Active Versus Conventional Side Branch Protection Strategy for Coronary Bifurcation Lesions
A Systematic Review and Meta-Analysis

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Summary
The side branch (SB) provisional stenting strategy is currently the recommended approach for most coronary bifurcation lesions. However, this strategy may result in SB deterioration, which is associated with an increased incidence of periprocedural myocardial infarction (PMI) and may adversely affect the long-term prognosis. Various techniques for SB protection (SB-P) have been developed to reduce SB occlusion and improve the clinical prognosis. This meta-analysis was performed to compare the outcomes of an active SB-P strategy of jailed balloon technique, balloon-stent kissing technique, and jailed Corsair technique versus the conventional SB-P strategy based on jailed wire technique.

This meta-analysis included 5 studies (4 randomized and 1 observational) involving a total of 1,174 patients in whom the active and conventional SB-P strategies were compared. Fixed- and random-effects models were used to calculate summary risk ratios (RRs).

The risk of SB occlusion was significantly lower in active SB-P strategy [RR 0.47, 95% confidence interval (CI) 0.30-0.73 in fixed-effect model; RR 0.52, 95% CI 0.31-0.87 in random-effect model]. The risk of PMI was similar between the two strategies (RR 0.63, 95% CI 0.31-1.33 in fixed-effect model; RR 0.71, 95% CI 0.20-2.48 in random-effect model). The rate of long-term major adverse cardiovascular events was similar between the groups (RR 0.48, 95% CI 0.15-1.48 in fixed-effect model; RR 0.49, 95% CI 0.16-1.52 in random-effect model).

The active SB-P strategy in coronary bifurcation lesions is associated with reduced SB deterioration, but it does not decrease PMI or improve the long-term prognosis.

Key words: Percutaneous coronary intervention, Periprocedural myocardial infarction, Long-term major adverse cardiovascular events

Coronary bifurcation lesions are common and comprise 15% to 20% of indications for percutaneous coronary intervention (PCI).1–2 PCI of bifurcation lesions is considered to be technically difficult and associated with a high incidence of periprocedural complications and a poor cardiac long-term prognosis.3 In the last few years, the optimal stenting strategy for bifurcation PCI has not been well established. Many clinical trials reported that the provisional side branch (SB) stenting strategy (stenting the main vessel and the additional stenting of the SB only in case of occlusion risk) was similar or even superior to the up-front two-stent strategy (planning stenting of the main vessel and SB) for bifurcation lesions based on clinical outcomes.4–5 Therefore, the current guidelines recommended the provisional SB stenting strategy for the vast majority of bifurcation lesions except for those with complex anatomy and diffuse atherosclerotic involvement of both the main vessel and the SB where up-front two-stent strategy may be considered.6–9 In the provisional SB stenting strategy, release of the main vessel stent often causes SB compromise because of plaque or carinal shift.10 Moreover, SB occlusion is associated with a higher rate of periprocedural myocardial infarction (PMI) and worse long-term clinical outcomes than is the absence of SB occlusion.11,12 Next, the conventional SB protection (SB-P) strategy refers to embedding a guidewire in the SB before main vessel stenting, which facilitates rewiring and subsequent stenting in the SB when occlusion occurs.13 Unfortunately, because the jailed wire technique (JWT) cannot directly prevent plaque or carinal shift in the SB, it demonstrates a limited role in avoiding SB occlusion.14 Several innovative approaches recently emerged as more active SB-P strategies, such as the jailed balloon technique (JBT), balloon-stent kissing technique (BSKT), and jailed Corsair technique (JCT). Previous single-arm studies of active SB-P strategies consis-
tently demonstrated their effectiveness in reducing SB occlusion with excellent immediate- and long-term clinical outcomes.\textsuperscript{14-16} However, whether an active SB-P strategy is superior to the conventional SB-P strategy remains controversial, and most comparative studies exhibited small sample sizes.\textsuperscript{17-21} Therefore, we performed a meta-analysis to better characterize the outcomes of these two strategies.

**Table I.** Endpoint Definitions in Each Study

| Study |Endpoint Definitions |
|-------|---------------------|
| Dou 2020\textsuperscript{21} | SCAI definition: CK-MB elevation > 0 times the upper limit of normal value (or 5 times if new electrocardiographic Q waves are present). |
| Jin 2019\textsuperscript{20} | NA |
| Study | PMI | MACEs |
| Qu 2019\textsuperscript{22} | Cardiac death, myocardial infarction, and target lesion revascularization |
| Lai 2018\textsuperscript{23} | Cardiac death, myocardial infarction, and target lesion revascularization |
| Kuno 2019\textsuperscript{24} | Cardiac death, acute myocardial infarction |

PMI indicates periprocedural myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions; CK-MB, creatine kinase-MB; NA, not available; and MACEs, major adverse cardiovascular events.

**Methods**

**Study eligibility and selection:** Here, we report this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) Statement,\textsuperscript{22} and we registered it with the International Prospective Register of Systematic Reviews (CRD 42020195868). We searched PubMed/Medline, EMBASE, and the Cochrane Library from database conception to 20 Jul. 2021 without language limits. The search terms used were “JWT,” “JBT,” “BSKT,” and “JCT.” The reference lists of the retrieved articles were also searched for additional studies not identified from the initial database search. The following inclusion criteria were used: (1) studies involving patients with bifurcation lesions who received an active SB-P strategy of the JBT, BSKT, or JCT versus the conventional SB-P strategy of the JWT, and (2) measurement and comparison of the difference in outcomes between the two strategies.

A coronary bifurcation lesion is defined as a coronary artery stenosis that occurs adjacent to and/or involving the origin of a significant SB.\textsuperscript{25} The conventional SB-P strategy of the JWT consists in reserving a wire in the main vessel while implanting a stent in the main vessel.\textsuperscript{24} Active SB-P strategies involve placement of a balloon or Corsair microcatheter in the SB instead of a wire for higher occupation of the SB ostium. The major difference between the JBT and BSKT is that in the JBT, the SB balloon is inflated when necessary after deployment of the stent in the main vessel, while in the BSKT, the SB balloon and main vessel stent balloon are inflated simultaneously.\textsuperscript{24}

**Data collection and quality assessment:** Two of the authors (Q.Q. and J.L.) independently screened the titles and abstracts, reviewed the full-text articles, and determined each study’s eligibility. Disagreements were resolved by the corresponding author. The following data were independently extracted by the two authors (Q.Q. and J.L.): the type of study, year of publication, time period of patient enrollment, total number of participants, follow-up period, baseline patient and lesion characteristics, procedural characteristics, and procedural and long-term outcomes. The quality of eligible studies was assessed by the Cochrane Collaboration’s tool for randomized controlled trials\textsuperscript{26} and the Newcastle-Ottawa scale for nonrandomized studies.\textsuperscript{26} Quality evaluation of each study was also independently performed by the same two authors (Q.Q. and J.L.).

**Outcomes:** The endpoints of interest in the overall analysis included SB occlusion, a decrease in the Thrombolysis in Myocardial Infarction (TIMI) flow grade in the SB, absence of blood flow in the SB, PMI, and long-term major adverse cardiovascular events (MACEs). SB occlusion was defined as any decrease in the TIMI flow grade or absence of flow in the SB immediately after full apposition of the main vessel stent. Table I shows the detailed definitions of the other outcomes of the included studies.

**Statistical analysis:** Categorical data are summarized as frequencies and percentages, whereas summary statistics for continuous variables are presented as means and standard deviations. The weighted mean follow-up duration was calculated according to study size. Both fixed- and random-effects models were used to calculate the pooled estimate rates and 95% confidence intervals (CIs) of the study outcomes. All tests were two-tailed, and a $P$ value $\leq 0.05$ was considered statistically significant. Next, heterogeneity testing was performed using the Higgins I$^2$ test, and an I$^2$ value of $>50\%$ was considered to indicate significant heterogeneity. Also, we performed a sensitivity analysis to evaluate whether the summary estimate of the effect could have been significantly affected by a single study. For this purpose, pooled estimates were recalculated using a random-effects model by excluding one study at a time. Publication bias was calculated using the Egger method ($P$ for significant asymmetry, $<0.1$). All analyses were conducted using STATA software Ver. 15.5 (StataCorp, College Station, TX, USA).

**Results**

Of 175 publications retrieved through the electronic
search, 5 studies comparing an active SB-P strategy versus the conventional SB-P strategy were identified and included (Figure 1). Quality assessment of the included studies is shown in Tables II, III. Due to the lack of disclosure of crucial information in these studies, some of the items assessed by the Cochrane Collaboration’s tool were rated as an unclear risk of bias.

Table IV shows the main characteristics of the included studies. Four were randomized controlled trials, and one was a retrospective cohort study. In the study by Dou et al., patients with an SB reference vessel diameter (RVD) of < 2.5 mm were randomly assigned to either the JBT or JWT group (other patients with an SB RVD of ≥ 2.5 mm were assigned to either an elective two-stent strategy or provisional stenting). However, most patients enrolled in the study received the JBT or JWT because
about 85.6% of patients exhibited an SB RVD of < 2.5 mm. In the other four studies, the patients were directly assigned to either an active or conventional SB-P strategy. Of the five included studies, three evaluated the long-term outcome of the two SB-P strategies with a mean follow-up period of 12.5 ± 6.0 months (range, 6-19.0 months). The baseline patient and lesion data are shown in Table V. Most of the patients were male, and the average age was > 60 years. Bifurcation lesions involving a lesion site in the left main artery accounted for a small proportion of the total population, and the lesions were mainly distributed in the left anterior descending artery. The patients demonstrated a high percentage of true bifurcation lesions, mainly type 1,1,1 by the Medina stratification.

Compared with the conventional SB-P strategy, the use of an active SB-P strategy was associated with a lower risk of SB occlusion [risk ratio (RR) 0.47, 95% CI 0.30-0.73 in fixed-effect model; RR 0.52, 95% CI 0.31-0.87 in random-effect model; I² = 11.9%] and a TIMI flow grade decrease in the SB (RR 0.38, 95% CI 0.21-
**Table V.** Baseline Patient and Lesion Characteristics of the Included Studies

| Study      | Dou 2020(1) | Jin 2019(2) | Qu 2019(3) | Lai 2018(4) | Kuno 2019(5) |
|------------|-------------|-------------|------------|-------------|-------------|
| Age, years | 60.8 ± 9.3/60.7 ± 10.1 | 65.4 ± 10.4/66.0 ± 8.8 | 62.0 (12) /59.5 (13) | NA          | 69.1 ± 8.3/67.8 ± 9.7 |
| Male       |             |             |            |             |             |
| Diabetes   |             |             |            |             |             |
| Angina     |             |             |            |             |             |
| Target lesion location |             |             |            |             |             |
| LM         |             |             |            |             |             |
| LAD        |             |             |            |             |             |
| LCX        |             |             |            |             |             |
| RCA        |             |             |            |             |             |
| Medina classification |             |             |            |             |             |
| 1,1,1      |             |             |            |             |             |
| 1,0,1      |             |             |            |             |             |
| 0,1,1      |             |             |            |             |             |
| Others     |             |             |            |             |             |
| LVEF, %    | 62.9 ± 8.8/61.2 ± 8.9 | NA          | 59.2 ± 10.1/60.4 ± 8.0 | NA          | NA          |
| PCI indications |             |             |            |             |             |
| STEMI      |             |             |            |             |             |
| NSTEMI     |             |             |            |             |             |
| MI elective PCI |             |             |            |             |             |

Data are presented as median ± standard deviation or median (interquartile range) for continuous and as percentage for categorical variables. NA indicates not available; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LM, left main artery; LAD, left anterior descending artery; LCX, left circumflex artery; and RCA, right coronary artery.

Figure 2. Forest plot of SB occlusion, TIMI flow grade decrease in SB and absence of blood flow in SB in fixed- (A) and random- (B) effect models. SB indicates side branch; and TIMI, thrombolysis in myocardial infarction.
of the absence of blood flow in the SB, PMI, and long-
term MACEs, the pooled RRs did not substantially change
after excluding each study in turn. No publication bias
was found, as assessed by Egger’s test ($P = 0.55$), for the
outcome of SB occlusion. Lastly, we did not evaluate the
publication bias for other endpoints because of the limited
number of studies involved.

Discussion

Because a provisional SB stenting strategy is associ-
ated with a risk of SB occlusion after main vessel stenting
in bifurcation lesions, different SB-P techniques have been
developed to preserve the patency of the SB. The conven-
tional SB-P strategy of the JWT has been proven to be as-
sociated with reduced SB occlusion. More active SB-P
strategies such as the JBT, BSKT, and JCT are thought to
be more effective in this regard because of more pro-
nounced space occupation in the SB ostium. However,
this advantage of active SB-P strategies has only been
supported by single-arm studies, thus, weakening the
conviction. Only a few studies directly compared the ef-
fects of conventional and active SB-P strategies, and the
results of the studies were inconclusive. To obtain a
more precise estimation of these two strategies, we per-
formed a meta-analysis of 5 studies involving 1,174 pa-
tients with bifurcation lesions.

The three main findings of the present meta-analysis
can be summarized as follows. (1) An active SB-strat-
egy was associated with a lower rate of SB occlusion,
mainly driven by a significantly lower incidence of a
TIMI flow grade decrease. (2) No significant difference
was found in the rate of PMI between conventional and
active SB-P strategies. (3) The two groups showed a simi-
lar incidence of MACEs at the long-term follow-up.

Different from the conventional SB-P strategy, active
SB-P strategies are characterized by higher occupation
of the SB ostium by a balloon or microcatheter, leading to
maximization of SB patency. However, the pooled RR was significantly changed, suggesting that the
result of the comparison of SB occlusion between the two
groups was not sufficiently reliable and should be inter-
preted with caution. The possible reasons for the sensitiv-
ity of this study are as follows. First, the patients enrolled
in the study by Dou, et al. presented with bifurcation le-
sions with a high risk of SB occlusion, defined as a V-
RESOLVE score of ≥12 points, and detecting the ad-
advantage of reducing SB occlusion might be easier in the
active than conservative SB-P group. Second, a small sub-
set of patients in the authors’ experimental group received
an elective two-stent strategy (SB RVD of ≥2.5 mm),
which may have decreased the incidence of SB occlusion
in the active SB-P group of our study, although it has
been well demonstrated that the effect of reducing SB oc-

Figure 3. Forest plot of PMI in fixed- (A) and random- (B) effect models. PMI indicates periprocedural myocardial infarction.

Figure 4. Forest plot of long-term MACEs in fixed- (A) and random- (B) effect models. MACEs indicates major adverse cardiovascular events.
clusion in the experimental group is driven mainly by a provisional SB stenting strategy with the JBT technique. 30) PCI of coronary bifurcation lesions is associated with an increase in PMI, and patients with SB occlusion (even those with a small SB occlusion) exhibit a significantly higher incidence of PMI than those without SB occlusion. 31,32) Our meta-analysis showed that the active SB-P group tended to exhibit a lower incidence of PMI in the context of decreasing SB occlusion, but the difference was not statistically significant. Several possible reasons for this result may exist. First, PMI was not the primary endpoint of the included studies; thus, the sample size for the evaluation of PMI was insufficient. 39-41) Second, the definitions of PMI of the included studies were relatively conservative. 39,41) They only reflected a large MI and thus, lost diagnostic sensitivity. 51) However, most of the patients in our analysis exhibited a small SB RVD, so occlusion of the SB may not be sufficient to cause PMI, as defined in the studies, and the role of SB-P strategies may also be underestimated. Notably, as previously reported, any increase in the creatine kinase-MB concentration after PCI is associated with varying degrees of statistically significant adverse clinical outcomes. 46,47) Third, the successful salvage of acute SB occlusion through rewiring and subsequent intervention in the SB by experienced interventionists in these studies may have further reduced the incidence of PMI. 39-41) Finally, although SB occlusion is the most common mechanism of PMI, other significant causes include distal embolization, slow flow or no reflow, and other conditions 35,36) that were not detailed in the included studies. 39-41) PMI of these causes can hardly be reduced through improvement of an SB-P strategy.

As shown in our meta-analysis, no significant difference was found in long-term MACEs between the active and conventional SB-P strategies. Some previous studies showed that patients with and without SB occlusion exhibited a comparable prognosis with respect to MACEs during follow-up. 19,21) Conversely, Hahn, et al. showed that patients with SB occlusion exhibited worse clinical outcomes than patients without SB occlusion, and they attributed this discrepancy to a larger SB and inclusion of left main bifurcation lesions in their study. 40) Patients included in our meta-analysis mainly exhibited a small SB with few left main lesions, 19,18,20) so the lack of a prognostic benefit of an active SB-P in decreasing SB occlusion was not unexpected. In addition, in a study with a 2.7-year follow-up, the JBT was associated with a significantly lower rate of MACEs than were non-JBT procedures. 41) Therefore, our analysis may be limited by the scarcity of published long-term data, and we can expect to observe the advantage of active SB-P strategies in reducing MACEs by extending the follow-up time.

Our study demonstrated several limitations. First, the quality of included studies was relatively low, especially RCT studies highlighting a number of methodological weaknesses including the inadequate description of methods of randomization, allocation concealment, and blinding. Second, most of the included studies exhibited a small sample size and a short follow-up time, which limit our ability to draw firm conclusions. Third, five of the five studies included in this meta-analysis, one was an observational study, which may have introduced confounders and resulted in biased results. However, no significant heterogeneity was found in our analysis, and the sensitivity analysis showed that the combined RRs of all endpoints were consistent and without apparent fluctuation after omitting this observational study. Fourth, the SB of bifurcation lesions involved in our analysis was relatively small and may not be representative of all lesions. Most of the included studies did not assess the complexity of the bifurcation, which prevented us from further differentiating the SB-P strategies most suitable for lesions of varying degrees of complexity. Finally, all data in this meta-analysis were from Asian (mostly Chinese) medical centers, reducing the ability to generalize our results to other populations.

Conclusion
In patients with coronary bifurcation lesions undergoing a provisional SB stenting strategy, the active SB-P strategy was associated with a significantly lower rate of SB occlusion than was the conventional SB-P strategy. No significant difference was found in the incidence of PMI or long-term MACEs between active and conventional SB-P strategies.

Disclosure
Conflicts of interest: All authors declare that no conflict of interest requiring disclosure exists.

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