Outcomes of Saphenous Vein Graft Intervention With and Without Embolic Protection Device

A Comprehensive Review and Meta-Analysis

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Background—Current guidelines give a class I recommendation to use of embolic protection devices (EPD) for saphenous vein graft (SVG) intervention; however, studies have shown conflicting results. The objective of this meta-analysis is to compare all-cause mortality, major adverse cardiovascular events, myocardial infarction (MI), or target vessel revascularization in SVG intervention with and without EPD.

Methods and Results—Literature was searched through October 2016. Eight studies (n=52 893) comparing SVG intervention performed with EPD (n=11 506) and without EPD (n=41 387) were included. There was no significant difference in all-cause mortality (odds ratio [OR], 0.79; confidence interval [CI], 0.55–1.12; *P*=0.19), major adverse cardiovascular events (OR, 0.73, CI, 0.51–1.05; *P*=0.09), target vessel revascularization (OR, 1.0; CI, 0.95–1.05; *P*=0.94), periprocedural MI (OR, 1.12; CI, 0.65–1.90, *P*=0.69), and late MI (OR, 0.80; CI, 0.52–1.23; *P*=0.30) between the 2 groups. Sensitivity analysis excluding CathPCI Registry study showed no difference in periprocedural MI, late MI, and target vessel revascularization; however, it favored EPD use in all-cause mortality and major adverse cardiovascular events. Further sensitivity analysis including only observational studies revealed no difference in all-cause mortality, major adverse cardiovascular events, target vessel revascularization, and late MI. Additional analysis after excluding CathPCI Registry study revealed no difference in outcomes.

Conclusions—This study including 52 893 patients suggests no apparent benefit in routine use of EPD during SVG intervention in the contemporary real-world practice. Further randomized clinical trials are needed in current era to evaluate long-term outcomes in routine use of EPD, and meanwhile, current guideline recommendations on EPD use should be revisited. **(*Circ Cardiovasc Interv*. 2017;10:e005538. DOI: 10.1161/CIRCINTERVENTIONS.117.005538.)**

Key Words: embolic protection device ■ meta-analysis ■ mortality ■ myocardial infarction ■ percutaneous coronary intervention

Percutaneous coronary intervention (PCI) of saphenous vein grafts (SVG) is associated with higher periprocedural complications compared with native vessel PCI because of distal embolization of atheroma from degenerative graft lesions leading to no-reflow phenomenon and periprocedural myocardial infarction (MI).[1,2] Current guidelines give the use of embolic protection device (EPD) a Class I indication (Level of Evidence B) for SVG intervention when technically feasible to minimize distal embolization.[3] The guideline recommendations are mainly based on only 1 randomized controlled trial (RCT) that compared distal EPD versus no-EPD in SVG intervention.[4] Several studies published later on the use of EPD in SVG intervention have shown conflicting results.[5–10] A large National Cardiovascular Data Registry (NCDR) CathPCI Registry study showed no benefits in routine use of EPD during SVG intervention, with an association between EPD use and a higher incidence of periprocedural complications.[11] Despite modifications and newer versions, EPD use can increase procedural time and complexity and may be associated with procedure-related complications.[4,11,12] Moreover, in the recent era, no-reflow and periprocedural MI during SVG intervention has decreased[13,14] likely because of

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WHAT IS KNOWN

- A randomized trial (SAFER trial [Saphenous Vein Graft Angioplasty Free of Emboli Randomized Trial]) published in 2002 showed embolic protection device (EPD) in saphenous vein graft intervention lowered major adverse cardiovascular events at 30 days mainly driven by lower myocardial infarction and no-reflow phenomenon.
- National Cardiovascular Data Registry CathPCI Registry study published in 2015 revealed no benefits in routine use of EPD during saphenous vein graft intervention and associated with a slightly higher incidence of periprocedural complications.

WHAT THE STUDY ADDS

- This study suggests that routine use of EPD during saphenous vein graft intervention is not associated with a reduction in all-cause mortality, major adverse cardiovascular events, myocardial infarction, or target vessel revascularization.
- Contrary to the expected benefit of the use of EPD, it was associated with 1.5-fold higher periprocedural myocardial infarction.
- With lack of evidence from >1 randomized trials, the present study adds further evidence on lack of benefit in routine use of EPD, supporting the need for re-evaluation of current guideline recommendations on EPD use during saphenous vein graft intervention in the current era.

the use of more potent antiplatelet therapy and improved procedural techniques and stents.[15] Thus, the role of routine use of EPD in SVG intervention has been questioned.[11] The objective of this meta-analysis is to compare all-cause mortality, major adverse cardiovascular events (MACE), MI, and target vessel revascularization (TVR) between EPD use and no-EPD use in SVG intervention.

Methods

This meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statements for reporting systematic reviews.[16,17] General guidelines of Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0, were used in developing methodology, and meta-analysis was conducted in adherence to these guidelines.[17] We searched the National Library of Medicine PubMed, National Institutes of Health clinical trials registry, and the Cochrane Central Register of Controlled Trials to include clinical studies comparing all-cause mortality, MACE, MI, and TVR in SVG intervention with and without the use of EPD. Studies conducted through October 2016 were included. Two independent investigators (S.B. and T.K.P.) performed extensive literature search and reviewed all titles from the search results, and articles were selected for final data extraction. Initial search was open-ended using key words SVG, saphenous vein graft, embolic protection device, EPD, percutaneous SVG intervention, SVG intervention, saphenous vein graft intervention, SVG–PCI, saphenous vein graft PCI, mortality, major adverse cardiovascular events, and MACE. Additional searches were performed, and related articles were reviewed. Reference lists of all related retrieved studies were also reviewed to complete our search. Two independent investigators performed the data collection from included studies (S.B. and T.K.P.). Data collection was then matched and reviewed by a third investigator (H.B.P.) for accuracy. All inconsistencies were resolved by discussion among all 3 investigators. The inter-rater agreement was 90%, and disagreements were resolved by consensus.

The main objective of this study was to compare all-cause mortality and MACE in patients who underwent SVG intervention using EPD versus without EPD. To be selected for analysis, a study had to meet all inclusion criteria: (1) study compares outcomes of SVG intervention using EPD versus without EPD and (2) study reports at least one of the following outcomes: all-cause mortality, MACE, periprocedural MI, late MI, and TVR. Studies that did not meet any of the above criteria were excluded.

After identifying all relevant articles, we extracted data from each study including authors, year of publication, study design, sample size, follow-up duration, and baseline clinical characteristics of patient population (Table 1). End points extracted were all-cause mortality, MACE, periprocedural MI, TVR, and late MI up to 3 years after the procedure. Periprocedural MI was defined as an elevated creatine kinase (CK-MB) fraction >2 to 3 times the upper limit of normal within 24 hours of index procedure or during index hospitalization. Late or subsequent MI was defined as CK-MB elevation >3 times the upper limit of normal beyond index hospitalization up to 3 years of follow-up in any subsequent clinically driven measurements as available. When multiple follow-ups were available, we used the longest follow-up data.

Newcastle-Ottawa quality assessment scale was used to evaluate quality of the included studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). Briefly, studies were quoted by prespecified variables on patients' selection (representativeness and selection of patients and ascertainment of exposure), comparability of cohorts, and assessment of outcomes (recording and adequacy of follow-up). Score for each item was added, and a cumulative study quality score (maximal score, 9) was calculated. Two independent reviewers (H.B.P. and T.K.P.) performed the Newcastle-Ottawa Scale grading, and all discrepancies were resolved with consensus.

RevMan 5.3 statistical software was used to calculate odds ratios (OR) across all studies with corresponding 95% confidence interval (CI) for each end point (The Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity of the studies was assessed for each end point. Heterogeneity was defined as I^2>50% and χ^2 P value <0.01 as shown in Table 2. All primary analyses were performed by random-effect model, and results were shown. Further analyses were performed by fixed-effect model for comparison of the results between the 2 models as shown in Table 3. Sensitivity analysis was performed excluding studies and separately according to the types of the study. Publication bias was assessed using funnel plot and Egger test. A P value of <0.05 was considered to be statistically significant.

Results

Eight studies met the inclusion criteria and were included for the analysis.[4–11] Literature search and the selection process are shown in Figure 1. Studies overview, baseline patient characteristics, Newcastle-Ottawa quality assessment score, and outcomes are included in Table 1. All studies received a score of >7 consistent with good quality. Publication bias and heterogeneity for each outcome are demonstrated in Table 2. There was no publication bias for any of the outcome based on Egger test.

This meta-analysis included 52 893 patients who underwent SVG intervention with EPD (n=11 506, 21.7%) and without EPD (n=41 387). Studies were homogenous for the outcomes of all-cause mortality, periprocedural MI, and TVR

Table 1. Baseline Study Characteristics and Quality Assessment

Studies	Types of Study	EPD Group: Age in Mean (IQR) or Mean±SD	No-EPD Group: Age in Mean (IQR) or Mean±SD	EPD Used	Maximum Follow-Up, mo	Newcastle-Ottawa Scale	Outcomes
Iqbal et al[7]	British Columbia Cardiac Registry	n=96	n=1263	FilterWire	24	8	Death, TVR
		Age: 74 (65–81)	Age: 73 (66–79)				
		Men: 82.3%	Men: 85%				
		ACS: 71.9%	ACS: 71.1%				
Brennan et al[11]	NCDR CathPCI Registry study	n=10 432	n=38 893	SpideRX (n=640)	36	7	Death, MACE, periprocedural MI, late MI, TVR
				Spider FX (n=558)			
		Age: 75 (70–80)	Age: 75 (70–80)	FilterWire EX (n=3204)			
		Men: 77%	Men: 75%	FilterWire EZ (n=6113)			
		ACS: 72%	ACS: 68%	Combination (n=23)			
Sadr-Ameli et al[10]	Prospective observational study	n=22	n=128	Not provided	6	8	Death, MACE, periprocedural MI, late MI, TVR
		Age: 63.23±9.3	Age: 62.53±8.65				
		Men: 86.4%	Men: 72.7%				
		ACS: None	ACS: None				
Golwala et al[6]	Retrospective study	n=93	n=71	Proxis (7%)	12	8	Death, MACE, periprocedural MI, late MI, TVR
		Age: 65.4±9.7	Age: 67.8±9.4	FilterWire (55%)			
		Men: Not provided	Men: Not provided	Spider (35%)			
		ACS: 64.8%	ACS: 72.1%	GuardWire (1%)			
Lavi et al[8]	Prospective study	n=198	No-EPD suitable: n=175	Not provided	36	7	Death, MACE, periprocedural MI, late MI
		Age: 70.4±8.9					
		Men: 85%	Age: 69.4±10.2				
		ACS: 60%	Men: 80%				
			ACS: 66%				
			No-EPD, not suitable: n=161				
			Age: 67.6±10				
			Men: 85%				
			ACS: 53%				
Matar et al[9]	Retrospective study	n=108	n=94	Not provided	1	7	Death, MACE, late MI, TVR
		Age: 69±9	Age: 68±10				
		Men: 80.6%	Men: 79.8%				
		ACS: not provided but urgent procedure in 24.1%	ACS: not provided but urgent procedure in 31.5%				
Dixon et al[5] (TRAP trial)	Randomized controlled trial	n=173	n=185	TRAP vascular filtration system	1	9	Death, MACE, late MI, TVR

(Continued)

Table 1. Continued

Studies	Types of Study	EPD Group: Age in Mean (IQR) or Mean±SD	No-EPD Group: Age in Mean (IQR) or Mean±SD	EPD Used	Maximum Follow-Up, mo	Newcastle-Ottawa Scale	Outcomes
		Age: 69.9±10.3	Age: 70.4±9.9				
		Men: 82.1%	Men: 20.5%				
		ACS: not provided, MI excluded	ACS: not provided, MI excluded				
Baim et al[4] (SAFER trial)	Randomized controlled trial	n=406	n=395	GuardWire	1	9	Death, MACE, late MI
		Age: 68±10	Age: 69±9				
		Men: 82%	Men: 84%				
		ACS: Not provided, MI excluded	ACS: Not provided, MI excluded				

ACS indicates acute coronary syndrome; EPD, embolic protection device; MACE, major adverse cardiovascular events; MI, myocardial infarction; mo, months; n, total number; NCDR, National Cardiovascular Data Registry; SAFER, Saphenous Vein Graft Angioplasty Free of Emboli Randomized Trial; and TVR, target vessel revascularization.

and heterogenous for MACE and late MI. There was no significant difference in all-cause mortality (OR, 0.79; CI, 0.55–1.12; *P*=0.19; Figure 2), MACE (OR, 0.73; CI, 0.51–1.05; *P*=0.09; Figure 3), TVR (OR, 1.0; CI, 0.95–1.05; *P*=0.94; Figure 4), late MI (OR, 0.80; CI, 0.52–1.23; *P*=0.30; Figure 5), and periprocedural MI (OR, 1.12; CI, 0.65–1.90; *P*=0.69; Figure 6) between EPD use and no-EPD use. However, there was a significant difference noted in periprocedural MI (OR, 1.51; CI, 1.32–1.73; *P*<0.00001) favoring no-EPD use compared with EPD use when fixed-effect model was used. There was no periprocedural MI outcome in RCTs, and only 4 observational studies reported this outcome.

Sensitivity analysis was performed excluding NCDR CathPCI Registry study showing studies were homogenous for all outcomes. There was no statistically significant difference in periprocedural MI (OR, 0.78; CI, 0.41–1.49; *P*=0.46), TVR (OR, 0.85; CI, 0.52–1.38; *P*=0.51), and late MI (OR, 0.68; CI, 0.43–1.06; *P*=0.09; Figures I through III in the Data Supplement). However, all-cause mortality (OR, 0.57; CI, 0.36–0.90; *P*=0.02) and MACE (OR, 0.64; CI, 0.45–0.92; *P*=0.02) differed significantly between the 2 groups favoring EPD use (Figures IV and V in the Data Supplement). Further sensitivity analysis was performed including only observational studies (6 studies) that showed studies were homogenous for all outcomes. There was no significant difference in late MI (OR, 1.05; CI, 0.69–1.61; *P*=0.82), all-cause mortality (OR, 0.89; CI, 0.64–1.23; *P*=0.48), MACE (OR, 0.82; CI, 0.52–1.29; *P*=0.38), and TVR (OR, 1.00; CI, 0.95–1.05; *P*=0.93). Additional analysis was performed after excluding NCDR CathPCI Registry study (5 studies), which revealed no statistically significant difference in all-cause mortality (OR, 0.62; CI, 0.36–1.04; *P*=0.07), MACE (OR, 0.69; CI, 0.34–1.40; *P*=0.30), late MI (OR, 92; CI, 0.33–2.56; *P*=0.87), and TVR (OR, 0.80; CI, 0.47–1.34; *P*=0.39). All analyses were duplicated by fixed-effect model, and comparisons with random-effect model are shown in Table 3. Overall, the results are consistent between the 2 models.

Discussion

Although RCTs have demonstrated efficacy and safety of EPDs in SVG intervention, the routine use of these devices has been controversial and continues to be a matter of debate. The results of this study including 52 893 patients revealed that all-cause mortality and MACE rate were similar in EPD versus no-EPD use in SVG PCI. Similarly, there was no difference in periprocedural MI, late MI, and TVR. Surprisingly, when fixed-effect model was used, contrary to the expected benefit of the use of EPD, it was associated with 1.5-fold higher periprocedural MI (*P*<0.0001) compared with no-EPD. Because the main goal of EPD is to reduce no reflow and prevent periprocedural MI, the results of the current analysis question the necessity of a routine use of EPD in SVG intervention. Except for late MI and MACE, studies were homogenous for the outcomes of all-cause mortality, periprocedural MI, and TVR.[11] NCDR CathPCI Registry study[11] has the largest sample size

Table 2. Test of Heterogeneity and Publication Bias for Each Outcome

Outcomes	χ^2	df	*P* Value	I^2, %	Heterogeneity	Publication Bias	Egger Test *P* Value
All-cause mortality	9.28	7	0.23	25	Homogeneous	No	0.692
MACE	17.31	6	0.008	65	Heterogeneous	No	0.836
TVR	3.86	5	0.57	0	Homogeneous	No	0.927
Late MI	16.06	5	0.007	69	Heterogeneous	No	0.209
Periprocedural MI	5.44	3	0.14	45	Homogeneous	No	0.779

MACE indicates major adverse cardiovascular events; MI, myocardial infarction; and TVR, target vessel revascularization.

Table 3. Outcomes Using Fixed-Effect Model and Random-Effect Model

Outcomes	Fixed Effect			Random Effect		*P* Value
	OR	CI	*P* Value	OR	CI	
All-cause mortality	1.05	1.00–1.10	0.07	0.79	0.55–1.12	0.19
Late MI	1.06	1.00–1.13	0.05	0.80	0.52–1.23	0.30
MACE	0.99	0.95–1.03	0.60	0.73	0.51–1.05	0.09
Periprocedural MI	1.51	1.32–1.73	<0.00001	1.12	0.65–1.90	0.69
TVR	1.00	0.95–1.05	0.91	1.00	0.95–1.05	0.94
Outcomes excluding NCDR Registry						
All-cause mortality	0.57	0.36–0.89	0.01	0.57	0.36–0.90	0.02
Late MI	0.64	0.47–0.88	0.006	0.68	0.43–1.06	0.09
MACE	0.62	0.47–0.82	0.0008	0.64	0.45–0.92	0.02
Periprocedural MI	0.77	0.41–1.44	0.41	0.78	0.41–1.49	0.46
TVR	0.79	0.49–1.27	0.33	0.85	0.52–1.38	0.51
Outcomes of all observational studies						
All-cause mortality	1.05	1.00–1.10	0.06	0.89	0.64–1.23	0.48
Late MI	1.08	1.02–1.15	0.01	1.05	0.69–1.61	0.82
MACE	1.00	0.95–1.04	0.89	0.82	0.52–1.29	0.38
TVR	1.00	0.95–1.04	0.90	1.00	0.95–1.05	0.93
Outcomes of observational studies excluding NCDR Registry						
All-cause mortality	0.60	0.36–1.01	0.06	0.62	0.36–1.04	0.07
Late MI	0.97	0.50–1.88	0.93	0.92	0.33–2.56	0.87
MACE	0.69	0.43–1.10	0.12	0.69	0.34–1.40	0.30
TVR	0.74	0.45–1.23	0.25	0.80	0.47–1.34	0.39

CI indicates confidence interval; MACE, major adverse cardiovascular events; MI, myocardial infarction; OR, odds ratio; and TVR, target vessel revascularization.

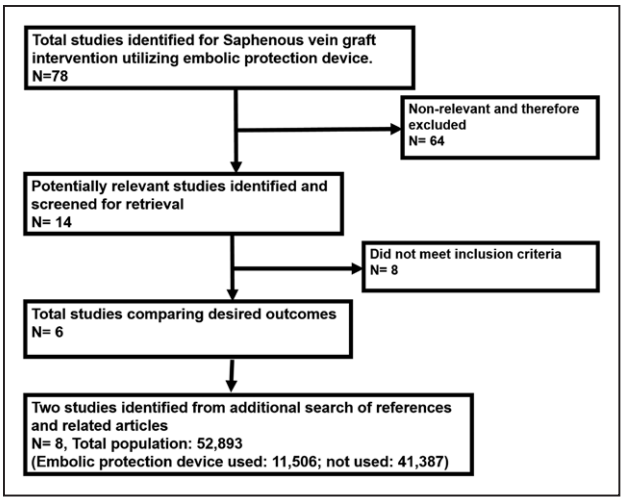

Figure 1. Study selection process.

compared with other studies, and this may skew the results of this study. Thus, sensitivity analysis was performed excluding NCDR CathPCI Registry study showing studies were homogenous for all outcomes. There was no significant difference in periprocedural MI, late MI, and TVR between EPD versus no-EPD groups. However, all-cause mortality and MACE differ significantly between the 2 groups favoring EPD use.

These pooled estimates of the 7 studies were compared directly with the results of the CathPCI Registry. Periprocedural MI was higher in EPD group in CathPCI Registry, but the pooled estimate showed no difference in periprocedural MI between the 2 groups. The CathPCI Registry study showed similar risk of late MI and TVR between EPD and no-EPD groups, which is consistent with pooled estimates. With regard to outcomes of all-cause mortality and MACE, there was no difference by CathPCI data, whereas pooled analysis showed a difference favoring EPD use. Further sensitivity analysis performed including only observational studies showed no difference in all-cause mortality, MACE, late MI, and TVR between the 2 groups. When fixed-effect model was used, a significant difference was observed in late MI favoring no-EPD use. Additional analysis on observational studies was performed after excluding NCDR CathPCI Registry study, which revealed no statistically significant difference in outcomes. When only observational studies were used for analysis, studies were homogenous for all the outcomes either including or excluding NCDR CathPCI Registry study. Of note, an initial analysis of 8 studies showed that studies were homogenous for all-cause mortality, periprocedural MI, and TVR even inclusive of the NCDR CathPCI Registry study. Therefore, probably NCDR CathPCI Registry data are not the main factor for different results when excluding this study from initial analysis. However, unknown confounders could not be determined in this meta-analysis. The analysis was not performed only including RCTs because there were 2 RCTs, and 1 of them was underpowered. Subgroup analysis based on study quality was not performed because all the included studies were of good quality.

The 2011 American College of Cardiology/American Heart Association guidelines recommend use of EPD as Class I indication (Level of Evidence B) during SVG intervention when technically feasible.[3] This guideline recommendation was based on only 1 RCT (SAFER trial [Saphenous Vein Graft Angioplasty Free of Emboli Randomized Trial], GuardWire distal protection device)[4] that compared EPD (balloon occlusion) versus no-EPD and showed a reduction in MACE with EPD use. This lower MACE at 30 days was mainly driven by lower MI and no-reflow phenomenon. Two additional randomized trials published in 2003 and 2007 were cited in guidelines. However, these 2 trials did not have no-EPD arm for comparison. They were noninferiority trials that compared 2 distal EPDs[18] and proximal versus distal EPD,[19] respectively. The FIRE trial (FilterWire EX Randomized Evaluation)[18] compared 2 distal EPDs (filter-based FilterWire EX versus the GuardWire balloon occlusion and aspiration system) showing similar MACE rates at 30 days between the 2 EPD groups, and filter wire was noninferior to GuardWire. The third trial compared proximal (PROXIMAL trial [Proximal Protection During Saphenous Vein Graft Intervention], Proxis embolic protection system)[19] versus distal

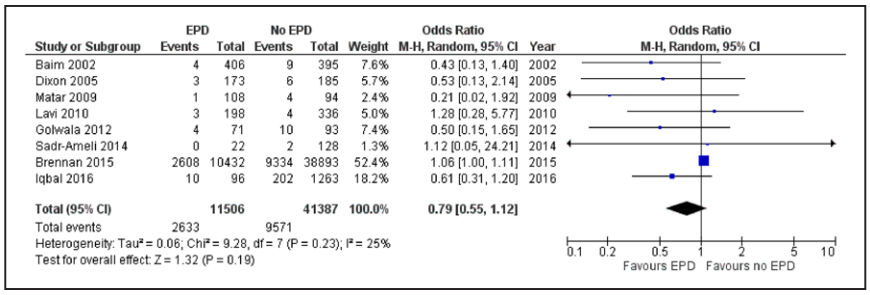

Figure 2. Meta-analysis comparison of all-cause mortality between embolic protection device (EPD) vs no-EPD groups.[4–11] Only Baim et al[4] and Dixon et al[5] are randomized controlled trials. CI indicates confidence interval.

EPD in SVG intervention showing similar 30-day MACE rate between groups. In these 2 trials, the benefit of EPD use was limited to a reduction in periprocedural MI. However, regardless of EPD use, the periprocedural event rates remained ≈10% across the studies, indicating that EPD use was not always successful.[4,9,18,20–22] It is also important to mention that none of these 3 randomized studies reported long-term follow-up data.

There were several studies published subsequently on the use of EPD in SVG intervention that have shown conflicting results.[5–10] Dixon et al[5] conducted a randomized multicenter trial (TRAP trial) that used the TRAP distal vascular filtration system showing no difference in MACE, all-cause mortality, MI, and TVR between TRAP and control group at 30 days. Because of slow enrollment, the study was terminated early as there was another approved distal protection device available at the same time. Thus, the study lacked power to detect a difference. Despite it being a randomized trial, lack of adequate power and absence of long-term follow-up data were major limitations of this study. A retrospective study of 202 SVG interventions demonstrated no statistically significant difference in MACE at 30 days (13.9% versus 9.6%; EPD versus no-EPD).[9] A prospective observational study including 534 patients who underwent SVG PCI showed similar in-hospital events including death, MACE, and MI.[7] Another retrospective study by Golwala et al[6] revealed that EPD use during SVG PCI did not improve the primary end point of periprocedural MI, but the secondary end point of MACE was significantly reduced at 1-year follow-up driven by reduced TVR because no difference in death and MI was noted. This lower TVR may be due to larger caliber vessels/stents because EPD is generally used in vessels between 3 and 5 mm, and larger stents decrease future revascularization rate. Moreover, a reduced TVR rate may be because of contemporary use of drug-eluting stents instead of bare metal stents rather than beneficial effect of EPD itself. Another prospective observational study showed no difference in death, MI, TVR, and MACE in-hospital, at 1- and 6-month follow-ups.[10] A propensity-matched analysis of British Columbia Cardiac Registry data including 1359 patients showed no difference in mortality at 1- and 2-year follow-ups.[7] TVR was lower at 1 year but similar at 2 years.[7] These data suggest that the short-term benefits observed in the SAFER trial may not have sustained at longer term follow-up not only for TVR but also for other outcomes because longer follow-up did not show any difference across studies including ours. Moreover, a large NCDR CathPCI Registry study showed no benefits in routine use of EPD during SVG intervention.[11] Rather, this registry showed that use of EPD was associated with slightly higher incidence of no-reflow, vessel dissection, perforation, and periprocedural MI. These results raised questions about the safety and efficacy of EPDs in routine SVG intervention and a concern about the relevance of existing randomized data to contemporary clinical practice.

Despite a Class I recommendation, we found the utilization of EPD in SVG intervention to be low (21.7%), which is consistent with previous literature,[7,11,23] with even a decreasing trend in EPD use over time.[7] There are several explanations for this lower rate of EPD use. The use of EPD increases the procedure time and complexity and cannot be used in all SVGs because of size, anatomic location, and lesion complexity.[4,12] Mathew et al[24] have shown that approximately half of the SVG lesions were not suitable for EPD; 42% and 57% of SVG lesions failed to meet the inclusion criteria for filter wire and balloon occlusion, respectively. Even if EPD can be used, it may not completely seal the distal vessel and be unsuccessful in preventing distal embolization. Additionally, EPD use is associated with procedural complications including vessel perforation, dissection, and device entrapment.[4,11] Simpler technique such as direct stenting,[25] undersizing stents with higher stent/lesion length ratio, and periprocedural vasodilator therapy[26] has been proven beneficial in preventing no-reflow phenomenon that may limit the benefits of EPD use. Studies showed that without visible thrombus, prophylactic use of intragraft abciximab and vasodilators including verapamil, adenosine, or nicardipine combined with or without direct stenting is a safe and effective strategy to prevent distal microembolization and no-reflow phenomenon in SVG intervention.[25–27] Anecdotally, aspiration catheters and low-dose intragraft tPA (tissue-type plasminogen activator) has

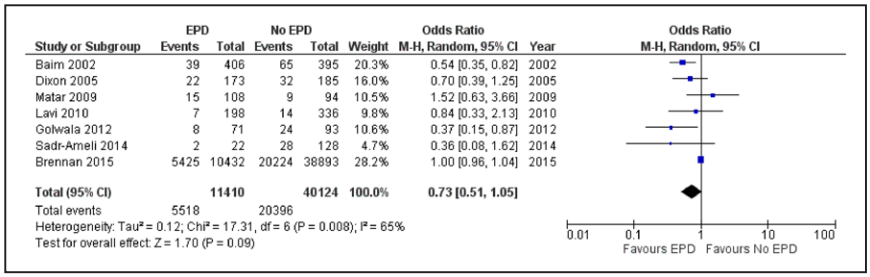

Figure 3. Meta-analysis comparison of major adverse cardiovascular events between embolic protection device (EPD) vs no-EPD groups.[4–6,8–11] Only Baim et al[4] and Dixon et al[5] are randomized controlled trials. CI indicates confidence interval.

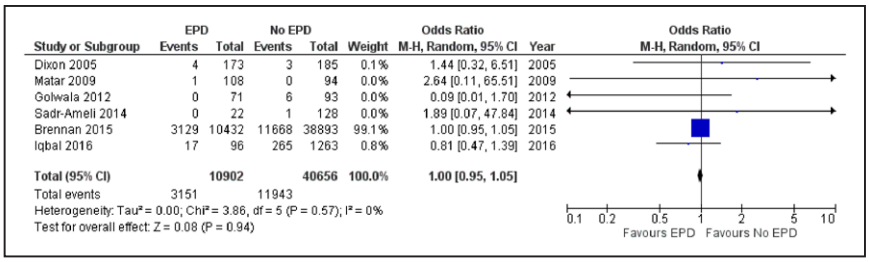

Figure 4. Meta-analysis comparison of target vessel revascularization between embolic protection device (EPD) vs no-EPD groups.[5,6,8–11] Only Dixon et al[5] is a randomized controlled trial. CI indicates confidence interval.

been used in SVG interventions by operators in selected cases with benefits to prevent or treat no-reflow where thrombus is visible.

The results of this meta-analysis showed no difference in clinical outcomes. Potential explanations are the currently available more potent pharmacotherapy, pretreatment with dual antiplatelet therapy, improved procedural techniques, and advent of contemporary interventional devices, which are less bulky and highly deliverable. Furthermore, devices for efficient vasodilator delivery to distal vessel have helped in managing no-reflow phenomenon in SVG PCI. Therefore, the routine use of EPD in SVG intervention may not be necessary and beneficial, but EPD utilization may still be useful in selected higher risk patients. EPD probably prevent macroembolization and may be beneficial in intervention of SVGs with heavy thrombus burden or large lipid-laden plaque with higher distal embolization risk.

With lack of evidence from >1 randomized trials, the present meta-analysis would add further evidence on lack of benefit of routine use of EPD supporting re-evaluation of the need for EPD in routine use during SVG intervention. It is difficult to make firm conclusions, given that the EPD patients were chosen by operators, and the unmeasured confounders make it difficult to be definitive. Future randomized controlled EPD trials are needed with the advent of new technologies and newer pharmacotherapies in current real-world practice. Meanwhile, guideline recommendation for routine use of EPD in SVG intervention may need to be revisited.

This meta-analysis has several limitations. Because this is not a patient-level meta-analysis, the effects of age, sex, race, and ethnic background on outcomes could not be assessed. Although there is a potential for publication bias as is true for all meta-analyses, this analysis shows that there is no publication bias for any outcome. Included studies did not provide data required for this study uniformly, and hence, for comparison of various outcomes, different set of studies were used. Power analysis was not performed in most of the studies, and many of these studies may have been underpowered. Importantly, there are only 2 RCTs comparing EPD versus no-EPD,[4,5] and rest are registry data,[7,11] prospective,[8,10] and retrospective[6,9] observational studies with wide range of sample sizes. Except NCDR CathPCI Registry, other studies including 2 RCTs (Baim, n=801, and Dixon, n=358) have small sample size (n=150–1359), as such evidence from these studies are diverse and may not be strong. The individual studies have their own limitations that also reflect on this analysis, especially prospective and retrospective observational studies that are prone to selection bias. One RCT was underpowered to detect the difference in outcomes.[5] The end points for each outcome were not reported homogenously across studies, and follow-up time varied such as in-hospital, 30 days, 6 months, 1 year, 2 years, and 3 years. The definition of MACE was not universal; although death, MI, and TVR were common components of the MACE,[6,8,9,11] 2 studies included coronary artery bypass surgery[4,5] and 1 study included in-stent thrombosis and target lesion revascularization as part of MACE. MI was defined as CK-MB level >3 times upper limit of normal[4–6,9] and >2 times upper limit of normal. The study by Iqbal et al[7] was excluded from the analysis for the outcomes of periprocedural and late MI as TIMI (Thrombolysis in Myocardial Infarction) 2 to 3 flow was used as a surrogate marker for MI. Individual study lacks data on angiographic subsets for the outcomes of the study for further analysis. Use of EPD in specific angiographic subset may gain more benefits compared with other subsets, and without angiographic subgroup analysis, it is hard to make definitive conclusion in this regard. Previous MI may be a potential confounder, and 2 RCTs excluded patients with recent or acute MI at baseline. Three observational studies included patients with history of MI and showed no difference in baseline characteristics between EPD and no-EPD groups.[7–9] Other 3 observational studies did not presented previous MI data in the baseline characteristics, but previous MI was included as a variable in the regression model for adjustment in the CathPCI Registry study. The strength of this meta-analysis is that there is no publication bias, and studies are homogenous for the outcomes when sensitivity analysis was performed. Additionally, quality assessment score demonstrated that all studies were of good quality. Furthermore, analyses were performed using both random- and fixed-effect models, and results were consistent across strata, strengthening the association of no difference in outcomes.

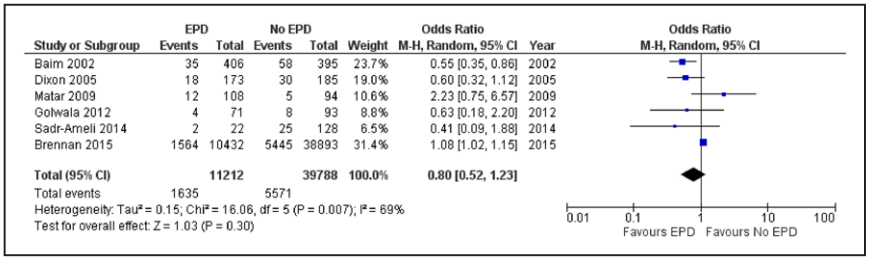

Figure 5. Meta-analysis comparison of late myocardial infarction between embolic protection device (EPD) vs no-EPD groups.[4–6,9–11] Only Baim et al[4] and Dixon et al[5] are randomized controlled trials. CI indicates confidence interval.

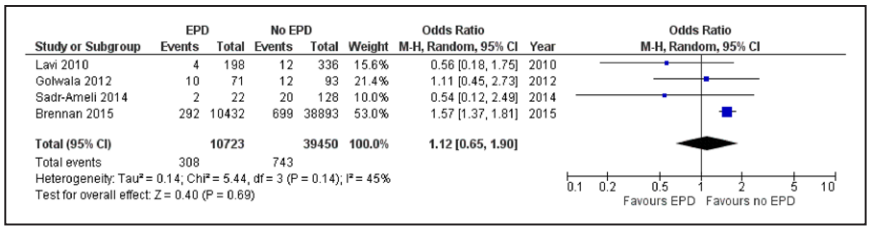

Figure 6. Meta-analysis comparison of periprocedural myocardial infarction between embolic protection device (EPD) vs no-EPD groups.[6,8,10,11] CI indicates confidence interval.

The results of this study including 52 893 patients suggest that routine use of EPD during SVG intervention is not associated with a reduction in all-cause mortality, MACE, MI, or TVR. Routine use of EPD in contemporary real-world practice does not show any apparent benefit. Further randomized clinical trials are needed in the current era to evaluate long-term outcomes with routine use of EPD during SVG intervention, and meanwhile, current guideline recommendations on EPD use should be revisited.

Disclosures

Dr Zhao is helping in clinical trials of BCS, Medtronic, and Abbott; is on the Advisory Board of BCS; and is a proctor/faculty for Medtronic and Edwards. Dr Rao is a consultant for Medtronic (modest), CSI (modest), Corindus (modest), and Svelte (modest). Dr Banerjee receives honoraria from Medtronic and Gore and institutional research grants from BCS and Merck. Dr Mehran receives research funding to institution from AZ, Bayer, DSI, Cardiokinetix, TMC, BMS, Claret, Abbott, BSC, Medtronic, and CSL Bhering consulting/honoraria (includes spouse) from Medscape, Abbott, Janssen, Abiomed, and Watermark. The other authors report no conflicts.

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Outcomes of Saphenous Vein Graft Intervention With and Without Embolic Protection Device: A Comprehensive Review and Meta-Analysis

Timir K. Paul, Samit Bhatheja, Hemang B. Panchal, Shimin Zheng, Subhash Banerjee, Sunil V. Rao, Luis Guzman, Nirat Beohar, David Zhao, Roxana Mehran and Debabrata Mukherjee

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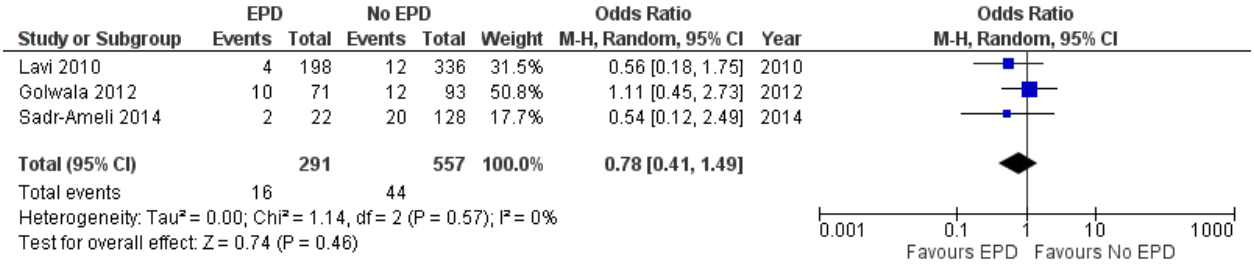
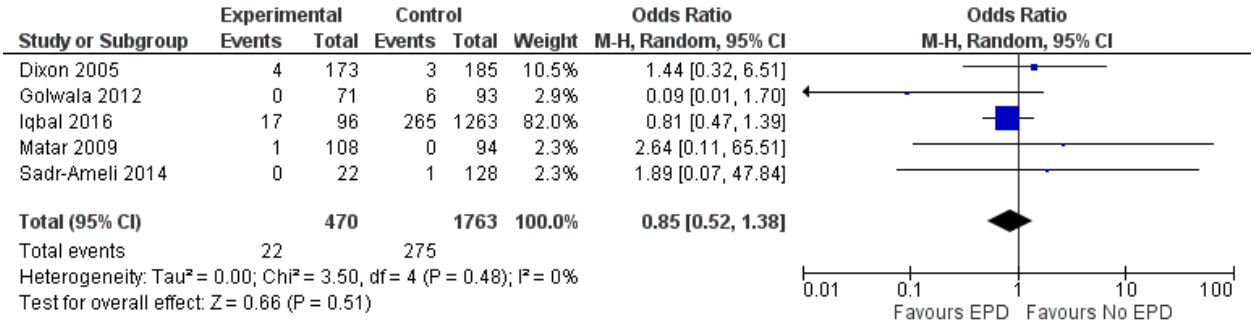
SUPPLEMENTAL MATERIAL

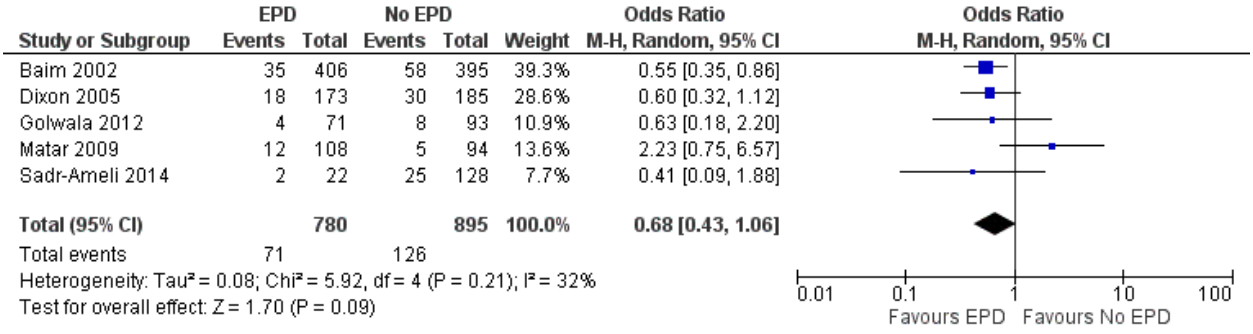
Supplemental Figure 1: Meta-analysis comparison of peri-procedural MI between EPD versus no-EPD groups excluding NCDR Cath PCI registry data[1-3]; EPD, embolic protection device, MI, myocardial infarction, NCDR, National cardiovascular data registry



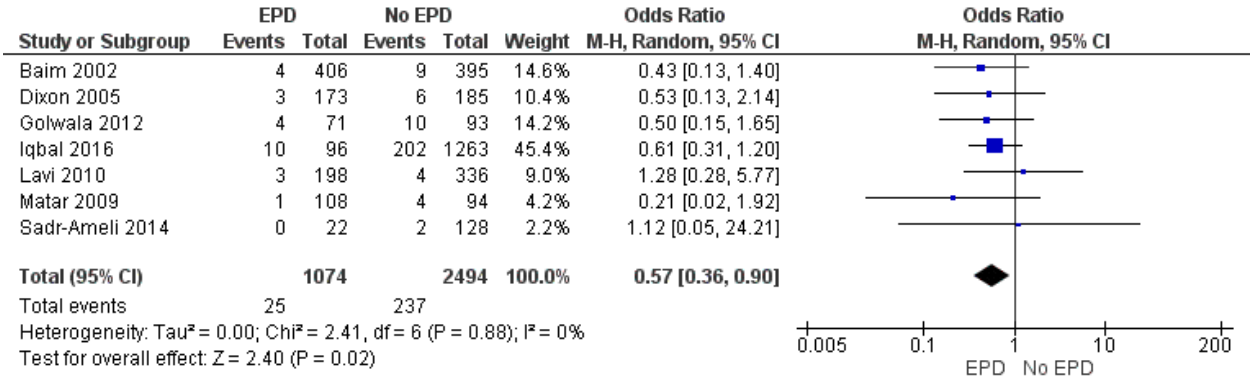
Supplemental Figure 2: Meta-analysis comparison of TVR between EPD versus no-EPD groups excluding NCDR Cath PCI registry data[1,3-6]; EPD, embolic protection device; TVR, target vessel revascularization, NCDR, National cardiovascular data registry. Only Dixon 2005 is a randomized controlled trial.



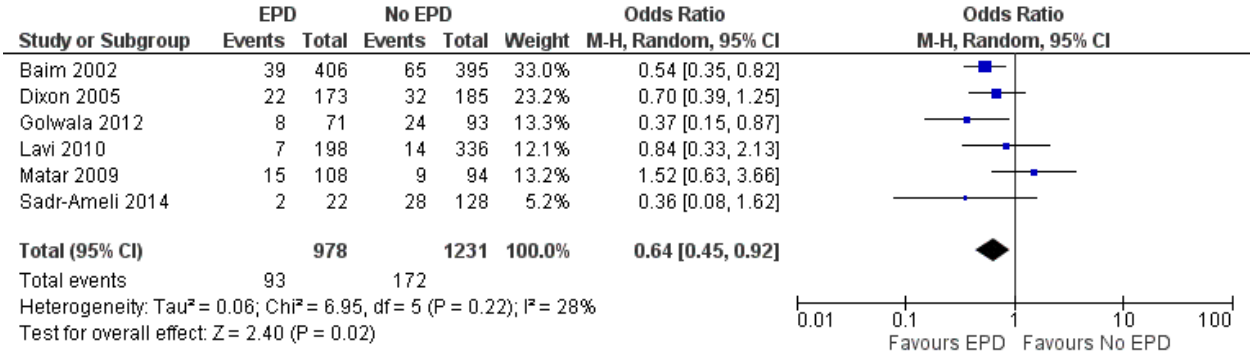
Supplemental Figure 3: Meta-analysis comparison of late MI between EPD versus no-EPD groups excluding NCDR Cath PCI registry data[1,3,4,6,7]; EPD, embolic protection device, MI, myocardial infarction, NCDR, National cardiovascular data registry. Only Baim 2002 and Dixon 2005 are randomized controlled trials.



Supplemental Figure 4: Meta-analysis comparison of all-cause mortality between EPD versus no-EPD groups excluding NCDR Cath PCI registry data[1-7]; EPD, embolic protection device, NCDR, National cardiovascular data registry. Only Baim 2002 and Dixon 2005 are randomized controlled trials.



Supplemental Figure 5: Meta-analysis comparison of MACE between EPD versus no-EPD groups excluding NCDR Cath PCI registry data[1-4,6,7]; EPD, embolic protection device; MACE, major adverse cardiovascular events, NCDR, National cardiovascular data registry. Only Baim 2002 and Dixon 2005 are randomized controlled trials.



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