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REVIEW

Coronary artery disease in heart transplantation: new concepts for an old disease

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SUMMARY

Cardiac allograft vasculopathy (CAV) remains one of the main long-term complications after heart transplantation. We performed a systematic review focused on articles published in the previous 6 years to reappraise the novel evidences supporting risk factors, pathology, prevention, and treatment of CAV. We identified a search string for a literature search on PubMed. We excluded articles specifically focused on diagnosis/biomarkers/imaging only or complications of other diseases. We included 98 studies out of our search. Forty-eight articles describe risk factors for CAV, 13 pathology, 24 prevention, and 13 treatment for CAV. While confirming known concepts, we found supportive evidence that CAV pathophysiology may vary according to the time post-transplant and the prevalence of metabolic versus immune-mediated risk factors. Selective revascularization of focal lesions in patients with CAV may result in some clinical benefit, but CAV prevention, rather than treatment, by controlling risk factors and by using targeted immunosuppressive therapies is the most evidence-based approach to reduce disease progression.

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cardiac allograft vasculopathy, graft dysfunction, heart transplantation, pathology, risk factors

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Introduction

Although the survival after heart transplantation (HT) has improved considerably in the last decade [1,2], cardiac allograft vasculopathy (CAV) remains one of the main long-term complications, as a major cause of death and the most frequent cause of late graft dysfunction [3]. According to data from the Registry of the International Society for Heart Transplantation (ISHLT), within 10 years after HT about half of recipients develop CAV, and its detection more than doubles the risk of death the following year [1].

Cardiac allograft vasculopathy is a rapidly progressive form of atherosclerosis, albeit characterized by a deceitful and silent development. Diffuse intimal hyperplastic lesions of the vascular tree, leading to vessel narrowing and eventually to allograft ischemia, represent CAV typical morphology, which makes standard coronary imaging tools insensitive [4]: its detection is uneasy and requires high-sensitive imaging and specifically developed classification criteria [5].

Because of the cardiac denervation, patients with CAV mostly do not suffer from chest pain, which can be typical in native coronary artery disease [6]. Ventricular arrhythmias, congestive heart failure, or even sudden cardiac death may often be CAV′s first clinical manifestation [7].

Cardiac allograft vasculopathy pathogenesis is characterized by a complex interplay between immune-mediated and non-immune-mediated mechanisms [8],

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rendering to a wide heterogeneity in vascular lesions, ranging from intimal thickening to complicated atheromas.

Therapeutic strategies for established CAV are limited. While interventions directed at reducing the impact of risk factors on CAV development showed some efficacy in pivotal studies [9,10], no specific drug therapy or revascularization strategy has evidence-based efficacy in limiting the clinical events in patients with CAV.

Altogether, this scenario still depicts CAV as an unavoidable destiny hanging over heart transplant recipients. Nevertheless, latest ISHLT registry data show a slight reduction in CAV incidence for patients transplanted in the most recent era [11], suggesting that current post-transplant management may have indeed led to an improvement in CAV-related outcomes.

To substantiate the rationale for this hypothesis, and highlight the basis for further improvement in the near future, we performed a systematic review of the literature published in the latest 7 years (i.e., 2011–2017), aiming to shed light on current developments about CAV risk factors, pathology, prevention, or treatment of CAV.

Methods

Search strategy

To reduce as much as possible potential selection biases in the articles chosen to be included in this review, we applied the systematic review approach using Medical Subject Heading (MeSH) terms by searching PubMed on the 10th of October 2017. The following search protocol was used:

> ((“Coronary Artery Disease/etiology”[Majr] OR “Coronary Artery Disease/pathology”[Majr] OR “Coronary Artery Disease/therapy”[Majr]) AND “Heart Transplantation/adverse effects”[Majr]) OR “cardiac allograft vasculopathy”[tiab] NOT (“Review”[Publication Type] OR “Letter”[Publication Type] OR “Comment” Type] OR “Editorial”[Publication Type] OR “News”-cation Type] OR “Rats”[Mesh] OR “Mice”[Mesh] OR “Rabbits”[Mesh]) AND “loattrfull text”[sb] AND “2011/10/10”[PDAT]: “2016/10/10”[PDAT] AND English [lang]

Relevance of articles was screened by titles and abstracts. Full-text of all selected articles was then reviewed and categorized as reported in Results section.

Study selection and data extraction

We included studies focusing on risk factors, pathology, and prevention or treatment of CAV. Because we aimed at gaining new knowledge on potential novel therapeutic targets and on the effectiveness of interventions, we excluded from the systematic review articles specifically focused on diagnosis/biomarkers/imaging only, or complications of other diseases, although they might have been considered when supportive of findings of the included studies. Animal studies, case reports, and reviews were excluded as well. Finally, we excluded studies in which CAV has been reported as ancillary outcome and not specifically aimed at.

Titles and abstracts of the retrieved articles were independently reviewed by two reviewers (ML and KM). If there was any disagreement about the articles to include, it was resolved by both reading the full article and debating with the other authors on which criteria the study would be included or excluded.

After the studies were included, the following data were extracted from each study: year of publication, journal of publication, on which of our three subjects the study was, study type, study population, mean age of the study population, average follow-up time, type of risk factor/pathologic component/prevention/intervention studied, and main outcomes of the studies.

Results

PubMed search

Two hundred ninety-nine studies were retrieved out of the search on PubMed. After application of our inclusion and exclusion criteria, we selected 98 studies. The flowchart in Fig. 1 shows how the studies were included and excluded.

Of the included studies, 48 describe risk factors for CAV, 13 pathology, 24 prevention, and 13 treatment of CAV.

Risk factors for CAV

Of the 48 articles investigating risk factors for CAV, six had a prospective design [12–17], seven were subanalysis of multicenter registries [16,18–23], and 36 were retrospective mostly single-center cohort studies [24–59] (Table 1). In most of the studies, several factors emerged from the analysis as associated with CAV, but it has to be noted that only few were consistently reported in all studies, which analyzed widely variable

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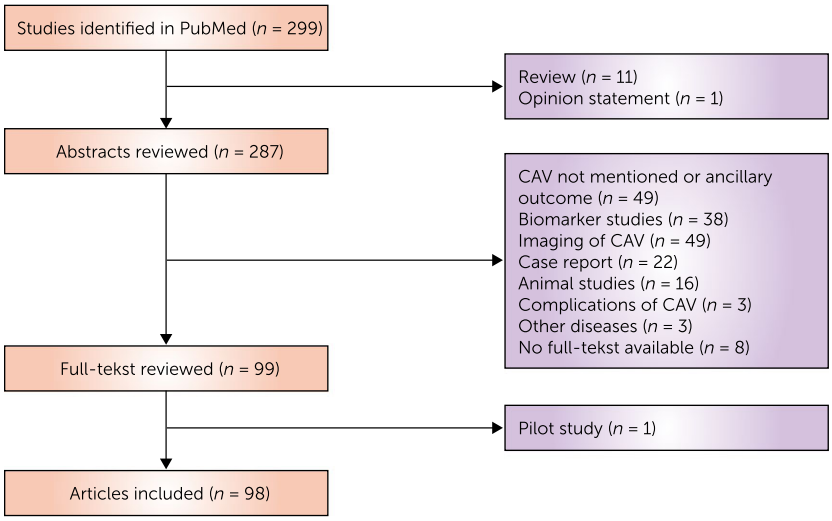

Figure 1 Study flowchart.

sets of risk factors. Donor age, and antibody-mediated rejection (AMR) or donor-specific antibodies (DSA) are the most consistently analyzed and reported risk factor associated with CAV, emerging as major players in 17 (34%) and 12 (24%) of these articles, respectively. Among other factors potentially implicated in CAV development, the analyzed studies reported metabolic abnormalities (including elevated cholesterol or triglycerides, diabetes, and high body mass index), cigarette smoking, African ethnicity, pretransplant ischemic cardiomyopathy, donor–recipient, gender mismatch, and cytomegalovirus (CMV) infection. Toxoplasma serology, heart rate, retransplantation, and primary graft dysfunction were not associated with CAV, while heart–lung or heart–liver transplantation appeared to be protective.

Pathology of CAV

We found thirteen articles studying CAV in terms of pathological description. In this group, we included in vivo imaging studies focusing on specific morphological features of coronary lesions [60–66], and on ex vivo or postmortem studies analyzing morphological and molecular phenotypes of CAV [67–72]. Table 2 describes the main characteristics and outcomes of the retrieved papers. In addition to descriptive studies on plaque morphology and histopathological phenotype in CAV, the immune-mediated and inflammatory pathophysiology of CAV had been investigated by studies analyzing pathological AMR in CAV, monitoring of immune function and CAV, ectopic lymphoid structures, and neovascularization. The major novelties include findings supporting distinct pathways in CAV pathogenesis varying with the time from transplant, and strong evidence relating B-cell lineage – both as graft-infiltrating cells and as antibody-producing cells – in CAV development.

Prevention of CAV

Twenty-four studies investigated strategies for CAV prevention. The main study characteristics and outcomes are shown in Table 3. Nine of these studies had a randomized controlled design, thus supporting strong evidence of the findings [73–81]. Most of studies (58%) investigated the effect of mTOR inhibitors (sirolimus or everolimus) in comparison with calcineurin inhibitors (CNIs, cyclosporin or tacrolimus) or to mycophenolate derivatives (MMF) [74,76–80,82–86]. The other agents investigated for CAV prevention included induction therapies, tacrolimus versus cyclosporine, Ace inhibitors, aspirin, statins and granulocyte–colony-stimulating factor [73,75,81,87–93].

Treatment of CAV

Thirteen of the included articles studied the treatment of CAV. In Table 4, the main study characteristics and outcomes are shown. Percutaneous coronary intervention (PCI) was used in twelve studies [66,94–104]. Four studies compared the use of bare metal stents (BMSs) with drug-eluting stents (DESs) [95,96,98,103]. Coronary artery bypass grafting (CABG) was used in four studies [94,97,99,104]. Three studies report about retransplantation as extreme treatment for CAV [94,99,105]. Of note, all were retrospective cohort

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Table 1. Characteristics of included studies on risk factors.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Olmetti *et al.* (2011) [24]	*De novo* HT recipients	Retrospective cohort study	*N* = 244	96 months	Donor age (sec)	Donor age was correlated with a significant higher risk of developing CAV (HR 1.02; 1.00–1.0; *P* = 0.022)
Sánchez-Gómez *et al.* (2012) [12]	*De novo* HT recipients	Prospective cohort study	*N* = 89	1 year after HTx	Lipids and cholesterol, Donor age (sec)	In a multivariate analysis, metabolic syndrome [OR: 7.97; confidence interval (CI): 2.77–22.96; *P* < 0.001] low high-density lipoprotein cholesterol (OR: 0.26; 95% CI: 0.09–0.71; *P* = 0.009) and hypertriglyceridemia (OR: 4.08; 95% CI: 1.45–11.50; *P* = 0.008) and donor age (years) (OR: 1.07; CI: 1.01–1.13; *P* = 0.019) were related to a higher risk of CAV
Khush *et al.* (2012) [19]	*De novo* HT recipients	Multicenter Registry subanalysis	*N* = 60 584	4.1 years	Gender, gender mismatch	Receipt of a female allograft was associated with a lower incidence of CAV. Specifically, male recipients of a female versus male allograft had a 19% lower odds of developing CAV (OR: 0.81; CI: 0.74–0.88). Similarly, female recipients of a female versus male allograft had 18% lower odds of developing CAV (multivariate OR: 0.82; CI: 0.72–0.93), where the effect of donor sex on CAV did not differ by recipient sex (*P* = 0.9)
Everitt *et al.* (2012) [25]	Patients receiving HT ≤18 years and with at least one endomyocardial biopsy	Retrospective cohort study	*N* = 76	5.1 years	Rejection (AMR)	Patients with at least 1 pathologic AMR 3 episode had lower freedom from cardiovascular mortality or cardiac allograft vasculopathy within 5 years of HT than those without pathologic AMR 3 (45% vs. 91%, *P* < 0.001)
Topilsky *et al.* (2013) [48]	HT recipients in whom anti-HLA antibodies were determined and who had baseline and 1-year follow-up IVUS study	Retrospective cohort study	*N* = 49	3.7 years	DSA	There were 36 (71%) of 51 patients who had grade I CAV or greater during a median follow-up period. Kaplan–Meier curves show considerable difference in the presence of angiographic CAV

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
						significantly affecting the DSA II+ group as compared to DSA− patients at 1 year (42.5 ± 18% vs. 19.6 ± 7%), 2 years (57.2 ± 18% vs. 36.2 ± 9%), and 4 years (100.0 ± 0% vs. 64.2 ± 9%, $P = 0.05$). There were seven patients (14%) who had grade II or greater CAV during the median follow-up period of 3.7 years. There was a clear trend for increased rate of developing grade II or greater CAV in DSA II+ patients as compared to DSA− patients at 1 year (16.6 ± 15% vs. 3.3 ± 3%), and 4 years (58.3 ± 30% vs. 18.2 ± 8%)
Kwon *et al.* (2013) [26]	HT recipients who required ECMO, open chest, and/or usage of an intra-aortic balloon pump within 72 h of transplantation	Retrospective cohort study	$N = 733$	–	Primary graft dysfunction	Of the 23 primary graft dysfunction patients with allograft survival beyond 30 days, two developed CAV (8.7%) at an average time of 1.4 year post-transplant. Of the 684 nonprimary graft dysfunction patients surviving past 30 days, 144 (21.0%) developed CAV at an average of 4.4 years after transplantation. The difference in incidence of CAV between the two groups is statistically significant ($P = 0.02$)
Kobayashi *et al.* (2013) [18]	Pediatric HT recipients with at least 1-year follow-up, re-HTx included	Multicenter Registry subanalysis	$N = 5211$	–	Re-HTx/donor age/recipient age/donor cigarette use	The risk of CAV was associated with the following variables: recipient age 1–4 years (HR 1.25), 5–9 years (1.45), 10–18 years (1.83), donor age >18 years (1.34), re-HTx (2.14), recipient black race (1.55), and donor cigarette use (1.54). Older recipient and donor age, recipient black race, donor cigarette use, and retransplantation were highly associated with shorter CAV-free survival

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
van Hellemond *et al.* (2013) [27]	HT recipients, also re-HTx	Retrospective cohort study	*N* = 582	8.3 years	*Toxoplasma gondii*	No difference was found in deaths due to cardiac allograft vasculopathy. After adjustment, the recipient Toxoplasma serostatus was not associated with mortality [hazard ratio, 1.21; 95% CI, 0.95–1.54]. With the Toxoplasma serostatus combination donor negative/recipient negative as a reference, univariate hazard ratios for the Toxoplasma serostatus combinations were D+/R− 0.52 (95% CI, 0.37–0.73), D−/R+ 0.65 (95% CI, 0.40–1.05), and D+/R+ 0.78 (95% CI, 0.57–1.07). Multivariate analysis, however, showed that donor Toxoplasma serostatus was not independently associated with mortality
Eskandary *et al.* (2014) [28]	HT recipients >16 years	Retrospective cohort study	*N* = 1190	10 years	Donor age/recipient age/gender	Survival was 80%, 77%, 69%, and 56% after 1, 2, 5, and 10 years, respectively Significant risk factors for CAV were donor age (HR, 1.4; CI: 1.3–1.5) and male recipient sex (HR, 1.5; CI: 1.0–2.2). Recipient age was inversely associated with initiation of CAV (HR, 0.8; CI: 0.8–1.0)
Guihaire *et al.* (2014) [29]	*De novo* HT recipients	Retrospective cohort study	*N* = 220	94 months	HLTx	CAV-free survival from and changes of CAV grade over the time among heart–lung transplant and heart transplant recipients. Survival of CAV grade ≥1 was better among HLTx recipients. Similarly, CAV grade after HTx was higher at each 2-year follow-up compared with HLTx. CAV severity increased progressively over the time after HLTx, suggesting that CAV was delayed rather than completely prevented in this group. $P < 0.01$ (HTx versus HLTx)

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Tehrani *et al.* (2014) [30]	HT recipients excluding known donor coronary artery disease	Retrospective cohort study	$N = 390$	5-year	Donor age	Donor age ≥50 years is a risk factor for CAV (HR, 1.9, CI: 1.2–2.9, $P = 0.004$)
Guddeti *et al.* (2014) [31]	HT recipients who had undergone at least two virtual histology IVUS examinations	Retrospective cohort study	$N = 165$	–	Ischemic cardiomyopathy	After multivariate adjustment, ICM was significantly associated with plaque progression (odds ratio 3.10; CI: 1.17–9.36; $P = 0.023$). Ten-year cardiovascular event-free survival was 50% in ICM patients compared with 84% in non-ICM patients (log-rank test $P = 0.003$). In multivariate Cox proportional hazard analysis, ICM was significantly associated with a higher event rate after HTx (hazard ratio 2.02; 95% CI: 1.01–4.00; $P = 0.048$)
Friedland-Little *et al.* (2014) [16]	HT recipients including re-HTx	Multicenter Registry subanalysis	$N = 106$	10 years	Re-HTx	There was no difference between third HTx patients ($n = 27$) and control second HTx patients ($n = 79$) with respect to survival (76% vs. 80% at 1 year, 62% vs. 58% at 5 years and 53% vs. 34% at 10 years, $P = 0.75$), early (<1 year from HTx) rejection (33.3% vs. 44.3%, $P = 0.32$), or CAV (14.8% vs. 30.4%, $P = 0.11$)
Milaniak *et al.* (2014) [32]	HT recipients	Retrospective cohort study	$N = 169$	1 year after HTx	BMI and diabetes/ gender mismatch (sec)/recipient age (sec)	Interaction found between entry BMI, fasting glucose, gender, and cardiovascular disease ($R = 0.378$; $R^2 = 0.143$; adjusted $R^2 = 0.097$; $F = 3$; 107; $P = 0.004$) Neither gender nor years after HTx and age of recipients appeared as significant predictors of CAV on multivariate logistic regression ($P > 0.05$)

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Correia *et al.* (2014) [46]	Male HT recipients	Retrospective cohort study	*N* = 200	4.35 ± 3.34 and 4.21 ± 2.95 years, respectively	Gender mismatch	In a cohort of male recipients, the overall mortality of those receiving male versus female donor was 27.3% and 21.8% (*P* = 0.446). Survival free from graft vascular disease at 1, 5, and 8 years was 97.1 ± 2.9%, 87.8 ± 6.9%, and 87.8 ± 6.9%, respectively, in Group A and 97.6 ± 1.4%, 87.2 ± 3.6%, and 72.8 ± 6.4% for Group B (*P* = 0.299)
Frank *et al.* (2014) [47]	HT recipients who had an endomyocardial biopsy	Retrospective cohort study	*N* = 109	–	DSA	Twenty-four (21%) of 112 grafts developed CAV, and 18 (75%) of 24 were positive for C4d. Patients with DSA (*n* = 51) against human leukocyte antigen class I (*n* = 5), II (*n* = 26), or both (*n* = 20) developed CAV at a rate of 40%, 38%, and 20% and a mean time to CAV of 89, 47, and 25 months, respectively. Of 61 grafts without DSA, only 13% developed CAV
Lopez-Fernandez *et al.* (2014) [13]	HT recipients and seven necropsies	Prospective cohort study	*N* = 113	2 years	Cardiogenic shock	The risk of CAV is 6.49 times higher after a cardiogenic shock at the time of transplant operation (95% CI: 1.86–22.7; *P* = 0.003)
Prieto *et al.* (2015) [33]	HT recipients with donors in specific age groups	Retrospective cohort study	*N* = 162	55 ± 32 months	Donor age	CAV was diagnosed in 22 patients (8.8%), with some difference in the incidence between the groups (15.6% vs. 7.4%; *P* = 0.081). Decreased survival from CAV at 8 years (65 ± 18% vs. 78 ± 7%; *P* = 0.06)
Roig *et al.* (2015) [59]	*De novo* HT recipients	Retrospective cohort study	*N* = 2102	10-year maximum	Donor age	Grafts from older donors had a higher incidence of CAV at 5 years (RR 1.67; 1.22–2.27; *P* = 0.001) and 10 years (RR 1.55; CI: 1.19–2.02; *P* = 0.001)
Chehrazi-Raffle *et al.* (2015)	HT recipients	Retrospective cohort study	*N* = 785	–	*Toxoplasma gondii*	No significant difference was found between pretransplant *T. gondii*-seronegative and *T. gondii*-seropositive recipients in 5-year outcomes after HT.

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
						However, in the donor-seropositive/recipient-seronegative subgroup (D+/R−), there was a significantly lower 5-year survival rate compared to the cohort of donor-seronegative/recipient-seronegative (D−/R−) patients (60% vs. 87%, $P = 0.04$). After adjustment by multivariate analysis, D+/R− status conferred a trend toward increased mortality (HR, 3.0, $P = 0.06$)
Chen *et al.* (2015) [14]	Pediatric HT recipients	Prospective cohort study	$N = 25$	3.8 years	DSA	Over the time period of the study, 11 patients (44%) had one coronary angiogram performed at a median of 3.5 years (IQR: 3.2–3.9 years) post-transplant; none demonstrated evidence of accelerated or early CAV
Coutance *et al.* (2015) [49]	HT recipients with late antibody-mediated rejection	Retrospective cohort study	$N = 20$	1-year maximum	Rejection	Among survivors at 3 months ($n = 12$), histologic persistence or recurrence of AMR, persistent left ventricular dysfunction, and fulminant CAV were common (33%, 33%, and 17% of patients)
Delgado *et al.* (2015) [50]	*De novo* HT recipients	Retrospective cohort study	$N = 166$	11 years	Donor age (sec)/rejection (ACR)/CMV infection	Independent variables associated with development of CAV were donor age [hazard ratio (HR), 1.028; 95% CI, 1.002–1.053; $P < 0.028$], presence of ACR ≥ 2R (HR, 1.764; 95% CI, 1.011–3.078; $P < 0.0414$), CMV infection (HR, 2.334;95% CI, 1.043–5.225; $P < 0.0354$)
Irving *et al.* (2015) [34]	Pediatric *de novo* HT recipients	Retrospective cohort study	$N = 108$	8.2 years	DSA	There was an increased incidence of CAV, rejection, and graft loss in those with persistent DSA. Outcomes were similar between the group with non-DSA antibodies and the group with no antibodies

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Johansson *et al.* (2015) [36]	HT recipients >14 years and without mortality in less than 30 days	Retrospective cohort study	$N = 226$	–	CMV infection/donor age/recipient age	CAV-free survival of patients without CMV infection was 6.7 years (95% CI: 6.0–7.4) and thus better compared with the survival of 4.2 years from patients with CMV disease (95% CI: 3.2–5.2; $P < 0.001$). An asymptomatic CMV infection also had less survival compared with no CMV infection (5.4 years; 95% CI: 4.3–6.4; $P = 0.013$) Donor age and recipient age were significantly associated with CAV-free survival
Prieto *et al.* (2015) [33]	*De novo* HT recipients	Retrospective cohort study	$N = 248$	3.8 ± 2.7 vs. 4.5 ± 3.1 years, respectively	Recipient age/ donor age	Donors to Group A were older (38.5 ± 11.3 vs. 34.0 ± 11.0 years; $P = 0.014$). Incidence of cellular/humoral rejection was similar, but incidence of cardiac allograft vasculopathy was higher (15.6% vs. 7.4%; $P = 0.081$)
Sato *et al.* (2016) [38]	*De novo* HT recipients	Retrospective cohort study	$N = 54$	6.6 ± 4.0 years	Rejection (ACR)/ donor age	ACR ≥ 2 and donor age >50 years were significantly associated with CAV development
Tran *et al.* (2016) [39]	Pediatric *de novo* HT recipients	Retrospective cohort study	$N = 105$	–	DSA	DSA-positive patients had significantly higher rates of coronary artery vasculopathy (CAV) compared with DSA-negative patients (36% vs. 13%). CAV-free survival at 1 year and 5 year post-transplant for DSA-negative patients was 90% and 25%, respectively, compared with 70% and 0%, respectively, for DSA-positive patients ($P < 0.01$). DSA-positive patients had 2.5 times more rejection events per year than DSA-negative patients. The 5-year graft survival rate was 72.4% for DSA-negative patients and 21% for DSA-positive patients ($P < 0.001$)

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Zheng *et al.* (2016) [15]	HT recipients	Prospective cohort study	*N* = 39	1 year	Rejection	Patients with history of high-grade rejection had larger plaque burden in distal coronary segments and higher maximum lipid core burden index
Wong *et al.* (2016) [40]	SHLT and HT recipients	Retrospective cohort study	*N* = 245	–	Heart–liver transplantation	Simultaneously transplanted liver allograft was associated with reduced risk of TCMR [odds ratio (OR) 0.003, 95% CI: 0–0.02; $P < 0.0001$], antibody-mediated rejection (OR: 0.04, 95% CI: 0–0.46; $P = 0.004$), and cardiac allograft vasculopathy (OR: 0.26, 95% CI: 0.07–0.84; $P = 0.02$)
Szyguła-Jurkiewicz *et al.* (2016) [41]	*De novo* HT recipients with at least 1 CAG	Retrospective cohort study	*N* = 198	63.6 ± 14.7 months	BMI and diabetes	The occurrence of diabetes (OR = 12.355 (1.417–35.750), $P < 0.001$) was an independent predictor of CAV
Javaheri *et al.* (2016) [42]	HT recipients	Retrospective cohort study	*N* = 35	–	Lipids and cholesterol	High cholesterol efflux capacity levels were associated with improved survival (HR = 0.26). At baseline and 1 year after transplantation, patients who had developed CAV had low cholesterol efflux capacity
Watanabe *et al.* (2016) [43]	*De novo* HT recipients	Retrospective cohort study	*N* = 42 (DA *N* = 24, No-DA *N* = 18)	–	Donor age	The DA group showed a significant increase in plaque volume ($P < 0.001$) at 1 year post-HTx compared to baseline. The frequency of angiographic new or progressive CAV in any coronary artery was likely to be higher in the DA group than in the DA-free group, this difference was not significant ($P = 0.069$)
Clerkin *et al.* (2016) [44]	HT recipients including 1 re-HTx	Retrospective cohort study	*N* = 68	–	Rejection (AMR)/ primary graft dysfunction	Patients with late AMR and graft dysfunction had accelerated development of *de novo* CAV (50% at 1 year; hazard ratio, 5.42; $P = 0.009$), whereas all other groups were all similar to the general transplant population

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Galli *et al.* (2016) [45]	*De novo* HT recipients	Retrospective cohort study	*N* = 495	–	CMV infection/ gender mismatch/ rejection/donor age/lipids and cholesterol	CMV serology mismatch and CMV disease in the univariate analysis were not risk factors for CAV (respectively *P* = 0.97 and *P* = 0.12). However, in the multivariable proportional hazard regression analysis, CMV disease and rejection were borderline associated with an increased risk for CAV in (*P* = 0.06). Male donor gender was significantly associated with CAV (HR, 1.6; *P* = 0.001). There is an increasing risk on CAV related with older donors. Comparing with the reference group, the HR increased (donor age 30–39: HR = 1.5, *P* = 0.018; donor age 40–49: HR = 2.2, *P* = <0.0001; donor age 50–59: HR = 2.8, *P* < 0.0001) Cholesterol levels at 1 year were higher in the CAV cohort as compared with the CAV-free cohort
Solé-González *et al.* (2016) [51]	HT recipients	Retrospective cohort study	*N* = 119	20 ± 12 months	Anti-HLA-AB	Multivariate analysis showed that anti-HLA-AB was the only significant predictor of the combined endpoint: cardiovascular mortality, AMR, and CAV [hazard ratio (HR) 3.1; CI: 1.3–7.5; *P* = 0.01]
Lim *et al.* (2017) [52]	HT recipients with CAV in the first year post-HT	Retrospective cohort study	*N* = 297	5.6 ± 5.2 years	Donor age, recipient age, ischemic time, postoperative renal replacement therapy, lipids and cholesterol	Predictors of CAV included donor age (HR, 1.06, 95% CI: 1.03–1.10: *P* < 0.001), recipient age [1.03 (1.003–1.06); *P* = 0.03], ischemic time >240 min [3.15 (1.36–7.28), *P* = 0.007], postoperative renal replacement therapy (RRT) [7.1 (2.3–21.8); *P* = 0.001], and triglyceride level at 1 year post-HT [1.005 (1.002–1.008), *P* = 0.003]

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Peled *et al.* (2017) [53]	HT recipients	Retrospective cohort study	*N* = 166	9.6 ± 5.2 years	Gender mismatch	The female donor–male recipient group experienced a significantly higher rate of cardiac allograft vasculopathy (43% vs. 20%; *P* = 0.01)
Kransdorf *et al.* (2017) [20]	HT recipients	Multicenter Registry subanalysis	*N* = 14 328	6.8 years (4.4–9.6 years)	Gender, donor age, BMI and diabetes, ischemic cardiomyopathy, creatinine, lipids and cholesterol, CMV, recipient age, donor cigarette use, HLA-DR mismatch, immunosuppressant management	This analysis of the ISHLT registry aimed to develop a prediction risk model to identify the likelihood to develop CAV. Recipients risk factors included the following: male sex, previous ischemic cardiomyopathy, higher BMI, higher creatinine, hyperlipidemia, and being seronegative for CMV. Donor risk factors included the following: older age, male sex, higher BMI, higher creatinine, and hypertension, cigarette use, diabetes mellitus, and brain hemorrhage or stroke as cause of death. A higher degree of donor–recipient HLA-DR mismatch was present in recipients that developed CAV. Immunosuppressant management at hospital discharge was also significantly different in recipients who developed CAV, with less utilization of induction immunotherapy and higher utilization of cyclosporine and azathioprine
Wever-Pinzon *et al.* (2017) [21]	HT recipients	Multicenter Registry subanalysis	*N* = 52 995	10 years	Younger recipient age	The overall incidence of CAV-related death at 10 years after transplant was 2.8%. The risk of death caused by cardiac allograft vasculopathy (HR, 2.85; *P* < 0.01) was highest in the youngest recipients (18–29 years) compared with the reference group (50–59 years)
Jalowiec *et al.* (2017) [54]	HT recipients	Retrospective cohort study	*N* = 347	3 years	Gender mismatch	The study found a higher incidence of CAV during the first 3 years after HT surgery in the female-mismatch patients (the same group with more rejections)

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Clerkin *et al.* (2017) [17]	HT recipients	Prospective cohort study	*N* = 221	2–5 years	DSA	Analyzing the freedom from CAV (ISHLT CAV1 or greater) after transplantation, statistically there was no significant difference, although there was a suggestion that the CAV risk may be increased for patients with AMR with DSA compared with patients without DSA or AMR (HR = 1.55; 95% CI, 0.76–3.19; *P* = 0.23). This risk did not differ by class of DSA (*P* ¼ 0.37)
Guihaire *et al.* (2017) [57]	HT recipients	Retrospective single-center study	*N* = 261	99 and 40 months in Groups A and B	Donor age, hypertension, CMV mismatch	Two groups of HTx recipients: those receiving transplants from 1996 to 2004 (Group A, *n* = 120) and from 2005 to 2013 (Group B, *n* = 141). Donor age and cardiovascular risk factors including hypertension were not associated with the development of CAV, whereas CMV mismatch was associated with the development of CAV (*P* = 0.002). Freedom from CAV at 5 years was 64% and 61%, respectively (*P* = 0.367)
Leong *et al.* (2017) [55]	HT recipients	Retrospective cohort study	*N* = 257	1 year	Prolonged QT interval	Patients with QTc interval >500 ms had a significantly lower 1-year freedom from CAV development
Madan *et al.* (2017) [22]	*De novo* HT recipients	Multicenter Registry subanalysis	*N* = 35 054	5 years	Donor age	Adult recipients of hearts from early adolescent donors had a trend toward reduced CAV [hazard ratio: 0.80 (95% CI: 0.62–1.01); *P* = 0.071], when compared with recipients of hearts from adult donors in the usual age group up to 5 years of follow-up. This trend was present even after adjusting for confounders [hazard ratio: 0.80 (95% CI: 0.62–1.02); *P* = 0.076]

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Table 1. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean follow-up time	Risk factor	Outcome
Clemmensen *et al.* (2017) [56]	HT recipients	Retrospective cohort study	$N = 79$	Median 7.5 years	DSA	Authors found a strong relation between DSA presence and presence of ISHLT CAV grade ≥II (odds ratio (OR) 5.5, 95% 1.8–17.2, $P < 0.01$)
Das *et al.* (2017) [58]	Pediatric HT recipients	Retrospective cohort study	$N = 127$	13-year maximum	DSA	Multivariate analyses identified C1q binding DSA as an independent risk for CAV with a hazard ratio (HR) of 3.25 (95% CI of 1.33–7.93, $P = 0.0095$)
Madan *et al.* (2017) [22]	*De novo* HT recipients	Multicenter Registry subanalysis	$N = 472$	5 years	LVSD	Transplant recipients of improved-donor LVEF hearts were not at increased risk of developing CAV, with up to 5 years of follow-up compared with recipients of donor hearts with normal LVEF

HT, heart transplant, HTx, heart transplantation, sec, secondary measure, IVUS, intravascular ultrasound, AMR, antibody-mediated rejection, DSA, donor-specific antigen, ECMO, extracorporeal membrane oxygenation, re-HTx, heart retransplantation, HLTx, heart–lung transplantation, ICM, ischemic cardiomyopathy, SHLT, simultaneous heart–liver transplantation, TCMR, T-cell-mediated rejection, CAG, coronarography, DA, donor-transmitted atherosclerosis, CMV, cytomegalovirus, CAC, coronary artery calcium, LVSD, left ventricular systolic dysfunction, PCWP, pulmonary capillary wedge pressure.

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Table 2. Studies about pathology features for CAV.

Study	Patients included	Study type	Number of patients	Mean follow-up time	Pathology and analyzed features	Outcome
Devitt *et al.* (2013) [67]	Patients who fit the criteria for cardiac organ donation and HT recipients who died and had one of the major coronaries for analysis	Histopathologic study	*N* = 44	–	Neovascularization	The study characterizes the donor-derived benign intimal thickening (BIT). Transplants harvested at 1, 4, or 10 days post-transplant confirmed retention of BIT after transplantation. Image analysis of later transplants supported a hypothesis of carryover BIT in CAV. The more luminal CAV layer more closely resembled naturally occurring atherosclerosis
Cassar *et al.* (2013) [60]	HT recipients who have coronary angiography and IVUS	Retrospective cohort study	*N* = 53	>48 months	Plaque morphology and histopathological phenotype	Segments with CAV plaque on IVUS were analyzed by OCT for specific CAV morphological characteristics within the framework of three groups according to follow-up time after heart transplantation. The prevalence of atherosclerotic characteristics (eccentric plaques, calcification, and lipid pools), vulnerable plaque features (thin-cap fibroatheroma, macrophages, and microchannels), and complicated coronary lesions (intimal laceration, intraluminal thrombus, and layered complex plaque) significantly increased by the time from transplant
Huibers *et al.* (2014) [68]	Sample of coronary arteries in patients post-HT, patients with noncardiac death (both adults and children)		*N* = 51		Plaque morphology and histopathological phenotype	Histologic CAV type was significantly related with time after transplantation, age at transplantation, the amount of atherosclerotic disease, and the occurrence of infection. In addition, morphometric analysis revealed that higher histologic CAV types have a relatively larger intimal area, that is compensated for by expansive arterial remodeling of the artery
Huibers *et al.* (2015) [69]		Retrospective study	*N* = 56	–	Ectopic lymphoid structure and	Ectopic lymphoid structures (ELS) were related to survival after transplantation

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Table 2. Continued.

Study	Patients included	Study type	Number of patients	Mean follow-up time	Pathology and analyzed features	Outcome
	Sample of the proximal region of one of the major coronary arteries				immune monitoring	(P = 0.013) and histologic composition of CAV (P < 0.001). ELS contain B and T lymphocytes, macrophages, and antibody-producing [immunoglobulin (Ig) M and/or IgG] plasma cells. A subpopulation of B lymphocytes appeared to be cluster of differentiation (CD)20(+)CD27(+) memory B lymphocytes. The messenger RNA expression of TLO markers [lymphotoxin-β, and chemokine (C-C motif) ligand 19 and 21] was significantly higher in ELS than in the neointimal lesions
Okada *et al.* (2015) [61]	HT recipients with serial IVUS assessment at 1 and 12 months after HT	Retrospective cohort study	N = 100	Median follow-up 4.7 years	Coronary remodeling and prognosis	Paradoxical remodeling (i.e., vessel shrinkage) in the proximal LAD was associated with higher incidence of death and retransplantation [hazard ratio: 11.18; 95% confidence interval (CI): 2.39–83.23; P = 0.0015]. Mid- and distal LAD remodeling, and MIT change did not predict outcomes. Of note, pre-existing atherosclerosis did not predict outcome
Zheng *et al.* (2015) [62]	Patients who underwent coronary angiography and NIRS-IVUS imaging of the LAD and HT recipients	Retrospective cohort study	N = 55	–	Plaque morphology and histopathological phenotype	Maximum lipid core burden (maxLCB) was significantly greater among atherosclerotic patients than in transplant patients in both proximal and middle coronary artery segments, but not in the distal segment. There was a positive linear correlation between lipid core burden and maximum plaque burden in both groups, but atherosclerotic patients demonstrated a smaller maxLCB than transplant recipients among segments with plaque burden <40%. Among segments with a maximum plaque

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Table 2. Continued.

Study	Patients included	Study type	Number of patients	Mean follow-up time	Pathology and analyzed features	Outcome
						burden ≥40%, native atherosclerosis patients had a greater maxLCBI4 mm compared with transplant patients ($P = 0.015$). Calcification was present in 72.9% of native atherosclerosis and 14.7% of transplant segments ($P < 0.001$). Among the 165 analyzed segments, prevalence of lipid-rich plaque (LRP) with superficial attenuation (30.9% vs. 1.2%, $P < 0.001$) or calcified LRP (13.6% vs. 2.4%, $P = 0.03$) was significantly greater in native atherosclerosis compared with transplant patients. Conversely, the proportion of segments with non-LRP (46.4% vs. 11.1%, $P < 0.001$) was higher in transplant patients
Ichibori *et al.* (2016) [63]	HT recipients including re-HTx	Prospective cohort study	$N = 45$	1–16 years	Neovascularization	This study identifies microchannels as makers of neovascularization and coronary risk after transplant. The risks for microchannels were donor age [odds ratio, cytomegalovirus infection, diabetes, LDL cholesterol, and intimal volume. All microchannels were seen only in patients with intimal thickness >0.5 mm
Loupy *et al.* (2016) [70]	Explanted allografts from HT recipients who underwent retransplantation	Retrospective multicentre cohort study	40 explanted heart allografts patients and 402 biopsies	118 months	Antibody-mediated rejection	Explanted allografts with evidence of antibody-mediated rejection demonstrated higher endothelial and microvascular inflammation scores (0.89 ± 0.26 and 2.25 ± 0.28, respectively) compared with explanted allografts without antibody-mediated rejection (0.42 ± 0.11 and 0.36 ± 0.09, $P = 0.046$ and $P < 0.0001$, respectively). Antibody-mediated injury was observed in 62.1% of failing

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Table 2. Continued.

Study	Patients included	Study type	Number of patients	Mean follow-up time	Pathology and analyzed features	Outcome
						allografts with pure coronary arteriosclerosis and mixed (arteriosclerosis and atherosclerosis) pattern, while it was not observed in patients with pure coronary atherosclerosis ($P = 0.0076$)
Shan *et al.* (2016) [64]	HT recipients with and without history of rejection were compared with native atherosclerosis with OCT imaging of the LAD	Cohort study	$N = 120$	–	Segment level	Compared with patients with native atherosclerosis, patients with rejection history had similar intima areas but smaller external elastic lamina areas resulting in smaller lumen areas in distal segments and smaller lumen diameters in side branches. Compared with patients with native atherosclerosis, lesions in patients with HT were more homogeneous, involving the entire coronary vascular tree. Patients with rejection history had a higher prevalence of macrophages involving ≥1 quadrant in all three segments compared with patients with native atherosclerosis
Kitahara *et al.* (2016) [65]	Baseline and 1-year post-transplant IVUS in HT recipients	Retrospective cohort study	$N = 102$	4.7 years	Neovascularization	The proliferative periarterial small vessels group had greater progression of intimal thickening and a higher incidence of acute cellular rejection than the nonproliferative group, and the incidence of cardiac death over a median period of 4.7 years was significantly higher in the proliferative group than in the nonproliferative group
Huibers *et al.* (2017)	Coronary artery material available of patients that died after HT	Retrospective cohort study	$N = 56$	–	Ectopic lymphoid structure and immune monitoring	Plasma cells in ectopic lymphoid structures produce IgG and IgM antibodies; IgM levels are higher in patients with larger ectopic lymphoid structures; markers higher expressed in ELS are IL6, IL7, IL10, IL23, CD20, CXCR3, TNFα, IFNγ, and TGFβ

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Table 2. Continued.

Study	Patients included	Study type	Number of patients	Mean follow-up time	Pathology and analyzed features	Outcome
Cheng *et al.* (2016) [66]	HT recipients with annual angiograms and at least one immune monitoring assay	Retrospective cohort study	$N = 240$	Clinical follow-up = 4.6 years, angiographic follow-up = 4.0 years	Ectopic lymphoid structure and immune monitoring	Elevated immune monitoring (IM), as measured by adenosine triphosphate (ATP) release from activated lymphocytes, has been suggested to represent an under-immunosuppressed state. In multivariate analysis, elevated peak IM assay was found to be associated with angiographic CAV1, with a hazard ratio of 1.695 (95% CI: 1.029–2.793) ($P = 0.038$). Treated rejection trended toward being associated with angiographic CAV1, with a hazard ratio of 1.804 (95% CI: 1.000–3.256) ($P = 0.050$). Ischemic etiology, diabetes, pretransplant peak panel-reactive antibodies ≥10%, donor age, high-risk CMV mismatch, mTOR inhibitor use at 6 months, and ischemic time were not found to be statistically associated with angiographic CAV1
Chatterjee *et al.* (2017) [72]	Tissue specimens from a total of 56 cardiac transplants were used in this study	Retrospective cohort study	56 allografts with CAV, 49 native failed hearts, and 25 autopsy specimens	–	Graft-infiltrating B cells	B-cell infiltration was observed around coronary arteries in 93% of allograft explants with CAV. Comparatively, intragraft B cells were less frequent and less dense in the intraventricular myocardium from where routine biopsies are obtained. Plasma cells and macrophages were also detected in 85% and 95% of explants, respectively. Remarkably, B-cell infiltrates were not associated with circulating donor-specific antibodies (DSA) or prior episodes of antibody-mediated rejection

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Table 2. Continued.

Study	Patients included	Study type	Number of patients	Mean follow-up time	Pathology and analyzed features	Outcome
						(AMR). Among all B-cell clones generated from three explants with CAV, a majority secreted natural antibodies reactive to multiple autoantigens and apoptotic cells, a characteristic of innate B cells

HT, heart transplantation; CAV, cardiac allograft vasculopathy; LAD, left anterior descending artery; IVUS, intravascular ultrasound; NIRS, near-infrared spectroscopy; OCT, optical coherence tomography.

studies and three of them derived from multicenter large registries.

Discussion

In this paper, we performed a systematic review including original research articles dealing with risk factors, pathology, prevention, and treatment of CAV. Our aim was to summarize the evidences gained in the 2011–2017 period, and provide clinicians with up-to-date evidence, which could improve clinical practice in reducing the negative impact of CAV on post-transplant outcomes.

We selected eighty articles focusing on the four themes we identified per study design. Despite the fact that the vast majority of available "evidence" derives from single-center and retrospective studies, large registries overall confirm most of the findings of the smaller studies, in particular for the identification of CAV risk factors. The few prospective studies available, some of which multicenter and/or randomized, are focused on interventions for CAV *prevention*, while we regrettably were unable to find randomized studies supporting any strategy for CAV *treatment*: the only evidences available in this theme weakly stand on retrospective cohort studies. Regardless of the weakness of most studies, the consistency of some findings did provide a reasonable weight of evidence supporting meaningful advancement in the understanding of CAV.

Risk factors for CAV

The evidence from the analyzed studies supports a meaningful role in favoring CAV by donor age, DSA and AMR, metabolic abnormalities, donor/recipient gender mismatch, and, despite some controversies, CMV infection. Neutral effect was found for primary graft dysfunction, while combined heart–lung transplantation and heart–liver transplantation appear to be protective for CAV development.

Donor age, when analyzed, is consistently reported to be associated with CAV detection [12,18,20,21,23,24,28,30,33,36–38,43,45,50,59]. This concept is not novel [106] and is mainly related to the risk of transmission of donor coronary lesions to the recipient, as also suggested by studies finding that male donors – more likely to bear subclinical coronary lesions – may be associated with CAV development [45]. The selected studies, however, do not clarify the old-times debate whether donor-derived lesions from older grafts are more likely to progress than *de novo*

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Table 3. Characteristics of included studies on cardiac allograft vasculopathy prevention.

Study	Inclusion criteria	Study type	Number of patients	Mean age (year)	Mean follow-up time	Medication used	Outcome
Potena *et al.* (2011) [73]	*De novo* HT recipients	Open-label, single-site, prospective, randomized study	$N = 52$	54 ± 11 and 55 ± 10, respectively	1 year	Fluvastatin 20 mg ($N = 26$) or 80 mg ($N = 26$)	Early LDL levels and average LDL burden were lower in the maximal-dosing arm ($P < 0.05$). Few patients developed an increase in MIT of 0.5 mm, with numerical prevalence in the titrated-dosing arm [3 (12.5%) vs. 1 (5%); $P = 0.3$] Intimal volume increased in the titrated-dosing ($P < 0.01$) but not in the maximal-dosing arm (P: 0.1), which accordingly showed a higher prevalence of negative remodeling (P: 0.02)
Topilsky *et al.* (2012) [82]	*De novo* HT recipients	Nonrandomized, retrospective, single-center study	$N = 103$	48.6 ± 12.6 and 50.2 ± 14.2, respectively	–	Conversion CNI to SRL ($N = 45$) CsA ($N = 36$) TAC ($N = 22$)	Plaque index progression (plaque volume/vessel volume) was attenuated in the SRL group (0.7 ± 10.5% vs. 9.3 ± 10.8%; $P = 0.0003$) Five-year survival was improved with SRL (97.4 ± 1.8% vs. 81.8 ± 4.9%; $P = 0.006$), as was the incidence of all-cause mortality (5.6% vs. 18.6%; $P = 0.01$)
Arora *et al.* (2012) [74]	Maintenance HT recipients entering the study after year 1	Subgroup analysis of a randomized controlled trial	$N = 78$	56.2 ± 12.1 and 60.7 ± 9.1, respectively	–	EVE + low-dose CNI ($N = 30$) Standard CNI ($N = 48$)	No significant difference in volumetric CAV progression between the EVE and control group by measurement of Δ plaque index (1.9 ± 3.8% and 1.6 ± 3.9%, respectively, $P = 0.65$) Significant increase in calcified (2.4 ± 4.0% vs. 0.3 ± 3.1%; $P = 0.02$) and necrotic component (6.5 ± 8.5% vs. 1.1 ± 8.6%; $P = 0.01$) in EVE patients vs standard CNI

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Table 3. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (year)	Mean follow-up time	Medication used	Outcome
Guethoff *et al.* (2013) [75]	*De novo* HT recipients	Follow-up analysis of a randomized controlled trial	*N* = 60	55	9.1 ± 3.3 and 8.8 ± 4.0 years, respectively	TAC + MMF (*N* = 30) CsA + MMF (*N* = 30)	Freedom from CAV ISHLT ≥ CAV1 onset was 96.4% in the TAC group vs. 88.5% in the CsA group (log-rank 1.2, *P* = 0.281) after 1 year, 64.0% in the TAC group vs. 36.0% in the CsA group (log-rank 3.0, *P* = 0.085) after 5 years; and 45.8% in the TAC group vs. 8.0% in the CsA group (log-rank 9.0, *P* = 0.003) after 10 years
Kaczmarek *et al.* (2013) [76]	*De novo* HT recipients	Randomized controlled trial	*N* = 78	49.6 ± 13.2, 48.3 ± 12.3, 55.1 ± 8.6, respectively	5 years	TAC/MMF (*N* = 34) TAC/SRL (*N* = 29) SRL/MMF (*N* = 15)	Freedom from CAV at 5 years was highest in the SRL/MMF group (93.3%) compared with TAC/MMF (73.5%) and TAC/SRL (80.8%), not significant
Masetti *et al.* (2013) [83]	*De novo* HT recipient and long-term HT recipients with 0–1 year and 1–5 years paired IVUS	Retrospective analysis	*N* = 143 (*N* = 91 early, *N* = 52 late)	50.1 ± 9.2, 51.7 ± 11.7 and 55.1 ± 10.7, 55.6 ± 8.8, respectively	1 and 5 years	Early cohort: EVE (*N* = 20) MMF (*N* = 71) Late cohort: EVE (*N* = 19) MMF (*N* = 33)	MMF treatment was associated with higher occurrence of early CAV than EVE, both by ITT (22.8% vs. 5%; *P* = 0.04) and on-treatment (24.8% vs. 4.7%; *P* = 0.02) analyses No significant differences between EVE and MMF patients in the occurrence of late CAV (31.5% vs. 27.2%, respectively; *P* = 0.74), average MIT change (0.34 ± 0.53 mm vs. 0.27 ± 0.36 mm; *P* = 0.57), and average change of all vascular volume parameters
Vrtovec *et al.* (2013) [87]	HT recipients who presented with	Retrospective cohort study	*N* = 52	50 ± 15	1 year	G-CSF (*N* = 24)	Rejection or progressive allograft vasculopathy occured

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Table 3. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (year)	Mean follow-up time	Medication used	Outcome
	leukopenia (WBC count <2.5 × 10^9 cells/l) in the absence of active infection, rejection, or malignancy						in two patients in the G-CSF group and in 15 patients in the non-G-CSF group (8% vs. 53%; $P < .01$) Multivariate analysis showed for G-CSF therapy an OR of 0.09 (CI: 0.01–0.52; $P = 0.007$)
Matsuo *et al.* (2013) [84]	*De novo* HT recipients. Conversion if impaired renal function likely secondary to CNIs, CAV, severe CNI-related side effects, or those interested in conversion 3–6 months after transplantation.	Retrospective cohort study	$N = 146$	56 ± 11 and 53 ± 14, respectively	2.8 years	Conversion from CNIs to SRL ($N = 61$) CNI ($N = 85$)	A significantly less plaque volume progression in favor of SRL was found in patients who were converted early (−0.67 mm^3/mm/year; 95% CI, −1.10 to −0.25) Significant differences of necrotic core ($P = 0.02$ for interaction) and dense calcium volume progression ($P = 0.03$ for interaction) were found in favor of CNI in the late group (0.15 mm^3/mm/year, 95% CI: 0.00–0.29; and 0.10 mm^3/mm/year, 95% CI: 0.03–0.17, respectively)
Nytrøen *et al.* (2013) [88]	Clinically stable HT recipients	Prospective cohort study	$N = 43$	51 ± 16	1 year	High-intensity interval training ($N = 20$)	The rate of CAV progression was significantly lower in the high-intensity interval training group compared with controls – a smaller mean increase [Δ (95% CI)] in percent atheroma volume: 0.9% [0.3%–1.9%] vs. 2.5% [1.6%–3.5%] ($P = 0.021$); Δ total atheroma volume: 0.3 [0.0–0.6] mm^3/mm vs. 1.1 [0.6–1.7] mm^3/mm

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Table 3. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (year)	Mean follow-up time	Medication used	Outcome
							(P = 0.020); and Δ total plaque volume: 8.0 [0.3–15.7] mm^3 vs. 25.6 [14.8–36.4] mm^3 (P = 0.011)
Kobashigawa *et al.* (2013) [80]	*De novo* HT recipients	Subgroup analysis of a randomized controlled trial	N = 189	51.1 ± 11.8 and 49.5 ± 13.1, respectively	1 year	EVE (n = 88) MMF (n = 101)	EVE was significantly more efficacious than MMF in preventing CAV as measured by IVUS among heart transplant recipients after 1 year
Luo *et al.* (2014) [89]	*De novo* HT recipients	Prospective observational study	N = 132	43.6 ± 18	–	Statins (N = 74)	Overall 5-year survival was 85.6%. Cause of death was mainly related to cardiovascular events (13; 68.4%) Seven patients were retransplanted due to severe CAV
Andreassen *et al.* (2014) [77]	*De novo* HT recipients	Randomized controlled trial	N = 115	51 ± 12.9 and 51.5 ± 12.3, respectively	1 year	EVE (N = 56) CsA (N = 59)	Incidence of CAV at month 12 was significantly lower in the EVE group (50.0 ± 7.4%) than in the CsA group (64.6 ± 6.9%) (P = 0.003)
Guethoff *et al.* (2015) [85]	*De novo* HT recipients	Three prospective, open-label, single-center studies	N = 125	50 ± 12 and 51 ± 13	7.6 ± 1.2 and 6.8 ± 2.3 years	Low TAC/SIR (N = 61) TAC/MMF (N = 64)	No difference between the treatment groups regarding CAV. The freedom from ISHLT CAV grade ≥1 in the low TAC/SIR group vs TAC/MMF group was 94.6% vs. 91.7% (P = 0.489), 78.6% vs. 68.3% (P = 0.141), and 55.4% vs. 60.0% (P = 0.922) after 1, 5, and 8 years of follow-up

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Table 3. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (year)	Mean follow-up time	Medication used	Outcome
							There was no statistical difference in severity of CAV in the low TAC/SIR group versus the TAC/MMF group ($P = 0.618$)
Arora *et al.* (2015) [78]	*De novo* HT recipients	Randomized controlled trial	$N = 95$	49.9 ± 13.1	1 year	EVE ($N = 47$) CsA ($N = 48$)	Significantly reduced CAV progression in EVE group as compared to the CsA group with a mean increase in MIT of 0.03 ± 0.06 vs. 0.08 ± 0.12 mm, respectively ($P < 0.01$)
Wang *et al.* (2015) [90]	*De novo* HT recipients	Retrospective cohort study	$N = 13$	55 and 47.5, respectively	–	Basiliximab induction ($N = 7$)	In the control group, vessel volume exhibited positive remodeling (increase in volume growth of 49.39 mm^3), whereas in the basiliximab group, the effect was reversed (negative remodeling: −4.17 mm^3) ($P = 0.051$)
Azarbal *et al.* (2016) [91]	*De novo* HT recipients with performed baseline and 1 year IVUS	Retrospective cohort study	$N = 103$	55.8 ± 12.6	–	ATG induction ($N = 46$)	Coronary plaque progression was attenuated in ATG group compared with the control group changes in maximal intimal area (1.0 ± 1.2 vs. 2.3 ± 2.6 mm^2; $P = 0.001$), maximal percent stenosis (6.3 ± 7.9% vs. 12.8 ± 12.3%; $P = 0.003$), MIT (0.2 ± 0.2 vs. 0.3 ± 0.3 mm; $P = 0.035$), and plaque volume per 1 mm coronary segment (0.5 ± 0.7 vs. 1.0 ± 1.3 mm^3/mm; $P = 0.016$)
Watanabe *et al.* (2016) [43]	*De novo* HT recipients	Retrospective analysis	$N = 63$	41.0 ± 15.7 and 35.1 ± 12.5	1 year	Conversion tot EVE ($N = 24$)	Greater increase in MIT in the MMF group at the 1-year

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Table 3. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (year)	Mean follow-up time	Medication used	Outcome
						Maintained on MMF (N = 39)	follow-up (P = 0.039), while MIT in the EVE group did not change between study entry and the 1-year follow-up. The MMF group had a higher incidence of increased MIT (≥0.3 mm) (4.2% in the EVE group vs. 25.6% the MMF group, P = 0.029)
Greenway *et al.* (2016) [92]	*De novo* HT recipients transplanted during childhood or adolescence (age 5–18)	Retrospective cohort study	N = 964	13.24 ± 3.29 and 12.0 ± 3.64, respectively	–	Statins (N = 317)	No significant difference in overall survival up to 10 years post-transplant in children who received early statin therapy there was compared with children who were not treated with a statin (P = 0.34) A significantly higher incidence of rejection in the statin-treated group of children after 1 year of follow-up (P = 0.0008) The incidence of any degree of CAV was likewise not associated with statin use (P = 0.48)
Mirza *et al.* (2016) [79]	15 *de novo* HT recipients from the *Schedule* trial	Randomized controlled trial	N = 15	51 ± 10 and 48 ± 15	1 year	Conversion to EVE (N = 8) CsA (controls) (N = 7)	The EVE group showed a significant increase in FoxP3 (e.g. Treg) density from baseline to time of 1-year follow-up [median (IQR) = 4.78×10^{-7} Tregs/μm^2 (20.36), P = 0.046) while controls showed no significant change [median (IQR) = 3.07×10^{-7} Tregs/μm^2 (6.45), P = 0.116]
			N = 68		4 years	TAC (N = 68)	

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Table 3. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (year)	Mean follow-up time	Medication used	Outcome
Shuker *et al.* (2017) [141]	HT recipients who use TAC, with follow-up at 1 and 4 years after HT	Prospective observational study		50 (30–61) CAV progression 49 (24–65) No CAV progression			No significant difference in the proportion of patients with high tacrolimus intrapatient variability in the group that progressed to higher grades of CAV (n = 15) versus the group without progression (n = 71) at 4-year follow-up (60.0% vs. 47.9%; P = 0.57)
Kim *et al.* (2017) [93]	All HT recipients	Retrospective cohort study	N = 120	54.9 (47.3, 62.2) and 55.0 (44.1, 63.1), respectively	7 years	Aspirin (N = 59)	Aspirin therapy was associated with a lower rate of moderate or severe CAV at 5 years. Event-free survival was 95.9% for patients with and 79.6% for patients without aspirin exposure (log-rank $P < 0.005$) There was a powerful inverse association between aspirin use and moderate-to-severe CAV (adjusted hazard ratio 0.13; 95% CI: 0.03–0.59)
Fearon *et al.* (2017) [81]	*De novo* HT recipients who were >12 years of age and had a serum creatinine concentration of <2.0 mg/dl	Randomized controlled trial	N = 96	55 ± 15 and 52 ± 17, respectively	1 year	Ramipril (N = 47) Placebo (N = 49)	Plaque volumes at 1 year were similar between the ramipril and placebo groups (162.1 ± 70.5 mm^3 vs. 177.3 ± 94.3 mm^3, respectively; P = 0.73). Patients receiving ramipril had improvement in microvascular function as shown by a significant decrease in IMR (21.4 ± 14.7–14.4 ± 6.3; P = 0.001) and increase in CFR (3.8 ± 1.7–4.8 ± 1.5; P = 0.017), from baseline to

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Table 3. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (year)	Mean follow-up time	Medication used	Outcome
							1 year. EPCs decreased significantly at 1 year in the placebo group but not in the ramipril group
Rossano *et al.* (2017) [142]	*De novo* pediatric HT recipients	Retrospective review and propensity-matched analysis	$N = 2080$	7.37 ± 6.27 and 6.79 ± 6.23, respectively	1 year	SRL ($N = 144$)	SRL and non-SRL patients had similar survival in the overall cohorts and in the propensity-matched analysis There was a trend toward increased time to CAV ($P = 0.09$) and decreased time to infection ($P = 0.05$) among sirolimus-treated patients in the overall cohort ($P = 0.19$) but not in the propensity-matched cohort ($P = 0.17$)
Yardley *et al.* (2017) [132]	HT recipients with a stable clinical condition	Follow-up analysis of a randomized study	$N = 137$	49.1 ± 16.5	5 years	HIT ($N = 67$) Controls ($N = 70$)	This follow-up analysis showed that the group initially randomized to HIIT had a decline in peak VO_2, after the initial rise at year one, while it decreased along the entire study period in the control group. Despite initial benefit on CAV at 1 year in the HIT group, at 5 years no difference between study groups was found

HT, heart transplant; PV, plaque volume; SL, segment length; EVE, everolimus; SRL, sirolimus; CsA, calcineurin inhibitors; MMF, mycophenolate mofetil; MIT, maximal intimal thickness; HIIT, high-intensity interval training; mTORI, mammalian target of rapamycin inhibitors (= EVE/SRL); EEM, external elastic membrane; VVI, vessel volume index; PVI, percent plaque volume index; Re-HT, re-heart transplantation; CFR, coronary flow reserve.

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Table 4. Characteristics of included studies on cardiac allograft vasculopathy treatment.

Study	Inclusion criteria	Study type	Number of patients	Mean age (yr)	Mean follow-up time	Type of intervention	Outcome
Lee *et al.* (2012) [94]	*De novo* HT recipients with CAV who underwent PCI with a BMS or DES and had angiographic evidence of binary restenosis	Retrospective cohort study	*N* = 83 (*N* = 26 ISR, *N* = 57 no ISR)	53.7 and 56.9, respectively	7 years	First PCI (*N* = 83) Re-PCI (*N* = 17) Re-HT (*N* = 3) CABG (*N* = 1)	Lower freedom from the composite endpoint of death, myocardial infarction, or repeat HT in patients with ISR (27.9% vs. 63.2%, *P* = 0.006) Lower survival in ISR patients (38.5% vs. 84.2%, *P* < 0.001)
Lee *et al.* (2012) [94]	Pediatric patients (<19 years) who underwent PCI for CAV	Retrospective chart review	*N* = 12	15.1 ± 3.5	7.1 ± 4.9 years	BMS (*N* = 5) DES (*N* = 7)	Total survival at mean follow-up was 71.3%. Repeat HT was performed in 5/12 (41.7%)
Lee *et al.* (2012) [94]	*De novo* HT recipients with CAV who underwent first-vessel PCI	Retrospective cohort study	*N* = 105	54.34 and 56.49, respectively	–	BMS (*N* = 47) DES (*N* = 58)	BMS and DES were associated with similar rates of MACE (59.6% vs. 40.8%, *P* = 0.33), death (40.4% vs. 31.8%, *P* = 0.46), MI (11.3% vs. 12.2%, *P* = 0.98), and target vessel revascularization (26.5% vs. 25.5%, *P* = 0.76)
Prada-Delgado *et al.* (2012)	*De novo* HT recipients with significant CAV (CAV2 and CAV3)	Retrospective cohort study	*N* = 43	53.1 ± 12.5	3.0 ± 2.4 years	BMS (*N* = 4) DES (*N* = 4) CABG (*N* = 4)	MACE occured in 3/12 (25.0%) patients who underwent revascularization. In 12/20 of the nonrevascularizible patients (65%, *P* = 0.012), MACE occured
Azarbal *et al.* (2014) [100]	*De novo* HT recipients who presented with angina pectoris and/or a positive stress test and had hemodynamically significant angiographic stenosis >70%	Retrospective cohort study	*N* = 21	–	549 ± 221 days	EES	The use of EES in patients with TCAD is safe, associated with low incidence of major adverse cardiac events, no incidence of stent thrombosis, no deaths, and low rates of TLR or TVR. The incidence of TLR in OHT patients treated with EES is comparable to rates reported in patients with native coronary artery disease
Park *et al.* (2014) [98]	*De novo* HT recipients with CAV who underwent PCI for a	Retrospective chart review	*N* = 45	56 ± 7, 54 ± 11	–	BMS (*N* = 23) DES (*N* = 15)	No significantly different risk of cardiovascular outcomes for BMS versus DES (HR = 0.265,

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Table 4. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (yr)	Mean follow-up time	Type of intervention	Outcome
	previously untreated coronary lesion			and 40 ± 14, respectively		BMS/DES (*N* = 7)	CI: 0.042–1.673, *P* = 0.16) Mean luminal area ratio was higher in DES group (0.7957 vs. 0.4810 *P* = 0.0037)
Agarwal *et al.* (2014) [99]	*De novo* HT recipients with any coronary artery stenosis ≥30% on any coronary angiogram	Retrospective cohort study	*N* = 393	52.3 ± 12.3	11.7 ± 5.5 years	PCI (*N* = 90) CABG (*N* = 6) Re-HT (*N* = 4)	Reduction in the adjusted risk for mortality in PCI compared to non-PCI group at 2-year follow-up (adjusted OR: 0.26; 95% CI: 0.08–0.82) and at 5-year follow-up (adjusted OR: 0.28; 95% CI: 0.09–0.93) 46/90 patients who underwent PCI died, of which 20 to CVD. 29 Re-PCIs were performed 4/6 patients who underwent CABG died 1/4 patients who underwent re-HTx died
Jeewa *et al.* (2015) [101]	*De novo* pediatric HT recipients	Retrospective cohort study	*N* = 3156	13.4 ± 5.95	–	PCI (51 lesions in 28 pt) Balloon angioplasty (*N* = 13 lesions) Stent (*N* = 28 lesions)	Freedom from graft death post-PCI was 89%, 75%, and 61% at 1, 3, and 12 months 13/28 patients underwent re-HT after PCI 8/28 patients died
Dasari *et al.* (2015) [102]	Patients who underwent PCI to a non-bypass graft	Retrospective cohort study	*N* = 1 897 328 (*N* = 542 HT *N* = 1 896 786 no HT)	58.2 ± 15.4 and 64.0 ± 12.1, respectively	72 h	PCI	Similar rates of death (1.3% vs. 1.1%, *P* = 0.362), myocardial infarction (3.2% vs. 2.3%, *P* = 0.25), the composite endpoint of in hospital death/myocardial infarction/stroke (4.4% vs. 3.3%, *P* = 0.08), and bleeding events at 72 h (0.7% vs. 1.2%, *P* = 0.972) between the HT and non-HT groups

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Table 4. Continued.

Study	Inclusion criteria	Study type	Number of patients	Mean age (yr)	Mean follow-up time	Type of intervention	Outcome
Goldraich *et al.* (2016) [105]	*De novo* HT recipients who developed CAV	Retrospective cohort study	*N* = 4595	47.0 and 55.0, respectively	5 years	Re-HT (*N* = 65) Medical management (*N* = 4530)	No difference in survival between re-HT and medical management at 9 years (55% in retransplant vs. 51% in medical management, *P* = 0.88) Re-HT group had better survival versus medically managed patients with systolic graft dysfunction at 1 year
Turner *et al.* (2016) [103]	Pediatric HT recipients who underwent PCI for a diagnosis of CAV	Retrospective chart review	*N* = 23	16.4	10.4 months	Balloon angioplasty (*N* = 3) BMS (*N* = 2) DES (*N* = 18)	During the follow-up, 7/13 patients had re-PCI performed, 2/23 patients died, and 5/23 were retransplanted Freedom from death or retransplant by Kaplan–Meier analysis was 54% at 1 year
Kuroda *et al.* (2017) [104]	All HT recipients who were screened for CAV	Retrospective chart review	*N* = 96	–	83.0 ± 60.4 months	PCI with DES (*N* = 3) CABG (*N* = 2)	No perioperative complications occurred No angiographic restenosis occurred in two patients at 31 and 36 months after PCI All grafts were patent as assessed by use of CAG at 34 and 5 months after CABG
Cheng *et al.* (2017) [143]	HT recipients who underwent PCI with an EES for CAV	Retrospective cohort study	*N* = 48	52.7 ± 11.9	30.7 ± 18.8 months	PCI with EES (*N* = 132 stents)	1-, 2-, and 3-year freedom from death, nonfatal MI, re-HT, and VAD placement were 87.2 ± 4.9%, 82.3 ± 5.7%, and 75.8 ± 6.9%, respectively seven patients died, four patients had a re-HT, one patient had a VAD, four patients had a nonfatal MI

HT, Heart transplantation; ISR, in-stent restenosis; TVR, target vessel revascularization; MACE, major adverse cardiac event; EES, everolimus-eluting stent; MLA, mean luminal area; MLA ratio, follow-up MLA/baseline MLA; re-HT, re-heart transplantation; VAD, ventricular assist device.

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lesions from younger grafts [107]. In this regard is worth noting a study selected in the descriptive pathology section (Table 2) [67] reporting a specific morphology for donor-derived intimal hyperplasia, defined "benign" by the authors, and *de novo* intimal hyperplasia, more rich in inflammatory cells, and likely to be associated with rapidly progressing lesions. Interestingly, in pediatric patients, increasing recipient age is more strongly associated with CAV risk than donor age, which appears to carry an independent increased risk only for donors older than 18 [18]. Altogether, these findings support the concept that increased donor age may portend a risk *per se*, and minor transmitted coronary lesions may not impair the overall transplant benefit when allocated to candidates with an immediate adverse prognosis without transplantation. Donor–recipient gender mismatch and prolonged QT in donor ECG represent additional donor features associated with CAV development with a meaningful level of evidence. While the effect of gender mismatch could be explained by immune-mediated injury against gender-specific antigens [53], prolonged QT is associated with cerebral hemorrhage as cause of death of the donor, a condition known to increase catecholamine stress on donor heart, and probably endothelial injury [55].

As opposed to the consensus on donor age, the role of recipient age in favoring CAV development is controversial. Johansson *et al.* [36] found that age of recipients was associated with angiographic CAV only in univariate analysis, with just 1% relative risk increase per recipient year, and Milaniak *et al.* [32] found no significance for recipient age as risk factor for CAV. Kobayashi *et al.* [18], on the other hand, showed that recipient age was significantly associated with increasing risk for CAV in children. Nevertheless, older recipients do bear a higher risk for overall poor outcome. In a study focused on late CAV progression, our group found an independent effect of age on the risk of fatal and nonfatal cardiovascular events, but not on the risk of imaging-detected progression of CAV [108]. Similarly, a large study from Tjang *et al.* [109] found that post-transplant outcome in older recipients (>55 years) is less favorable than in younger recipients (<55 years), with CAV being one of the main causes for late mortality. Altogether, these data can be interpreted by the concept that although recipient age may not be directly involved in the process of coronary lesions progression, older recipients bear more often multiple comorbidities and metabolic abnormalities that are related to increased risk of "standard" cardiovascular disease, and thus poor outcome. In support of this concept, older recipients with a low comorbidity profile show good outcomes after transplantation [37].

Alloimmunity is the main drive of CAV development, as already noted by the pivotal study by Russel *et al.* [110] finding that CAV lesions are confined to the allograft, abruptly ending at the organ suture lines. More recently, DSA and manifestations of AMR have been extensively investigated as measurable markers of the immune activation against vascular alloantigens. In our review, we found that eleven of twelve studies supported DSA/AMR involvement with CAV development [17,25,34,39,44,47–49,51,56,58], with the only neutral study [14] likely underpowered by the very small sample size. Anti-HLA DSA class II and combination of class I and class II were found associated with angiographic CAV [47,48], while non-DSA HLA antibodies did not appear to bear meaningful risk [34]. These data reinforce results from older studies [111,112], and the parallel findings that pathology-defined AMR is associated with CAV [25,44]. The specific impact of cellular rejection on CAV risk remains debated, with three small studies that found an association [38,50,62] and a large one that did not [45]. These discrepancies may be explained by the known low reproducibility of biopsy-based diagnosis of cellular rejection or by the variable timings of CAV detection [8]. Altogether, available evidence clearly supports the concept that acute episodes of rejection may favor the onset of CAV, with DSA playing a pathogenic role by targeting HLAs expressed on the coronary endothelial layer [113,114].

A large bulk of debated evidences in the past supported a role for infections, in particular CMV, in CAV development [115] largely based on the findings that aggressive anti-CMV strategies appeared to reduce early CAV [116]. Recent studies, all based on retrospective cohort analyses, confirmed the uncertainties, providing suggestive, but weak, evidence supporting a role for CMV in CAV. In a large single-center retrospective cohort of patients receiving heterogeneous anti-CMV strategies, Johansson *et al.* [36] found that not only CMV disease but also subclinical infection reduced the CAV-free survival. In a current and homogeneously managed cohort of patients, Delgado *et al.* [50] confirmed these findings by showing that CMV disease and subclinical high-titer viremia are independently associated with the development of CAV. On the other hand, Galli *et al.* [45] found that in multivariable analysis the association between CMV disease and increased in risk of CAV did not reach full statistical significance, while in children it was found that CMV serology had no association with development of CAV [117].

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Toxoplasma serology has also been investigated as potentially associated with CAV in two studies. However, both showed no impact of toxoplasma on CAV development [27,35], but one found that the D+/R− recipients showed a lower 5-year survival rate than the D−/R− group.

Metabolic abnormalities including diabetes, insulin resistance, and dyslipidemia are known and established risk factors for CAV development [118]. Extensive use of statins in clinical practice has made the impact of cholesterol on CAV development less detectable in recent studies, than it was in historical series. In addition, a subanalysis of a large randomized trial on everolimus revealed that the impact of cholesterol on CAV may be influenced by the immunosuppressive strategy: Only in mycophenolate arm, low-density lipoprotein (LDL) concentrations were proportionally associated with intimal thickness increase, despite everolimus patients showed more often hypercholesterolemia [80]. This finding suggests that everolimus-induced hyperlipidemia may not be harmful [119] and that in transplant recipients cholesterol concentration *per se* may no longer represent a reliable marker of lipid-induced injury to vessel wall. In this context, more sophisticated measurements of cholesterol activity have been recently proposed, such as cholesterol efflux capacity [42], but the robustness of these findings and the clinical applicability still need to be confirmed [11].

Markers of resistance to insulin, on the other hand, are consistently identified as associated with CAV development and likely identify an undertreated condition in current clinical practice. In particular, among the studies we retrieved, we found that overt diabetes [41], high fasting glucose and elevated body mass index [32], and high concentration of triglycerides [108] – all markers of insulin resistance – are consistently associated with CAV development.

Kransdorf *et al.* accomplished a commendable result in integrating all these major risk factors associated with CAV in three prediction models derived from the ISHLT registry, developing a CAV risk calculator. In this paper, authors weighted the donor- and recipient-related factors at the moment of transplant in an algorithm allowing to predicting the risk of CAV 7 years after transplant. Of note, in these models, immunosuppressive therapy did not play any role in reducing CAV risk [20].

Pathology of CAV

Availability of advanced imaging tools such as virtual histology intravascular ultrasound (VH-IVUS) and optical coherence tomography (OCT) allowed meaningful improvement in the *in vivo* descriptive pathology of CAV. Although it was not among our scopes to revise studies dealing with allograft coronary imaging *per se*, we included in our review those IVUS and OCT studies providing novel insights on the specific pathophysiological features of CAV.

Using VH-IVUS, Matsuo *et al.* [84] described the multilayer appearance of coronary plaque in CAV patients. Multilayer appearance was associated with increase in plaque volume, necrotic core volume, and dense calcium volume and was found to be a potential predictor of plaque progression. OCT imaging also revealed that coronary microchannels, which indicate intimal neovascularization, are a novel and relevant morphological marker of CAV progression [63]. OCT imaging also confirmed typical features of CAV [64]. When compared with native atherosclerosis, CAV lesions were more homogeneous along the coronary tree and presented more macrophage-rich lesions [64]. Using a combined approach with IVUS and OCT, Cassar *et al.* [60] analyzed the time-dependent change of CAV lesions morphology. While uncomplicated "simple" intimal hyperplasia was a feature of early-stage CAV, longer after transplant authors describe increasing prevalence of complicated coronary lesions (i.e., thin fibrous cap, intimal laceration, thrombi) and of other plaque morphologies resembling the typical native atherosclerotic lesions of nontransplant patients. Similar findings have been reported in a postmortem study: Huibers *et al.* [68] who described inflammatory lesions in patients dying in the first years after transplant and fibrous lesions with outward remodeling in patients long after transplant. In a more recent series, Stanford group found that early constrictive remodeling portend an adverse prognosis [61]. The relevance of the outward remodeling, on the other hand, has been highlighted by our group, finding that increase in vessel volume is associated with higher risk of cardiovascular events long term after transplant [108].

Pathological correlates of the tight link between immune activation and CAV have been confirmed by several investigations. As already discussed, DSA and AMR are important risk factors for CAV, which can be viewed as the outcome of the chronic inflammatory injury mediated by non-complement-dependent mechanisms [114], inflammatory cytokine release [120,121], suggesting that cardiac allograft recipients have a persistent immune activation long term after transplantation. Pathological evidence of this link has been shown by Loupy *et al.* [70] who, analyzing postmortem heart

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allografts, found that pathology evidence of AMR was more often associated with specific phenotypes of coronary lesions, characterized by inflammation and myointimal hyperplasia, while it was not observed in patients with morphology of pure coronary atherosclerosis. Additional important observations supporting the role of allo- and autoimmunity in CAV development were consistently reported again by Huibers and by Chatterjee [69,72]. With different methodologies and study design, both authors found perivascular B-cell lineage infiltrates in CAV allograft explants. Of note, these cells appeared to produce not only HLA-directed antibodies, but also non-HLA natural antibodies reactive to multiple autoantigens, consolidating the contribution of HLA-independent immunological mechanisms implicated in CAV development [72], as already suggested by other several reports about anti-AT1r and anti-endothelial cell antibodies [122,123].

Prevention of CAV

Immunosuppressive treatments

The effect of induction therapy on CAV was analyzed by two observational studies. Use of antithymocyte globulins (ATG) [91] was associated with less IVUS-detected CAV in a study including 103 patients, 1 year after transplantation. Similarly, but in a study including just 13 patients [90], basiliximab was as well found associated with less IVUS-defined CAV progression. In the past, other studies found that ATG is associated with less CAV progression, providing substantial evidence in support of this effect [124]. However, none of these studies, neither large registry data, demonstrated a survival advantage of ATG induction over no induction. Efficacy of Basiliximab in preventing CAV, on the other hand, has not been confirmed by other studies, and recent registry reports suggest that it may be associated with increased mortality in heart transplantation, when compared with ATG or no induction.

Several randomized and nonrandomized studies analyzed the impact of mTOR inhibitors (everolimus and sirolimus) on CAV progression (Table 3). There is overall compelling evidence that either associated with low-dose CNI [80,83,86] or as replacement for CNI [77,82,84] mTOR inhibitors are associated with lower progression of early signs of CAV, as assessed by IVUS. It should be underlined, however, that CAV prevention effect has been consistently reported only when these drugs are initiated during the first months after transplantation, while there is currently no evidence whether their initial efficacy is retained long term after transplant, or the effect on IVUS endpoint translates into a net clinical benefit. In this context, Guethoff *et al.* [85] report a long-term analysis of patients initially randomized to sirolimus and low-dose tacrolimus (TAC) or TAC plus MMF. After initial benefit in renal function, sirolimus strategy did not provide any advantage in CAV development, or overall survival, 8 years after transplant, in the intention-to-treat analysis. The low long-term tolerability of sirolimus may partially explain these findings, because more patients were discontinued sirolimus, than MMF, possibly contributing to the balancing of the outcomes. In addition, two studies, one of which randomized [78,83], found that late conversion to everolimus or sirolimus seems ineffective, possibly related to the difference in plaque composition at various stages of CAV development, while another small retrospective study supports opposite results with everolimus delaying late CAV progression [86]. Overall, these findings are in line with the reports discussed above about pathology and the CAV risk factors, supporting the model of two stages and morphologies CAV development: a first phase more related to immuno-inflammatory injury, characterized by concentric intimal hyperplasia, and a later phase in which the contribution of metabolic risk factors becomes more relevant, resulting in a different plaque and morphology composition, resembling that of native atherosclerosis.

While the superiority of TAC over cyclosporine (CsA) in biopsy-proven rejection is quite well established, differences in CAV development are controversial. In one single study, the use of TAC versus CsA in combination with MMF was analyzed in the setting of a follow-up analysis of a small, randomized, single-center, controlled trial [75]. Freedom from angiographic CAV was 45.8% in the TAC group vs. 8.0% in the CsA group ($P = 0.003$) after 10 years, with the combination CsA-MMF found as an independent risk factor for CAV development (OR: 3.6; CI: 1.1–11.4; $P = 0.031$). However, there was no statistical difference in long-term survival between the treatment groups. By contrast, Sánchez-Lázaro and Kobashigawa [125] found no significant differences in early IVUS-defined or late angiographic CAV [126], again with no difference in long-term survival. In a small, randomized study, Klauss *et al.* [127] found greater progression of early IVUS-defined CAV in the TAC group compared to the CsA group (79% vs. 38%; $P = 0.082$).

Other drugs and therapeutic approaches

Statins are the cornerstone of prevention of native atherosclerosis, as well as CAV, following the pivotal

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randomized studies with pravastatin and simvastatin [9,128]. More recently, a small but randomized study found that high-dose fluvastatin was associated with lower early CAV development [73] and an observational study in adult heart recipients found that statin use was associated with lower mortality [89]. When used in pediatric patients however, these drugs do not appear to be as effective [92]. Nevertheless, at least in adult patients, these novel findings, altogether with the previous literature, strongly support a benefit on clinical outcomes of statin therapy [129,130].

Ace inhibitors and aspirin are other two cornerstone drugs in prevention and treatment of native coronary artery disease, but, in contrast to statins, only recently their effect on CAV has been adequately reported. A recent multicenter, double-blind, randomized study found that ramipril does not slow development of epicardial plaque volume 1 year after transplant, but does stabilize levels of endothelial progenitor cells and improve microvascular function, two surrogate measures associated with long-term survival [81]. Early administration of aspirin, on the other hand, appears to provide a meaningful benefit on long-term CAV development and CAV-related clinical events, although by the weaker evidence of a retrospective propensity score-based analysis [93].

Potentially intriguing insights for CAV prevention derive from small studies, suggesting a role for granulocyte–colony-stimulating factor (G-CSF) and for high-intensity interval training [87,88]. In a nonrandomized study, G-CSF was initially used in patients with leukopenia because of the regulating role of G-CSF in hematopoiesis and innate immune response. In patients who received G-CSF therapy, the incidence of rejection or progressive CAV was significantly lower (8% vs. 53%) [131]. In a small, randomized study, physical activity program has been analyzed as a therapeutic approach. Patients allocated to high-intensity interval training developed less increase in plaque volume as assessed by IVUS. The initial benefits, however, were not retained in the long-term follow-up, when high-intensity training was withdrawn [88,132].

Treatment of CAV

Treatment of established CAV is based on revascularization procedures and, at its extreme, on retransplantation. Numerous studies analyzed PCI and CABG: All of them are retrospective, and the angiographic efficacy has been only weakly translated in proven clinical benefits.

Percutaneous coronary intervention is the standard revascularization approach for CAV epicardial lesions. Patients with coronary lesions amenable to PCI or CABG had better prognosis than those with nontreatable lesions [97,99]. Of note, the Prada-Delgado paper also suggests that patients with CAV not associated with ischemia had similar outcomes than patients with no CAV [97]. In-stent restenosis and target vessel revascularization appears to be less frequent in patients receiving DES than BMS, although the benefit in clinical outcome is controversial [95,98,133,134]. Of note, in-stent restenosis identified patients at higher risk of subsequent death [94].

Coronary Artery Bypass Grafting surgery is rarely performed because of the diffuse nature of CAV [135] and because of historical data on high perioperative mortality in these patients. However, recent studies reporting small case series show that in selected patients with multivessel symptomatic disease CABG perioperative mortality may to date be significantly reduced, despite long-term outcomes remain poor patients most likely to benefit from this approach are those with symptoms and multivessel coronary disease resembling native atherosclerosis [97,99,136,137]. In this context, it is worth remembering the largest published series of HT recipients treated with CABG, although published out of the time frame of our interest, in which thirteen patients showed 83% survival after revascularization [136].

Retransplantation is a controversial approach of treatment for CAV because of the organ shortage and increased perioperative mortality. Of note, in current era, retransplantation shows similar outcomes to primary transplant in selected age categories and when first-year conditioned survival is analyzed [16,138–140]. A recent ISHLT registry analysis, however, found that patients retransplanted because of CAV show a similar outcome than patients with CAV treated with medical therapy, with a benefit suggested only for those with left ventricle dysfunction [105].

Study limitations

This systematic review has been designed to cover updates on the novelties emerged in the latest years about CAV. Given the complexity of the disease, the large amount of literature involved, and the diversity of study designs and scopes, we chose to focus our work only on risk factors, pathological features, prevention, and treatment. Despite we used a systematic approach to minimize biases in study selection, it is possible that we have missed relevant papers not retrieved by our

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search string, or excluded because dealing mainly with imaging or biomarkers. In addition, because of the retrospective design of most of the studies, presenting variable and sometimes nonstandardized endpoints, it has not been possible to apply a meta-analysis approach to the study findings. Thus, the sum of the evidences we found should be regarded as qualitative and cannot be weighted by statistical methods.

Conclusions

Despite improvements in surgical and medical management yielded to significant benefit in heart transplant outcomes, CAV remain a significant threat to long-term survival. In this systematic review of recent literature, while confirming known concepts, we found supportive evidence that the CAV pathophysiology may vary according to the time after transplant and the prevalence of metabolic versus immune-mediated risk factors. B-cell-mediated immunity appears to bear a growing importance and could represent a relevant therapeutic target for future interventional studies. Selective revascularization of focal lesions in patients with CAV may result in some clinical benefit, but CAV prevention, rather than treatment, by controlling risk factors and by using targeted immunosuppressive therapies is the most evidence-based approach to reduce disease progression. Customized therapeutic and preventive approaches based on patients' accurate risk stratification may represent an effective strategy to pursue in future studies to finally revert HT "unavoidable destiny."

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Conflict of interest

LP received consultancy fees from Novartis and Biotest, and travel grant by One Lambda.

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