR and TAVI in 30-day or 1-year all-cause mortality was
found in 810 matched patients [22], with no difference in 30-day mortality, stroke or myocardial infarction found in another study of 266 matched patients [23]. A meta-analysis including randomized and observational studies demonstrated no difference in major outcomes between TAVI and AVR (mortality, stroke, myocardial infarction, acute renal failure) [24]. There was, however, some evidence from this analysis that TAVI is associated with higher rates of vascular complications, permanent pacemaker implantation and post-procedural moderate/severe aortic valve regurgitation.

Although TAVI was introduced as a treatment option for patients deemed too high risk for AVR, its use in lower risk patients who would potentially be suitable for AVR is increasingly being explored. The logistic EuroSCORE of patients undergoing TAVI has reduced non-significantly over the study period, suggesting that a degree of ‘risk creep’ may be occurring. However, the observed increase in AVR activity suggests that any risk creep is unlikely to be significant. Increasing AVR activity following the introduction of a TAVI service has previously been observed in a single-centre study and is presumably due to greater awareness of the disease and its possible treatments [25].

Encouragingly, this study demonstrates that overall procedural mortality has significantly decreased in all procedural groups with a significant improvement in 1-year mortality following TAVI. Although the procedural mortality after TAVI has changed significantly over the study period, there has been a relative plateau in outcomes over more recent years. The observed improvement in outcomes is likely to be a result of a number of factors including the learning curve phenomenon, improvements in case selection through a heart team approach and improvements in equipment and techniques. It remains to be seen whether the procedural mortality will continue to change over time as the evidence base for TAVI develops.

There remain some questions about the durability of TAVI implants, which is of particular relevance when TAVI is performed in younger patients with less comorbidity and greater post-procedural life expectancy. There is also uncertainty about the healthcare resource implications of TAVI. The major clinical debate is the comparative outcomes, not for the highest risk patients who are unsuitable for AVR, but for the higher and intermediate risk patients in whom both treatment options are possible. A clear understanding of the comparative outcomes in those groups will only come from randomized clinical studies, which are currently under way.

**Limitations**

Although this study represents a comprehensive analysis of national AVR and TAVI activity and outcomes data, there are inevitable limitations. Owing to the nature of large clinical registries, data errors and missing data are unavoidable. As the TAVI registry was established much later than the NACSA registry and is managed by a separate committee, there are some differences between the registries with regard to risk factors, multiple
procedures and the level of missing data. To address conflicts between the registries, a rules-based approach for rationalization was developed. Despite the overall rate of missing outcome data being low, a limitation of the study is that missing outcome data are higher in the TAVI registry. Levels of missing data are expected to improve as the TAVI registry becomes more established and data validation processes become more robust. Discharge destination was not analysed and technical differences within procedural groups such as TAVI access route or minimal access AVR have not been addressed.

A potential limitation of this study is that while patients with concomitant coronary artery disease who also underwent revascularization at the time of AVR were identified and included, patients who underwent TAVI and percutaneous coronary intervention (PCI) were not identified. This is because the registry that captures data on PCI in the UK has not yet been reliably linked with the AVR and TAVI registries. Linkage or redesign of these registries to capture this information is important going forward. There are clearly significant differences between the procedural groups presented in this study with regard to underlying disease, comorbidities and procedure complexity. In addition, there are inevitable unmeasured confounders such as frailty that are not captured. As a result of this, no attempt has been made, or should be made to compare outcomes between the procedural groups based on these data.

CONCLUSIONS
Since the introduction of TAVI, there has been an increase in both TAVI and AVR activity. TAVIs now represent over 10% of all aortic valve implants performed in England and Wales. As would be expected, there are distinct differences between procedural groups with respect to patient risk factors. Outcomes following both AVR and TAVI have improved over time.

SUPPLEMENTARY MATERIAL
Supplementary material is available at EJCTS online.

DATA SHARING STATEMENT
The data sharing policy for NICOR data can be found at http://www.ucl.ac.uk/nicor.

ETHICS APPROVAL
NICOR has Section 251 (of the NHS Act 2006) approval, and pseudonymous, non-identifiable data were used for this study, meaning that ethical approval was not required.

ACKNOWLEDGEMENTS
The authors acknowledge all hospitals in England and Wales who contribute data to the SCTS and TAVI registries. The National Institute for Cardiovascular Outcomes Research, UCL, London, provided data for this study.

Funding
This work was supported by a grant from Heart Research UK [Heart Research UK Grant RG2583]. We also acknowledge the support by the MRC Health e-Research Centre, Farr Institute of Health Informatics (Grant: MR/K006665/1).

Conflict of interest: The authors declare the following relevant financial activities outside the submitted work: Neil Moat has received fees for consultancy and lectures from Medtronic. Mark de Belder has received fees for lectures from Edwards LifeSciences. Daniel J Blackman has received fees for travel, consultancy and lectures from Boston Scientific and consultancy from Medtronic. David Hildick-Smith has received fees for consultancy from Medtronic, Edwards LifeSciences and Boston Scientific. Ben Bridgewater has received fees for consultancy and lectures from Edwards LifeSciences.

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