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Observational Study

Role of coronary angiogram before transcatheter aortic valve implantation

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Abstract

BACKGROUND

Coexistent coronary artery disease is commonly seen in patients undergoing transcatheter aortic valve implantation (TAVI). Previous studies showed that pre-TAVI coronary revascularisation was not associated with improved outcomes, challenging the clinical value of routine coronary angiogram (CA).

AIM

To assess whether a selective approach to perform pre-TAVI CA is safe and feasible.

METHODS

This was a retrospective non-randomised single-centre analysis of consecutive patients undergoing TAVI. A selective approach for performing CA tailored to patient clinical need was developed. Clinical outcomes were compared based on whether patients underwent CA. The primary endpoint was a composite of all-cause mortality, myocardial infarction, repeat CA, and re-admission with heart failure.

RESULTS

Of 348 patients (average age 81 ± 7 and 57% male) were included with a median follow up of 19 (9-31) mo. One hundred and fifty-four (44%) patients, underwent CA before TAVI procedure. Patients who underwent CA were more likely to have previous myocardial infarction (MI) and previous percutaneous revascularisation. The primary endpoint was comparable between the two group (22.6% vs 22.2%; hazard ratio 1.05, 95%CI: 0.67-1.64, $P = 0.82$). Patients who had CA were less likely to be readmitted with heart failure ($P = 0.022$), but more likely to have repeat CA ($P = 0.002$) and MI ($P = 0.007$). In those who underwent CA, the presence of flow

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limiting lesions did not affect the incidence of primary endpoint, or its components, except for increased rate of repeat CA.

CONCLUSION

Selective CA is a feasible and safe approach. The clinical value of routine CA should be challenged in future randomised trials

Key Words: Transcatheter aortic valve implantation; Angiogram; Revascularisation; Coronary angiogram

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Core Tip: Previous studies showed that pre-transcatheter aortic valve implantation coronary revascularisation was not associated with improved outcomes, challenging the clinical value of routine coronary angiogram (CA). A selective approach for performing CA tailored to patient clinical need was developed. In 348 patients, the primary endpoint of all-cause mortality, myocardial infarction, repeat CA, and re-admission with heart failure was comparable between patients who underwent CA vs no CA (22.6% vs 22.2%; hazard ratio 1.05, 95%CI: 0.67-1.64, $P = 0.82$). Patients who had CA were less likely to be readmitted with heart failure ($P = 0.022$), but more likely to have repeat CA ($P = 0.002$) and myocardial infarction ($P = 0.007$). The clinical value of routine CA should be challenged in future randomised trials.

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INTRODUCTION

Aortic stenosis is the most common valve disease requiring intervention in Europe and North America and is largely a disease of older adults[1]. Transcatheter aortic valve implantation (TAVI) is now a standard treatment option for management of severe aortic stenosis[1,2]. Given the ageing population and increasing prevalence of disease, the volume of patients requiring valve intervention is likely to increase. Moreover, a paradigm shift towards the use of TAVI in lower-risk patients is becoming more evident[3,4].

Coexistent coronary artery disease (CAD) is commonly seen in those with severe aortic stenosis, with shared traditional cardiovascular risk factors[5,6]. Whether revascularisation for bystander coronary artery disease pre-TAVI can improve procedural and long-term outcomes remains a matter of debate. Current guidelines recommend routine coronary angiography and revascularisation of proximal lesions with $\geq 70\%$ stenosis prior to TAVI[1,2]. These recommendations are largely extrapolated from data in patients who underwent surgical aortic valve replacement[7-9]. Nonetheless, previous meta-analyses highlighted that pre-TAVI revascularisation was not associated with improved one-year mortality, and demonstrated increased 30-d major vascular complications and mortality[10,11]. Similarly, there was no significant difference between TAVI plus revascularisation versus TAVI alone in terms of 30-d mortality or morbidity with similar resolution of symptoms between the groups[12].

The lack of data showing consistent benefits in pre-TAVI revascularisation challenges the need for routine invasive coronary angiogram (CA) before TAVI procedure. However, there has not been any previous report on the safety of such approach or an attempt to identify a group of patients who may benefit from coronary angiography before TAVI. We report a single-centre experience using a selective approach to coronary angiography in patients with severe aortic stenosis referred for TAVI.

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MATERIALS AND METHODS

Study population

This was a retrospective observational analysis of consecutive patients undergoing TAVI at the Freeman Hospital in Newcastle-upon-Tyne over 4 years. Patients with inaccessible electronic follow-up were excluded. The TAVI programme is a regional service and ascertaining clinical follow up was an essential criterion to be included in this study.

The TAVI procedure and valve choice was left to the operators' discretion. Clinical, echocardiographic and procedural characteristics were prospectively entered into a dedicated TAVR database which was retrospectively interrogated. All patients had an echocardiogram and computed tomography (CT) prior to TAVI procedure.

Angiographic prior to TAVI

A selective approach to perform CA was developed during the study period. This was tailored to patient's clinical status and invasive angiogram was performed if: (1) Patient reported typical exertional chest pain which was relieved at rest and was suggestive of angina; (2) Impaired left ventricle systolic function (ejection fraction $\leq 50\%$), particularly if there were regional wall motion abnormalities; or (3) Extensive calcifications ($> 70\%$ of lumen diameter stenosis) involving the proximal segments of left or right coronary arteries detected on CT as part of TAVI work up.

Coronary revascularisation was recommended prior to TAVI, if patients had angiographically flow limiting lesions.

Study endpoints and follow up

The primary endpoint was a combination of all-cause mortality, myocardial infarction (MI), repeat CA, and re-admission to hospital with heart failure. Secondary endpoints included the individual or combination of two components of the primary endpoint. Procedural MI was excluded, and only spontaneous MI was included. Repeat CA after TAVI was indicated in the presence of symptoms, signs of ischaemia, or elevated cardiac biomarkers. Flow limiting lesion was defined as degree of stenosis $\geq 70\%$ on epicardial coronary artery of ≥ 2.5 mm in size.

Mortality data were provided by the Office of National Statistics. Other clinical endpoints were retrieved using dedicated electronic databases for clinical follow up. MI events were cross-checked by evaluating troponin measurements and referral letter for invasive CA. Heart failure readmissions were similarly assessed using reported chest X-ray.

Statistical analysis

Data were assessed for normality of distribution using the Shapiro-Wilk test. Normally distributed data were expressed as mean \pm SD or as median accompanied by inter-quartile range for non-parametric data. Continuous variables were compared by using unpaired T test or Mann-Witney U test as appropriate, while frequencies comparisons were made using Chi square test or Fisher's exact test, as appropriate. Kaplan-Meier methodology and the associated log-rank test were performed to determine the differences in the primary endpoint. All statistical analysis was performed using SPSS 26.0 (SPSS, Inc Chicago, IL, United States) and a $P < 0.05$ was considered statistically significant.

RESULTS

Of 480 patients undergoing TAVI, 348 (73%) patients with accessible electronic records were included in this analysis. Patients were followed for a median of 19 (9-31) mo.

The average age was 81 ± 7 and 57% of patients were male. Two-thirds of patients were markedly symptomatic with NYHA class III/IV. 295 (85%) patients received balloon expanding valve and 34 (10%) had self-expanding valves. Less than half of the cohort, 154 (44%) patients, underwent coronary angiography before TAVI procedure. Almost three-quarters of patients had their TAVI procedure in an elective setting. There were no differences between patients who did or did not undergo CA in terms of age, gender, cardiovascular risk, body mass index, kidney function, or other vascular disease. Baseline clinical characteristics stratified according to CA pre-TAVI are presented in Table 1. Patients who underwent CA were more likely to have previous MI (14% *vs* 8%, $P = 0.07$), and previous percutaneous coronary intervention

Table 1 Baseline clinical characteristics, stratified according to whether patients had invasive angiogram before their transcatheter aortic valve implantation procedure

	Whole group (n = 348)	No coronary angiogram group (n = 194)	Coronary angiogram group (n = 154)	P value
Age (mean \pm SD)	81 \pm 7	82 \pm 7	81 \pm 7	NS
Male gender, n (%)	197 (57)	109 (56)	88 (57)	NS
Obesity, n (%)	83 (34)	43 (31)	40 (37)	NS
Hypertension, n (%)	136 (55)	79 (57)	57 (53)	NS
NYHA III/IV, n (%)	232 (67)	127 (66)	105 (68)	NS
Diabetes, n (%)	68 (20)	39 (20)	29 (19)	NS
Smoking history, n (%)	166 (48)	94 (49)	72 (47)	NS
Previous MI, n (%)	38 (11)	16 (8)	22 (14)	NS
Previous PCI, n (%)	52 (15)	20 (10)	32 (21)	< 0.01
Previous CABG, n (%)	43 (12)	33 (17)	10 (7)	< 0.01
COPD, n (%)	58 (17)	34 (18)	24 (16)	NS
CVA/TIA, n (%)	29 (8)	14 (7)	15 (10)	NS
AF, n (%)	83 (24)	47 (24)	36 (23)	NS
PVD, n (%)	55 (16)	24 (12)	31 (20)	< 0.05
Creatinine (mean \pm SD)	112 \pm 97	114 \pm 117	110 \pm 65	NS
Elective admission, n (%)	271 (78)	149 (77)	122 (79)	NS

MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular event; TIA: Transient ischaemic attack; AF: Atrial fibrillation; PVD: Peripheral vascular disease; NS: No significant difference. Obesity was defined as body mass index > 30 kg/m².

(21% *vs* 10%, $P = 0.007$), but less likely to have previous coronary artery bypass graft (7% *vs* 17%, $P = 0.03$). There were no reported complications with any of the cases that underwent coronary angiography.

Echocardiographic and procedural characteristics are presented in [Table 2](#). There were no differences between the two groups in gradients, valve area, or left ventricle function. Transfemoral approach was performed in the majority of cases (89%). Patients who underwent CA were more likely to have undergone an alternative access TAVI *i.e.*, *via* subclavian, trans axillary, apical, or direct aortic. Similarly, general anaesthesia was more frequently used in CA *vs* no CA groups (12% *vs* 2%, $P < 0.001$).

The primary endpoint of all-cause mortality, MI, repeat CA, and re-admission to hospital with heart failure was comparable between the two groups [22.6% *vs* 22.2%; hazard ratio (HR) 1.05, 95%CI: 0.67-1.64, $P = 0.82$] ([Figure 1](#) and [Table 3](#)). All-cause mortality was comparable between the two groups (19% *vs* 17%; HR 1.18, 95%CI: 0.71-1.95, $P = 0.52$). Patients who had CA were less likely to be readmitted with heart failure (1.3% *vs* 6.2%, $P = 0.022$) but more likely to have repeat CA (5.8% *vs* 0.5%, $P = 0.003$). Likewise, patients in the CA group had higher rate of subsequent MI (3.9% *vs* 1.0%, $P = 0.07$), although this did not reach statistical significance.

We also assessed whether flow limiting lesions on CA before TAVI were associated with events post TAVI. One-third (54/154) of patients had flow limiting lesions on CA before TAVI. There were no differences in the incidence of the primary endpoint (29.6% *vs* 19.0%, $P = 0.13$), readmission with heart failure (3.7% *vs* 1.0%, $P = 0.24$), or spontaneous MI (7.4% *vs* 3.0%, $P = 0.21$) between patients with flow limiting *vs* those with no flow limiting lesions on CA, respectively ([Figures 2](#) and [3](#)). Repeat CA following TAVI was statistically more frequent in those with flow limiting lesions (9.3% *vs* 0%, $P = 0.005$) ([Figure 3](#)). Two patients had percutaneous coronary interventions at a median of 40 mo post TAVI. One patient with known flow limiting lesion which was not revascularised before TAVI while the second patient developed *de novo* flow limiting lesion.

Table 2 Echocardiographic and procedural characteristics, stratified according to whether patients had invasive angiogram before their transcatheter aortic valve implantation procedure

	Whole group (n = 348)	No coronary angiogram group (n = 194)	Coronary angiogram group (n = 154)	P value
Peak gradient (mean \pm SD)	74 \pm 23	73 \pm 22	74 \pm 24	NS
Mean gradient (mean \pm SD)	43 \pm 15	44 \pm 15	43 \pm 15	NS
Valve area (mean \pm SD)	0.70 \pm 0.20	0.71 \pm 0.18	0.69 \pm 0.22	NS
Preserved LV function, n (%)	274 (79)	158 (81)	116 (75)	NS
Moderate MR, n (%)	35 (10)	20 (10)	15 (10)	NS
PA pressure (mean \pm SD)	39 \pm 20	40 \pm 15	39 \pm 25	NS
Indication for AR or mixed AoV disease, n (%)	19 (6)	9 (5)	10 (7)	NS
Bioprosthetic valve, n (%)	17 (5)	14 (7)	3 (2)	< 0.05
GA, n (%)	23 (7)	4 (2)	19 (12)	< 0.01
BAV, n (%)	34 (10)	15 (8)	19 (12)	NS
Transfemoral approach, n (%)	311 (89)	183 (94)	128 (83)	< 0.01
Balloon-expanding, n (%)	295 (85)	161 (83)	134 (87)	NS
Valve size (> 23 mm), n (%)	222 (64)	125 (64)	97 (63)	NS

LV: Left ventricle; MR: Mitral regurgitation; PA: Pulmonary pressure; AR: Aortic regurgitation, AoV: Aortic valve disease; GA: General anaesthesia; BAV: Balloon valvuloplasty performed for pre-dilatation; NS: No significant difference.

Table 3 Clinical endpoints following transcatheter aortic valve implantation procedure

	Whole group (n = 348)	No coronary angiogram group (n = 194)	Coronary angiogram group (n = 154)	P value
Primary endpoint, n (%)	78 (22.4)	44 (22.6)	33 (22.2)	NS
Death, n (%)	63 (18.1)	37 (19.0)	26 (17.0)	NS
Myocardial infarction, n (%)	8 (2.3)	2 (1.0)	6 (3.9)	NS
Readmission with heart failure, n (%)	14 (4)	12 (6.2)	2 (1.3)	< 0.05
Coronary angiogram post valve intervention, n (%)	10 (2.9)	1 (0.5)	9 (5.8)	< 0.01
Death & myocardial infarction, n (%)	69 (19.8)	38 (19.5)	31 (20.3)	NS
Death & readmission with heart failure, n (%)	70 (20.1)	43 (22.1)	27 (17.6)	NS
Myocardial infarction & readmission with heart failure, n (%)	21 (6)	13 (6.7)	8 (5.2)	NS

Primary endpoint was defined as a composite of death, myocardial infarction, revascularisation, and readmission with heart failure. NS: No significant difference.

DISCUSSION

The main finding of this study was that our devised approach of selective CA tailored to patient clinical characteristics was safe and feasible over a relatively short follow up. Second, a composite of all-cause mortality, MI, repeat CA, and re-admission to hospital with heart failure was comparable irrespective of CA before TAVI procedure and importantly, there were no differences based on the obstructive nature of coronary lesions on CA before TAVI. Third, patients with flow limiting lesions pre-TAVI were more likely to have repeat CA following TAVI.

There is a strong association between CAD and aortic stenosis. In almost 16000 patients undergoing TAVI in the German Aortic Valve Registry, 50% of patients were

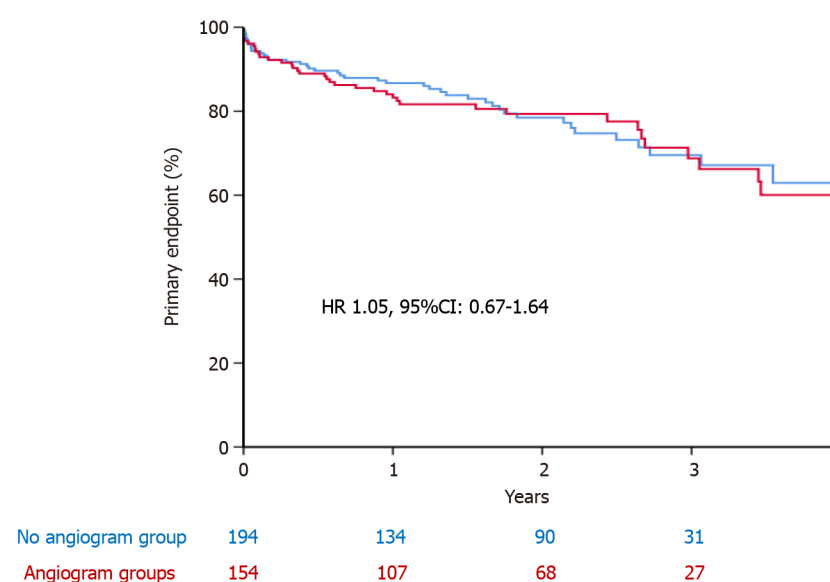


Figure 1 Primary endpoint of transcatheter aortic valve implantation patients stratified according to whether coronary angiogram was performed. Kaplan-Meier curves comparing cumulative incidence of all-cause mortality, myocardial infarction, repeat coronary angiogram, and re-admission to hospital with heart failure in patients with underwent coronary angiogram (in red) versus those who did not undergo coronary angiogram (blue). HR: Hazard ratio.

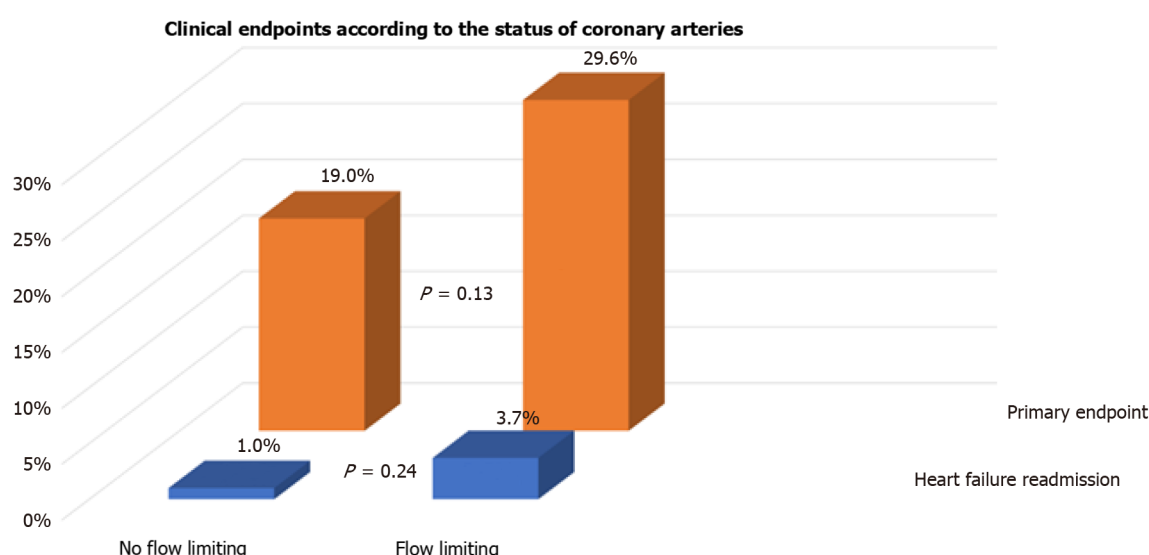


Figure 2 The incidence of the primary endpoint and heart failure readmission according to obstructive nature of coronary lesions. There was no difference in the incidence of the primary endpoint or readmission with heart failure between patients with obstructive versus non-obstructive coronary lesions.

reported to have concomitant coronary artery disease[13]. The management of CAD in this setting is controversial with previous studies highlighting the prognostic role of CAD in patients undergoing TAVI[14]. Moreover, observational data suggested a potential caveat when coronary arteries were not revascularised by demonstrating an association between rapid pacing and adverse outcomes in TAVI patients[15,16]. Coronary revascularisation was proposed to mitigate ventricular stunning and reduce prolong hypotension during rapid pacing, although this needs to be confirmed in randomised trials[17].

Nonetheless, percutaneous coronary intervention was not consistently associated with a reduction in adverse events following TAVI[10,18]. Recently, the percutaneous coronary intervention prior to TAVI (ACTIVATION) trial showed no difference in one-year survival or readmission to hospital according to whether coronary revascularisation was performed before TAVI[19,20]. This was the first randomised trial to test this hypothesis and challenges the current recommendation of performing routine coronary revascularisation for proximal CAD before TAVI[1,2]. Moreover, Snow *et al* [21] showed that the management of aortic stenosis and concomitant CAD can be

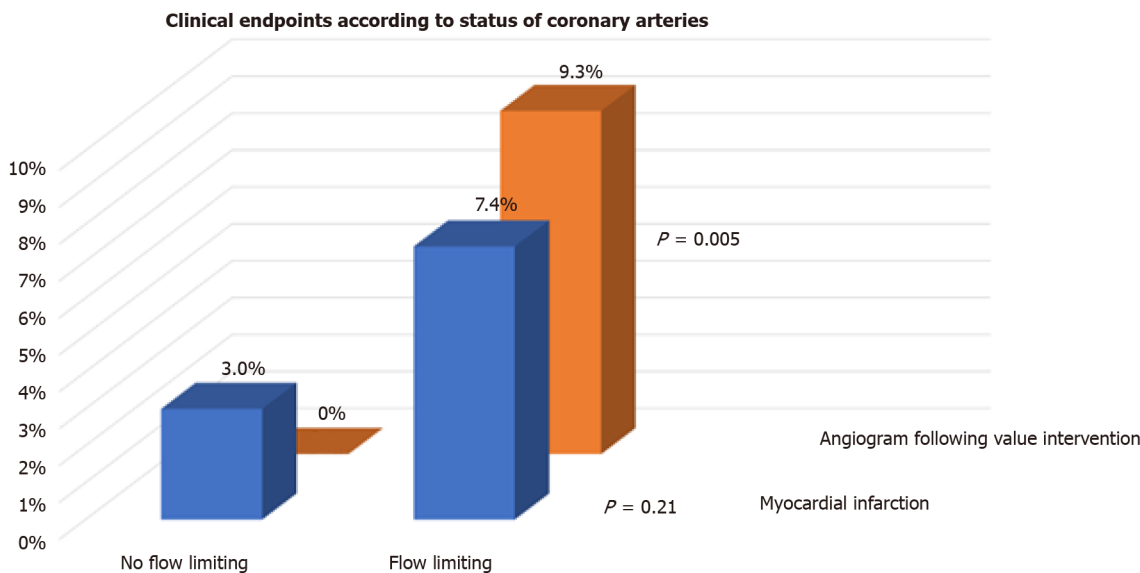


Figure 3 The incidence of the myocardial infarction and repeat coronary angiogram according to obstructive nature of coronary lesions. There was no difference in the incidence of myocardial infarction between patients with obstructive versus non-obstructive coronary lesions. Patients with flow limiting lesions were more likely to have repeat coronary angiograms following transcatheter aortic valve implantation procedure.

effectively managed by TAVI alone[21]. Importantly, our data are consistent with the results of these studies, and questions the need for CA, and revascularisation, before TAVI.

The current study suggests that the criteria for selective CA before TAVI is a safe and feasible. Patients with history of exertional chest pain suggestive of angina, left ventricle dysfunction, or extensive calcification on CT were deemed suitable for CA before TAVI. Up to 40% of patients with aortic stenosis may report angina symptoms and coronary revascularisation is indicated to relieve symptoms and improve quality of life. The presence of left ventricular dysfunction maybe related to CAD and suggests a second pathophysiological process, in addition to aortic stenosis, that needs to be addressed and managed. Advances in technology allowed CT-derived fractional flow reserve to assess CAD pre TAVI. This approach was illustrated to be safe and feasible in patients with severe aortic stenosis, and is currently assessed in the Functional Testing Underlying Coronary Revascularisation in aortic stenosis study[22].

Routine CA subjects patients to additional invasive procedure with associated risks, albeit small[23]. Contrast-induced nephropathy is a recognised risk with CA and is increased in the elderly and in patients with renal dysfunction[24,25]. These features are commonly observed in patients undergoing TAVI, and may exacerbate the renal risk associated following TAVI procedure itself[26]. Moreover, routine CA would add further delays to patients who are waiting for definitive valve intervention. There was an increase in mortality risk of almost 4% for each month delay while waiting for TAVI procedure[27].

Access to coronary arteries following TAVI has been reported to be challenging[28-30]. This was highlighted with self-expanding compared to balloon-expanding valves [31]. Therefore, it may be argued that upfront revascularisation of coronary lesions pre-TAVI would overcome the need to access the coronary arteries following TAVI. Nonetheless, these studies were of small sample size with success rate in engaging coronaries ranging from 50% to 100%[32]. Better understanding of the relationship between the bioprosthetic valve, particularly leaflets commissures, and coronary ostia would allow selective CA following TAVI[33].

Coronary events are relatively uncommon following TAVI. In our series, MI was reported in 2.3% of cases which was comparable to other contemporary studies[34]. Importantly, subsequent CAs did not always demonstrate culprit coronary lesions that required revascularisation. This should not be surprising since other mechanisms of MI were proposed such as coronary embolism secondary to subclinical leaflet thrombosis, late migration of the bioprosthetic valve, impaired coronary flow dynamic, and coronary hypo-perfusion related the valve bio-prosthesis[32]. Moreover, Faroux *et al*[30] showed that most coronary lesions were newly developed lesions that were not flow limiting prior to their valve procedure in patients presenting with acute coronary syndrome following TAVI[30]. This was reflected in our data whereby there

was no difference in events rates according to the presence of flow limiting lesions before TAVI. In other words, patients with non-obstructive CAD had similar incidence of ischaemic events to those with flow limiting lesions, and the use of CA did not identify a group of patients who were at a higher risk of future events. Interestingly, those with flow-limiting lesions were more likely to undergo repeat CA following TAVI. This is likely to reflect information bias as patients with known obstructive lesions will have a lower threshold to be brought back for CA compared to those with no flow limiting lesions.

Our study has several limitations. This was a retrospective single centre study associated with the inherent limitations of the design of the study. We had to exclude almost 25% of patients who underwent TAVI in our centre as their post procedural follow up could not be ascertained. Clinical endpoints were not adjudicated and were defined according to hospital discharge letters. This bias may have been mitigated by including hard events such as mortality and heart failure admissions.

CONCLUSION

Selective CA is a feasible and safe approach. It is not associated with high adverse outcomes. The role of CA before TAVI is increasingly undermined by the low ischaemic event rate. Additionally, the disconnect between CAD and subsequent cardiac events question the pre-emptive approach of coronary revascularisation in TAVI. Large randomised trials are required to test this hypothesis in the future.

ARTICLE HIGHLIGHTS

Research background

Routine coronary revascularisation pre-transcatheter aortic valve implantation (TAVI) was not associated with improved outcomes, yet, coronary angiogram (CA) is still performed as part of TAVI work up.

Research motivation

The lack of data showing consistent benefits in pre-TAVI revascularisation challenges the need for routine invasive coronary angiogram before TAVI procedure.

Research objectives

To assess whether a selective approach to perform pre-TAVI CA is safe and feasible.

Research methods

Retrospective analysis of consecutive patients undergoing TAVI who underwent CA *vs* those who did not was performed. Decision to undergo CA pre-TAVI was tailored to patients clinical characteristics.

Research results

The primary endpoint was a composite of all-cause mortality, myocardial infarction, repeat CA, and re-admission with heart failure was comparable between the two groups.

Research conclusions

Selective CA is a feasible and safe approach. The clinical value of routine CA should be challenged in future randomised trials.

Research perspectives

Future randomised clinical trials are required to test whether selective CA is safe.

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