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Prosthetic valve endocarditis following transcatheter aortic valve implantation

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Abstract

Aims

The aims were to report incidence and outcomes of transcatheter aortic valve implantation-infective endocarditis (TAVI-IE) from a high-volume TAVI centre in the United Kingdom, including how incidence varies relative to time from the procedure, and to assess the performance of modified Duke criteria in the diagnosis of TAVI-IE.

Methods

This retrospective, cohort study included all patients who underwent TAVI at Leeds Teaching Hospitals Trust during a 10-year period. Outcome measures were the incidence of TAVI-IE, the accuracy of the modified Duke criteria and mortality rate.

Results

1337 patients were followed up for a median of 2.3 years. Thirteen patients (0.97%) were diagnosed with TAVI-IE, mean age of 81.3 years (SD 5.1 years). Four patients (30.8%) fulfilled modified Duke criteria for definite IE. The remaining nine patients (69.2%) fulfilled the modified Duke criteria for possible IE. In the majority (7/13; 53.8%) the causative organism was streptococcal. Cumulative incidence of TAVI-IE has risen in line with the number of patients living with TAVI prostheses, and cumulative number of TAVI years. However, in relation to the number of 100-TAVI years, the infection rate has remained low and static over the last 6 years. The in-hospital mortality rate was 38.5%, all attributable to TAVI-IE.

Conclusion

The incidence of TAVI-IE was 0.97%, with an associated all-cause mortality of 53.8%. The incidence relative to the number of TAVI-years has remained low and static in recent years. The modified Duke

criteria has relatively low sensitivity in the diagnosis of TAVI-IE, meaning that a high index of suspicion is required.

Keywords

Transcatheter valve interventions; infective endocarditis

Classifications

Valvular heart disease; rheumatic and infective heart disease

Introduction

Transcatheter aortic valve implantation (TAVI) has revolutionised the management of severe, symptomatic aortic stenosis. Whilst surgical aortic valve replacement (AVR) previously represented the only viable therapy for this condition, a number of patients were precluded due to prohibitive surgical risk. The development of TAVI has provided an alternative treatment, and it is now the established therapy for patients unable to undergo AVR[1-3]. Increasing procedural familiarity and improvements in device technology have allowed for an expansion in the use of TAVI; it is now advocated by the European Society of Cardiology (ESC) as a viable alternative to AVR for selected patients at intermediate surgical risk[4]. Furthermore, TAVI is increasingly being used for the treatment of severe, bioprosthetic valve degeneration[5], and recent trials have shown promising results with the use of TAVI in low surgical risk cohorts[6,7]. The ever-broadening indications for TAVI necessitate a clearer understanding of the risks and complications associated with the procedure. Prosthetic valve endocarditis (PVE) is a recognised and serious complication following surgical AVR, with an incidence of 0.3-1.2% per year, and an in-hospital mortality of >20%[8,9]. The incidence and outcomes of PVE following TAVI are less well established. Previously published studies suggest the incidence of PVE in the first year following TAVI is 0.5-3.1%, the rate of in-hospital mortality 11-47%, and mortality during two years follow-up of 67%[10-13]. A recently published retrospective study from Denmark has also highlighted a 5-year incidence of TAVI-IE of 5.8%[14]. However, a number of questions remain unanswered, including the incidence of PVE per TAVI-year and the variation in incidence by year post-procedure.

Given the adverse outcomes associated with TAVI-IE, prompt diagnosis is of utmost importance. Modified Duke criteria remain the accepted diagnostic classification for infective endocarditis (IE), and these criteria have a sensitivity of around 80%[15]. However, the Duke criteria have been noted to

be less accurate in cases of PVE in the context of surgically-replaced valves[16]. The sensitivity of the modified Duke criteria in the diagnosis of TAVI-IE is unknown.

The aims of our study were two-fold: firstly, to report the incidence and outcomes of TAVI-IE from a high-volume TAVI centre in the UK, including an assessment of how incidence varies relative to time from the procedure. Secondly, to assess the performance of modified Duke criteria in the diagnosis of TAVI-IE.

Methods

This was a retrospective, cohort study of the incidence of TAVI-IE with a survival analysis, designed and reported using the STROBE statement[17]. The study was undertaken at Leeds Teaching Hospitals NHS Trust (LTHT), a tertiary referral centre for cardiology and cardiac surgery. LTHT comprises two large teaching hospitals and a smaller specialist hospital and has around 2500 inpatient beds. The trust serves a local population of over 700,000 people and receives tertiary referrals from a population of over 2 million.

Participants

All adult patients over 18 years of age undergoing TAVI at LTHT between 1st January 2008 and 31st December 2018 were eligible, and were identified from our institutional database. All patients who underwent TAVI did so for either severe, symptomatic aortic stenosis or for structural valve degeneration of surgical prostheses (valve-in-valve; ViV) following a multi-disciplinary Heart Team discussion. Patients who were diagnosed with TAVI-IE were treated with input by a specialist endocarditis team comprising a Consultant Microbiologist and a Consultant Cardiologist, the TAVI team and Cardiac surgical teams.

Procedure

Our institution uses a range of transcatheter heart valve prostheses, depending on the anatomical requirements. The most frequently used prostheses are the Medtronic Corevalve/Evolut, Boston Scientific Lotus valve and the Edwards Sapien 3. Antibiotic prophylaxis was routinely administered, with intravenous teicoplanin and gentamicin given in the hour pre-TAVI. Procedures were generally performed under sedation and the most commonly utilised access route was trans-femoral. Other access routes included subclavian and trans-apical. A trans-femoral temporary pacing wire was routinely inserted for patients without a permanent pacemaker (PPM) in situ, and a number of patients went on to require implantation of a PPM due to post-procedural conduction abnormalities.

Following TAVI, patients were initiated on aspirin and clopidogrel for three months, after which they were maintained on aspirin monotherapy indefinitely. As per the NICE guidelines, patients were advised that they did not routinely require antibiotic prophylaxis prior to dental procedures following TAVI [18].

Definitions

Modified Duke's criteria was used to define definite or possible endocarditis[18]. A patient's first episode of endocarditis was defined as the initial episode, and subsequent episodes were assessed to confirm if they were relapses or recurrence. A relapse was defined as TAVI-IE caused by the same bacterial species as the previous episode, occurring within 1 year and after an apparent clinical cure following completion of post-procedural antimicrobial therapy. A recurrence (or "reinfection") was defined as any new episode following the initial episode caused by a different pathogen to the index episode or episodes caused by the same pathogen as the initial episode occurring more than 1 year after the index episode[19].

Variables and data sources

Cases of TAVI-IE were identified from the Leeds Endocarditis Service database, which captures all patients referred for assessment by the Endocarditis service. Patients can be referred by clinicians, echo sonographers and microbiologists. A TAVI clinical database was used to identify all patients who have undergone TAVI. Once patients who had been diagnosed with TAVI-IE were identified, all clinical, microbiological, echocardiographic and outcome data was retrieved from electronic patient records, including the records of the Leeds Endocarditis Service. Data included patient demographics (age, sex), comorbidities (Charlson co-morbidity index), procedural information (date and indication for TAVI, type of implant, access route), time to development of TAVI-IE, the aetiology of infection (categorized as: oral *Streptococcus*, non-oral *Streptococcus*, *Staphylococcus aureus,* non-*aureus*

Staphylococcus spp., *Enterococcus* spp., other, culture-negative), echocardiographic findings, and outcomes following TAVI-IE (complications, relapse, mortality).

Microbiology

Microbial cause of infection was determined by blood cultures; whenever possible, three sets of cultures were taken from differing sites, 30 minutes apart, prior to administration of antibiotics.

Follow-up

Patients were routinely followed up in a specialist TAVI clinic post-procedure. For patients diagnosed with TAVI-IE, details of readmission, complications and outcomes were obtained from hospital and primary care records.

Outcomes

The primary outcome of interest was incidence of TAVI-IE. Secondary outcomes were incidence of TAVI-IE per TAVI-year, complications associated with TAVI-IE, mortality rate, and the diagnostic accuracy of the Modified Duke's criteria.

Ethics

Institutional approval was sought from the Research and Development department, on the basis of this study constituting a service evaluation, and therefore not requiring patient consent. Caldicott principles where adhered to when handling patient data and only de-identified data were shared between the research team or analysed, using secure nhs.net email.

Statistical analysis

Descriptive statistics have been reported for patient characteristics including patient demographics, comorbidities, procedural information, time to TAVI-IE, the aetiology of infection, and

echocardiographic findings. Continuous variables have been reported as mean (SD) if normally distributed or median (interquartile range) if not normally distributed. Frequency (percentage) has been reported for categorical variables. The incidence of TAVI-IE has been reported overall as well as by TAVI-year. The trend of incidence of TAVI-IE has been investigated through regression to TAVI-year. The secondary outcomes, such as complications associated with TAVI-IE, the mortality rate, and the diagnostic accuracy of the Modified Duke's criteria, have been summarized through descriptive statistics.

Results

During the 10-year study period (1st January 2008 - 31st December 2018), 1337 patients underwent TAVI. The total follow-up duration was 3721 TAVI-years, and the median follow-up duration was 2.3 years (interquartile range 1.3-4.0 years). In this time, 13 patients (0.97%) were diagnosed with TAVI-IE, and detailed information for each case is presented in Table 1. Out of these 13 patients, one presented within 30 days of TAVI (7.7%) and five presented in the first-year post-procedure (38.5%). The mean age of patients diagnosed with TAVI-IE was 81.3 years (SD 5.1 years), and the mean time between TAVI and diagnosis with TAVI-IE was 653 days (SD 541.9 days). The cohort of patients had a significant burden of co-morbidity; a median Charlson co-morbidity index of 5 indicated a 21% estimated 10-year survival at the time of TAVI-IE diagnosis.

The most frequently used TAVI prosthesis amongst the cohort of TAVI-IE patients was the Medtronic CoreValve (8/13; 61.5%), followed by the Boston Scientific Lotus valve (3/13; 23.1%) and the Edwards Sapien 3 (2/13; 15.4%). These frequencies correlate with the usage of the respective valves in the overall cohort of TAVI patients; the Medtronic CoreValve was used in 537 patients (40.2%), the Boston Scientific Lotus valve in 161 patients (12.0%) and the Edwards Sapien 3 in 235 patients (17.6%). All cases of TAVI-IE occurred following transfemoral TAVI, which is the default access route used at our institution.

Out of the 13 patients diagnosed with TAVI-IE, only four (30.8%) fulfilled the modified Duke criteria for definite IE. The remaining nine patients (69.2%) fulfilled the modified Duke criteria for possible IE. Only one patient (0.8%) had a vegetation seen on trans-oesophageal echocardiography (TOE), whilst one other had a possible aortic root abscess. Nine out of the 13 patients (69.2%) underwent TOE as part of the diagnostic work-up. Of the remaining four, two died before a TOE was possible and one was deemed too unwell to undergo the procedure. In the majority of cases (7/13; 53.8%) the causative organism was found to be streptococcal; oral-*Streptococcus* species in four patients

(30.8%) and non-oral *Streptococcus* spp. in three patients (23.0%). Out of the 13 patients diagnosed with TAVI-IE, two (15.4%) had undergone a recent dental procedure; one patient had treatment for a dental abscess including tooth extraction one month prior to presentation, whilst the other underwent a scale and polish procedure two months prior to presentation. Two other patients were noted to have poor dentition at the time of presentation, but had not undergone dental procedures.

The number of TAVIs performed within our institution has increased year-on-year, with the exception of 2018. The lowest number of TAVIs performed in a single year was 12, in 2008, whilst the highest was 258, in 2017. The cumulative incidence of TAVI-IE has risen in line with the number of patients living with TAVI prostheses and the cumulative number of TAVI years (figure 1). However, when assessed in relation to the number of 100-TAVI years, the infection rate has actually fallen from a peak in 2009 and has remained relatively static in recent years (figure 2). The infection rate per cumulative 100 TAVI-years has fallen from 3.6 in 2009 and has varied between 0.19-0.38 over the last 6 years. Meanwhile, the annual incidence of TAVI-IE per additional 100 TAVI-years gained per annum has fallen from a peak of 4.3 in 2009 and has varied between 0.17-0.77 in the last 4 years. Analysing the incidence of TAVI-IE relative to time after implantation, our data suggest show a peak between 300-600 days post-TAVI (figure 3).

All patients diagnosed with TAVI-IE were treated with guideline-directed antibiotics, and none underwent surgery. Of the 13 patients, seven died within the study period giving an all-cause mortality rate of 53.8%. For comparison, amongst the 1224 patients who underwent TAVI but did not develop TAVI-IE, 447 died during the study period giving an all-cause mortality rate of 36.5%. Out of the seven deaths within the TAVI-IE group, five occurred during the hospital admission, giving an in-hospital mortality rate of 38.5%, and these were all attributed to TAVI-IE or related complications. Details regarding the cause of death for the two out-of-hospital cases were limited, but there was no clear link to TAVI-IE.

Discussion

This observational, retrospective, single-centre study of 1337 consecutive patients who underwent TAVI during a 10-year period reports an overall incidence of TAVI-IE of 0.97%. This is in-keeping with previously published data which suggests an incidence of 0.5-3.1% in the first year following TAVI[10-13]. The all-cause mortality rate observed in our study is high, but also in accordance with prior studies (in-hospital mortality of 38.5% and an overall mortality of 53.8% after 2.3 years follow-up is similar to quoted figures of 11-47%, and 67% after 2 years respectively[10-13]). It is worth noting that 2 of the 7 deaths occurred more than 1 year following the diagnosis of TAVI-IE. In an observational study such as this, it is difficult to attribute them directly to TAVI-IE. Equally, whether or not the development of TAVI-IE shortened these patients' lifespan cannot be determined.

One of the main objectives of this study was to gauge how the incidence of TAVI-IE varies relative to time from the procedure. Our analysis has shown that the infection rate has actually fallen from a peak in 2009 and has remained relatively static in recent years. The explanation for the fall in infection rate is unclear. Possibilities include an improvement in TAVI procedural technique consistent with the operators' learning curve, or an improvement in procedural technology in recent years. However, we did not observe any relationship between valve-type and occurrence of TAVI-IE, despite use of self-expanding and balloon-expandable transcatheter heart valves. Interestingly, the finding that the peak incidence of cases of TAVI-IE occurred 300-600 days post implantation suggests transient bacteraemia to be the main cause of infection; when considering prosthetic valves, endocarditis linked to the insertion procedure generally occurs within 1-year of implantation. Irrespective, in light of recent trial evidence which points towards an expansion in the use of TAVI into lower risk cohorts[6, 7], these results provide welcome encouragement by demonstrating that increased rates of implantation are not necessarily associated with a commensurate increase in the rate of IE. Standardising measurement of incidence by device year may help monitoring infection rates and benchmarking between units.

Whilst the diagnostic accuracy of the modified Duke criteria has been shown to be reduced when assessing surgical AVR-PVE, there is little data regarding its sensitivity in the context of TAVI-IE. Our study has shown that less than a third of patients with TAVI-IE fulfilled the modified Duke criteria for definite IE. This is primarily due to the paucity of diagnostic echocardiographic findings, as only one patient from our cohort was found to have a vegetation. When assessing for PVE of a surgical AVR, paravalvular leak (PVL) as a result of valve dehiscence can often be one of the key diagnostic findings. Given that transcatheter aortic valves are expanded into the valve annulus without the requirement for sutures, TAVI–IE is unlikely to be diagnosed on the basis of new PVL. This places greater reliance on the presence of vegetations or abscesses, and makes echocardiographic diagnosis more challenging. The reduced sensitivity of the modified Duke criteria means that a high index of suspicion is required in the diagnosis of TAVI-IE, highlighting the importance of a specialist endocarditis team.

Limitations

The present study has certain limitations which must be borne in mind when appraising the results. Despite analyzing data from consecutive patients, our study is inherently limited by the fact that the data has been gained retrospectively, and from a single centre. Given the challenges associated with diagnosing TAVI-IE, it is also possible that a number of patients may have died following TAVI due to undiagnosed endocarditis, or been missed because they presented to other hospitals.

Not all of the patients diagnosed with TAVI-IE (4/13) underwent a TOE, which limits the assessment of the accuracy of the modified Duke criteria. In 2 of these cases, the patients died before they were able to have the test, and in the other 2 cases the patients was deemed too frail. This may be regarded as a limitation of the modified Duke criteria in the real world, as it is not always possible or appropriate to undertake invasive investigations. Furthermore, none of the patients underwent positron emission tomography/computed tomography (PET/CT) scans as part of the diagnostic

process. PET/CT is a recognised tool for the diagnosis of infective endocarditis, particularly when related to devices such as permanent pacemakers[19]. However, it has not been validated for use in TAVI-IE. Finally, as mentioned earlier, whilst we were able to present an all-cause mortality rate for this patient cohort, the observational and retrospective nature of this study limits our ability to provide definitive a mortality rate for TAVI-IE specifically.

Conclusion

The overall incidence of TAVI-IE was less than 1% after 2.3 years follow-up. After an initial higher rate, the rate of TAVI-IE has remained low and static in relation to the number of device years. The condition is associated with significant mortality, placing an emphasis upon prompt diagnosis and initiation of appropriate therapy. The modified Duke criteria appears to be less sensitive in the context of TAVI-IE, meaning that a high index of suspicion is required and investigation of better diagnostic tests is needed.

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Figure legends

Figure 1. Cumulative episodes of IE relative to cumulative number of TAVI years.

Figure 2. IE rate per 100 TAVI years relative to cumulative 100 TAVI years.

Figure 3. The relationship between diagnosis of TAVI-IE and the length of time of TAVI in situ.

Table 1. Demographics, co-morbidities, presentation, treatment and complications of patients diagnosed with TAVI-IE.

Cases are listed consecutively based upon the date of diagnosis of TAVI-IE.

(PVE – prosthetic valve endocarditis; TAVI – transcatheter aortic valve implantation; ViV – valve in valve; CCI – Charlson co-morbidity index; CABG – coronary artery bypass grafting; PPM – permanent pacemaker; AF – atrial fibrillation; THR – total hip replacement; Ca – carcinoma; CKD – chronic kidney disease; HTN – hypertension; T2DM – type 2 diabetes mellitus; BPH – benign prostatic hyperplasia; IHD – ischaemic heart disease; PMR – polymyalgia rheumatica; CVA – cerebrovascular accident; AIH – autoimmune hepatitis; COPD – chronic obstructive pulmonary disease; T1DM – type 1 diabetes mellitus; CCF – congestive cardiac failure; OA – osteoarthritis; SAVR – surgical aortic valve replacement; CRTD- cardiac resynchronisation therapy with implantable cardiac defibrillator; SoV – sinus of valsalva; TTE – trans-thoracic echocardiography; TOE –trans-oesophageal echocardiography; PVL – paravalvular leak)