Systematic Review

Percutaneous coronary intervention versus coronary artery bypass grafting in heart transplant recipients with coronary allograft vasculopathy: a systematic review and meta-analysis of 1,520 patients

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Background: Transplant coronary artery vasculopathy (TCAV) is the major cause of late allograft failure and death in heart transplant recipients. The aim of this systematic review was to examine the outcomes of percutaneous coronary interventions (PCIs) as compared to coronary artery bypass grafting (CABG) surgery in the management of TCAV. Our secondary objective was to compare the use and outcomes of drug eluting stents (DES) as compared to bare metal stents (BMS) in this patient population.

Methods: Electronic search was performed to identify all studies in the English literature examining PCI as compared to CABG for TCAV in heart transplant recipients. All identified articles were systematically assessed for inclusion and exclusion criteria.

Results: Of the 4,989 studies identified, 29 studies were included. Among 1,520 patients who developed TCAV, 1,470 patients underwent PCI and 50 patients underwent CABG. There were no significant differences in baseline demographics and comorbidities among the PCI and CABG cohorts. Compared to the PCI cohort, patients who underwent CABG had a higher early mortality (CABG 36.4% *vs.* PCI 4.3%, P<0.001) and overall mortality (CABG 42.3% *vs.* PCI 21.4%, P=0.049). When comparing DES versus BMS cohorts, there were no significant differences in the rate of in-stent stenosis (DES 14.5% *vs.* BMS 24.4%, P=0.476), overall mortality (DES 17.4% *vs.* BMS 30.8%, P=0.302) or cardiac related mortality (DES 7.7% *vs.* BMS 21.8%, P=0.415).

Conclusions: CABG and PCI are both feasible modalities for revascularization in patients with TCAV where PCI is associated with lower mortality. There were no differences in outcomes among patients who underwent PCI with DES as compared to BMS. Potential bias may exist due to heterogeneity in available data. Further studies are needed to delineate evidence-based guidelines to tailor the appropriate therapy, CABG or PCI, to the appropriate patient.

Keywords: Percutaneous coronary interventions (PCIs); coronary artery bypass grafting (CABG); revascularization; heart transplantation; transplant coronary allograft vasculopathy

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Introduction

Cardiac transplantation is the definitive therapy for patients with end stage heart failure refractory to medical management (1,2). Transplant coronary artery vasculopathy (TCAV) remains the most common cause of late allograft failure and death after 1 year (3). The prevalence of TCAV has been reported to be 8%, 30% and 50% at 1, 5 and 10 years post heart transplantation, respectively (3).

In contrast to coronary artery disease (CAD) that is associated with focal atherosclerotic calcium plaque formation, TCAV is a panarterial disease in which there is diffuse vessel narrowing due to concentric fibroproliferative lesion of the intima without calcium deposition (4). In addition to morphological differences, a different set of risk factors has also been suggested in the development of TCAV as compared to CAD. The pathophysiology of TCAV is multifactorial and involves both immunological and nonimmunological mechanism. Immunological factors that have been suggested include HLA mismatching, T cell activation, cytomegalovirus infection, older donor, younger recipient and presence of recipient pretransplant cardiovascular risk factors (5-7). Nonimmunological factors include endothelial injury, ischemia-reperfusion injury and risk factors for CAD, predominantly hyperlipidemia and diabetes (8,9).

Therapeutic strategies that exist in the prevention of TCAV are limited. Options for management of TCAV include immunosuppressive therapy, coronary allograft revascularization [percutaneous coronary intervention (PCIs), coronary artery bypass grafting (CABG)], or heart re-transplantation (10-12). Heart re-transplantation is the definitive management of TCAV in this group of patients, but is limited by the scarcity of suitable donor organs (13). Despite extensive literature regarding the use of PCI and CABG in the management of CAD, there is a paucity of data about the efficacy of such interventions in TCAV.

The primary objective of this systematic review was to examine the outcomes of PCI as compared to CABG in the management of TCAV. Our secondary objective was to compare the use and outcomes of drug eluting stents (DES) as compared to bare metal stents (BMS) among patients who underwent PCI for TCAV.

Methods

Literature search strategy

Thorough electronic searches were performed in August 2017 using Ovid Medline, Embase, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Web of Science, Scopus and CINAHL. To achieve the maximum sensitivity of the search strategy, we combined the terms: "heart transplant", "cardiac transplant", "coronary artery disease", "myocardial infarction", "myocardial ischemia", "vasculopathy", "coronary stenosis", "revascularization", "angioplasty", "stent" and "coronary artery bypass" as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies, assessed using the inclusion and exclusion criteria.

Selection criteria

Eligible studies for the present systematic review and meta-analysis included those that addressed TCAV amongst heart transplant recipients. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment with no overlapping time intervals. We excluded studies on patients <18 years of age, studies not published in the English language and those not involving human subjects. Furthermore, abstracts, case reports, conference presentations, editorials, reviews and expert opinions were also excluded.

Data extraction and critical appraisal

Data was extracted from article texts, tables and figures (JH Choi, JG Luc). Discrepancies between the two reviewers were resolved by discussion and consensus.

Statistical analysis

A meta-analysis of proportions was conducted for the available main perioperative and postoperative variables with logit transformation. Heterogeneity was evaluated using Cochran Q and I^2 test. Meta-regression was conducted using PCI *vs.* CABG as a subgrouping variable, or BMS *vs.* DES in case of our secondary objective. Studies included in the BMS *vs.* DES analysis did not include studies that report mixed techniques (BMS and DES combined) or those that do not specify stent type. R software, version 3.01 (R Foundation for Statistical Computing, Vienna, Austria) was used for all data analysis and visualization. The meta-analysis was performed using metafor package for Rusing continuity correction factor of 0.5. P values <0.05 were considered statistically significant.

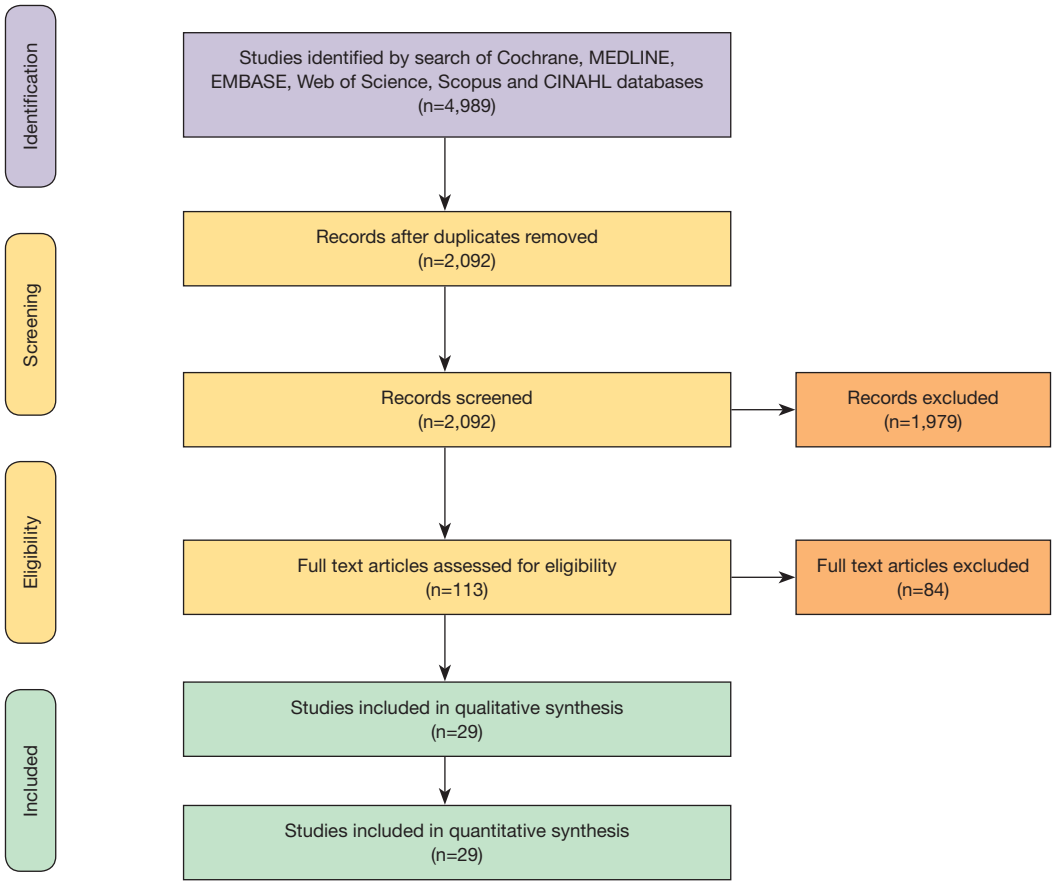

Figure 1 PRISMA schematic of search strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results

Study characteristics

Overall, 4,989 records were identified in the literature search that were published between 1968 and 2015. Following application of the inclusion and exclusion criteria, 29 studies were included for analysis, with a total of 1,520 patients and mean follow-up period of 30.8 months. A PRISMA flow diagram depicting the overall search strategy is provided in *Figure 1*. These studies included 28 single-center studies, and 1 multicenter registry. Of the studies, 28 studies had retrospective patient enrolment and 1 study had prospective patient enrolment. Manual search of references did not yield further studies.

Baseline demographics

Baseline demographics are shown in *Table 1*. Mean patient age was 54.4 years (95% CI, 52.66–56.06) with 78.6% being male. Patient comorbidities include hypertension (80.0%), diabetes (35.8%), dyslipidemia (69.5%), prior myocardial infarction (20.5%) and obesity (53.3%). Etiology of heart failure requiring heart transplantation was primarily ischemic cardiomyopathy (55.5%).

In terms of initial clinical presentation of TCAV, the majority of patients (55.4%) were asymptomatic with other variants of presentation including angina (24.8%), acute coronary syndrome (22.4%), congestive heart failure (18.3%) and myocardial infarction (10.6%) (*Table 2*). The majority of involved lesions were those of the left anterior descending coronary artery (67.8%), followed by right (38.1%), left circumflex (32.6%) and left main coronary artery (7.1%) (*Table 2*). Some patients had lesions in multiple areas.

PCI *vs.* CABG for TCAV cohorts

Among 1,520 patients who developed TCAV, 1,470 patients

Table 1 Baseline demographics of patients in CABG *vs.* PCI cohorts

Baseline demographics	PCI				CABG				Overall				P
	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	
Age (year)	18	–	54.353 (52.612, 56.094)	89.9	2	–	54.823 (47.954, 61.692)	0.0	20	–	54.356 (52.656, 56.056)	89.0	0.997
Male (%)	19	932/1,167	78.5 (74.4, 82.1)	31.4	3	18/22	81.0 (58.1, 92.9)	0.0	21	950/1,189	78.6 (74.7, 82.0)	25.4	0.793
White race (%)	5	574/717	79.3 (73.6, 84.0)	26.8	–	–	–	–	5	574/717	79.3 (73.6, 84.0)	26.8	–
Heart transplant to TCAV (months)	4	–	58.490 (49.758, 67.221)	0.0	1	–	21.800 (15.489, 28.111)	NA	5	–	53.966 (33.711, 74.221)	87.7	<0.001
Heart transplant to intervention (months)	18	–	89.694 (78.411, 100.976)	94.8	4	–	77.087 (49.535, 104.639)	84.7	19	–	88.317 (77.852, 98.781)	94.4	0.501
Smoking (%)	7	72/760	15.7 (7.8, 29.1)	83.6	–	–	–	–	7	72/760	15.7 (7.8, 29.1)	83.6	–
Hypertension (%)	16	790/972	80.0 (746, 0.845)	45.9	3	17/20	81.8 (57.4, 93.7)	0.0	17	807/992	80.0 (74.9, 84.2)	40.3	0.888
Diabetes (%)	16	386/1,012	35.4 (29.0, 42.3)	61.7	3	8/20	40.0 (21.4, 62.1)	0.0	17	394/1,032	35.8 (29.8, 42.2)	55.7	0.707
Dyslipidemia (%)	13	689/875	71.4 (60.9, 80.0)	76.6	3	11/20	55.0 (33.3, 75.0)	0.0	14	700/895	69.5 (59.4, 78.0)	74.2	0.233
Obesity (%)	3	47/85	58.4 (27.5, 83.9)	80.4	1	1/5	20.0 (2.7, 69.1)	NA	3	48/90	53.3 (25.7, 79.1)	77.7	0.332
Prior myocardial infarction (%)	3	120/585	20.6 (17.5, 24.1)	0.0	1	2/13	15.4 (3.9, 45.1)	NA	4	122/598	20.5 (17.4, 23.9)	0.0	0.647
Prior PCI (%)	5	308/687	25.2 (11.6, 46.4)	87.03	4	21/37	56.6 (35.4, 75.6)	33.38	8	329/724	36.1 (22.5, 52.4)	79.38	0.074
History of graft rejection (%)	2	17/37	47.5 (31.6, 63.9)	2.2	1	2/2	100.0 (100.0, 100.0)	NA	2	19/39	49.5 (33.0, 66.1)	6.3	0.282
CMV (+) (%)	4	59/149	33.4 (17.0, 55.2)	80.5	–	–	–	–	4	59/149	33.4 (17.0, 55.2)	80.5	–
Heart transplant indication—ischemic CM (%)	7	139/255	55.6 (47.3, 63.6)	35.6	–	–	–	–	7	139/255	55.6 (47.3, 63.6)	35.6	–
Heart transplant indication—nonvalvular CM (%)	6	75/196	37.6 (23.3, 54.5)	73.8	1	2/2	100.0 (100.0, 100.0)	NA	6	77/198	39.6 (25.0, 56.4)	71.5	0.208

CABG, coronary artery bypass grafting; CM, cardiomyopathy; CMV, cytomegalovirus; NA, not applicable; PCI, percutaneous coronary intervention; TCAV, transplant coronary allograft vasculopathy.

Table 2 Clinical presentations and coronary lesions involved in CABG *vs.* PCI cohorts

Clinical characteristics	PCI				CABG				Overall				P
	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	
Clinical presentations													
All symptomatic ischemia (%)	9	67/368	22.2 (13.4, 34.4)	76.3	2	4/17	24.9 (9.4, 51.5)	1.12	10	71/385	22.6 (14.4, 33.5)	71.4	0.817
No symptoms (%)	3	349/587	59.4 (55.4, 63.3)	0.0	2	5/18	28.1 (12.2, 52.4)	0.0	5	354/605	55.4 (45.6, 64.9)	27.1	0.014
Angina (%)	5	29/125	25.3 (11.6, 46.6)	73.8	1	1/5	20.0 (2.7, 69.1)	NA	6	30/130	24.8 (12.3, 43.7)	67.5	0.820
Noninvasive study positive (%)	5	114/657	32.7 (15.6, 56.2)	88.4	–	–	–	–	5	114/657	32.7 (15.6, 56.2)	88.4	–
TCAV on angiogram (%)	8	144/250	53.9 (42.7, 64.8)	57.6	1	5/12	41.7 (18.5, 69.2)	NA	8	149/262	52.9 (42.4, 63.2)	54.4	0.447
CHF symptom (%)	3	18/119	16.2 (9.6, 26.3)	27.1	2	4/19	22.7 (3.6, 69.7)	62.4	4	22/138	18.3 (10.6, 29.8)	37.2	0.326
ACS (%)	3	145/646	22.5 (19.4, 25.9)	0.0	1	1/7	14.3 (2.0, 58.1)	NA	4	146/653	22.4 (19.4, 25.8)	0.0	0.609
MI (%)	3	7/82	10.0 (4.2, 21.9)	21.0	1	1/7	14.3 (2.0, 58.1)	NA	4	8/89	10.6 (5.4, 19.9)	0.0	–
Vessels involved													
Left main (%)	10	18/471	5.8 (3.5, 9.3)	13.44	2	4/7	55.3 (16.7, 88.4)	20.36	12	22/478	7.1 (3.8, 12.8)	48.7	<0.001
LAD (%)	14	292/431	67.2 (57.7, 75.5)	65.7	1	6/7	85.7 (41.9, 98.0)	NA	15	298/438	67.8 (58.6, 75.9)	64.6	0.399
LCx (%)	15	154/487	32.2 (25.3, 39.9)	58.5	1	3/7	42.9 (14.4, 77.0)	NA	16	157/494	32.6 (25.8, 40.1)	56.3	0.623
RCA (%)	17	223/566	38.3 (31.9, 45.1)	53.6	1	2/7	28.6 (7.2, 67.3)	NA	18	225/573	38.1 (31.9, 44.8)	51.6	0.638

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CHF, congestive heart failure; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; RCA, right coronary artery; TCAV, transplant coronary allograft vasculopathy.

(96.7%) underwent PCI and 50 patients (3.3%) underwent CABG surgery. When comparing patients with TCAV who underwent PCI as compared to CABG, there were no significant differences in regards to mean age [PCI 54.4 (95% CI, 52.61–56.09) *vs.* CABG 54.8 years (95% CI, 47.95–61.69), P=0.997] or other comorbidities. Patients who underwent PCI were more likely to be farther out from their primary heart transplantation [PCI 58.49 (95% CI, 49.76–67.22) *vs.* CABG 21.80 months (95% CI, 15.50–28.11), P<0.001] and asymptomatic [PCI 59.4% (95% CI, 55.4–63.3) *vs.* CABG 28.1% (95% CI, 12.2–52.4), P=0.014] compared to the CABG cohort (*Table 2*).

Patients with left main TCAV were more likely to undergo CABG as compared to PCI [CABG 55.3% (95% CI, 16.7–88.4) *vs.* PCI 5.8% (95% CI, 3.5–9.3), P<0.001] (*Table 2*). There were no significant differences in the likelihood of patients undergoing CABG as compared to PCI for other coronary lesions, including the left anterior descending artery [CABG 85.7% (95% CI, 41.9–98.0) *vs.* PCI 67.2% (95% CI, 57.7–75.5), P=0.399], left circumflex artery [CABG 42.9% (95% CI, 14.4–77.0) *vs.* PCI 32.2% (95% CI, 25.3–39.9), P=0.623] or right coronary artery [CABG 28.6% (95% CI, 7.2–6.3) *vs.* PCI 38.3% (95% CI, 31.9–45.1), P=0.638].

For the entire cohort, early mortality, as defined as mortality within 30 days of TCAV intervention or hospital discharge, was 13.5% (95% CI, 5.0–31.6). Compared to patients who underwent PCI, those who underwent CABG had a higher early mortality [CABG 36.4% (95% CI, 20.0–56.7) *vs.* PCI 4.3% (95% CI, 2.1–8.8), P<0.001] and overall mortality [CABG 42.3% (95% CI, 28.4–57.5) *vs.* PCI 21.4% (95% CI, 14.4–30.7), P=0.049], but no difference in cardiac-related mortality [CABG 32.5% (95% CI, 19.7–48.5), PCI 22.7% (95% CI, 15.1–32.7), P=0.362]. CABG was accompanied with a trend towards decreased need for repeat intervention [CABG 15.4% (95% CI, 3.9–45.1) *vs.* PCI 37.2% (95% CI, 16.1–64.7), P=0.327] that did not reach statistical significance (P=0.327) during the same follow-up period [CABG 22.41 (95% CI, 24.259–39.388) *vs.* PCI 31.82 months (95% CI, 0–51.640), P=0.337] (*Table 3*).

Drug eluting versus BMS

Among the 303 patients who underwent PCI in studies reporting on stent type, 181 patients received DES (60%) and 122 patients received BMS (40%). Preoperative medications received among the cohorts are described in *Table 4*. Compared to the BMS cohort, patients in the DES cohort were more likely to receive the following medications in addition to aspirin: clopidogrel [DES 81.7% (95% CI, 56.1–94.0) *vs.* BMS 36.8% (95% CI, 18.7–59.7), P=0.004], angiotensin converting enzyme inhibitors/angiotensin receptor blockers [DES 56.4% (95% CI, 42.1–69.7) *vs.* BMS 33.1% (95% CI, 21.8–46.7), P=0.007], statins [DES 80.6% (95% CI, 73.1–86.4) *vs.* BMS 69.2% (95% CI, 56.8–79.3), P=0.077] and oral sirolimus [DES 43.5% (95% CI, 27.8–60.7) *vs.* BMS 21.6% (95% CI, 11.2–37.7), P=0.045]. Conversely, patients receiving BMS were more likely to receive oral azathioprine [BMS 53.1% (95% CI, 20.5–83.3) *vs.* DES 15.0% (95% CI, 8.5–25.2), P=0.014]. No differences in immunosuppressive therapy were seen between the DES and BMS cohort in regards to administration of cyclosporine, mycophenolate, or tacrolimus.

In terms of periprocedural details (*Table 5*), those who received a BMS were more likely to have a higher postprocedure minimal lumen diameter [BMS 3.075 (95% CI, 2.752–3.398) *vs.* DES 2.571 mm (95% CI, 2.433–2.708), P<0.001], stent diameter [BMS 3.197 (95% CI, 3.155–3.239) *vs.* DES 3.000 mm (95% CI, 2.963–3.037), P<0.001] and length [BMS 20.295 (95% CI, 18.284–22.307) *vs.* DES 18.740 mm (95% CI, 17.161–20.319), P<0.001].

There were no significant differences in the rate of in-stent stenosis [DES 14.5% (95% CI, 4.5–38.0) *vs.* BMS 24.4% (95% CI, 16.9–33.9), P=0.476], overall mortality [DES 17.4% (95% CI, 9.0–31.0) *vs.* BMS 30.8% (95% CI, 12.0–59.1), P=0.302] or cardiac related mortality [DES 7.7% (95% CI, 2.9–18.8) *vs.* BMS 21.8% (95% CI, 10.4–40.2), P=0.415] (*Table 5*). Furthermore, there were no significant differences between the DES and BMS cohorts in terms of survival (*Figure 2A*), event-free survival (*Figure 2B*) and freedom from restenosis (*Figure 2C*) at 1, 2 and 3 years post PCI.

Discussion

Coronary allograft vasculopathy following heart transplantation has an incidence of 30–50% at 5 years (14) and remains the most common cause of late allograft failure and the major determinant for long-term survival (3). The mainstays of treatment include CABG, PCI or heart retransplantation (15). Although the definitive management of TCAV is retransplantation, it is limited by the scarcity of suitable donor organs. Therefore, retransplantation is usually reserved for patients with disease progression despite revascularization or those with diffuse coronary

Table 3 Outcomes in CABG *vs.* PCI cohorts

Outcomes	PCI				CABG				Overall				P
	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	
Follow-up period (months)	13	–	31.824 (24.259, 39.388)	96.77	2	–	22.407 (0, 51.640)	88.47	14	–	30.800 (23.389, 38.211)	96.98	0.337
Early mortality (%)	4	6/184	4.3 (2.1, 8.8)	0.0	5	12/42	36.4 (20.0, 56.7)	18.8	8	18/226	13.5 (5.0, 31.6)	72.9	<0.001
Overall mortality (%)	19	223/1,261	21.4 (14.4, 30.7)	86.3	7	21/50	42.3 (28.4, 57.5)	3.3	24	244/1,331	25.3 (18.1, 34.1)	82.5	0.049
Cardiac mortality (%)	8	63/273	22.7 (15.1, 32.7)	48.5	5	13/42	32.5 (19.7, 48.5)	0.0	13	76/315	25.7 (19.2, 33.5)	29.9	0.362
Repeat procedure (all) (%)	4	103/231	37.2 (16.1, 64.7)	92.4	1	2/13	15.4 (3.9, 45.1)	NA	5	105/244	32.9 (14.7, 58.2)	90.8	0.327

CABG, coronary artery bypass grafting; NA, not applicable; PCI, percutaneous coronary intervention.

Table 4 Medications administered in DES *vs.* BMS subgroups

Medications	DES				BMS				Overall				P
	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	
Aspirin (%)	5	110/116	92.9 (85.9, 96.6)	0	5	57/65	86.9 (58.4, 96.9)	67.49	7	167/181	91.1 (80.9, 96.1)	51.2	0.163
Clopidogrel (%)	3	65/81	81.7 (56.1, 94.0)	67.15	1	7/19	36.8 (18.7, 59.7)	NA	3	72/100	72.4 (43.8, 89.8)	79.15	0.004
Ticlopidine (%)	3	25/30	84.3 (25.4, 98.8)	76.16	1	17/17	100.0 (100.0, 100.0)	NA	3	42/47	89.2 (43.5, 98.9)	74.43	0.319
Beta-blocker (%)	5	48/114	43.0 (25.4, 62.5)	73.91	3	20/58	33.2 (11.8, 64.9)	78.66	5	68/172	39.5 (25.6, 55.4)	72.35	0.533
ACEi/ARB (%)	5	66/114	56.4 (42.1, 69.7)	52.9	4	21/66	33.1 (21.8, 46.7)	11.97	6	87/180	46.3 (33.8, 59.2)	62.4	0.007
CCB (%)	2	9/39	23.5 (9.5, 47.3)	47.07	2	16/24	66.3 (45.6, 82.3)	0	3	25/63	43.3 (19.4, 70.9)	74.43	0.002
Statin (%)	6	119/146	80.6 (73.1, 86.4)	0	4	46/66	69.2 (56.8, 79.3)	0	7	165/212	76.6 (70.2, 82.0)	0.3	0.077
Prednisone (%)	4	67/99	66.3 (34.1, 88.2)	86.16	4	40/52	75.7 (52.1, 90.0)	45.1	6	107/151	71.5 (51.8, 85.5)	74.96	0.468
Azathioprine (%)	3	11/78	15.0 (8.5, 25.2)	0	4	24/52	53.1 (20.5, 83.3)	75.78	5	35/130	29.9 (14.3, 52.2)	71.98	0.014
Cyclosporine (%)	4	54/99	50.1 (23.2, 77.0)	84.09	4	37/52	70.2 (45.2, 87.0)	48.14	6	91/151	60.4 (41.4, 76.7)	71.79	0.251
Mycophenolate (%)	4	56/99	56.7 (40.9, 71.3)	56.45	2	21/35	60.0 (43.2, 74.7)	0	4	77/134	57.4 (46.8, 67.4)	29.99	0.701
Tacrolimus (%)	4	47/99	50.8 (29.2, 72.1)	77.91	2	16/35	45.7 (30.2, 62.1)	0	4	63/134	48.9 (34.4, 63.5)	63.53	0.758
Sirolimus (%)	7	75/163	43.5 (27.8, 60.7)	75.15	4	12/71	21.6 (11.2, 37.7)	27.38	7	87/234	35.1 (22.9, 49.8)	73.18	0.045

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMS, bare metal stent; CCB, calcium channel blocker; DES, drug eluting stent; NA, not applicable.

Table 5 Periprocedural details and postprocedural outcomes in DES *vs.* BMS cohorts

Variable	DES				BMS				Overall				P
	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	No. of studies	n/N	Weighted pool %/ mean (95% CI)	I^2 (%)	
Periprocedural details													
Procedure failure (%)	2	0/24	0 (0, 0)	0	3	1/58	3.6 (0.9, 13.2)	0	5	1/82	4.0 (1.3, 11.9)	0	0.757
Preprocedure LVEF (%)	2		58.662 (48.884, 68.439)	84.23	1		40.000 (28.913, 51.087)	NA	3		53.580 (43.051, 64.110)	86.12	0.013
Preprocedure diameter stenosis (%)	4		73.602 (58.393, 88.811)	98.8	3		78.804 (71.539, 86.069)	79.58	5		75.896 (71.312, 80.481)	97.76	0.484
Postprocedure diameter stenosis (%)	3		9.496 (6.148, 12.845)	60.47	2		6.260 (3.933, 8.588)	0	4		8.213 (6.186, 10.240)	48.73	0.134
Preprocedure minimal lumen diameter (mm)	3		0.881 (0.523, 1.239)	92.4	1		0.730 (0.485, 0.975)	NA	3		0.845 (0.563, 1.127)	89.29	0.556
Postprocedure minimal lumen diameter (mm)	3		2.571 (2.433, 2.708)	0	2		3.075 (2.752, 3.398)	49.83	4		2.772 (2.514, 3.031)	77.54	<0.001
Stent diameter (mm)	4		3.000 (2.963, 3.037)	0	3		3.197 (3.155, 3.239)	0	5		3.080 (2.974, 3.186)	87.56	<0.001
Stent length (mm)	5		18.740 (17.161, 20.319)	65.63	3		20.295 (18.284, 22.307)	38.83	6		19.195 (17.773, 20.617)	76.4	<0.001
Outcomes													
Follow-up period (months)	6	–	23.332 (10.707, 35.957)	98.35	4	–	33.902 (15.117, 52.687)	95.38	8	–	27.462 (17.569, 37.355)	97.63	0.184
Overall mortality (%)	6	23/133	17.4 (9.0, 31.0)	51.26	1	4/13	30.8 (12.0, 59.1)	NA	6	27/146	19.6 (11.4, 31.7)	44.67	0.302
Cardiac mortality (%)	2	4/53	7.7 (2.9, 18.8)	0	3	6/33	21.8 (10.4, 40.2)	0	4	10/86	14.0 (7.2, 25.5)	15.35	0.415
MI (%)	4	2/96	3.4 (1.1, 10.2)	0	2	2/35	8.5 (2.1, 28.5)	11.1	4	4/131	5.3 (2.3, 11.7)	0	0.653
Restenosis (all)	7	40/163	16.4 (5.2, 41.3)	86.01	4	29/99	30.2 (20.5, 42.1)	25.6	8	69/262	22.4 (12.4, 37.1)	78.71	0.294
In-stent restenosis (%)	8	38/166	14.5 (4.5, 38.0)	84.12	4	24/99	24.4 (16.9, 33.9)	0	9	62/265	19.4 (10.5, 33.0)	75.66	0.476
Target lesion revascularization (%)	4	19/89	13.0 (2.7, 44.5)	78.93	2	6/39	15.6 (7.2, 30.6)	0	4	25/128	15.2 (6.0, 33.3)	70.83	0.925
Target vessel revascularization (%)	4	12/96	14.1 (8.1, 23.2)	0	2	7/35	20.4 (10.0, 37.1)	0	4	19/131	16.1 (10.5, 23.9)	0	0.396
Heart retransplantation (%)	4	3/110	3.3 (1.2, 9.1)	0	2	0/35	0 (0, 0)	0	4	3/145	3.2 (1.3, 7.8)	0	0.851

BMS, bare metal stent; DES, drug eluting stent; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable.

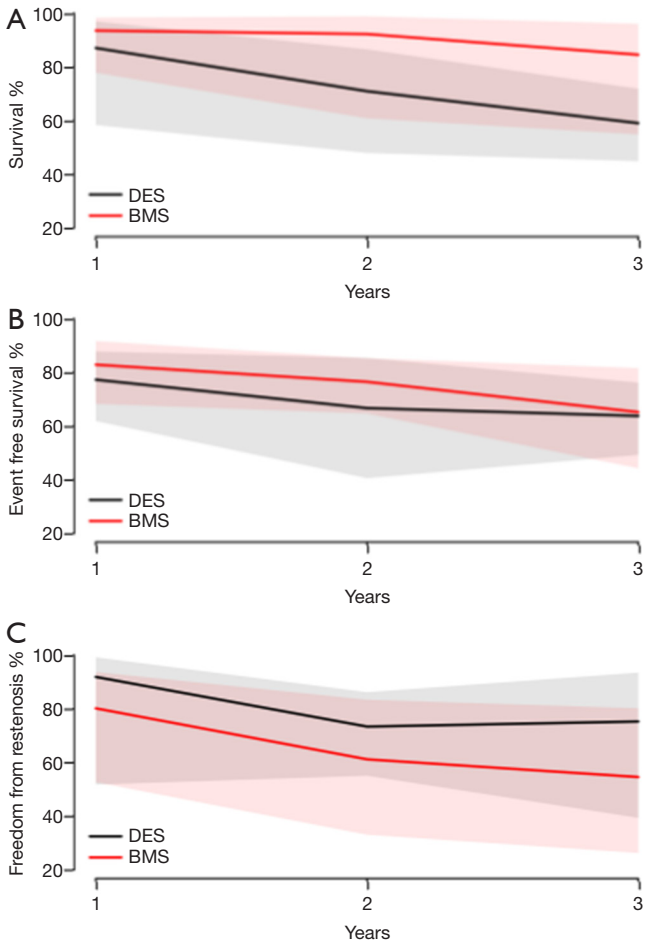

Figure 2 Comparison between DES and BMS in terms of (A) survival, (B) event-free survival and (C) freedom from restenosis at 1, 2 and 3 years of follow-up. DES, drug eluting stents; BMS, bare metal stents.

involvement (13). Limited studies have compared the outcomes of CABG and PCI in the management of TCAV.

In this systematic review and meta-analysis, we demonstrate that both CABG and PCI are feasible modalities for revascularization in patients with TCAV, where PCI is associated with lower mortality and no difference in cardiac mortality during the same follow up period. Furthermore, among those who underwent PCI, there were no differences in outcomes in terms of mortality, event-free survival or freedom from restenosis for patients who received a DES compared to a BMS.

In contrast to CAD in the general population, TCAV has significant morphological differences and risk factors (4), and has been thought to be a manifestation of chronic rejection (16). Preventative strategies for TCAV include treatment of immunological (anti-HLA, chronic inflammation and acute rejection via optimization of immunosuppressive therapy) and nonimmunological factors (e.g., hypertension, hyperlipidemia and pre-existing diabetes) (17). Early post-transplant coronary angiography is often obtained in recipients of higher risk donor hearts to screen for the presence of pre-transplant coronary artery disease as there has been shown a correlation between the presence of pre-transplant coronary artery disease and the incidence and severity of TCAV (18).

We demonstrate that CABG in patients with TCAV was associated with higher mortality (P<0.001), though no significant difference was found in cardiac-related mortality (P=0.362). Furthermore compared to PCI, CABG in patients with TCAV was accompanied with a decreased need for repeat intervention 15.4% *vs.* 37.2% that did not reach statistical significance (P=0.327) during the same follow-up period. Given the aforementioned outcomes, it is vital to interpret the results with care, whilst keeping in mind the threshold for revascularization in this often asymptomatic group of patients. There is significant heterogeneity in CABG early mortality outcomes for patients with TCAV (10,14,18,19), which is likely due to the limited number of patients in each study, differences in patient selection, treatment bias, and changes in medical management and surgical practice across the decades. Furthermore, in the present study, average time from heart transplantation to revascularization was shorter (P<0.001) with more patients with TCAV involving the left main coronary artery in the CABG subgroup as compared to the PCI group (P<0.001). As such, despite a higher incidence of TCAV with left main involvement in the CABG cohort, CABG cannot be advocated readily and indiscriminately given the significant early morbidity and mortality.

Prior decision algorithms have suggested that CABG can be performed in the subgroup of heart transplant patients with Type A lesions, whereby Type B/C lesions are not amenable to bypass surgery (20). However, the decision for CABG surgery should depend on other factors as well, factors including adequate artery size (minimum of 1.8 to 2 mm), whether the combination of lesions at different stages are bypassable, and whether the lesions are hemodynamically significant (14). Other factors that warrant consideration in patient selection include the patient's overall physiological and functional status, comorbidities, likelihood of achieving complete revascularization, and whether alternative surgical approaches such as off-pump

techniques are applicable (14).

PCI in patients with TCAV has been associated with greater restenosis rates compared to PCI in patients with native CAD (21). As DES has been shown to reduce restenosis when implanted in native coronary arteries (22-24), we compared the use and outcomes of DES *vs.* BMS among patients who underwent PCI for TCAV. In the present study, there was a non-significant higher freedom from restenosis at 1, 2 and 3 years among those who received a DES as compared to a BMS with no significant difference in mortality. Existing reports share a common experience (25,26). Similarly, a meta-analysis of six different studies found no difference in terms of major adverse cardiac events (MACE) or all-cause mortality between DES *vs.* BMS (27). Reasons postulated as to why DES did not affect MACE or all-cause mortality is that TCAV is a diffuse and progressive process, that a focal lesion is a marker of widespread disease (28), and that repeat intervention will remain common regardless of method of PCI.

Due to the denervation of the afferent cardiac nervous system and absence or incomplete reinnervation of the cardiac allograft, most heart transplant patients present asymptomatically, and if at all, with atypical angina (20), as is evidenced in our current study. Therefore, the first clinical manifestations of coronary allograft ischemia predominantly include congestive heart failure, ventricular arrhythmias, silent myocardial infarction, or sudden cardiac death (29). As such, given its asymptomatic nature and progressive nature of TCAV, close and frequent surveillance for heart transplant recipients is necessary. Noninvasive studies such as the treadmill test or myocardial perfusion studies have been demonstrated to have limited clinical utility due to poor sensitivity for TCAV, owing to the diffuse nature of the disease which does not allow for assessment of differential myocardial blood flow on radionuclide scans (16). Dobutamine echocardiographic stress test has been shown to be a more sensitive noninvasive screening test than the former noninvasive tests, nonetheless angiography remains the current gold-stand in diagnosis and characterization of lesions (16). The incremental levels of sensitivity from noninvasive to invasive tests for TCAV are demonstrated in the current study, where the majority of TCAV were found on angiography. However, angiography has been shown to underestimate the presence and severity of TCAV (20). Intravascular ultrasound imaging (IVUS) has been proposed as a more sensitive means of detecting intimal vascular wall thickening and may be an important tool for ensuring optimal stent deployment, reducing stent under-expansion, incomplete stent apposition, edge dissection or geographic miss (30).

Limitations

This meta-analysis has several key limitations and must be interpreted with care. Regional differences exist in patient and donor selection, center experience, heart transplantation techniques, immunosuppressive regimes used and clinical management of heart failure. We acknowledge that this heterogeneity in study population is a fundamental limitation that cannot be addressed due to inability to extract sufficient detail from the pooled data. Due to the lack of detail in the data, we were unable to stratify CABG outcomes by era or analyze and compare multi-lesion interventions separately. Pooled results may not correctly reflect the advancements made during the last five decades of this widely performed procedure. n/N variation amongst variables reported led to fluctuation in pooled number results. Moreover, the heterogeneity in results precludes broad generalization into prognostic terms. The impact of CABG and PCI in patients with TCAV on survival and freedom from restenosis is difficult to assess due to the limited number of patients, lack of detail precluding the ability to differentiate patients who underwent complete *vs.* partial revascularization, and incomplete clinical and angiographic follow-up for some of the patients. Furthermore, inconsistent definitions were used to describe the outcomes and CABG and PCI in terms of restenosis and clinically significant coronary lesions, with inconsistent criteria for the need for repeat reintervention. It is possible that patients undergoing PCI represented a population that was less sick than the population that underwent CABG, thereby overestimating the benefit of PCI. As well, patients who underwent CABG as compared to PCI may be different and represent different states in the natural course of progression of TCAV. It is also plausible that outcomes of revascularization may have been influenced by clinical presentation rather than treatment modality.

In view of improving success of cardiac transplantation, a larger number of patients with TCAV can be anticipated to present in need of therapy. It is hoped that advances in noninvasive methods to improve screening for TCAV using either imaging studies (31) or noninvasive markers (32) continue to expand for earlier diagnosis. Furthermore, ongoing research in TCAV and vascular biology to develop targeted preventive therapies, interventional and surgical

therapeutic approaches are needed to tailor management and improve outcomes. Decisions regarding CABG *vs.* PCI are likely to continue to remain difficult and it is our hope that the present study forms the basis for future studies as well as provides a platform for dialogue and collaboration amongst multiple disciplines to work towards reducing the number of grafts lost to TCAV. Randomized controlled trials or prospective registry analysis with clinical and angiographic data comparing outcomes of CABG *vs.* PCI for patients with TCAV would be invaluable.

Conclusions

The results of our systematic review of 29 studies consisting of 1,520 patients with TCAV demonstrate that CABG and PCI are both feasible modalities for revascularization in patients with TCAV, with PCI being associated with lower mortality. There were no differences in outcomes among patients who underwent PCI with DES as compared to BMS. Further studies are needed to delineate evidence-based guidelines to tailor the appropriate therapy, CABG or PCI, to the appropriate patient with TCAV.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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