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Coronary microvascular dysfunction in patients undergoing transcatheter aortic valve implantation

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ABSTRACT

Objectives This study aimed to evaluate the prognostic value of coronary microvascular dysfunction (CMD) at long term after transcatheter aortic valve implantation (TAVI) and to explore its relationship with extravalvular cardiac damage (EVCD). Moreover, we sought to test the correlation between angiography-derived index of microcirculatory resistance (IMR_{angio}) and invasive IMR in patients with aortic stenosis (AS).

Methods This was a retrospective analysis of the Verona Valvular Heart Disease Registry (Italy) including 250 patients (83 (80–86) years, 53% female) with severe AS who underwent TAVI between 2019 and 2021. IMR_{angio} was calculated offline using a computational flow model applied to coronary angiography obtained during the TAVI workup. CMD was defined as IMR_{angio} ≥30 units.
The primary endpoint was the composite of cardiovascular death and rehospitalisation for heart failure (HF). Advanced EVCD was defined as pulmonary circulation impairment, severe tricuspid regurgitation or right ventricular dysfunction.
The correlation between IMR and IMR_{angio} was prospectively assessed in 31 patients undergoing TAVI.

Results The primary endpoint occurred in 28 (11.2%) patients at a median follow-up of 22 (IQR 12–30) months. Patients with CMD met the primary endpoint more frequently than those without CMD (22.9% vs 2.8%, p<0.0001). Patients with CMD were more frequently characterised by advanced EVCD (33 (31.4%) vs 27 (18.6%), p=0.024). CMD was an independent predictor of adverse outcomes (adjusted HR 6.672 (2.251 to 19.778), p=0.001) and provided incremental prognostic value compared with conventional clinical and imaging variables. IMR_{angio} demonstrated fair correlation with IMR.

Conclusions CMD is an independent predictor of cardiovascular mortality and HF after TAVI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Coronary microvascular dysfunction was previously described in aortic stenosis but its relationship with extravalvular cardiac damage and its prognostic impact remain unknown.

WHAT THIS STUDY ADDS

⇒ Coronary microvascular dysfunction is associated with advanced extravalvular cardiac damage, and it is a strong predictor of cardiovascular mortality and heart failure at long-term follow-up after transcatheter aortic valve implantation (TAVI).

⇒ Angiography-derived index of microcirculatory resistance is a valuable alternative to invasive diagnostic tools to identify coronary microvascular dysfunction in patients with aortic stenosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If confirmed by prospective dedicated multicentric studies, patients with coronary microvascular dysfunction and aortic stenosis undergoing TAVI may be considered for close monitoring for the high risk of heart failure.

INTRODUCTION

Aortic stenosis (AS) leads to left ventricle pressure overload with compensatory changes (hypertrophy, fibrosis, reduced capillary density) that[1–4] adversely affects blood flow in the coronary epicardial arteries and microcirculation. Indeed, coronary microvascular dysfunction (CMD) was described in AS[2–11] and it was associated with adverse cardiac remodelling, left atrial dysfunction and myocardial fibrosis.[6 10]

Recently, advanced extravalvular cardiac damage (EVCD), characterised by right ventricular dysfunction, pulmonary vasculature impairment and severe low-flow phenotype, was associated with adverse clinical outcomes.[12 13] Moreover, preliminary data have suggested an association between low-flow phenotype and CMD.[6] However, whether CMD is associated with EVCD and worse clinical outcome in patients with severe AS undergoing transcatheter aortic valve implantation (TAVI) remains undetermined.

Angiography-derived index of microcirculatory resistance (IMR_{angio}) has been recently developed and validated to assess CMD, but it was never tested in AS.[14–16]

In this study, we aimed to assess if the presence of CMD was associated with EVCD and long-term adverse clinical outcomes in patients undergoing TAVI. Furthermore, we sought to test the correlation between IMR_{angio} and invasive IMR in patients with severe AS undergoing TAVI.

METHODS

Study design and population

This single-centre observational study consisted of two phases. In the first phase, we tested the correlation between IMR_{angio} and pressure/thermodilution wire-based IMR in a prospective cohort of patients with severe AS undergoing TAVI (derivation cohort). In the second phase, the long-term prognostic value of IMR_{angio}-defined CMD was assessed in a larger cohort of patients treated with TAVI and prospectively enrolled in the Verona Valvular Heart Disease Registry (prognostic cohort) (online supplemental figures 1 and 2). The main exclusion criteria were previous coronary artery bypass graft, severe angiographic stenosis of the left anterior descending artery (LAD) (>70%), significant angiographic stenosis (>50%) of the left main coronary artery and recent (<30 days) acute coronary syndrome. Details about the enrolment and the exclusion criteria of the two cohorts are provided in the online supplemental methods 1.

The clinical follow-up of patients included in the prognostic cohort was prospectively assessed with outpatient clinic visits or telephone contacts at 1, 6, 12, 24, 36 and 48 months after TAVI. Clinical events were adjudicated by dedicated research personnel blinded to the IMR_{angio} data. Discordance was resolved by consensus.

TAVI procedure and invasive assessment of coronary microvascular function

TAVI was performed in all cases under conscious sedation and local anaesthesia with transfemoral access. Technical decisions were all left to the operator's discretion. All patients underwent coronary angiography as part of the TAVI workup.

In the derivation cohort, coronary microvascular function was invasively assessed as previously described.[17] Briefly, a pressure and temperature-sensor guidewire (PressureWire X, Abbott, Santa Clara, California, USA) was advanced in the distal third of the LAD after careful equalisation of distal pressure and aortic pressure at the tip of the guiding catheter. Coronary pressures and mean transit times were measured and analysed with the Coroflow software (Coroventis, Uppsala, Sweden) during rest and steady-state hyperaemia obtained with the intravenous infusion of adenosine (140 µg/kg/min) (figure 1). IMR was calculated as:[17]

$$IMR = \textit{distal pressure}\ (\textit{hyperaemia}) \times \textit{mean transit time}\ (\textit{hyperaemia})$$

IMR >25 units was considered abnormal as previously described.[17 18]

Angiography-derived index of microcirculatory resistance

IMR_{angio} was assessed offline by expert quantitative flow ratio (QFR)-certified operators blinded to imaging data and clinical outcome (FDM, SA, MF) using standard coronary angiographic views obtained during TAVI workup.[14 15] Dedicated view angles according to the target coronary vessel were selected (online supplemental table 1). Coronary angiograms were acquired at 15 frames/s. Contrast media injection was performed in all patients using a standard contrast delivery system (ACIST CVi). Briefly, two angiographic views of the LAD were analysed using the QAngio XA three-dimensional (3D) software (Medis, Leiden, the Netherlands) to obtain the 3D vessel reconstruction and the QFR as a surrogate of the fractional flow reserve. The characterisation of coronary blood flow was based on the analysis of the number of frames required for contrast to reach the distal landmark of the vessel. IMR_{angio} was subsequently derived using the following formula[15]:

$$IMR_{angio} = Pa \times QFR \times \frac{n\ frames}{frame\ rate\ acquisition}$$

Where Pa is the mean aortic pressure at rest during the coronary angiography, and *n frames* are the number of angiographic frames for contrast dye to travel from the catheter to the distal part of the LAD at rest (figure 1 and online supplemental figure 3).

The recommendations recently proposed by Mejía-Rentería *et al* were applied to maximise standardisation (online supplemental methods 2).[19]

Conventional and speckle-tracking echocardiography

During the TAVI workup, all patients underwent conventional transthoracic echocardiography using commercially available ultrasound systems (Epiq 7C, Philips), and parameters were collected accordingly to international guidelines.[1 20]

Data were saved digitally and subsequently analysed offline using the TomTec software by two independent expert operators (PS, AD) blinded to the data on microvascular assessment and clinical outcome. Advanced speckle-tracking echocardiography was performed with TomTec Autostrain software for the assessment of global longitudinal strain (GLS) and peak atrial longitudinal strain (PALS) as recommended.[21–23]

EVCD assessment

The extent of EVCD was previously categorised into five stages according to a model described by Genereux *et al*.[12 13] To evaluate the interaction between CMD and EVCD and increase the statistical power, cardiac damage was dichotomised into stages 0–2 (group 1) corresponding to isolated left heart dysfunction, and stage 3 or 4 (group 2), corresponding to damage extending to the pulmonary circulation and right heart (advanced EVCD).[24] Details about the evaluation of EVCD are provided in online supplemental methods 3.

Study endpoints

The primary endpoint of the study was the composite of cardiovascular mortality and rehospitalisation for heart failure (HF) at long-term follow-up after TAVI.

HF was defined accordingly to international guidelines[25] as the evidence of central and/or peripheral congestion and/or peripheral hypoperfusion requiring hospitalisation for appropriate therapy. Cardiovascular death was defined as death attributable to HF, myocardial infarction, cerebrovascular accident or cardiac arrest because of other or unknown causes. Mortality was considered cardiovascular unless an alternative cause was documented.

Secondary endpoints were the correlation between IMR_{angio} and wire-based IMR and measures of EVCD.

Statistical analysis

Continuous variables were reported as median and IQR, while categorical variables were reported as numbers and percentages.

Continuous variables were compared with the Mann-Whitney test, whereas the Fisher's exact test was used to compare categorical variables.

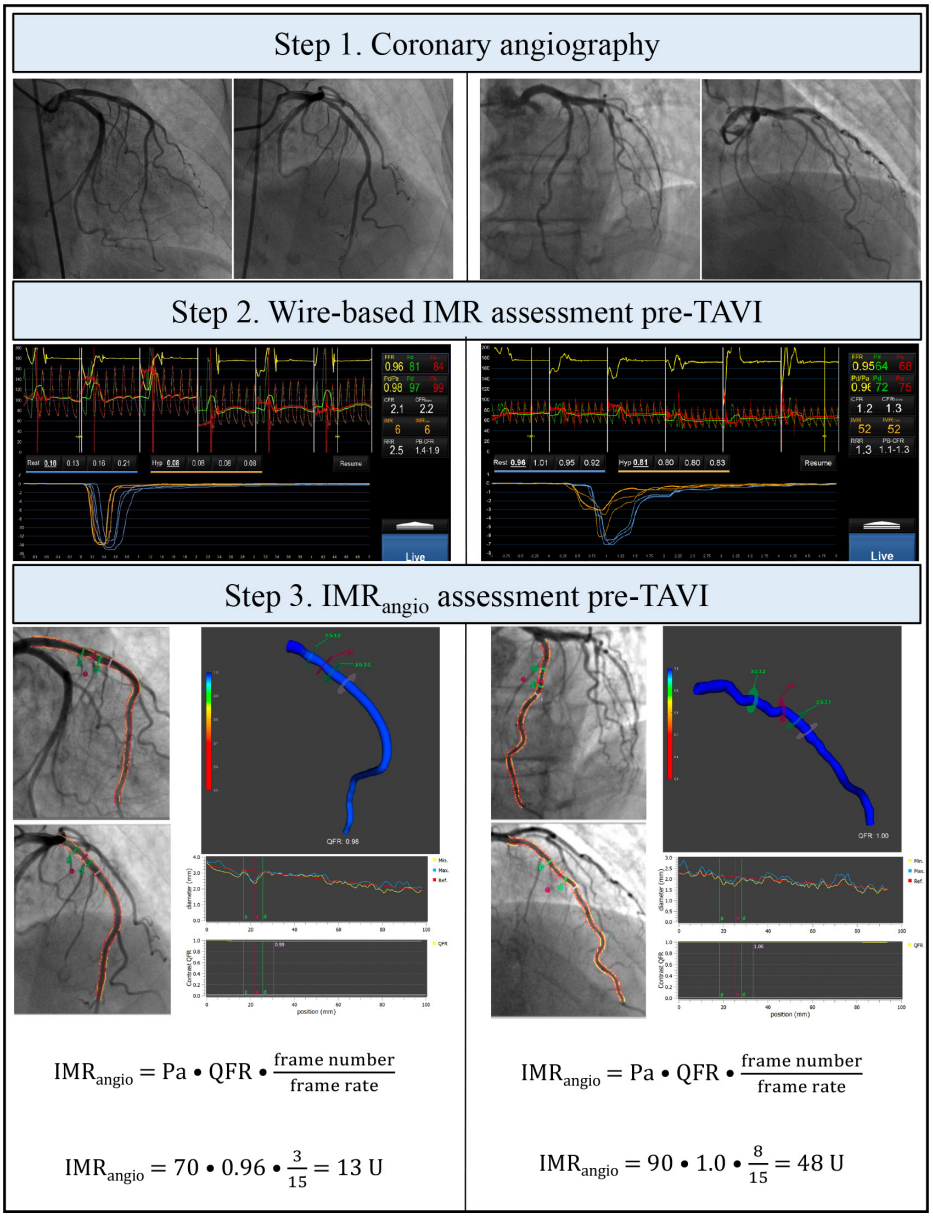


Figure 1 Wire-based and angiography-derived CMD assessment in the derivation cohort. Clinical example of wire-based IMR and IMR_{angio} assessment. IMR_{angio} is obtained using standard coronary angiography as the product of the measured mean aortic pressure, QFR and the ratio between the number of frames required for the dye to reach the distal landmark of the coronary vessel and the acquisition frame rate. CMD, coronary microvascular dysfunction; IMR, index of microcirculatory resistance; IMR_{angio}, angiography-derived index of microcirculatory resistance; QFR, quantitative flow ratio; TAVI, transcatheter aortic valve implantation.

To assess interoperator reliability, intraclass correlation coefficients (ICC) estimates and their 95% CIs were calculated. Spearman correlation coefficients were calculated to assess the linear correlation between IMR_{angio} and IMR, GLS and PALS using a non-parametric approach. The agreement between IMR_{angio} and invasive IMR was assessed using Bland-Altman plot analysis.

Areas under the curve (AUCs) of the receiver operating characteristic (ROC) curves were used to test the diagnostic accuracy of IMR_{angio} in predicting CMD defined by IMR >25 units and in predicting the primary endpoint. The best cut-off was determined with the analysis of the ROC curve to maximise sensitivity and specificity.

Survival analysis and endpoint comparison between groups were performed with the Cox regression analysis for the calculation of HR with 95% CI and the log-rank test. Survival analysis was adjusted for variables with $p<0.10$ at the univariable analysis. The test for proportional-hazards assumption was applied to confirm the validity of the model.[26] Logistic regression analysis was performed to identify determinants of the primary endpoint at 36 months of follow-up. AUCs were calculated and compared with the DeLong's method.[27]

The continuous association of IMR_{angio} with the primary endpoint was tested dividing the prognostic cohort in tertiles of IMR_{angio} and in four different groups according to the presence or absence of IMR_{angio}-defined CMD and/or advanced EVCD. Moreover, the analysis was conducted also in prespecified subgroups stratified by left ventricular ejection fraction (LVEF) <50%, presence of atrial fibrillation (AF) and older

age (≥median age of the study cohort). Interaction analysis was conducted to assess the impact of given variables on the IMR_{angio}-based prognostic stratification.

All the tests were two tailed and a $p<0.05$ was considered significant. Statistical analysis was performed with SPSS V.26 (IBM) and Stata V.15.1 (StataCorp, College Station, Texas, USA).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination of our research.

RESULTS

Correlation between invasive IMR and IMR_{angio}

Overall, paired invasive IMR and IMR_{angio} measurements were available in 31 out of 42 patients with severe AS undergoing TAVI (online supplemental figures 1 and 2).

Baseline clinical, echocardiographic and procedural characteristics of the derivation cohort are shown in online supplemental table 2. The correlation between IMR_{angio} and IMR was moderate but significant ($r=0.41$, $p=0.024$). The agreement between the two indices is shown in figure 2. At ROC curve analysis, IMR_{angio} showed an AUC of 0.81 (0.65–0.97, $p=0.009$) in predicting IMR >25 units.

Prognostic value of IMR_{angio} in patients with AS undergoing TAVI

Overall, 250 patients with severe AS undergoing TAVI were included in the prognostic cohort. Satisfactory ICC was observed for IMR_{angio} assessment (0.86 (95% CI 0.69 to 0.94), $p<0.0001$). The primary endpoint occurred in 28 patients (11.2%) at a median follow-up time of 22 months (12–30 months) and it was mainly driven by rehospitalisation for HF (22 of 28 events, 78.6%). Patients who experienced

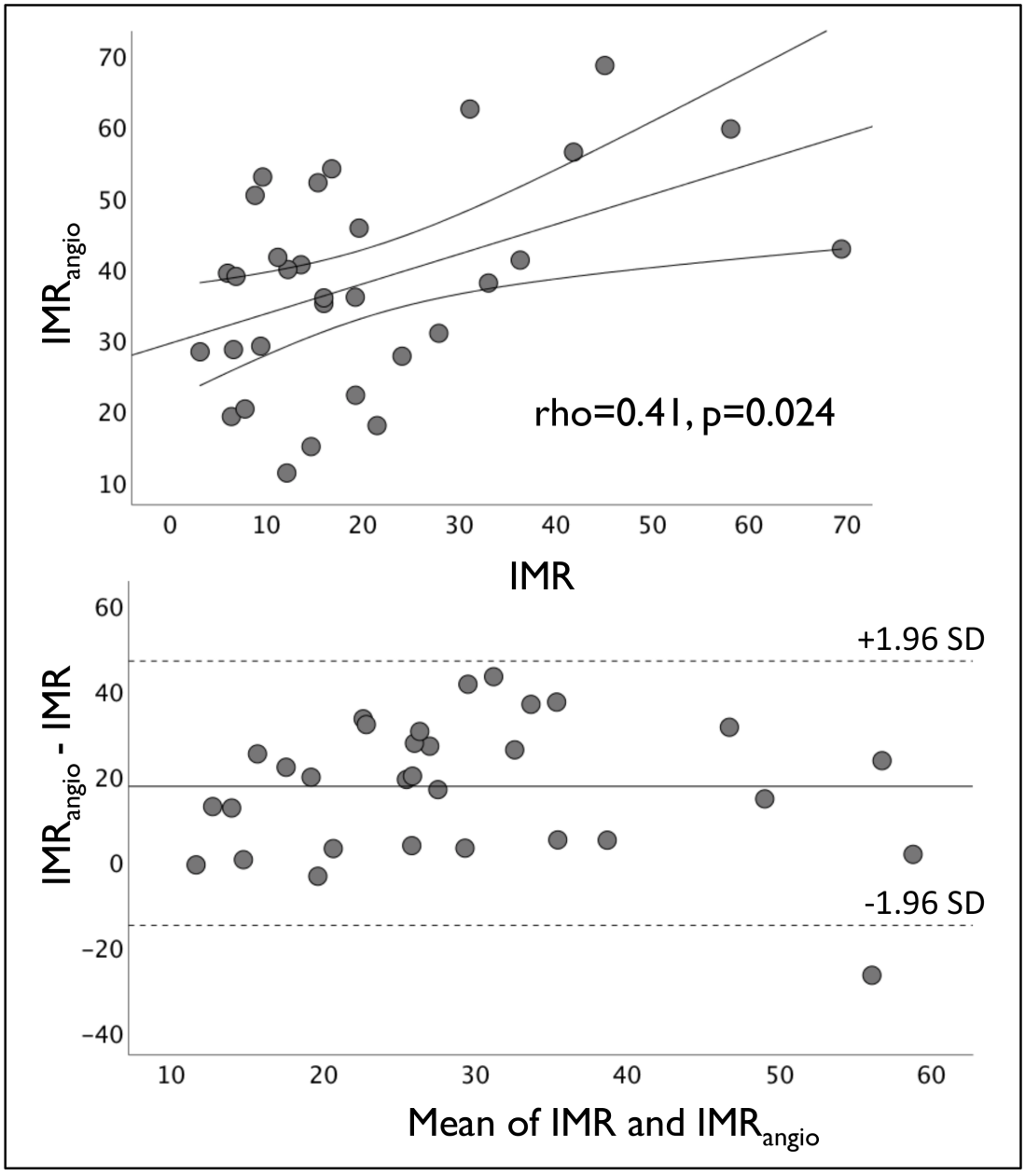


Figure 2 Correlation between IMR_{angio} and wire-based IMR in patients with AS undergoing TAVI. Scatter plot and Bland-Altman analysis showing the correlation and agreement between IMR_{angio} and invasive pressure wire-based IMR in our derivation cohort. AS, aortic stenosis; IMR, index of microcirculatory resistance; IMR_{angio}, angiography-derived index of microcirculatory resistance; TAVI, transcatheter aortic valve implantation.

Table 1 Clinical, procedural data and CMD assessment in patients suffering or not the primary endpoint

	Prognostic cohort			
	All patients	Primary endpoint	No primary endpoint	P value
Clinical data				
No (%)	250 (100)	28 (11.2)	222 (88.8)	–
Female (%)	132 (52.8)	15 (53.6)	117 (52.7)	>0.999
Age (years)	83 (80–86)	83 (80–87)	83 (79–86)	0.341
BMI (kg/m^2)	26 (23–29)	27 (24–29)	26 (23–29)	0.249
Hypertension (%)	223 (89.2)	25 (89.3)	198 (89.2)	>0.999
Dyslipidaemia (%)	156 (62.4)	15 (53.6)	141 (63.5)	0.309
Diabetes (%)	65 (26.0)	6 (21.4)	59 (26.6)	0.653
Smoker (current or former) (%)	63 (25.2)	10 (35.7)	53 (23.9)	0.174
eGFR CG (mL/min/1.73 m^2)	56 (45–72)	56 (40–72)	56 (47–72)	0.504
History of atrial fibrillation (%)	81 (32.4)	19 (67.9)	62 (27.9)	**<0.0001**
Peripheral vascular disease (%)	47 (18.8)	7 (25.0)	40 (18.0)	0.440
Previous AMI (%)	22 (8.8)	0 (0.0)	22 (9.9)	0.147
STS score (%)	2.386 (1.758–3.365)	2.941 (2.035–4.310)	2.335 (1.738–3.295)	**0.050**
Echocardiographic data				
Peak transvalvular velocity (m/s)	4.2 (3.9–4.6)	4.0 (3.8–4.5)	4.2 (3.9–4.6)	0.233
Mean gradient (mm Hg)	42 (37–51)	40 (32–48)	43 (37–51)	0.156
LVEF (%)	59 (52–64)	56 (42–61)	59 (53–64)	0.109
LV EDV index (mL/m^2)	59 (50–70)	61 (49–77)	59 (50–70)	0.714
LV mass index (g/m^2)	114 (93–133)	124 (110–157)	113 (92–130)	**0.024**
E/E'	14 (11–16)	11 (10–17)	14 (11–16)	0.254
More than mild mitral regurgitation	45 (18.0)	10 (35.7)	35 (15.7)	**0.010**
LAVi (mL/m^2)	47 (39–57)	55 (49–65)	45 (38–55)	**0.001**
sPAP (mm Hg)	40 (32–50)	45 (37–60)	39 (32–48)	**0.007**
More than mild tricuspid regurgitation	44 (17.6)	11 (39.2)	33 (14.9)	**0.001**
TAPSE (mm)	21 (19–23)	19 (17–22)	21 (19–23)	**0.003**
Genereux stages 3–4 (advanced EVCD)	60 (24.0)	15 (53.6)	45 (20.3)	**<0.0001**
Procedural data				
Balloon expandable valve (%)	160 (64.0)	18 (64.3)	142 (64.0)	>0.999
Contrast medium dose (mL)	117 (90–150)	110 (80–137)	120 (90–150)	0.634
Total procedural time (min)	67 (52–85)	66 (54–73)	67 (52–85)	0.800
Valve implant success (%)	250 (100)	28 (100)	222 (100)	–
CMD assessment				
IMR_{angio} (units)	27 (20–38)	37 (30–44)	26 (20–36)	**<0.0001**
IMR_{angio} ≥30 (units)	105 (42.0)	24 (85.7)	81 (36.5)	**<0.0001**
QFR	0.94 (0.89–0.98)	0.94 (0.88–0.98)	0.94 (0.89–0.98)	0.935

Estimates are n (%) or median (IQR). P values in bold are considered statistically significant (p<0.05).
AMI, acute myocardial infarction; BMI, body mass index; eGFR CG, estimated glomerular filtration rate–Cockcroft-Gault; CMD, coronary microvascular dysfunction; EDV, end-diastolic volume; EVCD, extravalvular cardiac damage; IMR_{angio}, angiography-derived index of microcirculatory resistance; LAVi, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; QFR, quantitative flow ratio; sPAP, systolic pulmonary arterial pressure; STS, Society of Thoracic Surgeons; TAPSE, tricuspid annular plane systolic excursion.

the primary endpoint presented higher Society of Thoracic Surgeons (STS) score (2.941 (2.035–4.310) vs 2.335 (1.738–3.295), p=0.050), larger left atrial volume index (55 (49–65) vs 45 (38–55), p=0.001), higher rate of AF (67.9% vs 27.9%, p<0.0001) and advanced EVCD (15 (53.6%) vs 45 (20.3%), p<0.0001), with lower tricuspid annular plane systolic excursion (TAPSE), higher systolic pulmonary arterial pressure and left ventricular mass index, and higher rate of more than mild mitral and tricuspid regurgitation (table 1).

IMR_{angio} was significantly higher in patients who met the primary endpoint (37 (30–44) vs 26 (20–36), p<0.0001), and overall, IMR_{angio} demonstrated fair discriminatory power in predicting the composite endpoint (AUC 0.72 (0.63–0.80), p<0.0001) (figure 3). IMR_{angio} ≥30 units demonstrated the best performance in predicting the primary endpoint (online supplemental table 3, figure 3 and online supplemental figure 4). CMD (defined as IMR_{angio} ≥30 units) was present in 105 (42%) patients.

Patients with CMD showed significantly worse clinical outcomes in terms of cardiovascular mortality and rehospitalisation for HF compared with patients with preserved microvascular function (22.9% vs 2.8%, p<0.0001) (figure 4).

The continuous association of IMR_{angio} with the primary endpoint was confirmed by dividing the prognostic cohort in tertiles of $IMR_{angio.}$ Notably, the number of adverse events was 2.4%, 10.6% and 20.5% in the first, second and third tertiles, respectively (p<0.0001) (figure 4).

At multivariable Cox regression analysis, CMD (adjusted HR (aHR) 6.672 (2.251 to 19.778), p=0.001), AF (aHR 2.621 (1.105 to 6.217), p=0.029) and advanced EVCD (aHR 2.196

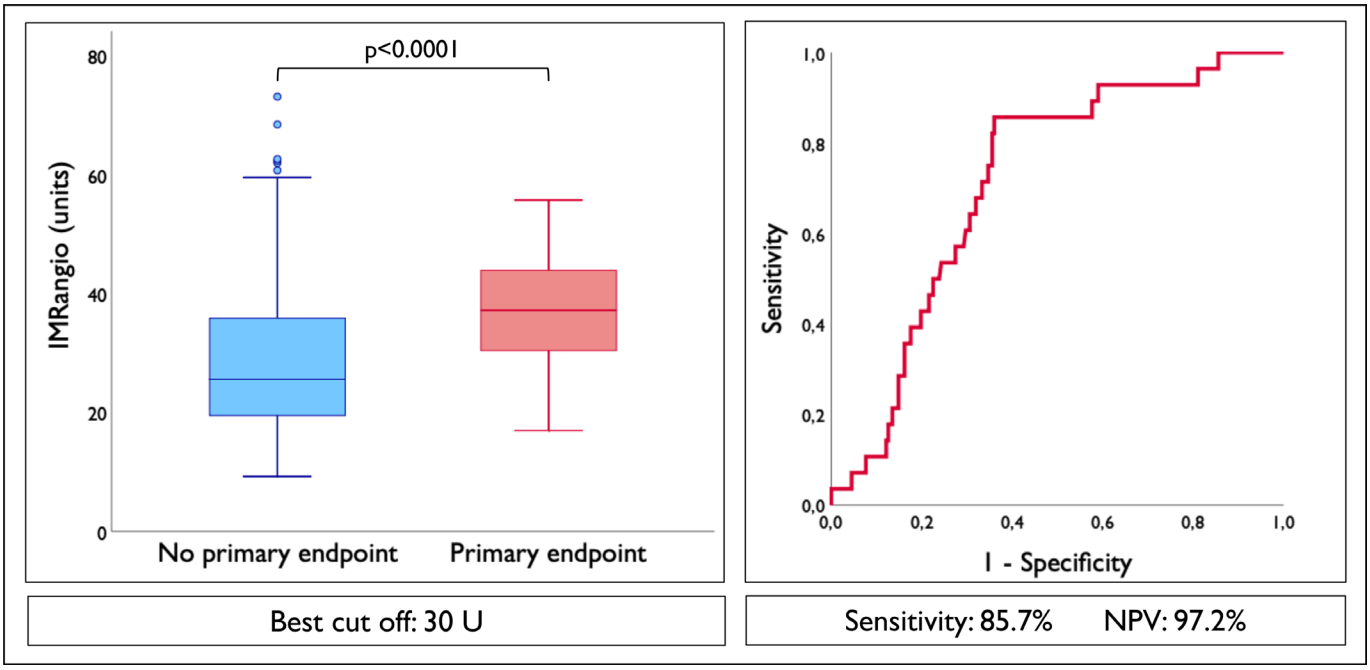


Figure 3 IMR_{angio} in patients who met the primary endpoint. IMR_{angio} was significantly higher in patients who met the primary endpoint (left panel). IMR_{angio} demonstrated fair diagnostic accuracy in predicting the primary endpoint at ROC curve analysis (right panel). The ROC-defined IMR_{angio} cut-off ≥30 units (Youden index 0.49) demonstrated a sensitivity, specificity, NPV and PPV of 85.7%, 63.5%, 97.2% and 22.9%, respectively. IMR_{angio}, angiography-derived index of microcirculatory resistance; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics.

(0.999 to 4.828), p=0.050) were independent predictors of the primary endpoint (online supplemental tables 4 and 5).

Sensitivity analyses excluding patients who underwent a percutaneous coronary intervention to the LAD (10.8% patients) (aHR 4.844 (1.614 to 14.537), p=0.005) and patients with QFR ≤0.80 (8.4% patients) (aHR 5.073 (1.693 to 15.202), p=0.004) confirmed the independent prognostic value of CMD (online supplemental figure 5).

CMD and adverse cardiac remodelling in the prognostic cohort

Clinical features of patients stratified by CMD are summarised in table 2. Briefly, patients with CMD showed a higher rate of AF (42.9% vs 24.8%, p=0.004), lower peak transvalvular velocity (4.0 (3.8–4.5) vs 4.2 (3.9–4.6), p=0.028), lower mean transvalvular gradient (40 (34–48) vs 44 (38–53), p=0.024), larger left atria (49 (40–58) vs 45 (37–55), p=0.042) and higher QFR (0.95 (0.90–0.99) vs 0.94 (0.87–0.97), p=0.002). Importantly, patients with CMD were more frequently characterised by an advanced EVCD (Genereux stages 3–4) (33 (31.4%) vs 27 (18.6%), p=0.024), with lower TAPSE and higher rates of more than mild mitral and tricuspid regurgitation (table 2).

Pre-TAVI speckle-tracking echocardiography was available in 125 (50%) patients. GLS was not significantly different in patients with and without CMD (−14.4% (−9.0 to −17.2) vs −14.0% (−10.0 to −16.7), p=0.993). Conversely, PALS was significantly lower in patients with CMD with borderline significance (14.5% (9.0–26.0) vs 18.7% (13.0–26.7), p=0.050)

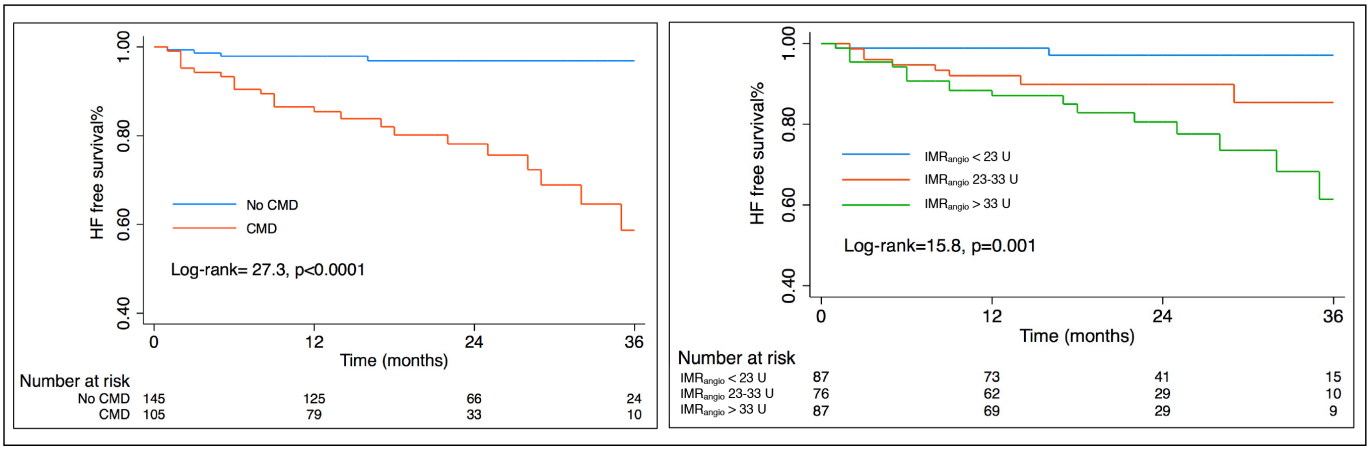


Figure 4 Survival analysis. Kaplan-Meier curves of patients with and without CMD defined by IMR_{angio} ≥30 units (left panel) and of patients stratified by tertiles of IMR_{angio} (right panel). CMD, coronary microvascular dysfunction; HF, heart failure; IMR_{angio}, angiography-derived index of microcirculatory resistance.

Table 2 Clinical, procedural data and outcomes in patients with and without CMD — prognostic cohort

	All patients	No CMD	CMD	P value
Clinical data				
No (%)	250 (100)	145 (58)	105 (42)	–
Female (%)	132 (52.8)	74 (51)	58 (55.2)	0.524
Age (years) (%)	83 (80–86)	83 (79–86)	83 (80–86)	0.552
BMI (kg/m^2)	26 (23–29)	25 (23–29)	27 (24–29)	0.094
Hypertension (%)	223 (89.2)	126 (86.9)	97 (92.4)	0.216
Dyslipidaemia (%)	156 (66.4)	91 (62.8)	65 (61.9)	0.896
Diabetes (%)	65 (26)	36 (24.8)	29 (27.6)	0.662
Smoker (current or former) (%)	63 (25.2)	37 (25.5)	26 (24.8)	>0.999
eGFR CG (mL/min/1.73 m^2)	56 (45–72)	54 (44–70)	60 (47–75)	0.141
History of atrial fibrillation (%)	81 (32.4)	36 (24.8)	45 (42.9)	**0.004**
Peripheral vascular disease (%)	47 (18.8)	32 (22.1)	15 (14.3)	0.141
Previous AMI (%)	22 (8.8)	16 (11.0)	6 (5.7)	0.177
STS score (%)	2.386 (1.758–3.365)	2.398 (1.776–3.320)	2.374 (1.699–3.367)	0.904
Echocardiographic data				
Peak transvalvular velocity (m/s)	4.2 (3.9–4.6)	4.2 (3.9–4.6)	4 (3.8–4.5)	**0.028**
Mean gradient (mm Hg)	42 (37–51)	44 (38–53)	40 (34–48)	**0.024**
LVEF (%)	59 (52–64)	59 (52–63)	60 (52–65)	0.490
LV EDV index (mL/m^2)	59 (50–70)	60 (52–70)	59 (48–72)	0.574
LV mass index (g/m^2)	114 (93–133)	115 (93–133)	114 (93–138)	0.375
E/E'	14 (11–16)	15 (12–17)	12 (10–16)	**0.012**
More than mild mitral regurgitation	45 (18.0)	18 (12.4)	27 (25.7)	**0.007**
LAV index (mL/m^2)	47 (39–57)	45 (37–55)	49 (40–58)	**0.042**
sPAP (mm Hg)	40 (32–50)	40 (32–49)	40 (32–53)	0.373
More than mild tricuspid regurgitation	44 (17.6)	17 (11.7)	27 (25.7)	**0.004**
TAPSE (mm)	21 (19–23)	21 (20–24)	21 (19–23)	**0.023**
Genereux stages 3–4 (advanced EVCD)	60 (24.0)	27 (18.6)	33 (31.4)	**0.024**
Procedural data				
Balloon expandable valve (%)	160 (64)	94 (64.8)	66 (62.9)	0.790
Contrast medium dose (mL)	117 (90–150)	120 (80–160)	110 (90–140)	0.563
Total procedural time (min)	67 (52–85)	65 (52–84)	69 (52–86)	0.354
Valve implant success (%)	250 (100)	145 (100)	105 (100)	–
QFR	0.94 (0.89–0.98)	0.94 (0.87–0.97)	0.95 (0.90–0.99)	**0.002**
IMR_{angio} (units)	27 (20–38)	22 (17–25)	40 (34–50)	–
Clinical outcomes				
Primary endpoint (%)	28 (11.2)	4 (2.8)	24 (22.9)	**<0.001**
Cardiovascular death (%)	6 (2.4)	2 (1.4)	4 (3.8)	0.242
Rehospitalisation due to HF (%)	22 (8.8)	2 (1.4)	20 (19.0)	**<0.001**

Estimates are n (%) or median (IQR). P values in bold are considered statistically significant (p<0.05).
AMI, acute myocardial infarction; BMI, body mass index; eGFR CG, estimated glomerular filtration rate–Cockcroft-Gault; CMD, coronary microvascular dysfunction; EDV, end-diastolic volume; EVCD, extravalvular cardiac damage; HF, heart failure; IMR_{angio}, angiography-derived index of microcirculatory resistance; LAV, left atrial volume; LV, left ventricular; LVEF, left ventricular ejection fraction; QFR, quantitative flow ratio; sPAP, systolic pulmonary arterial pressure; STS, Society of Thoracic Surgeons; TAPSE, tricuspid annular plane systolic excursion.

(online supplemental figure 6). Moreover, GLS was not significantly correlated with IMR_{angio} (r=0.014, p=0.874), while PALS showed a significant inverse correlation with IMR_{angio} (r=−0.191, p=0.033) (online supplemental figure 6).

Prognostic value of EVCD in patients with AS undergoing TAVI

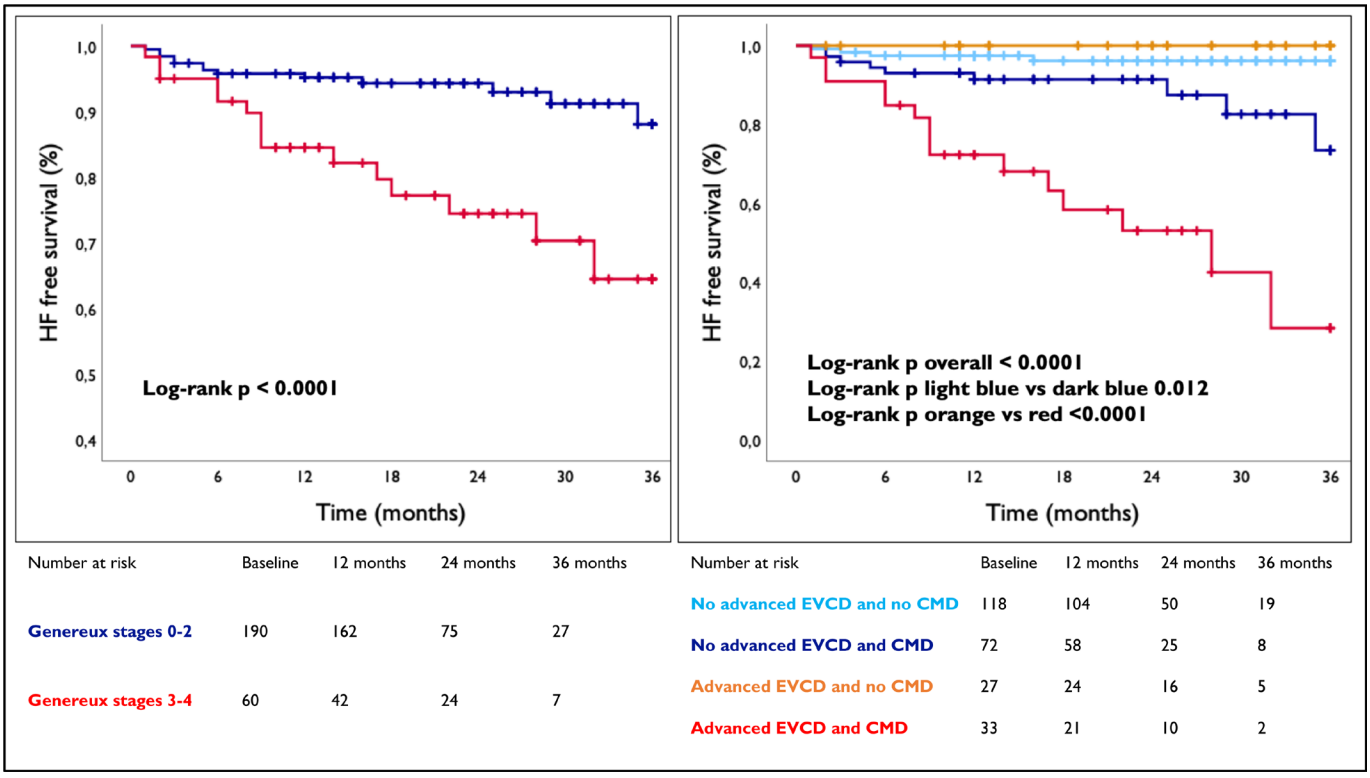
Patients with advanced EVCD met the primary endpoint more frequently compared with the rest of the study cohort (25.0% vs 6.8%, p<0.0001). Importantly, the coexistence of advanced EVCD and CMD portended significantly worse clinical outcomes compared with patients with EVCD or CMD in isolation (p<0.0001) (figure 5).

Incremental prognostic value of CMD in predicting cardiac mortality and HF after TAVI

The logistic regression model including age, AF, STS score, LVEF <50%, advanced EVCD (Genereux stages 3–4) and CMD (IMR_{angio} ≥30 units) showed an AUC of 0.86 (0.79–0.92) in predicting the primary endpoint, demonstrating a modest but significant prognostic gain compared with models including only clinical variables (age, AF and STS; p for AUC comparison=0.025) or clinical and echocardiographic parameters (age, AF, STS, LVEF and advanced EVCD; p for AUC comparison=0.042) (figure 6).

Subgroup analysis

IMR_{angio} was an effective risk-stratification tool in all the prespecified subgroups including patients with LVEF



Number at risk	Baseline	12 months	24 months	36 months
Genereux stages 0-2	190	162	75	27
Genereux stages 3-4	60	42	24	7

Number at risk	Baseline	12 months	24 months	36 months
No advanced EVCD and no CMD	118	104	50	19
No advanced EVCD and CMD	72	58	25	8
Advanced EVCD and no CMD	27	24	16	5
Advanced EVCD and CMD	33	21	10	2

Figure 5 Survival analysis stratified by CMD and advanced EVCD. Patients with advanced EVCD (Genereux stages 3–4) suffered more cardiovascular death and rehospitalisation for heart failure (HF) 36 months after TAVI compared with patients with Genereux stages 0–2 (left panel). Patients with CMD and EVCD were characterised by a significantly worse prognosis compared with patients with advanced EVCD and no CMD (right panel). Similarly, patients with CMD and no advanced EVCD showed worse clinical outcomes compared with patients without CMD and no advanced EVCD. CMD, coronary microvascular dysfunction; EVCD, extravalvular cardiac damage; TAVI, transcatheter aortic valve implantation.

<50% vs LVEF ≥50% (p for interaction=0.426), patients with and without AF (p for interaction=0.428) and patients aged <83 years vs ≥83 years (p for interaction=0.328) (online supplemental figure 7).

DISCUSSION

In this study, we observed that IMR_{angio} is a valuable alternative to wire-based IMR for the evaluation of CMD in patients undergoing TAVI.

CMD defined as high IMR_{angio} is associated with EVCD and adverse cardiac remodelling at non-invasive imaging. More importantly, CMD is an independent predictor of cardiovascular death and rehospitalisation for HF at a median follow-up time of 22 months after TAVI.

To the best of our knowledge, this is the first study to establish a direct link between CMD and long-term adverse clinical outcomes in patients with severe AS undergoing TAVI. In a previous study,[6] we demonstrated that, in patients with AS, CMD was associated with impaired left atrial function and with a chronic low-flow phenotype. Importantly, this was likely mediated via an association between high microvascular resistance, reduced vasodilatory capacity and adverse cardiac remodelling. Furthermore, patients with CMD were more frequently characterised as low-flow low-gradient AS, a phenotype notoriously associated with poor clinical outcomes.[6]

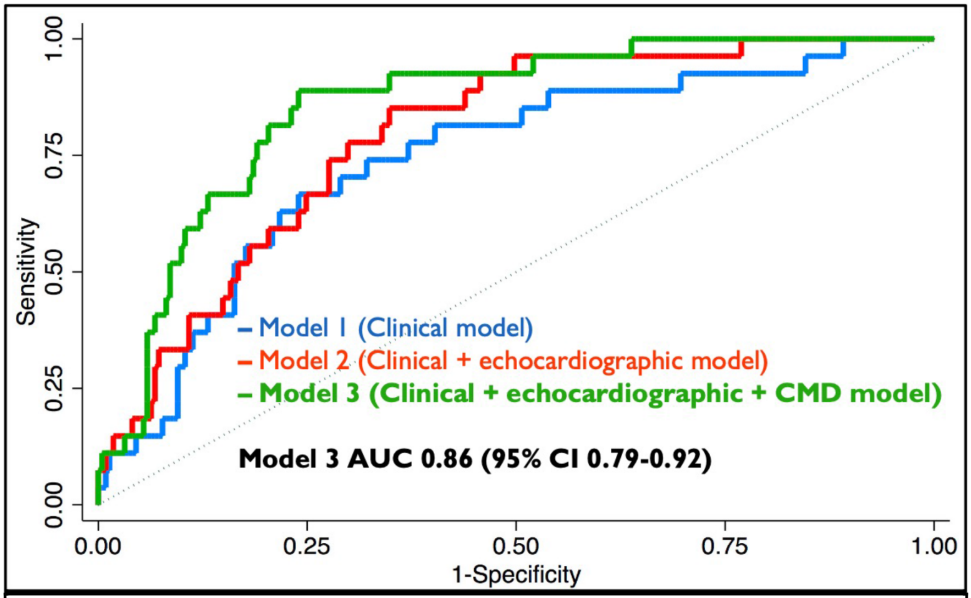
In AS, the left ventricular response to the valve narrowing is initially adaptive but it becomes soon maladaptive with excessive left ventricular hypertrophy and concentric remodelling.[4] CMD contributes to myocardial ischaemia which ultimately leads to further adverse cardiac remodelling, EVCD and symptoms.[28]

Although the association between CMD, adverse cardiac remodelling and adverse events was expected, whether CMD was associated with EVCD and the risk of cardiac mortality and HF in patients undergoing TAVI was not determined.[9] We demonstrated that the risk of adverse clinical outcomes at long-term follow-up after TAVI was continuously associated with impaired coronary microvascular function. This was mediated via adverse cardiac remodelling as demonstrated by the association between CMD, advanced EVCD, impaired atrial function and low-flow phenotype.[6] Consistently, previous histopathological studies suggested a relationship between left ventricular fibrosis and lower values of PALS in patients with AS undergoing surgical aortic valve replacement.[29] In addition, CMD has been previously correlated with the degree of left ventricular function recovery after TAVI beyond the acute effect of left ventricular unloading induced by the aortic valve replacement.[6]

IMR_{angio}-based risk stratification

The assessment of CMD may contribute to refine the long-term risk stratification of patients undergoing TAVI. In particular, being based on standard coronary angiography performed during the workup for TAVI and obviating the need for coronary artery instrumentation, IMR_{angio} may emerge as a practical tool to detect CMD overcoming most of the common limitations of pressure wire-based microvascular assessment.[30]

Importantly, IMR_{angio} demonstrated that a continuous risk stratification of the composite primary endpoint, as shown by the progressive higher rate of events of patients in the second and third tertiles of IMR_{angio}, should be provided (figure 4). Moreover, although the Genereux staging retains its excellent prognostic value in patients



Logistic regression models

Models	Variables	aOR (95% CI)	p value	AUC (95% CI)	AUC comparison p value
Model 1	Age	1.02 (0.93-1.12)	0.669	0.74 (0.64-0.84)	
	Atrial fibrillation	4.98 (2.11-11.77)	<0.001		
	STS score	1.17 (0.97-1.40)	0.099		
Model 2	Age	1.01 (0.92-1.12)	0.819	0.79 (0.71-0.87)	Model 2 vs Model 1
	Atrial fibrillation	4.01 (1.61-9.98)	0.003		0.167
	STS score	1.14 (0.94-1.39)	0.166		
	Advanced EVCD	2.62(1.09-6.34)	0.032		
	LVEF < 50%	2.24 (0.88-5.74)	0.090		
Model 3	Age	1.01 (0.91-1.12)	0.853	0.86 (0.79-0.92)	Model 3 vs Model 1
	Atrial fibrillation	3.61 (1.37-9.52)	0.009		0.025
	STS score	1.11 (0.90-1.37)	0.312		Model 3 vs Model 2
	Advanced EVCD	2.21 (0.86-5.69)	0.101		0.042
	LVEF < 50%	2.56 (0.93-7.04)	0.070		
	CMD	7.95 (2.55-24.81)	<0.001		

Figure 6 Incremental prognostic value of CMD in patients undergoing TAVI. The logistic regression model including CMD on top of imaging and clinical variables demonstrated the best accuracy in predicting cardiovascular death and rehospitalisation for HF after TAVI. aOR, adjusted OR; AUC, area under the curve; CMD, coronary microvascular dysfunction; EVCD, extravalvular cardiac damage; HF, heart failure; LVEF, left ventricular ejection fraction; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

with AS undergoing TAVI also in our cohort, IMR_{angio}-defined CMD demonstrated further stratification of the risk of cardiovascular death and rehospitalisation for HF in patients characterised by advanced EVCD (Genereux stages 3–4) (figure 5). Furthermore, CMD demonstrated that the prognostic value in different subgroups of patients characterised by a baseline high risk of adverse events, such as low LVEF, AF and older age, should be maintained (online supplemental figure 7).

Limitations

Our study has limitations, including the need for external validation due to its retrospective, single-centre nature, making our initial findings hypothesis-generating. Moreover, the sample size of the derivation cohort was limited and it did not allow to define the best cut-off of IMR_{angio} for detecting IMR >25 units. The absence of independent event adjudication is another limitation; however, the Verona Valvular Heart Disease Registry relies on trained researchers blinded to coronary physiology data for adjudication. In our series, a considerable proportion of patients did not demonstrate an adequate angiographic quality and were excluded from the analysis (online supplemental figure 2). Indeed, specific recommendations should be applied in order to increase the accuracy of IMR_{angio} assessment, including a recommended acquisition rate of at least 15 frames/s.[19]

Additionally, the diagnostic performance of IMR_{angio} was compared with IMR but not with myocardial perfusion imaging which may be considered the gold standard for CMD evaluation in the whole left ventricle. In fact, we only assessed CMD in the LAD, which may limit generalisability, but given its role in myocardial perfusion and the absence of prior anterior myocardial infarction history, it is a reasonable proxy for the whole coronary microcirculation.

CONCLUSIONS

CMD, being associated with adverse cardiac remodelling and advanced EVCD, is a major determinant of cardiac mortality and rehospitalisation for HF after TAVI. IMR_{angio} demonstrated a continuous association with adverse clinical outcomes after TAVI and showed incremental prognostic value compared with conventional clinical and echocardiographic risk stratification.

Correction notice This article has been corrected since it was first published. The OA license type has been updated to CC BY-NC. 18th November 2024.

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