UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA" BUCHAREST

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DOMAIN: MEDICINE

PERFORMANCE OF NOVEL BIOMARKERS AND IMAGING TECHNIQUES IN THE ASSESSMENT OF NATIVE AND BIOPROSTHETIC AORTIC VALVE DISEASE

PhD THESIS SUMMARY

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Background

Native aortic valve disease, and in particular aortic valve stenosis, as well as bioprosthetic aortic valve disease, have been major public health concerns over the past few years. Aortic stenosis is the most common valvular heart disease in developed countries, with a steadily increasing prevalence due to the ageing population [1], which also leads to higher rates of bioprosthetic heart valve implantation along with the advantages of avoiding long-term anticoagulation and the emergence of transcatheter aortic valve implantation [2].

Currently, there are no effective therapies to prevent or slow the development of aortic stenosis. At the same time, despite the efforts made during the past few years to develop more durable bioprosthetic valves, their limited durability continues to represent a major concern.

Given the above-mentioned issues, a better understanding of native and bioprosthetic aortic valve disease pathophysiology leading to feasible, widely available methods of investigation as well as potential therapies in these pathologies are required.

Aortic stenosis develops slowly over the course of years or decades and incorporates two phases. The *initiation phase* shares numerous similarities with atherosclerosis involving endothelial injury, the infiltration and oxidation of lipid particles, and an inflammatory response characterised by macrophages, T lymphocytes and small numbers of mast cells [3,4]. The subsequent *propagation phase* is characterised by progressive fibro-calcific valve thickening driven by a vicious cycle of mechanical injury, inflammation and a subsequent healing response including both fibrosis and calcification. Inflammation is therefore believed to play a central role in the pathogenesis of aortic stenosis throughout its duration [5].

Previous studies have used 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and computed tomography (CT) to investigate valve inflammation in aortic stenosis, demonstrating increased PET uptake in patients with aortic sclerosis and stenosis compared with control subjects [6]. Importantly, baseline valve 18F-FDG uptake was also associated with subsequent aortic stenosis progression and adverse clinical outcomes [7]. Whilst encouraging, PET-CT is an expensive tool, with limited use in routine clinical practice, thus a cheaper and more available technique to better understand the role of inflammation in aortic stenosis is needed.

In the coronary arteries, coronary plaque inflammation can be assessed by measuring pericoronary adipose tissue (PCAT) attenuation, on the basis that such inflammation alters the composition of the adjacent pericardial fat. PCAT CT attenuation measurements range between -190 to -30 Hounsfield units (HU) per voxel, with coronary vascular inflammation believed to increase the aqueous content of the surrounding adipose tissue resulting in higher densities [8]. In principle, this same imaging approach could be modified to facilitate the assessment of aortic valve inflammation.

Structural bioprosthetic aortic valve degeneration shares many risk factors with aortic stenosis and demonstrates many pathological similarities including oxidized lipid deposition, foam cell formation and inflammation [9-11]. Most notably, leaflet calcification plays a central role in both conditions, acting as a key driver of disease progression and clinical events [12,13]. Lipoprotein(a) [Lp(a)] is now well recognised as an important risk factor for incident aortic stenosis [14]. Moreover, patients with aortic stenosis and elevated serum Lp(a) concentrations demonstrate increased calcification activity within the valve, faster disease progression on echocardiography and CT, and more rapidly require aortic valve replacement [15-18].

Current research proposes two potential novel markers for the assessment of native aortic valve stenosis and bioprosthetic aortic valve degeneration.

The first study hypothesis was that a novel cardiovascular biomarker - serum lipoprotein(a) - would be associated with the development of bioprosthetic aortic valve degeneration, and the second study hypothesis was that a new imaging technique - the measurement of the perivascular adipose tissue computed tomography attenuation around the aortic valve - would be a useful tool for imaging the presence and severity of aortic stenosis, as well as disease activity and progression.

Aims and hypotheses

The aims of this thesis are:

1. To investigate the role of serum lipoprotein(a) concentrations as a marker of bioprosthetic aortic valve degeneration in patients with bioprosthetic aortic valves.
2. To investigate the utility of the perivascular adipose tissue CT attenuation around the aortic valve in detection and prediction of severe aortic stenosis.

The hypotheses of this thesis are:

1. Serum lipoprotein(a) concentrations can be a determinant or mediator of bioprosthetic aortic valve degeneration.
2. Perivascular adipose tissue CT attenuation around the aortic valve can provide an accurate and reproducible technique to assess aortic stenosis presence and severity, disease activity and subsequent disease progression.

General methodology

This chapter provides an overview of the study populations, clinical and paraclinical study assessments and statistical analysis employed in the current thesis. Detailed methodology of each study is described in the corresponding chapters.

Study populations

The research conducted as part of this thesis represents post hoc analyses of data from patients enrolled in three prospective studies.

The first study is a post hoc analysis of data from a study investigating bioprosthetic aortic valve degeneration: 18F-Fluoride Assessment of Aortic Bioprosthesis Durability and Outcome (18F-FAABULOUS). The patients were recruited at different periods of time from an aortic valve intervention and underwent multimodality imaging assessments as part of the study [12,13]. Although this was a multicentre observational study, only patients enrolled in a single centre (Edinburgh) were eligible for the current analysis.

The second study is a post hoc analysis of data from two double-blinded, randomised, placebo-controlled studies: the Study Investigating the Effects of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis (SALTIRE II) and the Dual Antiplatelet Therapy to Reduce Myocardial Injury (DIAMOND) study [19,20]. Patients from the SALTIRE II study represented the main cohort for the second study investigating aortic stenosis, whereas patients from the DIAMOND study represented the cohort used to select our control group of patients with no aortic stenosis. These control patients were selected to be similar to the aortic stenosis patients with respect to age, sex and coronary calcium score. The SALTIRE II study was designed to investigate the ability of calcium modulators, denosumab and alendronic acid, to modify disease progression in aortic stenosis. Participants underwent serial assessments with echocardiography, CT and 18F-sodium fluoride PET-CT as part of the study [19]. The DIAMOND study was designed to determine whether ticagrelor reduces plasma troponin concentrations in patients with high-risk coronary plaque. Participants were evaluated with CT and 18F-sodium fluoride PET-CT as part of the study [20].

Study assessments

Participants were identified by a study identification number. Date of birth, sex, ethnicity, cardiac symptoms, smoking habit, and alcohol intake were recorded at their first study visit. They were asked about significant medical history, current medication and history of adverse medication reactions were also documented.

A standard clinical examination was performed in each participant and abnormal findings were noted. Height, weight, blood pressure and heart rate were assessed in all participants.

Blood samples were collected at baseline and at specific periods of time according to each study protocol. Blood samples were used for routine clinical biochemistry and haematology, and according to each study protocol cardiac biomarkers, and bone turnover biomarkers. The remaining blood was stored at -80 °C until further use.

A 12-lead electrocardiogram (ECG) was performed in all patients. The ECG was examined for presence of arrhythmia, conduction disease, left ventricular hypertrophy, strain pattern, and ischaemic changes.

Two-dimensional and Doppler echocardiography was performed at baseline and at predefined intervals in all studies participants in accordance with current guidelines recommendations [21,22]. Standard 2-dimensional views and pulsed and continuous wave Doppler measurements were acquired. Aortic valve Doppler measurements were routinely assessed from the apex, suprasternal notch, and right sternal edge to measure the peak aortic jet velocity, the mean gradient, the aortic valve area in native valves, and the effective orifice area of the bioprostheses. Mean values were taken from 3 measurements when subjects were in sinus rhythm and from 5 measurements if they were in atrial fibrillation.

The CT and PET images were acquired using the same hybrid scanner (Biograph mCT, Siemens Medical Systems, Erlangen, Germany) using the previously published image acquisition protocol [12,13,19,20]. Unless contraindicated, intravenous or oral metoprolol was administered to patients with a heart rate >65 beats per minute to optimise image quality and limit radiation exposure. Non-contrast CT was centred on the aortic valve and acquired with ECG-gating during held expiration (40 mAs/rot [CareDose], 120 kV tube voltage, pitch 0.24, field of view 210 mm). Contrast-enhanced CT was timed to obtain peak arterial enhancement in the aortic root, with a 20-mL test bolus of contrast given to determine the appropriate trigger delay and, depending on body mass index, 80-100 mL of contrast (400 mgI/mL; Iomeron, Bracco, Milan, Italy) administered for the

acquisition. This was performed with either prospective (heart rate <60 min) or retrospective (heart rate >60 min) ECG-gating during held expiration (330 ms rotation time, 100-120 kV tube voltage, 160-245 mA tube current and 3.8 mm/rotation table feed). Patient radiation exposure was recorded and regularly reviewed by the medical physics department. Patients were observed for at least 5 minutes after scanning for evidence of adverse reactions before being released from the department.

A target dose of 125 Megabecquerel (MBq) of 18F-sodium fluoride was administered intravenously by PET-trained radiographers, with an expected effective radiation dose of 3 millisievert (mSv). After 60 minutes, participants were asked to empty their bladder in dedicated facilities and transferred to the scanner. They were asked to lie supine with both hands above their head and were attached to a 3- lead ECG monitor. A low-dose attenuation correction CT scan was performed (without contrast enhancement, 120 kV, 50 mA, slice thickness 5 mm, increment 3 mm), followed by acquisition of PET data using a single 30-min bed position centered on the valve in 3-dimensional mode. A simultaneously acquired ECG allowed segregation of PET data into 4 phases based on the R-R interval. Intravenous iodinated contrast was given after PET acquisition, followed by ECG- gated contrast CT acquisition in diastole (CARE Dose4D, Siemens; 0.75-mm slice thickness, spiral acquisition, 50%–75% R-R interval, expiratory breath-hold).

Statistical analysis

Parametric continuous variables were expressed as mean and standard deviation and non-parametric continuous variables were expressed as median and interquartile range. Data normality was tested using the Shapiro-Wilk normality test and by inspection of histograms. Categorical variables were presented as count and percentage. Paired and unpaired parametric continuous variables were tested using paired and unpaired Student's *t*-test respectively. Statistical testing of paired and unpaired non-parametric continuous variables was performed using the Wilcoxon signed-rank test and the Mann-Whitney U test. Categorical variables were compared using chi-square or Fisher's exact test. Non-parametric data were log transformed to achieve normality before inclusion in regression models and correlations.

Statistical analysis was performed in SPSS (IBM SPSS Statistics for Windows, Versions 26.0 and 28.0.1.0, IBM Corp), Graphpad Prism (GraphPad Prism version 9.3.1 for Mac, GraphPad Software, San Diego, CA, USA) and RStudio (RStudio Inc, USA; version 4.1.2). A two-sided *p*-value of < 0.05 was considered statistically significant.

Summary of results

1. Serum Lipoprotein(a) and Bioprosthetic Aortic Valve Degeneration

Study population

One hundred and five patients were recruited although 8 patients were unable to complete the baseline assessment. The remaining 97 patients (mean age of 75.3±7.3 years, 54% males) had a high prevalence of traditional cardiovascular risk factors and coronary artery disease and a baseline prosthetic valve velocity of 2.7 [2.3 to 3.0] m/s. Overall, 76 (78%) patients had a surgical bioprosthesis (56 bovine pericardial tissue bioprostheses, 20 porcine valve tissue bioprostheses) and 21 (22%) a transcatheter bioprosthesis. At baseline, 14 (14%) patients had echocardiographic evidence of structural valve degeneration, 20 (21%) patients had CT evidence of structural valve degeneration (calcification, HALT or pannus), 29 (30%) showed increased 18F-NaF uptake in leaflets and 5 (5%) patients had bioprosthetic valve failure.

The median serum Lp(a) concentration was 19.9 [8.4 to 76.4] mg/dL, and patients in the highest tertile had a median serum Lp(a) concentration of 91.8 [76.4 to 117.6] mg/dL, while patients in the middle and lower tertiles had median concentrations of 19.0 [12.8 to 24.5] mg/dL, and 5.7 [3.6 to 7.8] mg/dL respectively, with similar baseline characteristics. Comparing the upper tertile with the other 2 tertiles, both as a group and individually, there were no differences in baseline echocardiography, CT findings or 18F-NaF PET uptake.

Serum Lp(a) concentrations were similar in patients with or without evidence of structural valve degeneration of any stage (15.9 [7.7 to 62.7] mg/dL versus 31.8 [13.2 to 87.7] mg/dL), but also in patients with or without bioprosthetic valve failure (18.6 [7.9 to 77.2] mg/dL versus 24.8 [22.9 to 38.8] mg/dL) ($p>0.05$ for all). There were also no differences in serum Lp(a) concentrations between patients with normal or increased leaflet 18F-NaF uptake on PET (18.6 [7.9 to 76.5] mg/dL versus 21.0 [10.3 to 74.0] mg/dL; $p=0.725$).

Follow up

No differences were found between tertiles, considered either individually or tertile 1 and 2 as a group versus tertile 3 regarding hemodynamic progression of bioprosthetic

function expressed as annualized change in peak bioprosthetic valve velocity, mean pressure gradient, effective orifice area and Doppler velocity index ($p>0.05$ for all).

No correlation was observed between serum Lp(a) concentrations considered as a continuous variable and the subsequent annualized change in bioprosthetic valve peak velocity ($r=-0.032$, $p=0.768$), mean pressure gradient ($r=-0.024$, $p=0.823$), effective orifice area ($r=0.108$, $p=0.349$) or Doppler velocity index ($r=0.056$, $p=0.643$) on echocardiography.

On univariable analysis, only 18F-NaF uptake was associated with deterioration in bioprosthetic valve function, expressed by annualized change in bioprosthetic valve peak velocity.

Several multivariable linear regression models were constructed with the annualized change in peak bioprosthetic valve velocity as the dependent variable. Two models considered gender, baseline peak velocity, abnormal CT findings, 18F-NaF uptake and Lp(a) concentration (as a continuous variable in the first model and as a categorical variable defined by the presence in the highest tertile in the second model) as independent variables. In all the models considered, 18F-NaF uptake remained the only predictor of deterioration in bioprosthetic valve function. Serum Lp(a) concentration was not associated with deterioration in prosthetic valve function when it was considered either as a continuous variable (unstandardized coefficient -0.001 [95% confidence interval: -0.002 to 0.000]; $p=0.300$), or as a categorical variable (unstandardized coefficient -0.067 [95% confidence interval: -0.166 to 0.031]; $p=0.177$), nor were sex, baseline peak velocity or abnormalities on CT.

During follow up, 11 patients had progression of, or developed new, bioprosthetic valve dysfunction of which 2 with valve regurgitation, 7 with valve stenosis, and 2 with mixed dysfunction. Serum Lp(a) concentrations were similar in these patients compared to the remaining population (24.9 [0.3-92.0] mg/dL versus 15.9 [7.7-72.4] mg/dL, $p=0.503$). We found no differences between tertiles for patients who did or did not have evidence of structural valve degeneration during the follow up period. Two patients developed bioprosthetic valve failure during 2-year follow up, both had serum Lp(a) concentrations within the second tertile (median serum Lp(a) concentration of 19.0 [12.8 to 24.5] mg/dL).

Sensitivity analyses

Studies in coronary artery disease have examined serum Lp(a) concentration thresholds of >50 and >70 mg/dL as being associated with increased cardiovascular risk

[14,23,24]. The lower limit for serum Lp(a) concentration in tertile 3 was 50 mg/dL. Further analysis based on a serum Lp(a) concentration threshold of >70 mg/dL demonstrated results consistent with the tertile analysis.

When the same analyses were restricted to the SAVR cohort (76 patients), and within the SAVR cohort to the bovine valves and, respectively, porcine valves subgroups, we observed similar results with no clear association between Lp(a) levels and imaging markers of bioprosthetic valve degeneration.

2. Aortic Valve Perivascular Adipose Tissue Computed Tomography Attenuation in patients with Aortic Valve Stenosis

Study populations

We assessed the eligibility of 152 patients with aortic stenosis from the SALTIRE II study. Twenty-three patients were excluded due to CT angiogram artefacts that affected measurements of the aortic valve perivascular adipose tissue attenuation. A further 9 patients did not have interpretable coronary calcium scores, resulting in a final cohort of 120 patients with aortic stenosis. These patients were compared to 80 control patients without aortic stenosis, selected from the DIAMOND study to be similar to the aortic stenosis patients in terms of age, sex and coronary calcium score.

Patients with aortic stenosis versus control subjects

Whilst we explored 6 image analysis methods, we preferentially report results from the analysis method that assessed perivascular adipose tissue attenuation in regions of interest extending 3 mm away from the aorta and which extended from the base of the aortic valve up 10 mm distally towards the aortic root. This was based upon the good interobserver and intraobserver agreement of this approach and also because this focused approached limits the potential for signal contamination from the coronary arteries.

There were no differences in perivascular adipose tissue attenuation around the aortic valve between patients with aortic stenosis and control subjects with normal aortic valves (-62.4 [-68.7 to -56.5] HU versus -61.2 [-65.3 to -55.6] HU, p = 0.099). A weak correlation was observed between perivascular adipose tissue attenuation around the aortic valve and pericoronary adipose tissue attenuation of the RCA (r = 0.32, p=0.001).

In this larger patient population, univariable analysis demonstrated that the only variables associated with perivascular adipose tissue attenuation around the aortic valve were obesity ($p < 0.001$), current smoking habit ($p = 0.016$), PCAT attenuation of the right coronary artery ($p < 0.001$) and the presence of aortic stenosis ($p = 0.048$). However, on multivariable linear regression analysis obesity (unstandardized coefficient -0.077 [95% confidence interval: -0.112 to -0.033]; $p = 0.001$) and PCAT attenuation of the right coronary artery (unstandardized coefficient 0.005 [95% confidence interval: 0.002 to 0.008]; $p<0.001$) were the only factors that remained associated with perivascular adipose tissue attenuation around the aortic valve.

Patients with different severities of aortic stenosis

Baseline characteristics were similar between patients with mild, moderate and severe aortic stenosis, including the burden of coronary artery disease assessed with CT calcium scoring. There were no differences in perivascular adipose tissue attenuation around the aortic valve amongst patients with mild, moderate or severe aortic stenosis (-60.2 [-66.9 to -55.1] HU versus -62.8 [-69.6 to -56.8] HU versus -62.3 [-69.3 to -55.4] HU respectively, all p values > 0.05).

There was no association between perivascular adipose tissue attenuation and baseline echocardiographic assessments of aortic stenosis severity. Similarly, no associations were observed with CT aortic valve calcium scores, or with disease activity assessed by aortic valve ^{18}F-NaF PET uptake. In this population with aortic stenosis, obesity (unstandardized coefficient -0.074 [95% confidence interval: -0.128 to -0.019]; $p = 0.009$) and PCAT attenuation of the right coronary artery (unstandardized coefficient 0.005 [95% confidence interval: 0.002 to 0.008]; $p = 0.002$) were again the only factors associated with perivascular adipose tissue attenuation around the aortic valve on multivariable analysis.

Disease progression

No correlation was observed between baseline aortic valve perivascular adipose tissue attenuation measurements and subsequent disease progression as assessed by the annualized changes in aortic valve peak velocity ($r = 0.072$, $p = 0.458$), CT calcium score ($r = 0.108$, $p = 0.265$),^{18}F-NaF TBR_{max} ($r = -0.036$, $p = 0.719$) or ^{18}F-NaF TBR_{mean} ($r = -0.031$, $p = 0.759$).

Other Imaging Analysis Methods

Results were similar using the other methods for analysing perivascular adipose tissue attenuation at the level of the aortic valve with no clear association observed between aortic valve perivascular adipose tissue values and aortic stenosis presence, severity, disease activity or progression.

Conclusions and personal contributions

In this thesis, we investigated two potential novel markers for the assessment of native aortic valve stenosis and bioprosthetic aortic valve degeneration.

1. Serum Lipoprotein(a) and Bioprosthetic Aortic Valve Degeneration

In the first study, we investigated whether serum lipoprotein(a) concentrations would be associated with the development of bioprosthetic aortic valve degeneration in a post hoc analysis of data from patients enrolled in a prospective multimodality imaging study investigating bioprosthetic aortic valve degeneration: 18F-Fluoride Assessment of Aortic Bioprosthesis Durability and Outcome (18F-FAABULOUS).

In this study we demonstrate that serum Lp(a) concentrations are not associated with incident or progressive structural bioprosthetic aortic valve degeneration. This lack of association was consistent across echocardiography, CT and PET imaging which provided a comprehensive assessment of valve function in nearly 100 participants.

We conclude that serum Lp(a) concentrations do not appear to be a major determinant or mediator of bioprosthetic aortic valve degeneration [25].

Further research is now required to improve our understanding of the pathophysiology of bioprosthetic valve degeneration and to accelerate the development of novel treatments to prevent or inhibit its progression.

2. Aortic Valve Perivascular Adipose Tissue Computed Tomography Attenuation in patients with Aortic Valve Stenosis

In the second study, we investigated whether the measurement of the perivascular adipose tissue computed tomography attenuation around the aortic valve would be a useful tool in the assessment of inflammation in patients with aortic stenosis and that this would be associated with aortic stenosis presence, severity, disease activity and progression.

In the first part of our study, we were unable to demonstrate a difference in perivascular adipose tissue attenuation in patients with aortic stenosis compared to patients with normal aortic valve who had been matched in terms of age, sex and the burden of coronary atherosclerosis

The second part of our study focused on aortic valve perivascular adipose tissue attenuation in patients with different severity of aortic stenosis, and its relationship with

different imaging parameters of disease activity and progression. We found no significant differences between aortic valve perivascular adipose tissue in patients with mild, moderate or severe aortic stenosis using any of the perivascular adipose tissue analysis approaches, nor did we see any association with baseline echocardiographic measures, CT calcium scores or disease activity assessed with molecular PET. Also, we did not observe any associations with baseline perivascular adipose tissue attenuation and subsequent disease progression as assessed by both changes in CT calcium score or echocardiography.

In conclusion, our study indicates that while for coronary artery disease pericoronary adipose tissue attenuation is of significant value as imaging marker of inflammation [26], in aortic stenosis perivascular adipose tissue attenuation does not appear to be similarly informative. Alternative methods are required to provide a reliable readout of valve inflammation in aortic stenosis.

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THEME: NATIVE AND BIOPROSTHETIC VALVE DISEASE

First author

Articles

- **Botezatu SB***, Tzolos E*, Kaiser Y, Cartlidge TRG, Kwiecinski J, Barton AK, Yu X, Williams MC, van Beek EJR, White A, Kroon J, Slomka PJ, Popescu BA, Newby DE, Stroes ESG, Zheng KH, Dweck MR. Serum lipoprotein(a) and bioprosthetic aortic valve degeneration. European heart journal. Cardiovascular Imaging 2023; jeac274. Advance online publication. (Impact Factor 9.130) (Chapter 5) https://doi.org/10.1093/ehjci/jeac274
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- **Botezatu SB***, Tzolos E*, Kaiser Y, Cartlidge TRG, Kwiecinski J, Barton AK, Yu X, Williams MC, van Beek EJR, White A, Kroon J, Slomka PJ, Popescu BA, Newby DE, Stroes ESG, Zheng KH, Dweck MR. Serum lipoprotein(a) and bioprosthetic aortic valve degeneration. Oral presentation – The 61st National Congress of Cardiology, September 21st-24th 2022 – Young Investigator Award Session – 3rd prize

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- **Botezatu SB**, Beladan CC, Călin A, Rosca M, Mateescu AD, Iosifescu AG, Platon P, Ginghină C, B.A. Popescu BA. Acute Heart Failure after 15 years with a bioprosthetic mitral valve, Clinical Case Poster session 6, European Heart Journal - Cardiovascular Imaging, Volume 18, Issue suppl_3, 1 December 2017, Pages iii365–iii378 (Impact Factor 9.130).

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