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# *Cardiac allograft vasculopathy – Incidence and predictors in a single centre series*

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**Índice**

**List of Abbreviation**

BMI – Body Mass Index

BMS – Bare Mental Stent

BVS – Bioresorbable Vascular Scaffold

CAV – Cardiac Allograft Vasculopathy

CI – Confidence Interval

CMV – Cytomegalovirus

DES – Drug Eluting Stent

FFR – Fractional Flow Reserve

ICA – Invasive Coronary Angiography

IHD – Previous Ischemic Heart Disease

ISLHT – International Society for Heart & Lung Transplantation

IVUS – Intravascular Ultra-Sound

HLA – Human Leukocyte Antigen

HR – Hazard Ratio

OCT – Optical Coherence Tomography

OHT – Orthotopic Heart Transplantation

PCI – Percutaneous Coronary Intervention

2R – Moderate or severe acute rejection

**Abstract**

**Aims:** We aimed to investigate CAV incidence and predictors in a large cohort of OHT patients.

**Methods:** We conducted a retrospective analysis on a prospective cohort of 233 patients who underwent OHT at our institution from November 2003 to May 2014. OHT recipients younger than 18 years (n=3) and those who died less than a year after OHT were excluded (n=28). Baseline data was extracted from a main database; we analysed all invasive coronary angiograms (ICA) (n=712) performed as part of the structured follow up program of these patients. CAV was defined by at least one ICA with visible coronary lesions.

**Results:** We included 157 male and 45 female recipients. Median age was 66 years and median BMI was 24.7 $kg.m^{-2}$. Regarding risk factors for atherosclerosis, 17.3% were smokers, 36.8% had hypertension and 46.8% were dyslipidemic. A third of patients had established vascular disease before OHT, either an abnormal carotid doppler (39.6%), peripheral vascular disease (30.3%) or ischemic heart disease (IHD) (35.6%). Acute moderate or severe rejection occurred in 42 patients (21.3%) during the first year.

The donor group was composed by 154 males and 48 females. Median age was 35 years and median BMI 24.1 $kg.m^{-2.}$ Over a median follow-up of 2920 (1825-3650) days after HT, 37 patients (18.3%) were diagnosed with CAV. Incidence rate of CAV in our overall population was 2.91 cases per 100 person-year. Regarding lesion type, 14 had CAV 1 (38%), 12 had CAV 2 (35%) and 9 had CAV 3 (24%). PCI was performed in 15 (41%) patients. Diabetes (p=0.17) and IgG for CMV positive (p=0.42) showed statistical significant difference when comparing recipients from CAV (+) group and CAV (-) group. When considering CAV (+) group, abnormal carotid doppler [hazard ratio (HR) 2.44 95% confidence Interval (CI) 1.27–4.71, p<0.01], IHD [HR 2.32, 95% CI 1.21–4.45, p=0.01] and donor's age [HR 1.04, 95% CI

1.00–1.07, p=0.01] were significantly associated with CAV. Conversely, risk factors as hypertension [HR 1.46, 95% CI 0.75–2.86, p=0.26], diabetes [HR 1.59 95% CI 0.79-3.25, p=0.20], dyslipidaemia [HR 1.68, 95% CI 0.86–3.25, p=0.13] and smoking [HR 1.77, 95% CI 0.85–3.65, p=0.13] were not associated with CAV.

**Conclusion:** In a retrospective analysis of a single centre OHT cohort, abnormal carotid doppler at the time of OHT, a prior history of IHD and donor's age were independently associated with CAV. This may suggest that a prior history of IHD or an abnormal carotid doppler at the time of OHT might influence post-OHT outcomes and may elicit a specific follow-up program, focused on the progression of the systemic vascular disease.

**Keywords:** Orthotopic heart transplantation, allograft vasculopathy, donor's age, ischemic heart disease, abnormal carotid doppler, incidence, predictors

**Resumo**

**Objetivos:** Investigar a incidência e preditores da vasculopatia do enxerto numa população de transplantados cardíacos.

**Métodos:** Foi conduzida uma análise retrospetiva de um coorte prospetivo de 233 transplantados no nosso centro entre Novembro de 2003 e Maio de 2014. Transplantados com idade inferior a 18 anos (n=3) e os que faleceram menos de um ano após o transplante (n=28) foram excluídos. Todas as características pré-transplante foram extraídas de uma base de dados principal. As angiografias coronárias invasivas (n=712) realizadas no âmbito do estruturado programa de acompanhamento dos doentes pós-transplante foram analisadas. Foi definida vasculopatia do enxerto na presença de uma angiografia com lesões coronárias.

**Resultados:** No grupo dos recetores foram incluídos 157 homens e 45 mulheres. A idade média era 66 anos e o índice de massa corporal médio de 24,7 $kg.m^{-2}$. Relativamente aos fatores de risco ateroscleróticos, 17,3% eram fumadores, 36,8% eram hipertensos e 46,8% tinham dislipidemia. Um terço dos doentes apresentavam doença vascular estabelecida antes do transplante, doppler carotídeo anormal em 39,6%, doença vascular periférica em 30,3% e doença cardíaca isquémica em 35,6%. Durante o primeiro ano de follow up, verificou-se rejeição aguda moderada ou severa em 42 doentes (21.3%).

O grupo de dadores era composto por 154 homens e 48 mulheres. Idade média era de 35 anos e o índice de massa corporal médio de 24.1 $kg.m^{-2}$. Durante um período médio de follow-up pós-transplante de 2920 (1825-3650) dias, 37 doentes (18.3%) foram diagnosticados com vasculopatia do enxerto. A taxa de incidência de vasculopatia do enxerto no nosso centro foi de 2,91 casos por 100 pessoa-ano. De acordo com a classificação das lesões, 14 tinham grau 1 (38%), 12 grau 2 (35%) e 9 grau 3 (24%). Angioplastia coronária percutânea foi realizada em 15 (41%) doentes. Diabetes (p=0,17) e IgG positiva para CMV (p=0,42) no grupo dos recetores foram as diferenças encontradas estatisticamente significativas comparando as

características pré-transplante nos doentes com angiografias com e sem lesões. Quando considerado o grupo com vasculopatia, doppler carotídeo anormal [hazard ratio (HR) 2,44 95% confidence interval (CI) 1,27–4,71, p<0.01], doença cardíaca isquémica [HR 2.32, 95% CI 1.21–4.45, P=0.01] e idade do dador [HR 1,04, 95% CI 1,00–1,07, p=0,01] foram significativamente associados ao desenvolvimento da vasculopatia do enxerto. Por outro lado, fatores de risco ateroscleróticos como hipertensão [HR 1,46, 95% CI 0,75–2,86, p=0,26], diabetes [HR 1,59 95% CI 0,79-3,25,p=0,20], dislipidemia [HR 1,68, 95% CI 0,86–3,25, p=0.13] e tabagismo [HR 1,77, 95% CI 0,85–3,65, p=0,13] não mostraram associação com a vasculopatia.

**Conclusão:** Numa análise retrospetiva de um coorte de doentes transplantados cardíacos de centro único, doppler carotídeo anormal à data do transplante, doença cardíaca isquémica e idade do dador foram independentemente associados ao desenvolvimento de vasculopatia do enxerto. Tal pode sugerir que tanto doppler carotídeo anormal como doença cardíaca isquémica pré-transplante podem ter influência no sucesso do transplante e por isso, poderão beneficiar de um programa de follow up específico, focado na progressão de doença vascular sistémica.

**Palavras-chave:** transplante cardíaco, vasculopatia do enxerto, idade do dador, doença cardíaca isquémica, doppler carotídeo anormal, incidência, preditores

## Introduction

Orthotopic heart transplantation (OHT) remains the treatment of choice for refractory end-stage heart failure.[1–4] It is reserved for patients with severe hemodynamic compromise or ischemic cardiopathy limiting daily life activity.[5]

According to the International Society for Heart and Lung Transplantation (ISHLT), nowadays, one-year and ten-years post-OHT survival rates exceed 85 and 50%, respectively.[6] Actually, in our centre, the equivalent post-OHT survival rates are 87 and 79%.[7] ISLHT registry of 2017 defines cardiac allograft vasculopathy (CAV) as one of the most post-OHT limiting long-term complications and common form of chronic rejection.[8]

CAV is defined as an accelerated fibroproliferative disease with severe narrowing of epicardial and intramyocardial arteries in OHT patients.[9] It results in progressive luminal narrowing and reduced myocardial blood flow.[10] CAV appears to develop first on the distal vessels and progress centripetally to the large coronary vessels.[9,11] It contrasts with focal, eccentric, proximal epicardial lesions in classical coronary artery disease, however, both pathologies seem to have a atherosclerotic process in common.[9]

CAV results from an interaction between numerous immunologic and non-immunologic donor and recipient's features, that are still not very well established.[12–14] Donor history of hypertension, diabetes, smoking, higher body mass index (BMI), older age and male gender are being studied as likely CAV predictors.[4,14–16] On the side of the recipient, previous ischemic heart disease (IHD), higher BMI, dyslipidaemia, hypertension and diabetes were recognised as possible pre-OHT features predicting CAV.[4] Also, recipient cytomegalovirus (CMV) infection is known to be associated with CAV, because it generates a proatherogenic environment and exacerbates the nitric acid production leading to immune-mediated endothelial injury.[9,14]

Patients with CAV are usually asymptomatic because of allograft denervation.[9]

Invasive Coronary Angiography (ICA) remains the standard diagnostic routine technique.[9] However, the diffuse nature of CAV limits its sensitivity, especially during the first year post-OHT.[9,10] Therefore, intracoronary image techniques like intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have an emerging importance in CAV diagnosis.[9,17–19]

Modification of underlying classical cardiovascular risk factors and optimization of immunosuppression are the main focus of CAV therapy.[10]

Statins are recommended early after OHT, regardless of cholesterol levels.[20] They slow CAV progression and improve endothelial dysfunction as shown in the mid-1990s landmark trials.[10,21]

Once a patient is diagnosed with CAV, Sirolimus or its derivates Everolimus is included in the immunosuppressive regimen.[22] They inhibit proliferation signal and target of rapamycin, slowing CAV progression.[23]

Percutaneous Coronary Intervention (PCI) is a palliative option for patients with focal disease who present symptoms or evidence of ischemia.[24] Coronary artery bypass grafting is rarely indicated because of CAV lesions distal nature.[20] Re-transplantation is the only definitive treatment capable of improving rate survival in highly selected candidates.[13,20]

The primary objectives of this study are to investigate the incidence of CAV after OHT in our institution and to identify CAV predictors.

## Methods

Study Protocol

Patients consented to the use of anonymised data for research purposes at the time of the OHT.

The current study is a single-institution retrospective observational analysis on a prospective cohort.

We identified 233 consecutive patients who underwent first OHT in our centre, between November 2003 and May 2014. Recipients younger than 18 years (n=3) and those who died less than a year after OHT were excluded (n=28) for the present analysis. ICA data were extracted from 3rd April 2017 until 11th October 2017 from two databases of the Cardiology department. Pre-OHT baseline clinical data of the recipients and donor were prospectively collected and retrospectively analysed from a dedicated institutional database, inserted in the OHT national registry. For all the recipients we extracted the following data: age, gender, BMI, hypertension, previous vascular disease, previous ischemic heart disease (IHD), smoker, diabetes, dyslipidaemia, abnormal carotid doppler, IgG positive for CMV and moderate or severe acute rejection during (≥2R) the first year post-OHT. From the donor's pre-transplant baseline we analysed age, gender and BMI. All variables are present in Table 1.

Patients underwent a routine ICA 1,3,5,8, 10 and 12 years after OHT and additional ones if clinically justified. A total of 712 ICA were analysed.

We identified 143 reports describing some type of coronary lesions, their films were reviewed by two interventional cardiologists from our department.

All information present in these reports were classified according to ISHLT : ISHLT CAV0 (Not significant): No detectable angiographic lesion; ISHLT CAV1 (Mild ): Angiographic left main (LM) <50%, or primary vessel with maximum lesion of <70%, or any branch stenosis

<70% (including diffuse narrowing) without allograft dysfunction; ISHLT CAV2 (Moderate): Angiographic LM <50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction; ISHLT CAV3 (Severe): Angiographic LM ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF <45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology.

Study population

The recipients group included 157 male and 45 female. Median age was 66 (57-71) years, 62 recipients were older than 70 years. Median BMI was 24.69 (23.37-26.46) $kg.m^{-2}$.

The donors group was composed by 154 males and 48 females. Median age was 35 (24-43) years and 20 (10%) donors were more than 50 years old. Median BMI was 24.11 (21.91-27.00) $kg.m^{-2}$.Population baseline pre-OHT features is represented in table 1. To identify CAV predictors patients were categorized into CAV (+) and CAV (-) groups.

Statistical analysis

Data were analysed using statistics software (SPSS version 23.0).

Categorical variables were presented as frequency and percentage, and comparisons were performed by chi-square test or fisher's exact test. All continuous variables had a non-normal distribution so they were presented as median (interquartile range) and comparisons between groups were performed with Kruskal Wallis test. For predictors' analysis, univariate analyse were performed using the Cox proportional hazards model. CAV incidence rate was computed with STATA 14.0 statistical software. The follow-up period for each patient was calculated from the date of OHT to the date of last contact.

A *p*-value of less than 0.05 was considered statistically significant.

**Results**

Over a median follow-up of 2920 (1825-3650) days after OHT, 37 patients (18.3%) were diagnosed with CAV. Seven (35%) patients with donors older than 50 years were CAV (+). From the ones who had a donor younger than 50 years old, thirty (16.5%) patients were CAV (+). There was a significant statistical association between CAV and older donors (p=0.04), as shown in Graphic 1.

After the first, third and fifth year, 3.3, 5.1 and 9.7% of all patients had angiographic findings compatible with CAV, respectively. Prevalence is higher over the remaining follow-up: eight, ten and twelve years after the transplant, respectively, 17.6, 15.9 and 20.0% of the patients present CAV lesions, as shown in Graphic 2. Incidence rate of CAV in our overall population was 2.91 cases per 100 person-year.

Regarding lesion type, 14 had CAV 1 (38%), 12 had CAV 2 (35%) and 9 had CAV 3 (24%). During the follow-up period, six (16%) patients showed disease progression. Four patients first classified with CAV 1 showed progression to the next grade and two CAV 2 patients progressed to CAV 3. The remaining patients demonstrated a stationary CAV course during follow-up. The most frequent lesion was on left main coronary artery territory, proximal and mid segments of anterior descending coronary artery, affecting 26 (96%) patients with CAV. PCI was performed in 18 (49%) patients, for 27 CAV 2 and 3 lesions. Seventeen drug-eluting stents (DES) with either Everolimus, Sirolimus or Zotarolimus and one of them a bioresorbable vascular scaffold (BVS), were implanted in ten of these patients. The patient with BVS stent presented a restenosis ten months later, as illustrated on figures 1-3. PCI with Bare metal stents (BMS) was performed in five patients in a total of ten lesions, with a single case of restenosis during follow-up. PCI's details of the remaining three patients were not available. Four patients underwent OCT-guided PCI. Physiological assessment with fractional flow reserve (FFR) was performed during four procedures, before and after PCI.

A comparison of pre-OHT baseline characteristics of CAV (+) and CAV (-) groups is provided in Table 2. On the side of the recipient, diabetes (p=0.17) and IgG for CMV positive (p=0.42) showed statistical significant difference when comparing patients from CAV (+) group and CAV (-) group, as shown in Table 2. Univariate analysis is shown in Table 3. When considering CAV (+) group, abnormal carotid doppler [hazard ratio (HR) 2.03 95% confidence interval (CI) 0.99–4.14, p=0.06], IHD [HR 1.88, 95% CI 0.91–3.90, p=0.09] and donor's age [HR 1.04, 95% CI 1.00–1.07, p=0.01] were significantly associated with higher CAV prevalence. Conversely, recipient's risk factors such as hypertension [HR 1.46, 95% CI 0.75–2.86, p=0.26], diabetes [HR 1.59, 95% CI 0.79–3.25, p=0.20], dyslipidaemia [HR 1.68, 95% CI 0.86–3.25, p=0.13] and smoking [HR 1.77, 95% CI 0.85–3.65, p=0.13] were not significantly associated with CAV over the follow-up. Multivariate analysis was not performed because pre-IHD and abnormal carotid doppler at the time of OHT showed a strong statistical association between them (p=0.00).

**Table 1**- Baseline population features pre-OHT.

| | **Frequency** |
|---|---|
| **RECIPIENTS** | |
| Age (years) | 66.0 (57.0-71.0) |
| Gender (M) (%) | 157 (77.7) |
| BMI ($kg.m^{-2}$) | 24.69 (23.37-26.46) |
| Hypertension n(%) | 74 (36.8) |
| Diabetes n (%) | 48 (26.8) |
| Previous vascular disease n(%) | 61 (30.3) |
| Previous IHD n(%) | 72 (35.6) |
| Smoker n(%) | 35 (17.3) |
| Dyslipidaemia n(%) | 94 (46.8) |
| Abnormal Carotid Doppler n(%) | 80 (39.6) |
| IgG CMV (+) n(%) | 147 (80.3) |
| Acute rejection≥2R $1^{st}$ year n(%) | 42 (21.3) |
| **DONORS** | |
| Age (years) | 35.0 (24.0-43.0) |
| ≥50 (years) (%) | 20 (9.9) |
| Gender (M) n (%) | 154 (76.2) |
| BMI donor ($kg.m^{-2}$) | 24.11 (21.91-27.00) |

BMI: body mass index, CMV: cytomegalovirus, IHD: ischemic heart disease,M: masculine, OHT: orthotopic heart transplantation, 2R: moderate or severe.

**Table 2** - Pre-OHT baseline characteristics of CAV (+) and CAV (-) groups

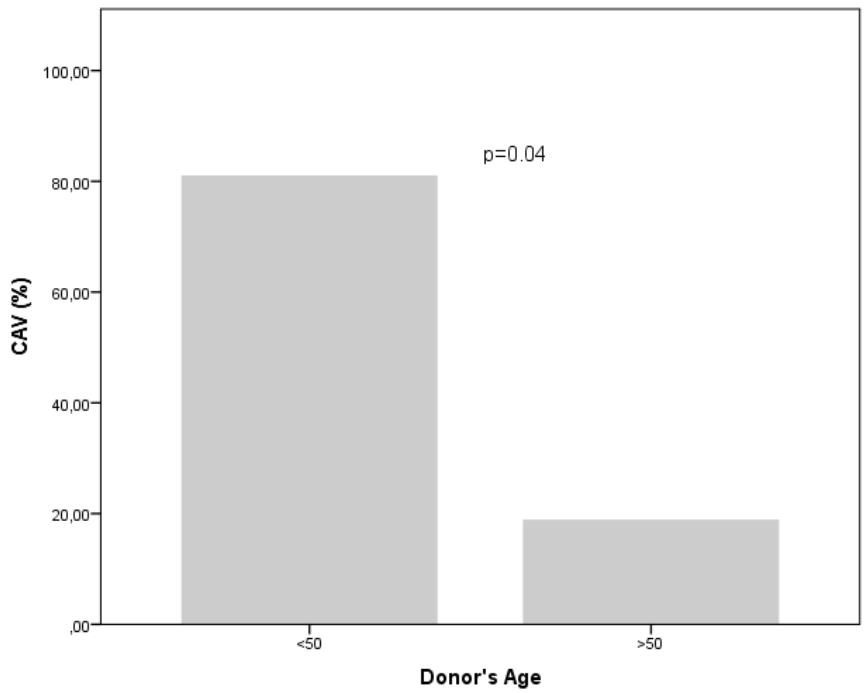
| | CAV (+) group **(n=37 18.3%)** | CAV (-) group **(n=165 81.7%)** | p-value |
|---|---|---|---|
| **RECIPIENTS** | | | |
| Age (years) | 65.0 (57.0-71.0) | 67.0 (57.0-72.0) | 0.55 |
| Gender (M) n(%) | 31 (83.8) | 126 (76.4) | 0.33 |
| BMI ($kg.m^{-2}$) | 23.53 (21.81-25.99) | 23.60 (21.50-25.51) | 0.72 |
| Hypertension n(%) | 14 (37.8) | 60 (36.6) | 0.89 |
| Diabetes n(%) | 12 (36.4) | 36 (24.7) | 0.17 |
| Previous vascular disease n(%) | 13 (35.1) | 48 (29.3) | 0.55 |
| Previous IHD n(%) | 14 (48.6) | 54 (32.7) | 0.07 |
| Dyslipidaemia n(%) | 18 (48.6) | 76 (46.3) | 0.80 |
| Smoking n(%) | 10 (27.0) | 25 (15.2) | 0.09 |
| Abnormal Carotid Doppler n(%) | 19 (51.4) | 61 (37.0) | 0.14 |
| IgG CMV (+) n(%) | 29 (85.3) | 118 (79.2) | 0.42 |
| Acute rejection >2R $1^{st.}$ year n(%) | 10 (27.8) | 32(19.2) | 0.30 |
| **DONORS** | | | |
| Age (years) | 37 (25-46) | 34 (24-42) | 0.07 |
| ≥50 (years) n(%) | 7 (35.0) | 13 (65.0) | 0.04 |
| Gender donor (M) n(%) | 32 (86.5) | 122 (73.9) | 0.11 |
| BMI donor ($kg.m^{-2}$) | 24.38 (23.15-27.10) | 24.91 (23.44-26.31) | 0.10 |

BMI: body mass index, CAV: cardiac allograft vasculopathy, CMV: cytomegalovirus, IHD: ischemic heart disease, M: masculine, 2R: moderate or severe.

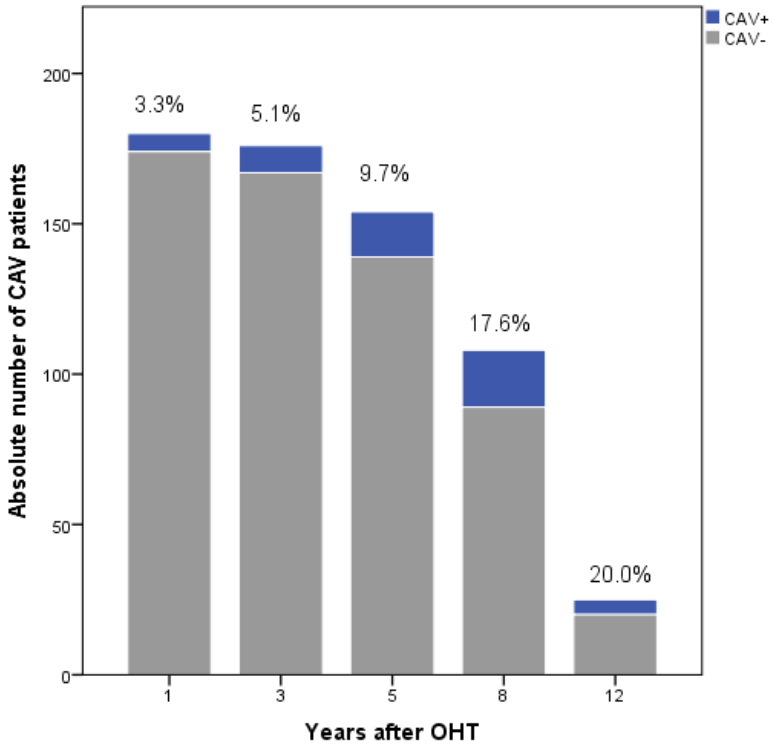
**Table 3** - Univariate analysis for CAV predictors (Cox regression).

| **RECIPIENTS** | **HR (CI 95%)** | **p-value** |
|---|---|---|
| Age (years) | 0.99 (0.97 - 1.02) | 0.62 |
| Gender (M) | 1.78 (0.75 - 4.27) | 0.20 |
| BMI ($kg.m^{-2}$) | 0.99 (0.94 - 1.05) | 0.84 |
| Hypertension | 1.47 (0.75 - 2.86) | 0.26 |
| Diabetes | 1.59 (0.79 - 3.25) | 0.20 |
| Previous vascular disease | 1.54 (0.78 - 3.02) | 0.21 |
| Previous IHD | 2.32 (1.21 - 4.45) | 0.01 |
| Smoker | 1.77 (0.85 - 3.65) | 0.13 |
| Dyslipidaemia | 1.68 (0.87 - 3.25) | 0.13 |
| Abnormal Carotid Doppler | 2.44 (1.27 - 4.71) | <0.01 |
| IgG CMV (+) n(%) | 0.93 (0.36 - 2.43) | 0.93 |
| Acute rejection≥2R $1^{st}$ year | 1.40 (0.68 - 2.91) | 0.36 |
| **DONORS** | | |
| Age (years) | 1.04 (1.00 - 1.07) | 0.01 |
| Gender (M) | 2.14 (0.83 - 5.52) | 0.12 |
| BMI donor ($kg.m^{-2}$) | 1.01 (0.90 - 1.12) | 0.88 |

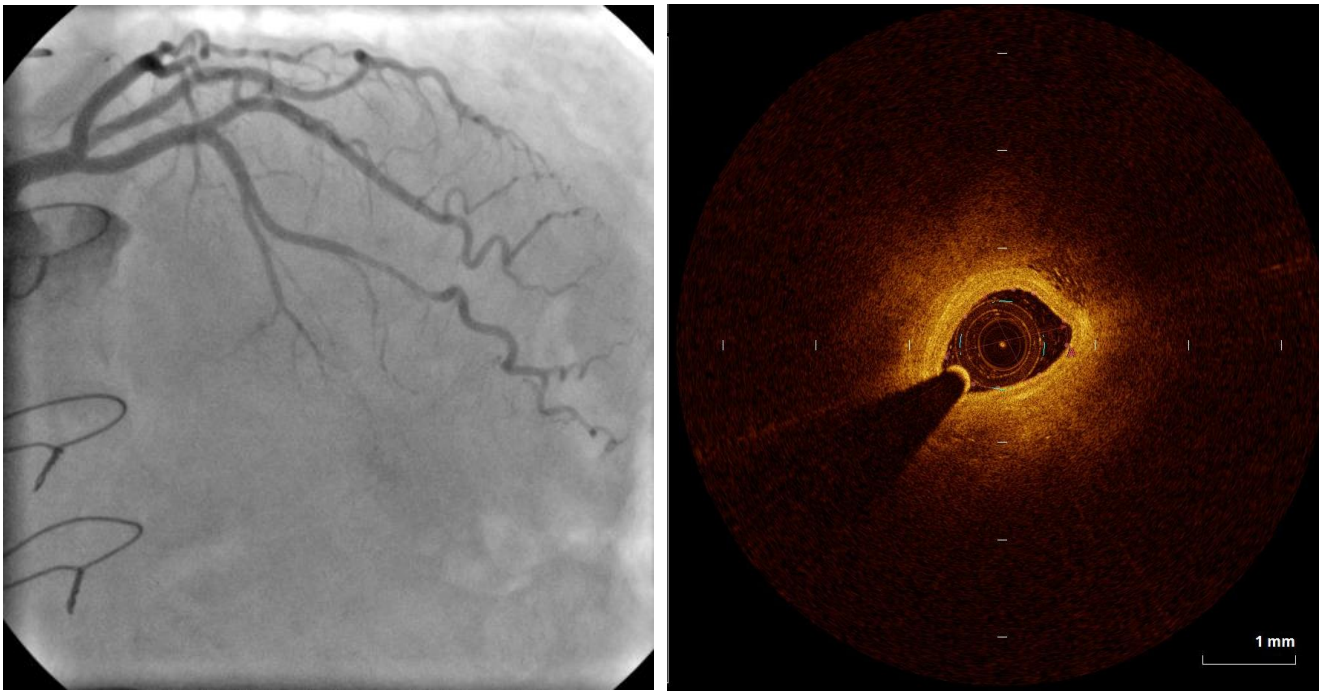
BMI: body mass index, HR: hazard ratio, CI: confidence interval, IHD: ischemic heart disease, M: masculine, 2R: moderate or severe.




**Graphic 1.** CAV prevalence according to donor's age.

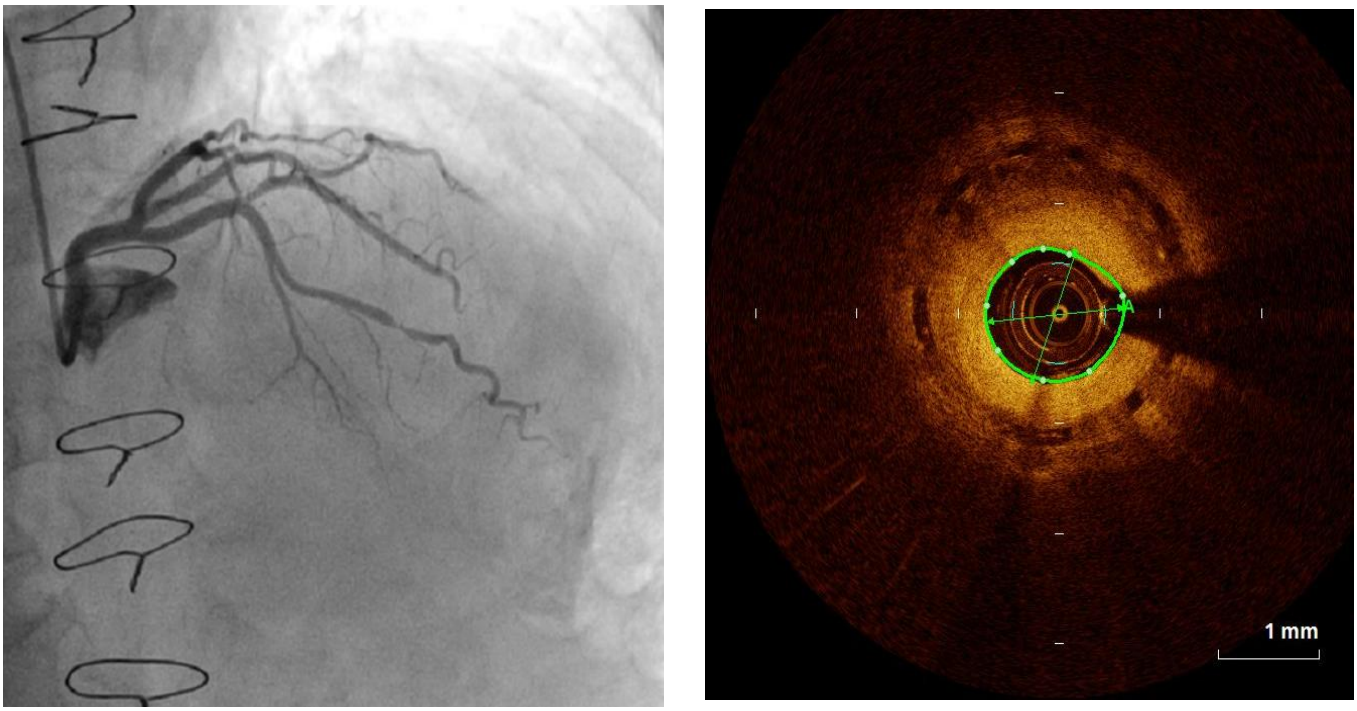



**Graphic 2**. Absolute number of CAV patients in each follow-up year.




**A.** **B.**

**Figure 1**. **A**- Coronary angiography showing an intermediate stenosis in the mid segment of left anterior descending artery. **B** - Optical coherence tomography (OCT) showing intimal thickening (minimal luminal area of 0.98 $mm^2$).




**A.** **B.**

**Figure 2**. **A** - Coronary angiography showing a severe in-stent restenosis in the mid segment of left anterior descending artery.**B** - Optical coherence tomography (OCT) showing focal in-stent restenosis (minimal luminal area of 1.26 $mm^2$).

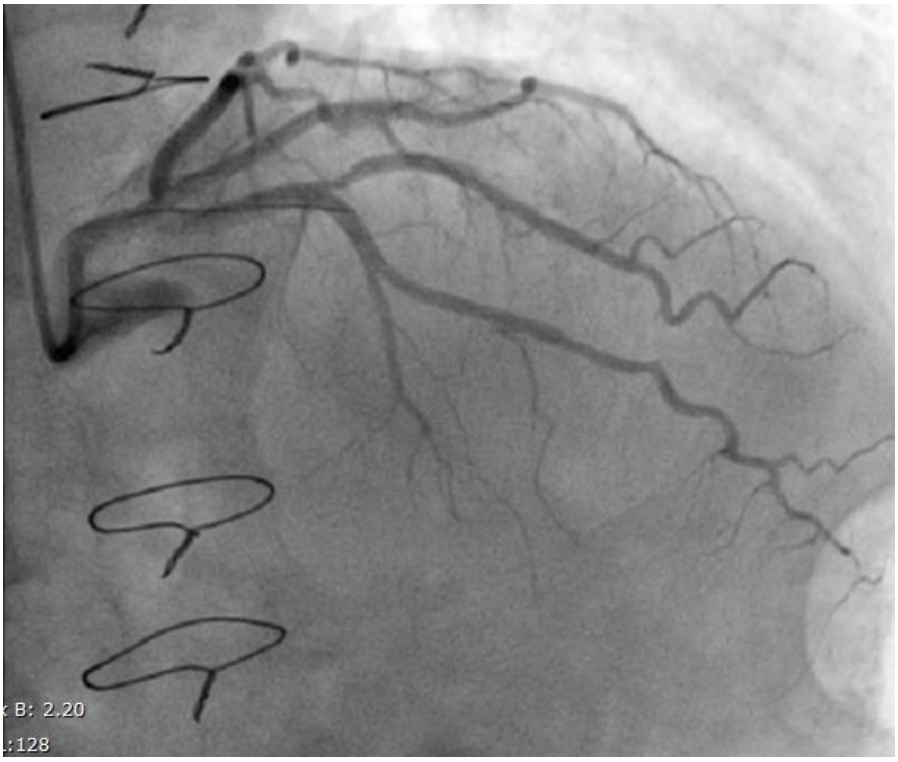



**Figure 3.** Coronary angiography showing left anterior descending artery after paclitaxel-coated balloon angioplasty.

**Discussion**

The incidence of CAV at our institution was 2.91 cases per 100 person-years, moreover, CAV prevalence was 3.3, 9.7 and 20% at 1, 5, and 12 years post-OHT, respectively. Furthermore, the grade of CAV, in most cases, was grade 1 (38%) and 2 (35%). According to the official 2015 ISHLT report, CAV prevalence is 29 and 40%, five and eight years after OHT, respectively.[25] A single centre retrospective study, based on a prospective cohort, enrolling 495 OHT patients and using ICA for CAV diagnosis, showed a CAV prevalence of 48.1%, much higher than our results.[26] Another study with a similar design but a smaller population (54) using both ICA and IVUS for CAV diagnosis presented a CAV prevalence of 46.2%.[27] On our centre, prevalence was much lower, however, their progressively importance with increasing time after OHT was concordant. The incidence rate in our cohort was, also, satisfyingly low. We identified abnormal carotid doppler at the time of OHT, prior history of IHD and donor's age as independently associated with CAV.

At least two single centre observational retrospective studies enrolling 361 and 113 OHT patients and using ICA for CAV diagnosis presented recipient previous IHD as a powerful independent predictor for CAV [HR 9.7, 95% CI 2.3–41.1, P<0.01] and [HR 5.8 , 95% CI 2.3–14.8], P<0.01].[15,28] None of the single centre cohort presented above included abnormal carotid doppler at the time of OHT in their analysis, maybe because of differences on pre-OHT protocol. However, considering that IHD and carotid disease share similar predictors, it would not be surprising if they reach similar association testing this predictor in their patients. Both immunologic and non-immunologic donor and recipient's features behind CAV are unestablished, however, IHD cardiovascular risk factors were thought to take part in CAV physiopathology.[29] In our population, none of the classical cardiovascular risk factors showed such association. However, both IHD and abnormal carotid Doppler at the time of the OHT suggest that recipients who presented CAV after OHT had some of the cardiovascular factors

at the time of the OHT. Therefore, even if each one of classical cardiovascular factors showed no association with CAV in our cohort, our findings reinforce the common atherosclerotic basis between CAV and classical coronary artery disease in non-transplanted patients. Both, IHD and carotid disease imply persistence of classical cardiovascular risk factors that might be associated with coronary plaque progression after OHT.[30,31]

Donor age, on the other hand, was one of the CAV predictors that we could find in our cohort. Another retrospective analysis looking at CAV prevalence of 162 OHT patients in our centre according to donor' age, concluded that the 50 years cut-off was significant.[32] A single centre retrospective study based on prospective cohort enrolling 495 OHT patients presented this variable as a CAV predictor [HR 2.2, 95% CI 1.94–4.84, P<0.01] .[26] A retrospective large cohort single centre study, similar to ours but using IVUS to CAV diagnosis reached a consistent conclusion.[4] For ethical reasons, usually, older donors' hearts are implanted in older recipients with more cardiovascular risk factors, themselves.[32] Also, when CAV appears early after OHT, hypothesis of pre-existing donor's disease should be consider.[33] This association represents a predictable consequence of the donor selection's expansion to older ages. We hypothesize that patients who had received hearts from older donors may benefit from a more intensive follow-up program.

Assuming the immunological process behind CAV, an history of acute cellular rejection assessed by endomyocardial biopsy was suggested on previous single centre cohorts as a predictor of CAV development.[27,34] We did not find such association in our population during the first year post-OHT.

Age limit is a controversial topic in OHT, and according to the international guidelines carefully selected patients older than 70 years may be considered.[3] In our study 62 patients were older than 70 years and recipient age was not statically associated with CAV development.

CAV diagnosis with ICA is in agreement with recent ISHLT recommendations, however, it has limited capability to detect early stages of CAV.[20] According to the American College of Cardiology Clinical Expert Consensus Document, IVUS is the optimal method for CAV detection.[35] A non-randomized single-centre prospective cohort enrolling 30 OHT patients showed that although ICA showed angiographic CAV lesions in only 14% of the patients, 75% of the population had significant intimal thickening, according to IVUS imaging, one year after OHT, confirming the high incidence of intimal lesions that are not detected by coronary angiography.[33] Observational single centre studies comparing ICA with IVUS have demonstrated a positive predictive value and negative predictive value for the diagnosis of CAV that range from 90% to 92%, and 27% to 57%, respectively.[17] OCT allows an even more precise measurement of intimal-media thickness.[19] Two single centre prospective studies performed OCT and IVUS in OHT patients and demonstrated higher sensitivity for the former for early CAV diagnosis.[18,19] Inclusion of IVUS or OCT in our centre follow up program would allow us to detect abnormalities earlier after OHT and study CAV predictors more accurately, although this would increase significantly the program expenses.

Revascularization procedures are associated with poor long-term results and are considered palliative due to the diffuse and progressive nature of vascular changes.[14] In the setting of triple vessel disease, for example, PCI is associated with only 27 % two-years freedom from cardiac death or graft loss.[24] Small single centre experiences suggest a higher (90% to 98%) initial procedural success but a restenosis prevalence of 35% to 100% for PCI alone and 20% to 56% for PCI with a stent during the first year[36,37] The higher restenosis rate in CAV compared to IHD is explained by the lymph proliferative response present in OHT patients.[11] Nevertheless, in our population, PCI had very good results. DES were chosen for the majority of CAV lesions described in our series. Large-scale randomised trials have shown substantial improvement in event-free survival with contemporary DES compared with BMS at 40

months' follow up.[38,39] BVS are a new stent drug-eluting generation made with a resorbable polymer. The only one patient in our series that had a stent of this kind implanted had a restenosis ten months after PCI. Four major randomised trials with the most widely used BVS in non-OHT patients presented comparable outcomes with metallic DES at one year.[39] However, a seven studies meta-analysis concluded that BVS was associated with increased risk of target vessel-related myocardial infarction and stent thrombosis, one to two years post intervention compared with metallic DES.[39] Nevertheless, a recently published clinical series of three CAV patients showed excellent long-term results performing PCI with these BVS, therefore, their application requires large controlled randomized trials.[40]

The treatment of the established CAV is disappointing, hence, the primary effort should be directed to early diagnosis and prevention. For that, identifying CAV predictors should be a priority.

Study Limitations

Firstly, due to the retrospective nature of this analysis, comparison between CAV (-) and CAV (+) groups could be biased because of potential confounding factors. Also, as a single-centre study the external validity is limited, with heterogeneity in the follow up program, for instance.

Secondly, our study population is relatively small. Larger populations may provide a greater statistical power to demonstrate the natural course and outcome of CAV.

Thirdly, ICA was the only exam included in our study. The results reported here may not be entirely applicable to centres that routinely use IVUS or OCT for CAV diagnosis and staging.

Lastly, exclusion of patients who died within the early postoperative period resulted in a survival bias, so data presented in our study cannot be applied to early post-OHT risk.

## Conclusion

In this retrospective analysis of a single centre OHT cohort, an abnormal carotid doppler at the time of OHT, prior history of IHD and donor's age were independently associated with CAV. This may suggest that an abnormal carotid doppler at the time of OHT, prior history of IHD or an older donor might influence post-OHT outcomes. OHT recipients with one of these features could be included in a special follow up program. Earlier CAV is diagnosed, earlier specific therapy can be prescribed and slower its progression.

The high number of OHT performed in our centre and the high quality of the ICA follow up program gave us great results, however, our sample size and statistical power remained modest.

Randomized controlled multicentre trials are required to establish the best diagnostic technique to include in the OHT patients' follow-up program for CAV prevention. Larger cohorts with a larger number of well-studied immunological and non-immunological donor and recipient's features are recommended to establish CAV predictors.

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