Incidental Non-Cardiac Findings on Computed Tomography (CT) Angiography Do Not Adversely Affect Survival Following Transcatheter Aortic Valve Implantation (TAVI)

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Aims and objectives

Introduction

The last ten years have seen an exponential growth in the number of transcatheter aortic valve implantation (TAVI) procedures being performed. Well over 50,000 cases have now been carried out worldwide - mostly in Europe - and in Germany it has been estimated that approximately 30% of aortic valves are currently implanted via a transcatheter route\(^1\). Nonetheless, important questions remain to be answered regarding optimal patient selection, and in the UK the National Institute for Clinical Excellence (NICE) recommends that all patients are initially assessed by a multi-disciplinary team (MDT)\(^2,3\).

A particular challenge lies in determining which patients are likely to gain the greatest long-term benefit from TAVI\(^4\). Recent two-year follow-up of the PARTNER trial found that over a third of all patients who had died at two years did so from a non-cardiovascular cause\(^5\), leading the investigators to suggest that comorbidities play an important role in late mortality following TAVI. Similarly, the FRANCE 2 registry found that of all patients who had died at one year post TAVI, over 40% did so from a non-cardiovascular cause\(^6\). Thus the identification of patients who are likely to succumb to non-cardiovascular conditions in the short- to medium-term remains an important goal of TAVI research.

While echocardiography remains the fundamental mode of valve assessment, several other imaging techniques can be used to assess an individual patient's suitability for TAVI. In particular, many centres now perform CT angiography of the aorta as part of the pre-procedural work-up in order to assess imaging angles, access routes, and annular size\(^7-9\). During CT aortography, images are acquired throughout the thorax and abdomen, where potentially significant incidental findings can be detected\(^10,11\). However, there are currently no published data on the incidence and nature of incidental findings in a TAVI cohort, which given the high average age of the TAVI population might be expected to be more common\(^12\). Furthermore, it has not been investigated whether incidental findings (IFs) found on CT scans performed prior to TAVI could impact on the clinical outcomes and cost-effectiveness of the procedure. The goal of this study was to investigate these issues in a cohort of patients referred for TAVI at our centre over a four-year period.
Methods and materials

Study Population

The study population comprised 380 consecutive patients who were referred for possible TAVI at the Royal Brompton Hospital between 2007 and 2011. Of these, 219 underwent TAVI, while 161 did not. All cases were formally discussed at a multidisciplinary team meeting - which included cardiothoracic surgeons, cardiologists, and radiologists - where all available imaging was reviewed. Only patients who underwent a CT TAVI protocol to image the thoracic and abdominal aorta were included in the analysis (188 patients who underwent TAVI, 91 patients in the control group). All patients gave written informed consent prior to the procedure.

TAVI

Selection and technical aspects of TAVI were consistent with published guidelines\textsuperscript{13}. Both the Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) and Edwards SAPIEN valve (Edwards Lifesciences, Irvine, California) were implanted. The decision to proceed with TAVI was determined by consensus at a multidisciplinary team meeting after reviewing all available imaging modalities.

Cardiovascular CT Imaging and analysis

The CT TAVI protocol consisted of three separate acquisitions: a coronary calcium score scan, a coronary CT angiogram, and lastly an acquisition of the ascending and descending aorta. Angiographic imaging was routinely performed using a prospective scanning protocol (acquisition time 0.5 to 5s, tube current, 370 mA [with electrocardiography-gated milliampere modulation control]; tube voltage, 100 or 120 kV [depending on a patient's weight]; gantry rotation time, 0.28s to 0.5s; and scanning field of view, 200 mm), unless the heart rate exceeded 75 beats/min or a significant arrhythmia was present, in which case a retrospective protocol was used [acquisition time, 7.5 to 8.5 s; tube current], 320 mA [with electrocardiography-gated milliampere modulation control]).

CT angiographic images were reconstructed at a slice thickness of 0.75mm every 0.5mm (0.6mm for the coronaries). Mediastinal and abdominal images were reconstructed at 2.1 mm thickness every 1 mm, and lung windows at 1mm thickness every 1mm. Aortic images were reconstructed (Aquarius Workstation, Terarecon, Inc., San Mateo, California) using the best diastolic phase images to allow assessment of aortic root dimensions. Total radiation dose was 8 to 11 mSv for prospectively gated studies and 23 to 30 mSv for retrospectively gated CCT and CTA of the thoracic and abdominal aorta.
A total of 150mls of contrast was used; 60mls for the coronary CT angiogram and 90mls for the CT aortogram.

**Incidental Findings and Patient Follow Up**

Two radiologists, both blinded to the final decision on whether or not to perform TAVI, reviewed all CT scans for IFs. Where opinions differed as to the significance of an IF, consensus was obtained following a third person review. Based upon the radiology reports, noncardiac findings were considered "incidental" if an abnormality was identified without antecedent clinical suspicion or previously known disease. IFs were diagnosed where an abnormality was found without previous clinical suspicion or known disease, and were categorised as: clinically significant (CS, when findings were clearly pathological and/or diagnostic), indeterminate (I, when additional investigations were required to clarify diagnosis), or clinically insignificant (CI). Patient follow-up was obtained from the office of national statistics (ONS) national mortality database, or by telephone interviews and/or correspondence with primary care physicians.

**Further Investigations and Cost determination**

Fleischner Society Guidelines were used to determine the follow-up of lung nodules\(^{14}\), and the Bosniak classification was used for renal cysts\(^{15}\). Liver lesions not showing the typical hallmarks of a cyst were investigated by further ultrasound or MRI if necessary. Patients with thyroid cysts were referred for ultrasound and, where the cyst exceeded 1.5cm in size, fine needle aspiration. For all other findings, National Institute of Clinical Excellence (NICE) Quality Standards for optimal care were used to assess which further investigations would be necessary.

All procedures recommended according to these guidelines were classified using UK Office of Population Censuses and Surveys codes in the first instance, and costs taken from the UK Department of Health Payment Tariff (2011-2012 financial year). Costs were defined as the sum of direct medical costs incurred as a result of investigating the IF, excluding any subsequent treatment required. Therefore, costs do not include those for medical or surgical therapy/intervention after diagnosis (e.g., chemotherapy) nor do they include hospital or community care costs.

**Statistical Analysis**

Analysis was performed using SPSS version 21.0 (SPSS Inc., Chicago, Illinois) and Stata 12. Continuous variables with normal distributions were expressed as mean (Standard Deviation). Variables with skewed distributions were expressed as median (IQR). Categorical variables were expressed as frequency (percentage). Differences at baseline between patients with and without events were tested with Pearson Chi-Square.
or Fisher's exact test in case of categorical variables and Student's \( t \)-test or Mann-Whitney \( U \)-test in case of continuous variables and a value of \( p<0.05 \) was considered statistically significant.

The prognostic value of incidental findings for predicting death was assessed for the study population. Survival distributions were calculated using Kaplan-Meier curves and compared using the log-rank test. For the risk-adjusted analysis, Cox proportional hazards models were used to assess the prognostic value of IFs, with results presented as hazard ratios and 95% confidence intervals.
Results

A total of 380 consecutive patients were referred for consideration of TAVI. Of these 279 underwent CT scanning of the thoracic and abdominal aorta as part of their assessment; 188 of these patients subsequently underwent TAVI and 91 were turned down. When compared to those patients where TAVI was not performed, more patients who underwent TAVI had undergone previous cardiac surgery (32.8% vs. 17.4%, \(P=0.009\)), prior treatment to the valve (8.2% vs. 0%, \(P=0.007\)), and previous PCI (23.0% vs. 7.4%; \(P=0.003\)). Amongst the TAVI cohort, patients with clinically significant or incidental findings were older (81.9 years vs. 77.2 years; \(P<0.001\)).

Incidental Findings

A total of 103/188 patients undergoing TAVI (54.8%) had at least one incidental finding (IF) of any kind (clinically significant/indeterminate/clinically insignificant), compared to 64/91 patients who were declined for TAVI (70.3%, \(P=0.01\)). 34/188 TAVI patients (18.1%) had clinically significant findings, compared to 20/91 patients (22.0%) declined for the procedure (\(P=0.440\)). Indeterminate findings were more common in patients not undergoing TAVI (25.3% vs. 15.4%; \(P=0.048\)). Overall, the presence of a clinically significant or an incidental finding was more common in patients declined for TAVI than in those accepted for TAVI (47.3% vs. 33.0%; \(P=0.02\)).

Pulmonary incidental findings were the most common overall; 56 in patients undergoing TAVI, compared to 45 in patients not undergoing TAVI. While a majority of these findings where either clinically significant or incidental (29/56 in the TAVI group, 25/40 in patients not undergoing TAVI), vascular incidental findings were most commonly felt to be clinically significant or indeterminate (16/16 in patients undergoing TAVI, 6/9 in patients not undergoing TAVI). Examples of some of the incidental findings noted are shown in Figure 1.
Fig. 1: Examples of incidental findings seen on TAVI assessment scans. A, top left: An area of fibrosis and calcification is seen in the periphery of the right lung. B, top right: An irregular mass is seen to arise from the left kidney. This was subsequently confirmed as a renal carcinoma. C, bottom left: the contour of the liver is irregular, and a round nodule of uncertain aetiology is noted, D, bottom right: an irregular filling defect of the bladder is seen.

References: Departments of Cardiology, Radiology, and Surgery, Royal Brompton Hospital - London/UK

Additional Investigations and Costings

Overall an additional 45 further investigations were recommended to clarify IFs in the TAVI group. Of the six cases of noncalcified lung nodules found in the TAVI group, one was subsequently confirmed as a malignancy. The total cost of these investigations was £6146, at an average of £32.69 per patient. By comparison, 30 additional investigations were needed for the 91 patients with CT scans who did not ultimately undergo TAVI, at a total cost of £5398 (average cost of £59.32 per patient). The total cost of investigating
incidental findings for the entire cohort according to current guidelines was estimated at £11,544. In both groups the most commonly recommended subsequent examination was ultrasound, however significant lung findings meant that overall 10 extra CT scans were recommended for the entire patient group. The median time from scan to TAVI procedure was slightly longer in patients with clinically significant or incidental findings (56.5 days versus 48 days; P=0.597).

Mortality Data

Follow-up mortality data were available for all patients up to three years. Overall there were 46 deaths in the TAVI group (24%), and 47 in those patients declined for TAVI (52%); the median survival time for patients not undergoing TAVI was 2.25 years (Figure 2).

![Survival curve](image)

**Fig. 2:** Survival to three years of the 279 patients who underwent CT, from time of the initial scan. A clear survival advantage is seen for patients undergoing TAVI (P<0.01), however the presence of a clinically significant incidental finding in TAVI group did not significantly alter outcomes (P=0.99). Similarly, in patients not undergoing TAVI, no significant difference in mortality was seen at three years (P=0.149), although there
was a trend towards more deaths at one year in patients with clinically significant or incidental findings (P=0.06).

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In patients undergoing TAVI, no statistically significant difference was found in survival when comparing patients with any form of incidental finding compared to those without (P=0.312, Figure 3). Specifically, patients with clinically significant or indeterminate findings also fared no worse when compared to those without (P=0.438, Figure 3). These findings were consistent whether survival was calculated from the time of CT scan or the time of TAVI procedure. Of patients who did not undergo TAVI, one year survival rate was 70.1% in patients with no clinically significant or indeterminate findings, compared to 51.0% in those with findings (Figure 4).
**Fig. 3:** Kaplan-Meier curves of outcomes in all patients undergoing TAVI (dotted line represents patients with incidental findings). Top, no significant difference is seen in survival to three years after TAVI in patients with any form of incidental finding compared to those without (P=0.531). Bottom, survival of patients with clinically significant or indeterminate findings did not differ from all other patients in the TAVI cohort (P=0.438).

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Fig. 4: Kaplan-Meier curves of patients not undergoing TAVI. No significant difference in mortality was seen at three years, either in patients with clinically significant (top, P=0.439) or indeterminate findings (bottom, P=0.345).

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For all patients with severe aortic stenosis being referred for consideration of TAVI, univariate analysis revealed that patients with clinically significant or incidental findings on CT had a 61% increase in all-cause mortality (Hazard Ratio [HR] 1.61; 95% CI 1.08 to 2.4; P=0.02) compared to those without. Similarly an incidental finding on its own was associated with a 63% increase (HR 1.02-2.58; 95% CI 1.02-2.58; P=0.039). TAVI procedure, pulmonary arterial hypertension, number of vessels with coronary artery
disease, and previous cardiac surgery also predicted outcome on univariate analysis. However, after multivariate analysis, only TAVI, pulmonary hypertension, and the number of coronary vessels with coronary artery disease remained as independent predictors of outcomes.
Fig. 1: Examples of incidental findings seen on TAVI assessment scans. A, top left: An area of fibrosis and calcification is seen in the periphery of the right lung. B, top right: An irregular mass is seen to arise from the left kidney. This was subsequently confirmed as a renal carcinoma. C, bottom left: the contour of the liver is irregular, and a round nodule of uncertain aetiology is noted, D, bottom right: an irregular filling defect of the bladder is seen.

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Fig. 4: Kaplan-Meier curves of patients not undergoing TAVI. No significant difference in mortality was seen at three years, either in patients with clinically significant (top, P=0.439) or indeterminate findings (bottom, P=0.345).

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Conclusion

This study found that over half of patients undergoing CT angiography of the aorta prior to TAVI had incidental non-cardiac findings, many of which were clinically significant or indeterminate and required further investigation.

The need for a sum total of only 75 extra tests in a population of 380 patients referred for TAVI - the majority of which were relatively low-cost ultrasound scans - would suggest that the impact of additional testing on the cost-effectiveness of the procedure is unlikely to be substantial.

However, the need for additional tests to clarify the nature of an incidental finding could potentially lead to a delay in the time to TAVI. Although this did not reach statistical significance in our study, the finding of a median scan to procedure time that was over a week longer in patients with clinically significant or indeterminate incidental findings raises the possibility that many of these patients - who are often already in a critical cardiovascular condition - could be kept waiting for longer for a TAVI procedure. Although some minor delays may be unavoidable, the majority of patients in this cohort required only ultrasound scanning to help clarify diagnosis or follow-up incidental findings, which can usually be performed quickly. However, seven additional CT scans were also recommended in patients awaiting TAVI. Although these scans are associated with an additional radiation burden, the overall impact of this in an elderly population that is already high-risk for all-cause mortality is likely to be low.

In this prospective observational study, we followed up all patients up to three years for mortality outcomes. Importantly, this analysis found no indication of poorer outcomes after TAVI for patients with any form of incidental finding, including patients with clinically significant or indeterminate findings.

The two-year follow-up results of the PARTNER trial found a high mortality in patients who had undergone TAVI or surgical aortic valve replacement, leading the authors to conclude that coexisting conditions may instead play a role in late mortality. Similarly, a multicentre registry of TAVI procedures performed in Canada found that late mortality was due to non-cardiac comorbidities in more than half the patients studied. In this regard, TAVI patients with incidental findings - particularly those that are clinically significant or indeterminate - might be expected to be at greater risk of death due to their increased disease burden, but this was not found to the case in the current study. A multicentre study involving more patients over a longer follow-up period is needed to confirm these findings, and specifically to examine whether the presence of a CT incidental finding identifies patients with a poor long-term prognosis (i.e. >3 years). In the interim, the findings of this study would suggest that the discovery of an incidental
finding on CT should not influence or delay the decision to perform TAVI in patients who are felt to be otherwise clinically suitable. These findings emphasise the importance of a collaborative, team-based approach to selecting and treating patients for TAVI.

**Study Limitations**

This was a single centre study. However, TAVI is currently only performed at certain specialist centres, and our referral base covered a large geographical area from Scotland to the most southern parts of England. Therefore, the study population is likely to be a valid representation of a general TAVI cohort in the United Kingdom.

It is possible that clinically significant or incidental findings led to some patients being declined for TAVI. However, we found no statistically significant difference in clinically significant findings between those patients who did and did not undergo TAVI. Furthermore, over half of the patients undergoing TAVI still had incidental findings, suggesting that they did not significantly bias the decision making process. Furthermore, the fact that clinically significant or indeterminate findings did not influence survival after TAVI emphasises the strength of a holistic, team-based approach to selecting suitable patients for the procedure, regardless of incidental findings.

Lastly, the costings used here represent those used to reimburse hospitals in the United Kingdom, and these costs may differ substantially in other parts of the world. In addition, our analysis included only the costs of any extra tests incurred, and did not include the cost of any subsequent treatment needed. Therefore, the true economic burden of the incidental findings described here may be higher.
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