Meta-analysis Comparing Outcomes of Percutaneous Coronary Intervention of Native Artery Versus Bypass Graft in Patients With Prior Coronary Artery Bypass Grafting

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Percutaneous coronary intervention (PCI) is common in patients with prior coronary artery bypass graft surgery (CABG), however the data on the association between the PCI target-vessel and clinical outcomes are not clear. We aimed to investigate long-term clinical outcomes of patients with prior CABG who underwent PCI of either bypass graft or native artery. We performed a systematic review and meta-analysis of observational studies comparing PCI of either bypass graft or native artery in patients with prior CABG. Twenty-two studies comprising 40,984 patients were included. The median follow-up duration was 2 (1 to 3) years. Compared with bypass graft PCI, native artery PCI was frequent (61% vs 39%) and was associated with lower major adverse cardiac events (MACE) (odds ratio [OR] 0.51, 95% confidence interval [CI] 0.45 to 0.57, p <0.001), lower all-cause death (OR 0.65, 95% CI 0.49 to 0.87, p = 0.004), lower myocardial infarction (OR 0.56, 95% CI 0.45 to 0.69, p <0.001), and lower target vessel revascularization (TVR) (OR 0.62, 95% CI 0.51to 0.76, p <0.001). There was no significant difference in the early incidence of major bleeding or stroke between the 2 cohorts. In 6 studies involving 2,919 patients with ST-elevation myocardial infarction, there was no significant differences between the 2 cohorts. The increase in TVR risk with bypass graft PCI was associated with MACE. In conclusion, in observational studies involving patients with prior CABG, native artery PCI was associated with lower MACE, all-cause death, myocardial infarction, and TVR compared with bypass graft PCI at a median follow-up of 2 years. Native artery PCI might be considered the preferred treatment for bypass graft failure. **(Am J Cardiol 2021;140:47−54)**

Saphenous vein graft (SVG) continues to be the most used conduit in patients undergoing coronary artery bypass graft surgery (CABG) owing to ease of harvesting. Despite secondary prevention measures, only approximately half of SVGs are patent at 10 years with poor long-term patency rates.[1] Repeat CABG is associated with increased morbidity and mortality and therefore percutaneous coronary intervention (PCI) is the preferred treatment strategy for SVG failure. SVG PCI accounts for approximately 6% of all PCIs, but is associated with increased risk of both periprocedural and late complications.[2] In contrast to PCI in native coronary arteries, drug-eluting stents (DES) do not improve outcomes compared with bare metal stents in SVG lesions.[3] In previous CABG patients presenting with SVG failure and need for revascularization, it remains controversial whether the SVG lesion or the corresponding native coronary artery lesion should be treated.

Methods

We performed a systematic review and meta-analysis of studies reporting long-term clinical outcomes after PCI of either bypass graft or native coronary artery lesions in patients with prior CABG. The study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement and Cochrane methodology. Our study also complies with the recommendations in the consensus statement outlined by the MOOSE (Meta−Analysis of Observational Studies in Epidemiology) group. We included all studies that reported clinical outcomes after at least 3 months of follow-up from the index procedure. Studies were excluded from the analysis if they were duplicates, single-arm studies, did not report clinical outcomes, reported only immediate (procedural or in-hospital) clinical outcomes with no long-term results, had indistinguishable bypass graft and native artery cohorts or

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Funding: None.

Ethics approval: All included studies in this meta-analysis obtained ethics approval.

Patient and public involvement: Not involved.

PROSPERO ID: CRD42020179499.

See page 53 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.10.062

were conducted in the thrombolysis or plain only balloon angioplasty era without stenting (Supplementary Figure 1).

Using PubMed, Scopus and the Cochrane Library, we performed searches of clinical studies published until April 30, 2020, without language restrictions. Eligible studies were identified using various combinations of the terms; native, graft, percutaneous, coronary, angioplasty, bypass, grafting, and intervention in the abstract or title. Reference lists of the retrieved articles were reviewed to identify further eligible studies. Two reviewers independently reviewed all titles, or titles and abstracts from the search results to identify articles that met the study inclusion criteria. Selected studies were compared, and disagreement was resolved by discussion and consensus. Data extraction was carried out independently and in duplicate by the study investigators. Articles selected for the final review were checked to avoid inclusion of data published in duplicate. Data was collected from each study on baseline characteristics and clinical outcomes at the longest follow-up period available.

The outcomes of interest were major adverse cardiac events (MACE), all-cause death, myocardial infarction (MI), target vessel revascularization (TVR), major bleeding and stroke, at the study-reported longest follow-up duration. All outcomes were defined according to the original study's protocol definition (Supplementary Table 1). Data on patients who underwent PCI in both bypass graft and native artery simultaneously in the same procedure were excluded. If TVR was not reported, we used target lesion revascularization.

Pooled odds ratio (OR) with 95% confidence interval (CI) were estimated for binary variables using a random-effects model by the method of DerSimonian and Lair. Heterogeneity between individual studies was explored by X^2 statistic and characterized with I^2 statistic. In sensitivity analyses, we examined; (1) studies that included only patients with ST-elevation myocardial infarction (STEMI), and (2) all studies after exclusion of the veterans affairs clinical assessment, reporting, and tracking program (VA-CART) study. We did meta-regression to investigate the following associations; (1) the log-transformed OR of the effect of bypass graft PCI on MACE risk and log-transformed OR of the effect of bypass graft PCI on death, MI or repeat revascularization risks, or the study-reported percentage of DES use at the longest follow-up duration, and (2) the log-transformed OR of the effect of bypass graft PCI on repeat revascularization risk at maximum follow-up duration and the study-reported percentage of patients with diabetes mellitus, acute coronary syndrome (ACS) presentation or DES use. Unpaired 2-sample mean comparison Student's *t* test was used to compare weighted means of different populations.

The results from meta-analysis were shown using forest-plots. Included studies were assessed using the modified Risk of Bias in Non−randomized Studies of Interventions tool. Publication bias was minimized by a comprehensive and inclusive literature search. Funnel plots were also used to investigate publication bias. All tests were 2-sided, and statistical significance was fixed at 0.05 level. Analysis was carried out using Review Manager Software (RevMan V. 5.3) and Stata V. 11.2 (StataCorp, College Station, Texas).

Results

Twenty-two observational studies were identified, including 40,984 patients with prior CABG and reporting long-term clinical outcomes after PCI of either bypass graft or native coronary artery (Table 1). The bypass graft was a SVG in all studies apart from 6 studies,[4−9] which also included a few arterial grafts. The study-quality was assessed using the modified Risk of Bias in Nonrandomized Studies of Interventions tool and is shown in Supplementary Table 2. The comparison groups were clearly defined in all the studies, and outcome data of interest were provided for all participants within each study. The overall risk of bias is considered low in the observational studies included. There was no evidence of publication bias (Supplementary Figure 2).

More than three-quarters of the patients were men, mean age 67 ± 10 years, 38.9% were diabetics, 81.9% had ACS, and 70.4% received DES (Table 1). An embolic protection device was used in 3,093 of 15,444 patients (20%) in 16 studies.[4,6−9,14,15,24,10,25,18,11,19,20,16,22] In 14 studies,[7−9,14,24,10,25,18,11,20,16,22,12,17] the CABG to index PCI interval was different between the 2 cohorts (3.6 ± 2.3 years in 4,337 bypass graft PCI patients vs 3.2 ± 2.2 years in 9,524 native artery PCI patients, p <0.001). The median follow-up duration for all studies was 2 (1 to 3) years (Table 1).

Compared with bypass graft PCI, native artery PCI was associated with lower MACE (OR 0.51, 95% CI 0.45 to 0.57, p <0.001) (Figure 1), lower all-cause death (OR 0.65, 95% CI 0.49 to 0.87, p = 0.004) (Figure 2), lower MI (OR 0.56, 95% CI 0.45 to 0.69, p <0.001) (Figure 3), and lower TVR (OR 0.62, 95% CI 0.51 to 0.76, p <0.001) (Figure 4). There was no significant difference in the incidence of major bleeding (OR 1.11, 95% CI 0.89 to 1.37, p = 0.36) (Figure 5), or stroke (OR 0.76, 95% CI 0.42 to 1.37, p = 0.36) (Figure 5) between the 2 cohorts, although these were mostly periprocedural reports. The exclusion of the VA-CART study did not have a significant effect on the results (Supplementary Figure 3).

In 6 studies that included 2,919 patients with STEMI, there were no significant differences between bypass graft PCI and native artery PCI (Supplementary Figure 4). There was significant association between MACE and repeat revascularization risks with bypass graft PCI (p = 0.007) (Supplementary Figure 5), but no significant association was found between MACE and MI (p = 0.189), or all-cause death (p = 0.105) risks, or the study-reported percentage of DES use (p = 0.526) (Supplementary Figure 6). Moreover, there was no significant association between repeat revascularization risk with bypass graft PCI and the study-reported percentage of patients with diabetes mellitus (p = 0.432), ACS presentation (p = 0.531) or DES use (p = 0.453) (Supplementary Figure 6).

Discussion

The major findings of our study are that in patients with prior CABG and as compared with bypass graft PCI, native coronary artery PCI is performed more frequently and is associated with lower incidence of MACE, all-cause death, MI and TVR at a median follow-up of 2 years (Figure 6).

Table 1
Baseline patient characteristics of included studies

Study/year	Design	Period	Population		Male	Age (year)	DM	CABG to index PCI interval (year)	DES	LM native artery	Follow-up (year)	ACS	Distal protection device
			BG	NA									
Meliga et al 2007[10]	Retrospective, single-center registry	Between 2002-2004	11	13	87.5 %	63±11	33.3 %	10 (1-20)†	100 %	0	3	29.2 %	38.4 %
Garcia-Tejada et al 2009[9]	Retrospective, single-center registry	Between 2005-2006	31	53	86.9 %	70±7	35.7 %	BG=8.9±5.1 NA=8.1±5.5	84.0 %	NR	1.5	45.2 %	32.2 %
Varghese et al 2009[11]	Retrospective, single-center registry	Between 2003-2006	63	79	98.6 %	66±10	56.3 %	BG=12±5 NA=9±6	74.1 %	11.0 %	2.5	79.5 %	28.0 %
D'Ascenzo et al 2010[12]	Retrospective, single-center registry	Between 2002-2004	28	25	90.5 %	74±8	41.5 %	BG=14.4±6.0 NA=9.7±6.3	19.0 %	0	3	69.8 %	NR
Welsh et al 2010[13]	Retrospective, post-hoc analysis of RCT	Between 2004-2006	63	55	86.0 %	68 (56-83)†	23.7 %	NR	NR	5.5 %	3	100 %	NR
Alidoosti el al 2011[14]	Retrospective, single-center registry	Between 2003-2007	63	163	77.9 %	59±9	29.6 %	BG=8.94±4.83 NA=5.67±4.11	42.9 %	0.9 %	9	0	26.9 %
Gaglia et al 2011[15]	Retrospective, single-center registry	Between 2000-2010	191	4001	65.9 %	62±13	29.3 %	NR	49.9 %	0.8 %	1	100 %	34.6 %
Xanthopoulou et al 2011[8]	Retrospective, single-center registry	Between 2004-2008	88	102	90.0 %	68±9	37.4 %	BG=10.1±5.7 NA=12.1±5.6	32.1 %	NR	2.3	71.1 %	43.4 %
Bundhoo et al 2011[16]	Retrospective, multicenter registry	Between 2005-2008	60	101	81.9 %	68±8	28.6 %	BG=10.4±4.9 NA=10.5±5.7	84.9 %	17.8 %	1	40.3 %	58.3 %
Leal et al 2012[17]	Retrospective, single-center registry	Between 2003-2008	123	533	73.0 %	66±9	33.2 %	BG=10.2±2.2 NA=10.2±2.3	83.2 %	NR	2	36.9 %	NR
Ho et al 2012[18]	Retrospective, single-center registry	Between 2005-2008	16	9	72.0 %	69±14	76.0 %	BG=6.4±6.2 NA=8.3±4.49	100 %	11.0 %	3	44.0 %	6.3 %
Nikolsky et al 2013[19]	Retrospective, post-hoc analysis of RCT	Between 2005-2007	33	50	86.0 %	65 (59-74)†	31.0 %	NR	78.0 %	0	3	100 %	14.0 %
Liu W et al 2013[20]	Retrospective, single-center registry	Between 2005-2011	30	110	81.0 %	62±10	49.0 %	BG=7.2±4.9 NA=5.3±3.9	100 %	2.7 %	2	100 %	30.0 %
Kohl et al 2014[21]	Retrospective, multicenter registry	Between 2003-2012	84	104	82.9 %	69±12	32.9 %	NR	NR	NR	5	100 %	NR
Liu Y et al 2015[22]	Retrospective, single-center registry	Between 2005-2010	75	190	73.0 %	63±8	53.0 %	BG=4.4±1.8 NA=4.0±2.6	82.7 %	NR	3	85.8 %	35.6 %
Garg et al 2015[23]	Retrospective, single-center registry	Between 2007-2012	25	22	83.0 %	65±10	11.0 %	NR	NR	NR	1.7	100 %	NR
VA CART 2016[24]	Retrospective, multicenter registry	Between 2005-2013	3616	7930	99.0 %	65 (61-73)†	55.0 %	BG=2.29(0.67-5.58) NA=2.17(0.81-4.24)	77.8 %	8.0 %	5	51.3 %	26.3 %
Iqbal et al 2016[4]	Retrospective, multicenter registry	Between 2007-2012	1490	1168	80.5 %	67±11	21.8 %	NR	52.1 %	10.2 %	1	100 %	9.4 %
Mavroudis et al 2017[25]	Retrospective, single-center registry	Between 2004-2010	89	103	83.9 %	73	32.3 %	BG=15 NA=7	83.0 %	13.6 %	3	41.4 %	52.8 %
ADAPT-DES 2017*,[5]	Retrospective, multicenter registry	Between 2008-2010	405	1063	84.4 %	69±10	43.6 %	NR	100 %	10.3 %	2	54.9 %	NR
Shoaib et al 2018[6]	Retrospective, multicenter registry	Between 2007-2014	9544	8825	80.0 %	71 (63-77)†	33.0 %	NR	70.0 %	26.0 %	1	100 %	18.0 %
Liu D et al 2019[7]	Retrospective, multicenter registry	Between 2009-2015	44	113	76.4 %	63±8	100 %	BG=9.8 NA=5.9	96.8 %	NR	3.7	63.0 %	22.7 %

ACS = acute coronary syndrome; BG = bypass graft; CABG = coronary artery bypass grafting; DES = drug-eluting stent; DM = diabetes mellitus; LM = left main; NA = native artery; NR = not reported; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

* Baseline characteristics of propensity score matching cohort in 388 BG PCI and 388 NA PCI.

† Values are median (Q1-Q3).

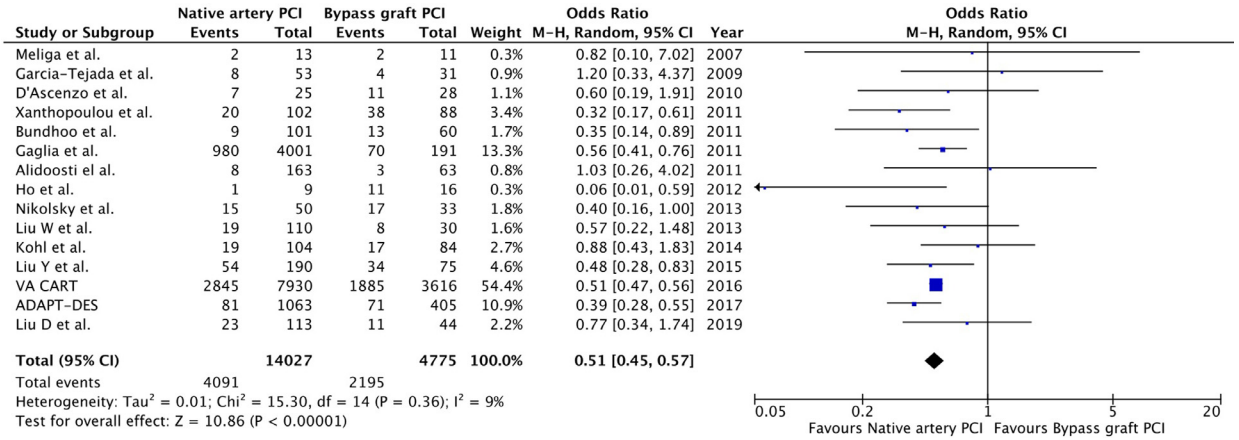

Figure 1. Major adverse cardiac events with native artery PCI versus bypass graft PCI in observational studies of patients with prior CABG.

There was no significant difference in the early incidence of major bleeding or stroke between the 2 study cohorts. The effect of bypass graft PCI on TVR was associated with MACE and did not depend on the patient's diabetes status, ACS presentation or DES use, suggesting that the late TVR with bypass graft PCI is a genuine risk probably related to the adverse characteristics of SVG disease.

In our review, native artery PCI was more frequent than bypass graft PCI in patients with prior CABG (61% vs 39%). This finding is in line with previous reports[26,27] and likely reflects higher difficulty of PCI in bypass graft and/or failure of ungrafted coronary arteries. In an analysis of 300,902 prior CABG patients who underwent PCI between 2004 and 2009, bypass graft PCI was independently associated with higher in-hospital mortality compared with native artery PCI.[26] Our study extends those findings by demonstrating worse clinical outcomes with bypass graft PCI during long-term follow-up.

Several potential mechanisms can help explain the worse outcomes after bypass graft PCI. First, the vast majority of bypass graft PCIs are performed on SVGs, which are known to develop friable atherosclerosis that can lead periprocedural MI. Embolic protection devices that could reduce the incidence of distal embolization have been underutilized in SVG lesions. Moreover, randomized trials have failed to show any benefit of adjunctive glycoprotein IIb and/or IIIa inhibitors during SVG stenting.[28] Second, degenerated SVG lesions tend to be more lipid-rich with poorly developed fibrous cap compared with native artery lesions. Therefore, SVG stenting may lead to greater inflammatory and thrombotic reaction. Third, DES do not reduce restenosis and the need for repeat revascularization in SVG lesions.[3] Fourth, stents placed in bypass grafts may be at higher risk of fracture, especially in aorto-ostial lesions.

Given better outcomes with native coronary compared with bypass graft PCI, why is not the former performed in all prior CABG patients in need of revascularization? There are several potential explanations. First, native artery lesions can be highly challenging to recanalize with frequent chronic total occlusions (CTO). A recent meta-analysis of CTO PCI in prior CABG patients showed lower

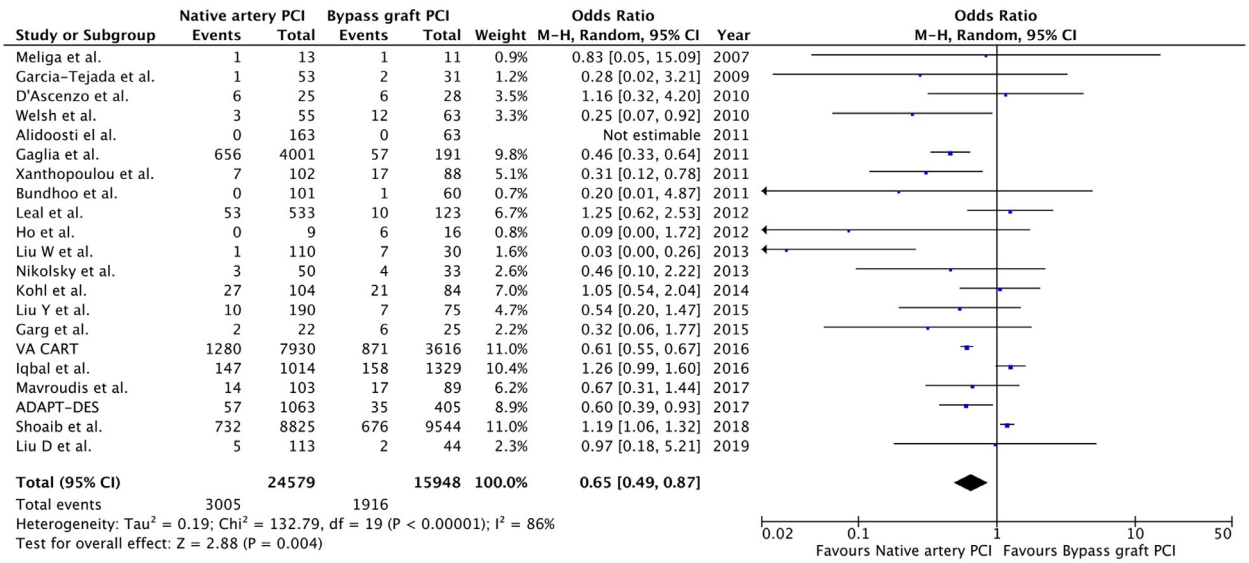

Figure 2. All-cause death with native artery PCI versus bypass graft PCI in observational studies of patients with prior CABG.

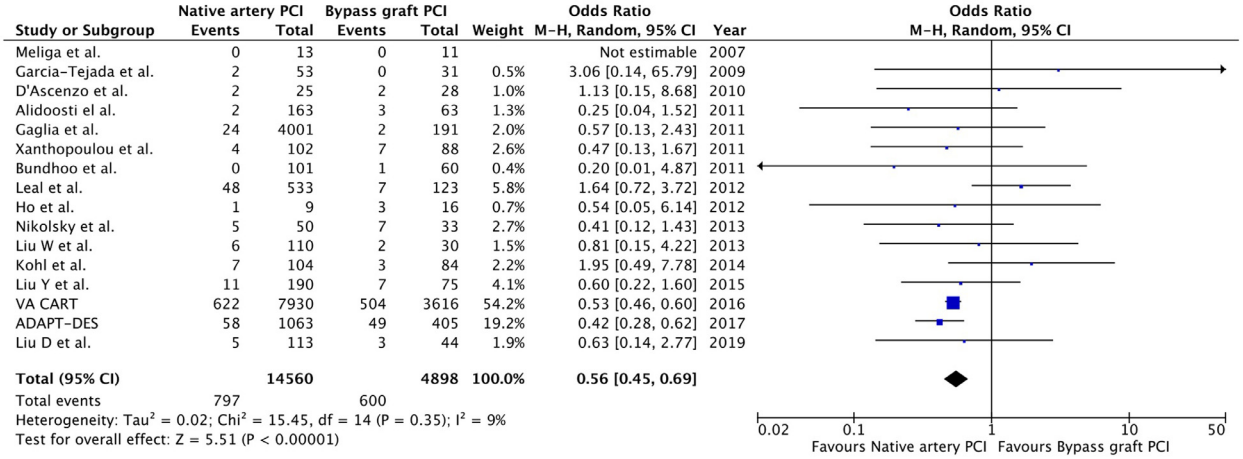

Figure 3. Myocardial infarction with native artery PCI versus bypass graft PCI in observational studies of patients with prior CABG.

technical success (80.7% vs 86.5%), higher contrast and fluoroscopy dose and higher risk of death compared with CTO PCI in nonprior CABG patients.[29] Second, the expertise and resources that may be required to perform complex native artery PCI are not universally available. Third, bypass graft lesions can sometimes be easy to recanalize raising concerns about the risk/ benefit ratio of treating native artery lesions. Fourth, prior CABG patients are often old with multiple comorbidities and may have limited time horizon to realize the benefits of a more complex, yet also more durable revascularization strategy.

The lack of a significant difference in long-term clinical outcomes between bypass graft PCI and native artery PCI in patients presenting with STEMI who had prior CABG in our study is not surprising. It is important to highlight that this is a result of sensitivity analysis with a relatively small number of studies and/or patients included. However, patients with previous CABG who present with STEMI usually pose a diagnostic and therapeutic challenge as baseline ECG and native artery and/or bypass graft anatomy are frequently unknown at the time of emergency presentation. These patients are also more likely to present with cardiogenic shock, undergo PCI to >1 vessel and have worse overall clinical sequalae.[4] Of note, the optimal reperfusion strategy for patients with acute SVG occlusion remains a challenge. Similarly, the logistic and/or technical challenges of dealing with complex native coronary disease may not be favorable in the acute setting. ''Staged revascularization'' has been proposed for such patients: the culprit SVG is initially treated followed by staged revascularization of the corresponding native coronary artery CTO, potentially optimizing both early and long-term outcomes.[30]

Our study has several limitations. First, all included studies are subjected to all the limitations of the retrospective observational design, such as selection bias. The ongoing PROCTOR trial (NCT03805048) is the first randomized trial investigating the outcome of native artery compared to SVG PCI in patients with prior CABG. Second, there is heterogeneity in the rationale for revascularization (stable vs ACS patients) and in turn the regime and/ or duration of antiplatelet treatment given. Third, the PCI lesions in the included studies were not matched for the same territory of myocardial ischemia. Fourth, some studies

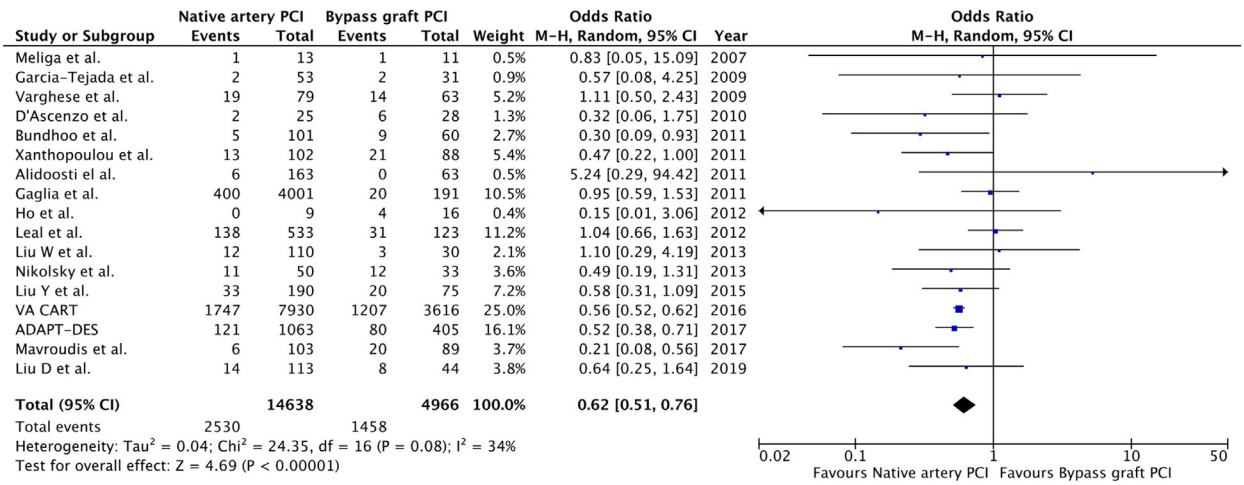

Figure 4. Target vessel revascularization with native artery PCI versus bypass graft PCI in observational studies of patients with prior CABG.

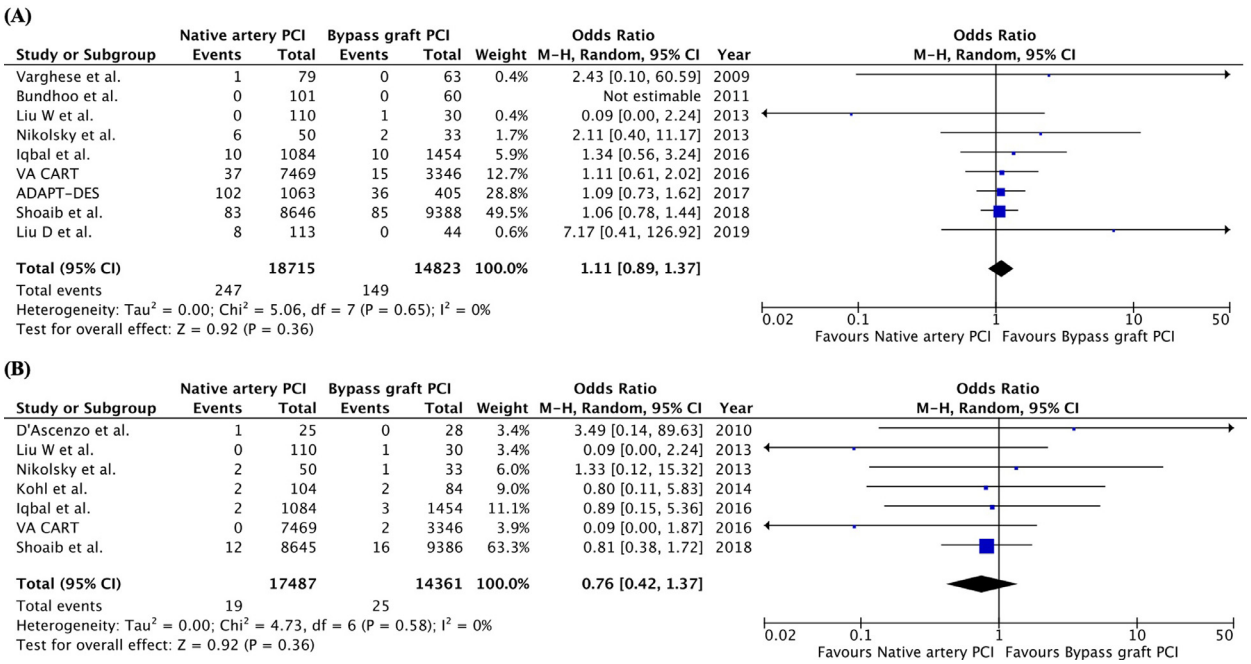

Figure 5. Native artery PCI versus bypass graft PCI in observational studies of patients with prior CABG (*A*) Major bleeding, and (*B*) Stroke.

are old and reported outcomes in only a small number of patients or were derived from cohorts in which contemporary pharmacotherapy was not used and PCI was undertaken in many patients using bare metal stents or plain only balloon angioplasty, hence the applicability of outcomes reported to contemporary practice is unclear. Fifth, a few studies reported outcomes for all bypass grafts, both venous and arterial.[4–9] This is unlikely to affect the results as the vast majority of bypass graft PCI is performed in SVGs with arterial grafts representing approximately 2.5% of all PCI procedures in prior CABG patients.[26] Sixth, although our regression analyses did not reveal a significant association between DES use and clinical outcomes, native arteries might have been treated more with DES. This is also unlikely to affect the results as DES do not seem to reduce adverse outcomes in SVG lesions.[3] Seventh, nearly half of the data came from a single study (VA-CART),[24] however our sensitivity analysis suggests similar findings with or

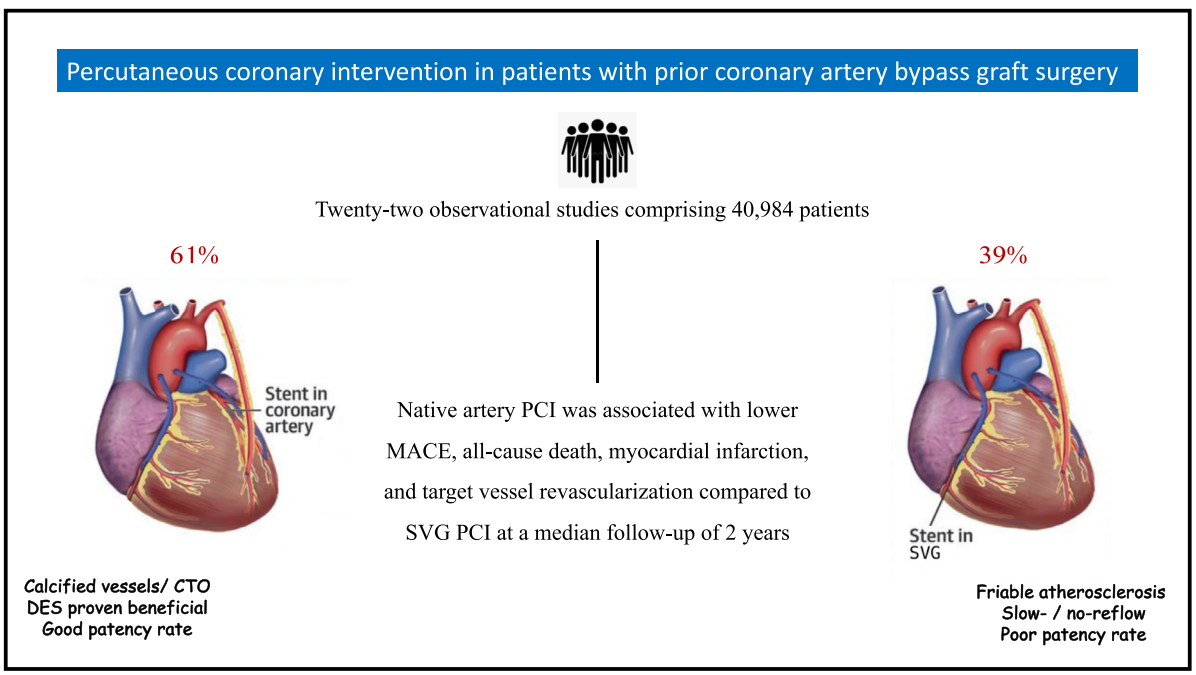

Figure 6. Native coronary artery PCI is associated with lower incidence of MACE, all-cause death, MI and TVR compared with bypass graft PCI at a median follow-up of 2 years.

without the VA-CART study. Moreover, important comorbidities such as left ventricular dysfunction and chronic kidney disease could potentially have affected the results although these were mostly comparable between the cohorts in included studies. Furthermore, the definition of MACE varied between included studies, however 15 of 22 studies standardized MACE as a composite of death, MI and repeat revascularization (Supplementary Table 1). Finally, in patients with prior CABG undergoing PCI before the stent era, it was observed that the native artery group had better long-term survival compared with the bypass graft group.[27] Our review included only studies conducted in the stent era with more than two-thirds of patients received DES, although likely first-generation DES, which are not used in contemporary PCI.

In conclusion, in observational studies involving patients with prior CABG, native coronary artery PCI was associated with lower MACE, all-cause death, MI and TVR at a median follow-up of 2 years compared with bypass graft PCI, suggesting that native coronary artery PCI is preferable to bypass graft PCI when technically feasible.

Authors' Contributions

Mohamed Farag: Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – Original draft & Review, Project administration; Ying X Gue: Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – Original draft; Emmanouil S Brilakis: Methodology, Investigation, Visualization, Supervision, Writing – Review; Mohaned Egred: Conceptualization, Methodology, Investigation, Visualization, Supervision, Writing – Review, Project administration.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.062.

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