REVIEW ARTICLE

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Crush is superior to Culotte in two-stent strategy for treatment of left main coronary artery bifurcations: A systematic review and meta-analysis

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Abstract

Purpose: Crush and Culotte techniques have been used increasingly to treat patients with complex unprotected left main coronary artery bifurcation lesions. This article compares published data on these two techniques.

Methods: Databases, including PubMed, Embase, Cochrane Library, Wanfang Data and China National Knowledge Infrastructure, were searched for articles published before Aug 21, 2019 to identify all relevant studies on left main coronary artery bifurcation lesions treated by Crush versus Culotte techniques. The pooled data were analyzed using either fixed- or random-effects model depending on heterogeneity (assessed via the I^2 index). The endpoints were major adverse cardiac events, target lesion revascularization, cardiac death, stent thrombosis, myocardial infarction and target vessel revascularization.

Results: Eight articles with a total of 1,283 patients were included, and 710 patients were treated with Crush, and 573 ones with Culotte. Crush group was trend to decreased major adverse cardiac event compared with Culotte group [Relative ratio (RR) 0.63,95% confidence interval(CI) 0.39-1.04, I^2 =72.7%], mainly driven by decreased cardiac death [RR 0.49, 95% CI(0.25-0.99), I^2 =0%], decreased myocardial infarction [RR 0.40, 95% CI(0.21-0.76), I^2 =21.6%],and lower stent thrombosis [RR 0.39, 95% CI(0.16-0.98), I^2 =39.4%]. There was no significant difference in target lesion revascularization and target vessel revascularization between Crush and Culotte [RR 0.77, 95% CI 0.46-1.28, I^2 =61.1%; RR 0.78, 95% CI (0.30-2.02), I^2 =73.1%, respectively].

Conclusion: Crush was superior to Culotte for treatment of left main coronary artery bifurcation lesions with a trend of lower incidence of long-term major adverse cardiac events, mainly derived from decreased myocardial infarction, stent thrombosis and cardiac death.

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Introduction

Left main coronary artery lesion (stenosis of left main lumen of over 50%, detected by angiography or other intracoronary imaging devices) accounts for approximately 4%–6% of all coronary angiograms and almost 70% of these lesions are bifurcations [1-3]. Coronary artery bypass grafting remains the standard recommendation for unprotected left main coronary artery lesion [4, 5].

With major progress in stent structure and eluted drugs for treatment of unprotected left main coronary artery bifurcation lesions (ULMCABLs) with low-to-moderate SYNTAX scores [6-7], an increasing number of trials supported the feasibility of percutaneous coronary intervention (PCI) in "real-world" study populations selected and treated in experienced medical centres [8,9]. The strategy for treating with ULMCABLs depends primarily on the SNYTAX score: the simpler lesions are more often treated with PCI, whereas the more complex lesions are more often treated with coronary artery bypass grafting [10,11].

When performing PCI for ULMCABLs, if the lesion of left main coronary artery involves one branch only (e.g., Medina 1, 1, 0 or 1, 0, 1), one-stent strategy should be suitable [12-13]. While both vessels are significantly diseased, two-stent strategy is mostly needed (actually about 30%-70% ULMCABLs required) [14-16]. There are numerous options for two-stent techniques; including T-stent, Y-stent, Crush-based and Culotte-based techniques. Of these, Crush and Culotte techniques are commonly used in clinical practice and many studies have confirmed that they are safe and efficacious [17-19].

Nevertheless, Crush and Culotte are complicated techniques and the surgical outcomes may be impacted by many factors, such as plaque load, artery anatomy, bifurcation artery angle and operator's experience. It remains unclear which technique is better for treating with ULMCABLs [10,15,19]. This meta-analysis was performed to compare the long-term clinical outcomes of Crush and Culotte techniques for treating ULMCABLs.

Materials and methods

Search strategy

We searched PubMed, Embase, Cochrane Library, Wanfang Data and China National Knowledge Infrastructure for articles published before Aug. 21, 2019 to identify all relevant studies on Crush versus Culotte stenting in patients with ULMCABLs. We searched studies using the following key words and strategy: (crush [Title/Abstract]) AND left main [Title/Abstract])) AND ((culotte [Title/Abstract]) AND left main [Title/Abstract]).

Study selection

Duplicated studies were excluded through Endnote software, and then remaining studies were screened according to their titles or abstracts. Further screening was then performed based on the full text. The inclusive criteria were as follows: (1) the study design was cohort study or randomized controlled trial; (2) the study subjects were patients with left main coronary artery bifurcation who underwent PCI using Crush versus Culotte technique; (3) data on any of the following clinical outcomes, such as major adverse cardiac events (MACE), target lesion revascularization (TLR), cardiac death (CD), stent thrombosis (ST), myocardial infarction (MI) and target vessel revascularization (TVR), were available; and (4) articles were written in English or Chinese. Articles were excluded if they met any of the following criteria: (1) study was not designed as the head-to-head study of Crush versus Culotte; (2) data on clinical outcomes could not be extracted; (3) written in language other than English or Chinese; and (4) reviews.

Xiao-Rui Chen and Di-Yu Cui searched the databases, included or excluded the papers, and assessed and extracted the data from the included studies. If these two reviewers could not reach a consensus on any question, the third and the fourth reviewers (Yunqing Chen and Tie-Sheng Niu) were consulted.

Data extraction

The quality of the non-randomized studies was assessed using the Newcastle-Ottawa Scale (with a slight modification) [20] according to three parameters: patient selection; comparability; and assessment of outcome. The risk of bias and the quality of the randomized trials were assessed using the Cochrane Collaboration Assessment Tool in the RevMan software (version 5.3) [21]. The data extraction was performed independently at least twice by two authors (Xiao-Rui Chen and Di-Yu Cui) to ensure accuracy. The following information were extracted from each retrieved article: corresponding author; publication year; treatment allocation; age; sex; smoking; diabetes; hypertension; hypercholesterolemia; final kissing balloon dilatation (FKBD) rate; Medina style; and SYNTAX score.

The end-points were MACE, CD, MI, ST, TVR and TLR. All endpoints were defined according to Academic Research Consortium definitions [22].

Statistical analysis

Relative ratio (RR) was used to measure the effect size. Heterogeneity tests were performed using I^2 statistics, which is a quantitative measure of inconsistency across studies [23]. Pooled RR was calculated for Crush versus Culotte groups. If I^2 was less than 50%, the fixed-effects model was chosen; otherwise the random-effects model was used. The 95% confident interval (CI) was also calculated. Sensitivity analysis was conducted by omitting one study in each turn in order to investigate the influence of a single study on the overall risk and to estimate and test the stability of the results. Publication bias was evaluated using Begg's [24] and Egger's test [25]. The results are presented in forest plots. The RevMan 5.3 and Stata 15.1 (Stata Corp LP, College Station, Texas) were used for analysis. A two-tailed *P* value <0.05 was considered statistical significant.

Results

Screening studies and characteristic and quality assessment of included studies

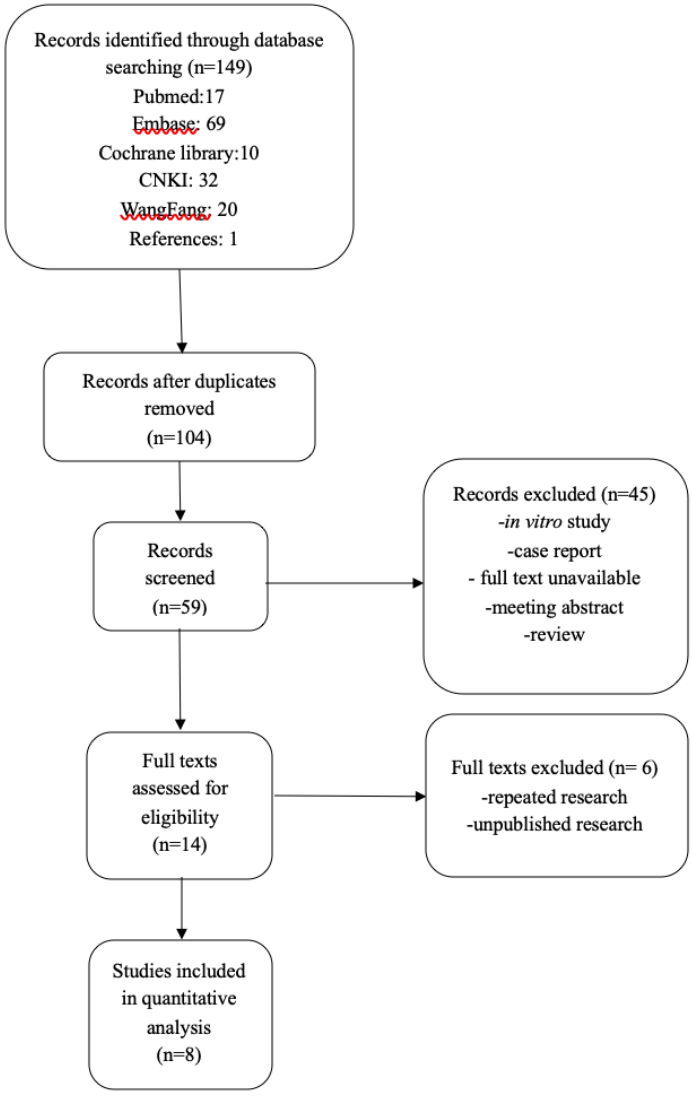
A total of 149 citations were screened and eight studies [15,26-32] were eventually included in the study. The process of study selection was shown in Figure 1. Of the eight included references, six references were full-text studies and two were abstract only. Two studies were randomized trials, and other six were observational studies, with a total of 1,283 patients, 710 patients treated with Crush and 573 with Culotte.

The characteristics of included studies are presented in Table 1, the clinical baseline characteristics in Table 2 and the follow-up of clinical outcomes in Table 3. The quality assessment was performed according to the randomized trial and the observational studies according to the Newcastle-Ottawa Scale (data are available upon request from the corresponding author).

Clinical outcomes.

Owing to absence of MACE data in Rigatelli 2018 [32], the MACE was analyzed using the other seven studies. Major adverse cardiac events tended to be lower in the Crush group [RR 0.63, 95% confidence interval (CI) (0.39-1.04), I^2 =72.7%] (see Figure 2). Because of the very small sample number in the study reported by Kervinen [15], fewer than 30 patients, this study was omitted and the data was reanalyzed: Crush significantly decreased the MACE compared with Culotte [RR 0.55,95%CI(0.34-0.88), I^2 =69.1%] (Figure 2).

FIGURE 1. Flow diagram showing the process of study selection



There was no significant difference in TLR and TVR between Crush and Culotte technique groups [RR 0.77, 95% CI (0.46-1.28), I^2 =61.1%; RR 0.78, 95% CI (0.30-2.02), I^2 =73.1%, respectively] (Figure 2).

Compared with the Culotte group, the Crush group decreased CD [RR 0.49, 95% CI(0.25-0.99), I^2 =0%], decreased MI [RR 0.40, 95% CI(0.21-0.76), I^2 =21.6%] and lowered ST [RR 0.39, 95% CI(0.16-0.98), I^2 =39.4%] (Figure 3).

Sensitivity analysis and publication bias

High heterogeneity was detected in MACE, TLR and TVR. We used several strategies to explore potential sources of heterogeneity and test the stability of the results. First, we performed sensitivity analysis by omitting each study in turn.

TABLE 1. Characteristic of included studies

Author/year	Type	Patients	Follow-up	Stent type	Comparison of procedure	Composite of MACE	MACE
		Crush/ Culotte					Crush/ Culotte (%), *P*-value
Chen 2015	RCT	210/209	3 years	1st-2nd DES	DK-Crush vs Culotte	CD, MI, TVR	8.2 vs 23.7, *P*<0.001
Kawamoto 2017	observational	135/90	5 years	1st-2nd DES	Mini-Crush vs Culotte	All-cause death, MI,TLR	36 vs 41.4, *P*=0.57
Pavani 2018	observational	104/68	2.27 years	2nd DES	Mini-Crush vs Culotte	All-cause death, MI,TVR	26.0 vs 31.0, *P*>0.05
Kervinen 2013	RCT	20/21	3 years	2nd DES	Crush vs Culotte	All-cause death, MI,TVR	40.0 vs 14.0, *P*=0.01
Maximkin 2017	NA	70/70	5 years	NA	Crush/Mini-Crush vs Culotte	MACE	0 vs 5.7, *P* <0.001
Rigatelli 2019	observational	32/33	27.4±10.8 months	2nd DES	Nano-Crush vs Culotte	CD, no-fatal MI, TLR	9.3 vs 54.4, *P* <0.05
Takagi 2014	observational	119/63	3 years	NA	Mini-Crush vs Culotte	CD, MI, TLR	24.4 vs 27.0, *P* =0.654
Rigatelli 2018	retrospective	20/19	3 years	2nd DES	Nano-Crush vs Culotte	NA	NA

Abbreviations: CD, cardiac death; DES, drug-eluting stent; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, no data available; RCT, randomized clinical trial; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization

TABLE 2. Clinical baseline characteristics of included studies (Crush vs. Culotte)

Author/ year	Age (years)	Female, %	Smoking, %	Diabetic, %	Hypertension, %	Hypercholesterolemia, %	FKBD, %	Medina, %		SNYTAX score
								1.1.1	0.1.1	
Rigatelli 2018	61.4±13.6/ 64.1±10.5	45/38.1	NA	30/19	NA	30/18.6	NA	85/76	NA	36.8±6.3/ 35.6±7.7
Kawamoto 2016	69.9±9.6/ 67.4±11.2	21.2/17.8	28.6/16.7	39.1/29.4	84.4/76.1	84.4/76.1	98.5/97.8	65.9/70	14.8/8.9	30.4±10.5/ 27.5±9.4‡
Chen 2015	64.3±10.3/ 63.3±9.2	22.9/20.1	45.2/43.5	31.9/30.1	70.5/61.2	41.4/42.1	99.5/99.5	98.7/94.8	1.3/5.2	NA
Rigatelli 2019	77.1±5.8/ 78.1±6.8	42.8/39.3	37.5/27.2	25/27.2	68.5/60.6	75/63.6	NA	75/51.5	25/48.1	26.3±7.2/ 21.4±4.8§
Pavani 2018	71±10/ 71±9.2	17.5/22	39/40	39.7/30	81/73.5	64.0/64.0	92.3/94.1	64.5/67.5	14.4/7.3	30±10.4/ 28±9.4 ns

Abbreviations: FKBD, final kissing balloon dilation; NA, no data available

* Study reported by Kervinen (2013) included patients with coronary artery bifurcations, so there were no details of left main coronary artery bifurcation lesions.

† Studies by Takagi (2014) and Maxinkin (2017) were abstract only and were therefore not included in this table.

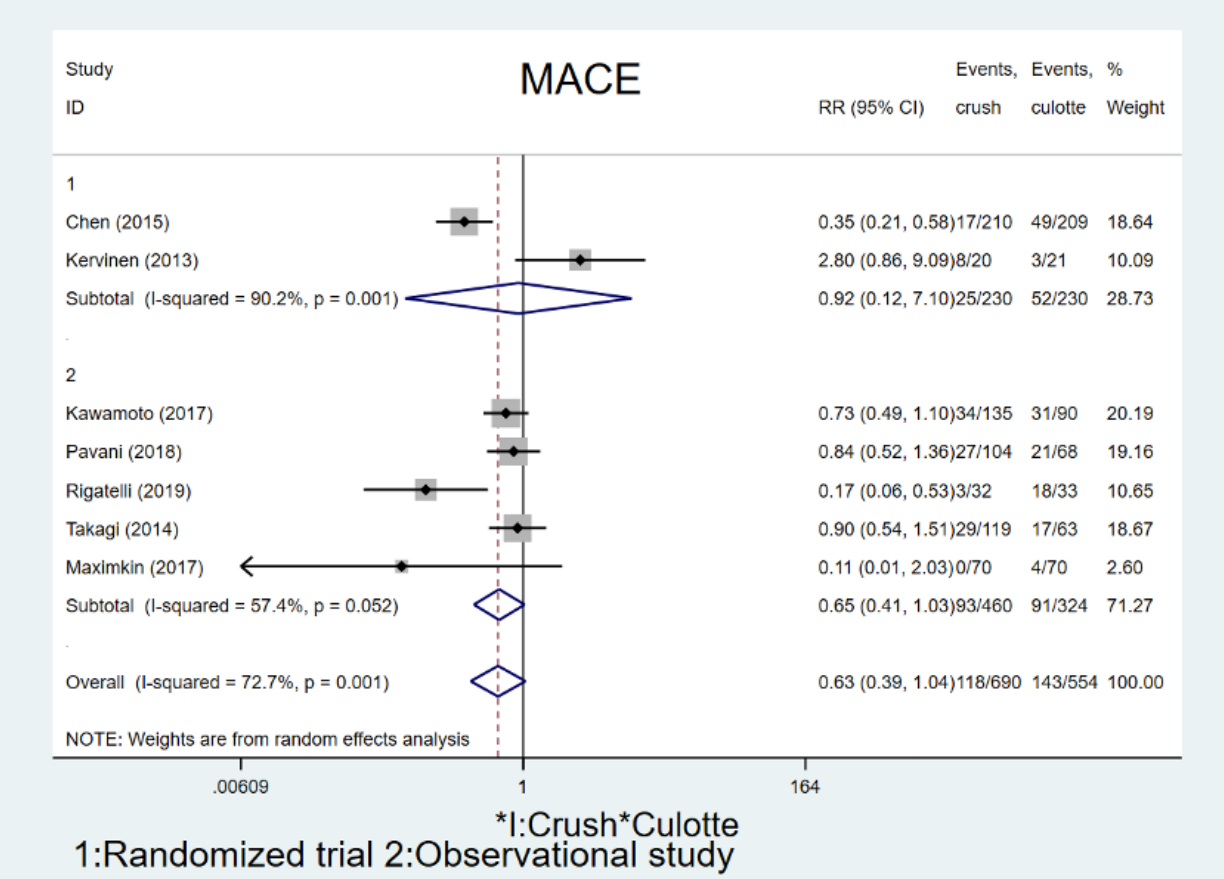
‡,§ Data are expressed as mean±SD; ‡*P*=0.04; §*P*=0.002

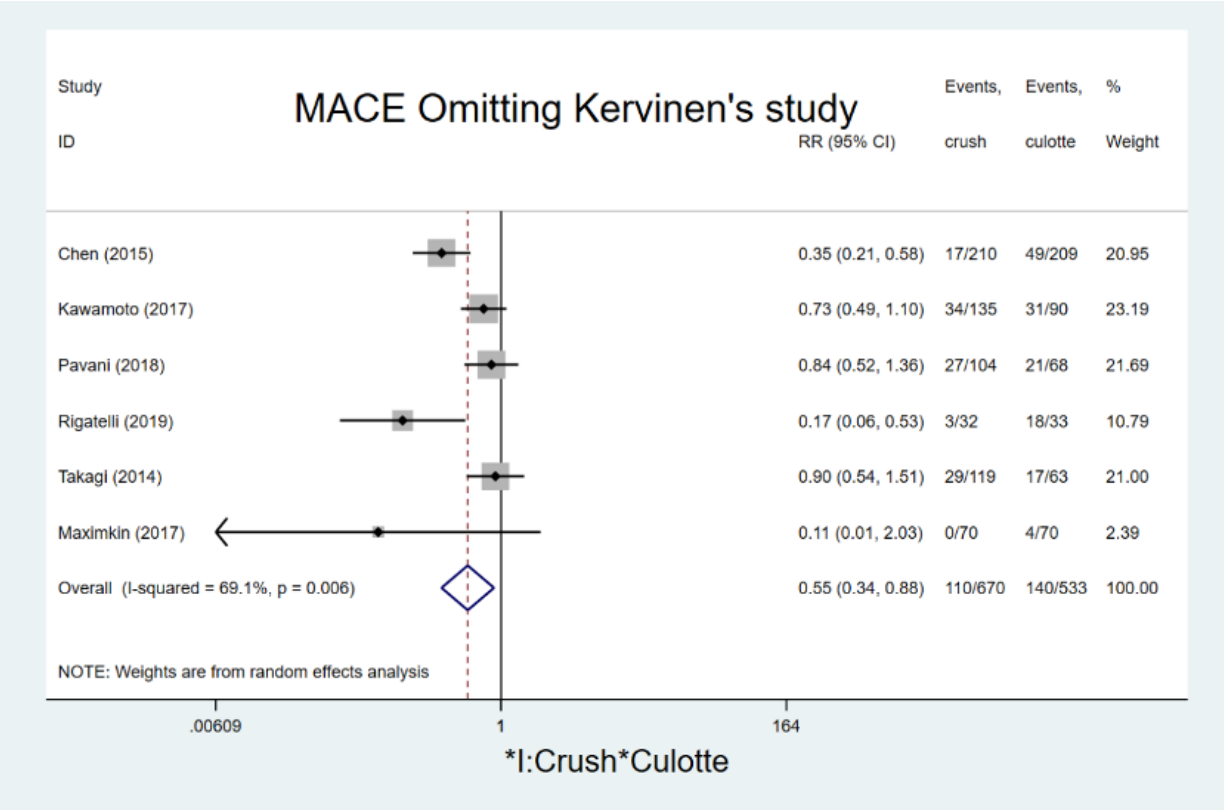
TABLE 3. Clinical outcomes of included studies

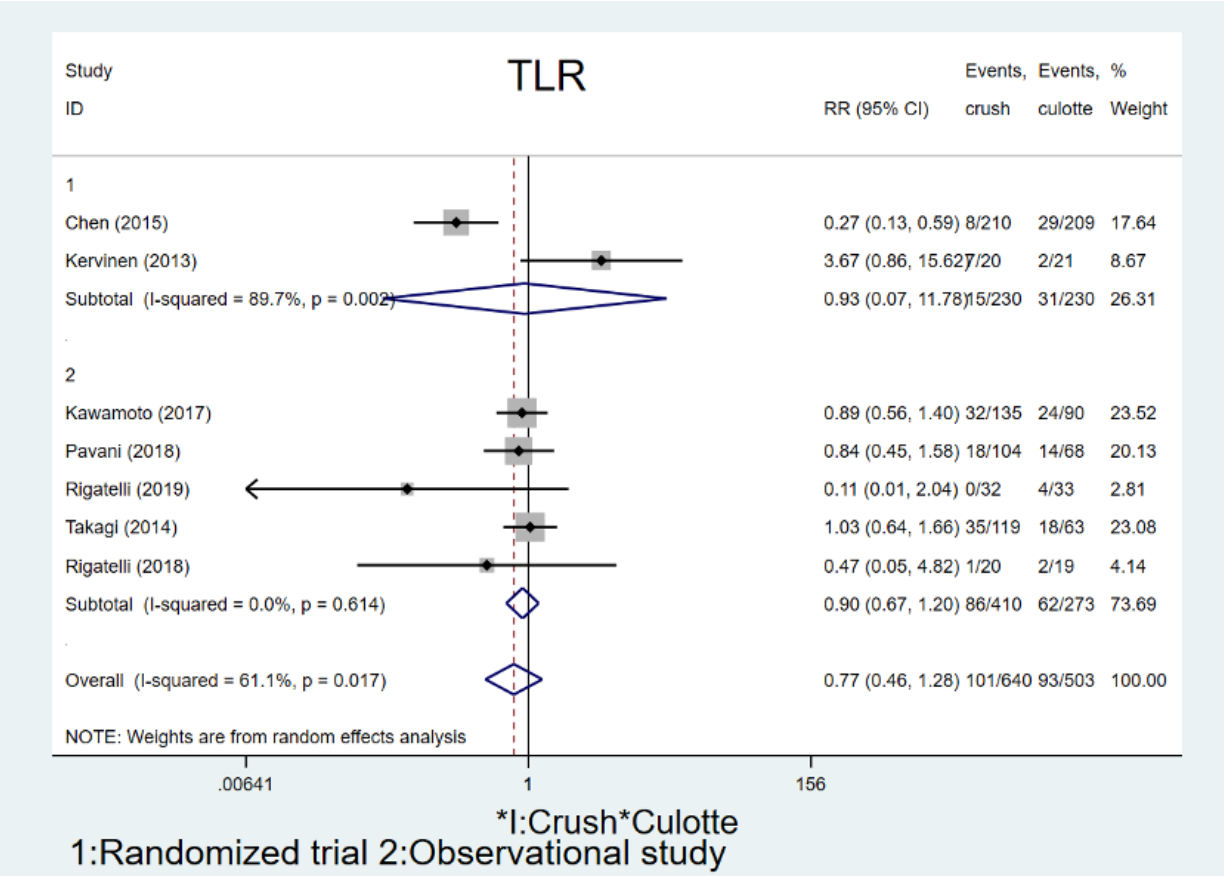
Author/ year	n		TLR		CD		MI		ST		TVR	
	Crush	Culotte	Crush	Culotte	Crush	Culotte	Crush	Culotte	Crush	Culotte	Crush	Culotte
Chen 2015	210	209	8(3.8%)	29(14.0%)	3(1.4%)	6(2.9%)	7(3.4%)	17(8.2%)	1(0.5%)	8(3.9%)	12(5.8%)	39(18.8%)
Kawamoto 2017	135	90	32(23.7%)	24(26.7%)	2(1.5%)	3(3.3%)	0(0%)	4(4.4%)	0(0%)	3(3.3%)	NA	NA
Pavani 2018	104	68	18(17.5%)	14(20.5%)	NA	NA	1(1.0%)	1(1.4%)	3(3.0%)	0(0%)	20(19.5%)	17(25%)
Kervinen 2013	20	21	7(35%)	2(9.5%)	1(5.0%)	0(0.0%)	2(10.0%)	0(0.0%)	1(5.0%)	0(0.0%)	7(35%)	2(9.5%)
Rigatelli 2019	32	33	0(0.0%)	4(12.1%)	2(6.2%)	8(24.2%)	1(3.1%)	6(18.1%)	0(0.0%)	2(6.0%)	NA	NA
Takagi 2014	119	63	35(29.4%)	18(28.6%)	3(2.5%)	2(3.2%)	NA	NA	NA	NA	NA	NA
Rigatelli 2018	20	19	1(5.0%)	2(10.5%)	1(5.0%)	2(10.5%)	NA	NA	NA	NA	1(5.0%)	1(5.2%)
Maximkin 2017	70	70	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

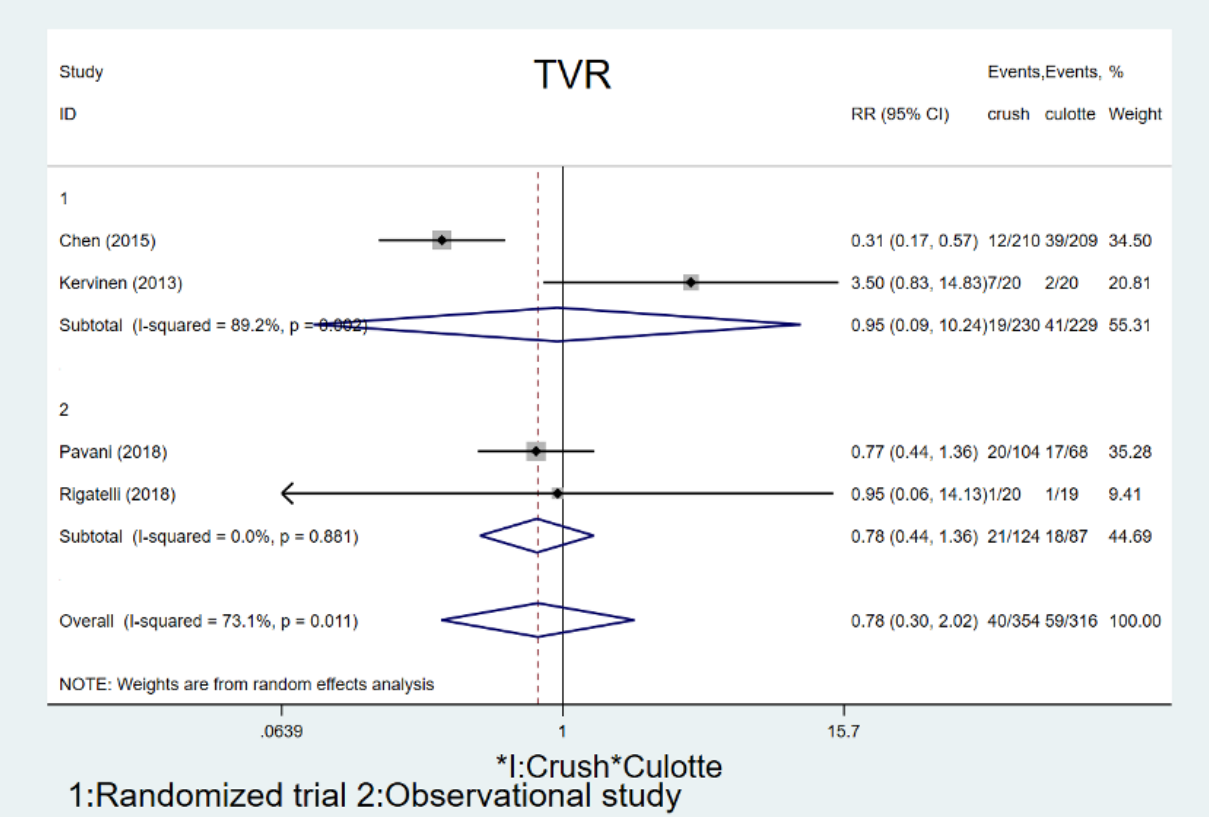
Abbreviations: CD, cardiac death; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization

FIGURE 2. Forest plots of MACE, TLR and TVR between Crush and Culotte groups.




Study
ID
MACE Omitting Kervinen's study
RR (95% CI)
Events, crush
Events, culotte
% Weight
Chen (2015) 0.35 (0.21, 0.58) 17/210 49/209 20.95
Kawamoto (2017) 0.73 (0.49, 1.10) 34/135 31/90 23.19
Pavani (2018) 0.84 (0.52, 1.36) 27/104 21/68 21.69
Rigatelli (2019) 0.17 (0.06, 0.53) 3/32 18/33 10.79
Takagi (2014) 0.90 (0.54, 1.51) 29/119 17/63 21.00
Maximkin (2017) 0.11 (0.01, 2.03) 0/70 4/70 2.39
Overall (I-squared = 69.1%, p = 0.006) 0.55 (0.34, 0.88) 110/670 140/533 100.00
NOTE: Weights are from random effects analysis
.00609
1
164
*I:Crush*Culotte


Study
ID
TLR
RR (95% CI)
Events, crush
Events, culotte
% Weight
1
Chen (2015) 0.27 (0.13, 0.59) 8/210 29/209 17.64
Kervinen (2013) 3.67 (0.86, 15.62) 7/20 2/21 8.67
Subtotal (I-squared = 89.7%, p = 0.002) 0.93 (0.07, 11.78) 15/230 31/230 26.31
2
Kawamoto (2017) 0.89 (0.56, 1.40) 32/135 24/90 23.52
Pavani (2018) 0.84 (0.45, 1.58) 18/104 14/68 20.13
Rigatelli (2019) 0.11 (0.01, 2.04) 0/32 4/33 2.81
Takagi (2014) 1.03 (0.64, 1.66) 35/119 18/63 23.08
Rigatelli (2018) 0.47 (0.05, 4.82) 1/20 2/19 4.14
Subtotal (I-squared = 0.0%, p = 0.614) 0.90 (0.67, 1.20) 86/410 62/273 73.69
Overall (I-squared = 61.1%, p = 0.017) 0.77 (0.46, 1.28) 101/640 93/503 100.00
NOTE: Weights are from random effects analysis
.00641
1
156
*I:Crush*Culotte
1:Randomized trial 2:Observational study



Abbreviations: MACE, major adverse cardiac events; TLR, target lesion revascularization; TVR, target vessel revascularization

The results did not materially alter the overall combined RR, with a range from 0.58 (95%CI: 0.42 to 0.80; p=0.001) to 0.68 (95%CI: 0.57 to 0.81; p<0.001). Second, according to the analysis of subgroup classified via randomized trial or observational study, high heterogeneity were found from randomized trial (Figure 2). Third, using Stata 15.1, the study of Chen [29] was found to contribute the source of heterogeneity (data are available upon request from the corresponding author).

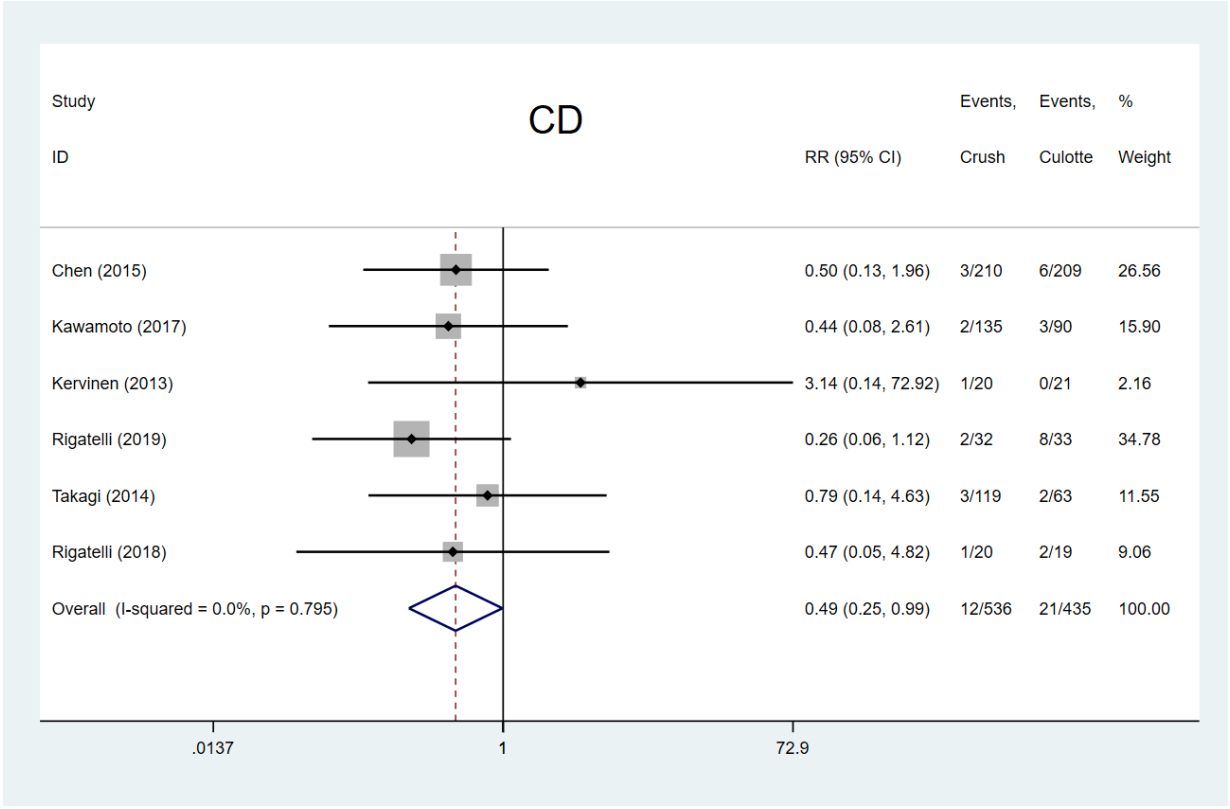
Publication bias was evaluated using Begg's and Egger's test, and no publication bias was found among the included studies for MACE (Begg test z=0.75, p=0.452;, p=0.71; Egger test, t=-0.09, p=0.931), TLR (Begg test z=0.38, p=0.707; Egger test, t=-1.41, p=0.231), TVR (Begg test z=0.34, p=0.734; Egger test, t=0.03, p=0.980), CD (Begg test z=0.24, p=0.806; Egger test, t=2.22, p=0.113), MI (Begg test z=0.0, p=1.0; Egger test, t=5.03, p=0.125) and ST (insufficient observations).

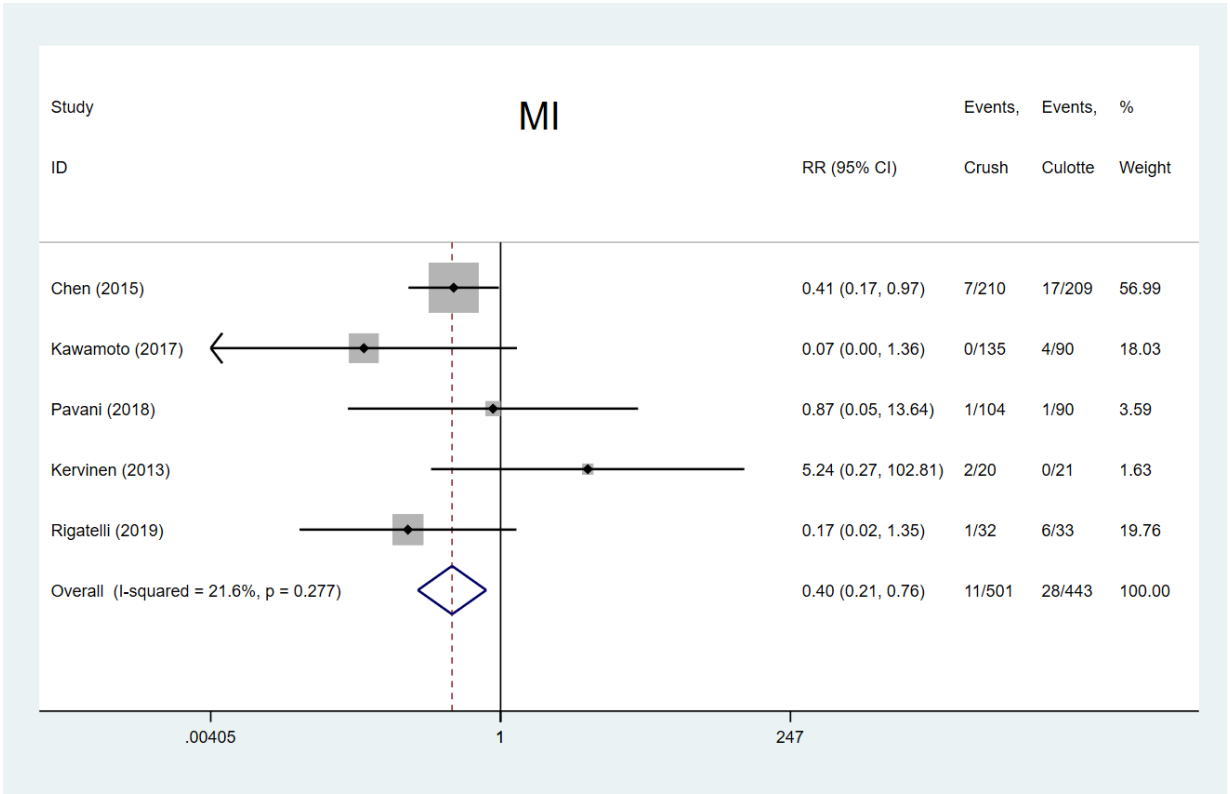
Discussion

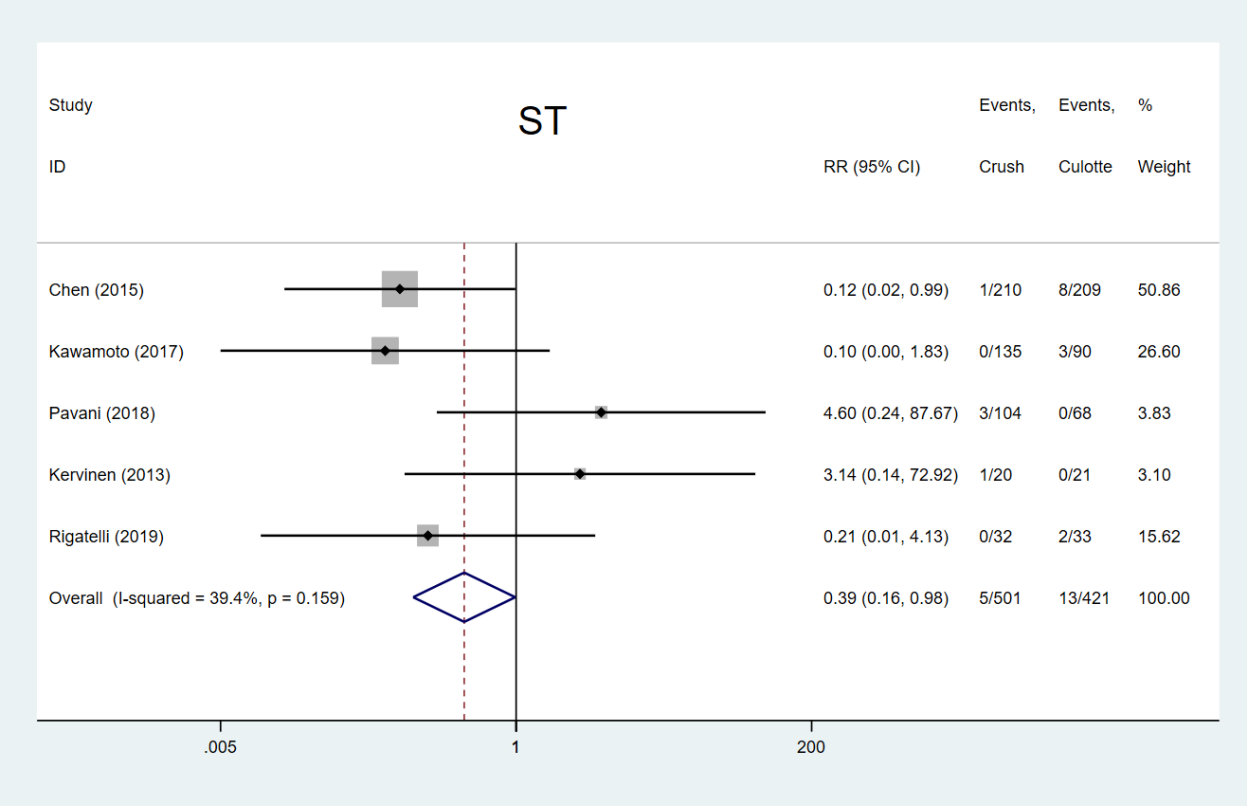
This meta-analysis is the first to evaluate the clinical outcomes of Crush versus Culotte techniques for treatment of ULMBs. The main findings were that, in comparison with the Culotte technique, the Crush technique tended to decrease the long-term MACE and significantly decreased CD, MI and ST. Thus, the Crush technique is superior to Culotte for treatment of ULMCABLs.

When PCI is needed to treat complex ULMCABLs—which often presents with two diseased branch arteries—two-stent strategies are usually used. Two-stent strategies include T-stent, Crush and Culotte techniques [17-19] and Crush and Culotte technique are now more and more commonly used. The Crush technique includes Step-, Nano-, Mini- and double dissing (DK) Crush (DK-Crush). Similarly, the Culotte technique includes Mini-, Inverted- and DK-Culotte. The major characteristic of Crush stenting is pre-staying a balloon for the Crushing side-branch (SB) stent (Step-Crush) before main-branch stent deployment. Mini-Crush means the length of the SB stent is less 3 mm. The major advantages of Crush technique are good coverage of SB ostium and facilitating to complete FKBD as well. The Culotte technique has overlapped stents of two branch stents in main artery. This may benefit for well stent covering of lesions in two branch arteries. But, Culotte is more complex in steps of procedure than that of Crush and need more time of operation and fluoroscopy, more contrast medium

FIGURE 3: Forest plots of CD, MI and ST between Crush and Culotte groups.







Abbreviations: CD, cardiac death; MI, myocardial infarction; ST, stent thrombosis

volume, and more dose area product [29, 30, 32]. The FKBD and the proximal optimization technique are needed to acquire a better immediate imaging effect and to decrease short- and long-term cardiovascular events. Increasingly, procedures of two-stent strategy for treatment of ULMBs are guided by intracoronary imaging system, such as optical coherence tomography and intravascular ultrasound [13-15].

The selection of the type of procedure for two-stent deployment, whether Crush or Culotte, is depended upon a number of factors, including the diameters of the main and branch coronary arteries, the angle of bifurcation of the arteries and the experience of operators [2]. Short- and long-term MACE are considered as key parameters to evaluate the safety and efficacy of dual stenting techniques. In this meta-analysis, there was a trend of lower long-term MACE in the Crush versus Culotte groups (Figure 2; RR 0.63, 95% CI: 0.39-1.04), despite of high heterogeneous (I2=72.7%). From the subgroup analysis, the high heterogeneous mainly come from the randomized studies group with I2 of 90.2%, while observational studies only with I2 of 57.4% (Figure 2). After analyzing the sensitivity of MACE using STATA software, we found that the study reported by Chen [29] was the main cause of the high heterogeneity, because better MACE was achieved using DK-Crush vs Culotte (data available upon request from the corresponding author). Chen reported that the DK-Crush technique significantly decreased the 3-year MACE compared with the Culotte technique (8.2% vs 23.7%, P<0.001) as described in the DKCRUSH-III Study [29]. When the study by Kevenen [15] was omitted because of the very small sample number, Crush significantly decreased the MACE compared with Culotte [0.55, 95%CI (0.34-0.88), I2 =69.1%] (Figure 2). This result was mostly was driven by improved clinical outcomes of CD, MI and ST (see Figure 3), and all of the heterogeneity was low. These results were different from the meta-analysis conducted by Chen [33], who reported that the clinical outcomes of MACE, CD, MI and ST were not significantly different when comparing Crush with Culotte in the treatment of coronary bifurcation lesions (CBLs). There were some similarities between two meta-analysis reported by Chen [33] and the results of our present study. Chen's study focused on CBLs, while ours focused on ULMCABLs. Therefore, although the bifurcation lesions are similar, the conclusions derived from CBLs may not be applicable to ULMCABLs due to the different artery anatomy, more important function and more restricted rules for intervening with ULMCABLs. The

MACE include all-cause death, MI, ST, TVR and TLR. The definitions of all-cause death were considered to be of cardiac origin, unless a noncardiac origin was established clinically or at autopsy in studies reported by Chen, Rigate and Takagi [29-31]. However, non-cardiac death was not reported in these studies. The population of death may mean all-cause death. Stent thrombosis is usually considered to be a very important index for the assessment of the procedural safety of stenting technique. The rate of ST impacts the results of MI, CD and MACE. In our meta-analysis, under very low heterogeneities, the Crush technique significantly improved the long-term outcomes of CD, MI and ST. From the included studies, only the DKCRUSH-III study [29] indicated that the DK-Crush significantly decreased MI and ST, and tended to lower the CD. Thus, decreased ST can significantly improve the clinical outcomes of CD and MI. These results may be attributed to two factors. First, DK-Crush had very high rate of FKBD, which was as high as 99.5% and much higher than that of other studies. The higher rate of FKBD may be attributable to the character of DK-Crush: an intermediate kissing balloon dilation prior to MB stenting facilitates rewiring or/and balloon crossing, resulting in a greater chance of successful FBKD, and successful FBKD has been shown to result in better long-term outcomes with the two-stent technique. Second, the differences in clinical outcome can be attributed to the different spatial relationships of two stents in the Crush vs Culotte techniques. Crush techniques are no named as the SB stent is crushed by the MB stent to vascular wall, with a side-to-side relationship between the two stents. But the Culotte technique results in the two stents overlapping each other. Technically, this tighter interaction between two stents has more chance to cause incorrect positioning between the two stent or between the stent and the vessel, and thus lead to ST [15-18]. These results from our meta-analysis also indicated that the Crush technique may lead to better long-term clinical outcomes in treatment of ULMCABLs than bifurcation lesions, with the exception of the left main coronary artery.

In this meta-analysis, TLR and TVR were similar between Crush and Culotte techniques, with high heterogeneity [RR 0.77, 95% CI (0.46-1.28), I^2 =61.1%; RR 0.78, 95% CI (0.30-2.02), I^2 =73.1%, respectively] (Figure 2). These results were similar to those of the meta-analysis reported by Chen [33]. A limitation is the TVR data cannot be extracted from three of the studies. Actually, many interventional cardiologists prefer TLR to assess the stent skill because TLR belongs to TVR and TLR is more important. The TLR is generally considered to be a key parameter for evaluation of the long-term efficacy of stenting techniques. From the included studies, only the DKCRUSH-III study showed that DK-Crush significantly decreased TLR and TVR compared with Culotte for treatment of patients with ULMCABLs.

In the present meta-analysis, the high heterogeneity of MACE, TLR and TVR were observed. First, using sub-group analysis according to the study design (randomized trial or observational study), the source of high heterogeneity was found from a randomized trial (Figure 2). Second, sensitivity analysis was conducted using STATA software, and found that the study reported by Chen [29] accounted for the main source of high heterogeneity of MACE, TLR and TVR (data are available upon request from the corresponding author). Because of the advantage of technique, the procedure of double kissing balloon, the DK-Crush technique significantly decreased the 3-year MACE, MI and ST compared with the Culotte technique. These results were better than others and showed that the DK-Crush technique resulted in the best long-term clinical outcomes among the dual-stent strategies for treatment of ULMCABLs.

Limitations

Nevertheless, there were some limitations to our study. First, the sample number was small, with a total of 1,283 patients included—710 patients were treated with Crush and 573 with Culotte techniques. Second, only two randomized trials were included in our study. High heterogeneity occurred in the two included randomized trials, and the DKCRUSH-III Study showed much better results than that of Kervinen's study. Third, the complexity of ULMCABLs, such as the angle, diameter and calcified degree of diseased arteries, the SYNTAX score and the generation of drug-eluting stents, was not analyzed. Fourth, the comparison was conducted between Crush and Culotte techniques, but each member of these types of two-stent techniques may cause different results. For the above confounders, well designed randomized clinical trial with larger sample size is needed to verify the efficacy of Crush and Culotte techniques for treatment of ULMCABLs.

Conclusions

According to our meta-analysis, as far as the treatment of unprotected left main coronary bifurcation lesions is concerned, although the long-term TLR and TVR were not different between the Crush and Culotte techniques, MACE was showed a decreased trend and CD, MI and ST were significantly improved in the Crush group vs the Culotte

group. Crush, particularly DK-Crush, appears to be superior to Culotte for treatment of ULMCABLs.

References

1. Ragosta M. Left main coronary artery disease: importance, diagnosis, assessment, and management. *Curr Probl Cardiol.* 2015;40 (3):93-126.
2. Lassen JF, Holm NR, Banning A, et al. Percutaneous coronary intervention for coronary bifurcation disease: 11th consensus document from the European Bifurcation Club. *EuroIntervention.* 2016; 12(1):38-46.
3. D'Ascenzo F, Chieffo A, Cerrato E, et al. Incidence and management of restenosis after treatment of unprotected left main disease with second-generation drug-eluting stents (from Failure in Left Main Study With 2nd Generation Stents – Cardiogroup III Study). *Am J Cardiol.* 2017; 119 (7):978-982. DOI: 10.1016/j.amjcard.2016.12.005
4. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014; 35(37):2541–619.
5. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/ AHA/ SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011; 58(24): e44–122.
6. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation*. 2010; 121(24):2645–53.
7. Capodanno D, Di Salvo ME, Cincotta G, et al. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. *Circ Cardiovasc Interv*. 2009; 2 (4):302–8.
8. Pyxaras SA, Hunziker L, Chieffo A, et al. Long-term clinical outcomes after percutaneous coronary intervention versus coronary artery bypass grafting for acute coronary syndrome from the DELTA registry: a multicentre registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment." *EuroIntervention.* 2016;12(5): e623-31. doi: 10.4244/EIJV12I5A102
9. Chieffo A, Tanaka A, Giustino G, et al. The DELTA 2 Registry: A Multicenter Registry Evaluating Percutaneous Coronary Intervention With New-Generation Drug-Eluting Stents in Patients With Obstructive Left Main Coronary Artery Disease. *JACC Cardiovasc Interv.* 2017; 10 (23):2401-10. DOI: 10.1016/j.jcin.2017.08.050
10. Burzotta F, Lassen JF, Banning AP, et al. Percutaneous coronary intervention in left main coronary artery disease: the 13th consensus document from the European Bifurcation Club. *EuroIntervention.* 2018; 14(1):112-120
11. Blachutzik F, Achenbach S, Röther J, et al. Percutaneous coronary intervention of unprotected left main stenoses–procedural data and outcome depending on SYNTAXI Score. *Cardiovasc Revasc Med.* 2018; 19 (7 Pt A):740-743.
12. Chen SL, Zhang JJ, Han Y, et al. Double Kissing Crush Versus Provisional Stenting for Left Main Distal Bifurcation Lesions: DKCRUSH-V Randomized Trial. *J Am Coll Cardiol.* 2017;70(21):2605-2617.
13. Song YB, Hahn JY, Yang JH, et al. Differential prognostic impact of treatment strategy among patients with left main versus non-left main bifurcation lesions undergoing percutaneous coronary intervention: results from the COBIS (Coronary Bifurcation Stenting) Registry II. *JACC Cardiovasc Interv.* 2014; 7 (3):255–63.
14. Kim YH, Park DW, Ahn JM, et al. Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study. *JACC Cardiovasc Interv.* 2012; 5(7):708-717.
15. Kervinen K, Niemela M, Romppanen H, et al. Clinical outcome after crush versus culotte stenting of coronary artery bifurcation lesions: the Nordic Stent Technique Study 36-month follow-up results. *JACC Cardiovasc Interv.* 2013; 6 (11):1160–5.
16. Jang WJ, Song YB, Hahn JY, et al. Impact of bifurcation stent technique on clinical outcomes in patients with a Medina 0,0,1 coronary bifurcation lesion: results from the COBIS (COronary BIfurcation Stenting) II registry. *Catheter Cardiovasc Interv.* 2014; 84 (5): E43–50.
17. Roh JH, Santoso T, Kim YH. Which technique for double stenting in unprotected left main bifurcation coronary lesions? *EuroIntervention.* 2015;11 Suppl V: V125-8.
18. Rigatelli G, Zuin M, Dell'Avvocata F, et al. Evaluation of coronary flow conditions in complex coronary artery bifurcations stenting using computational fluid dynamics: Impact of final proximal optimization technique on different

double-stent techniques. *Cardiovasc Revasc Med.* 2017;18(4):233-240.
19. Foin N, Alegria-Barrero E, Torii R,et al. Crush, culotte, T and protrusion: which 2-stent technique for treatment of true bifurcation lesions? - insights from in vitro experiments and micro-computed tomography. *Circ J*. 2013;77(1):73-80.
20. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
21. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011; 343: d5928.
22. Cutlip DE, Windecker S, Mehran R,et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344-51.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327:557–60.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-34.
25. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. *J Natl Cancer Inst*. 1989;81(2):107-15.
26. Kawamoto H, Takagi K, Chieffo A, et al. Long-term outcomes following mini-crush versus culotte stenting for the treatment of unprotected left main disease: Insights from the milan and New-Tokyo (MITO) registry. *Catheter Cardiovasc Interv.* 2017;89(1):13-24. doi: 10.1002/ccd.26654.
27. Pavani M, Conrotto F, Cerrato E, et al. Long-Term Outcomes of Different Two-Stent Techniques With Second-Generation Drug-Eluting Stents for Unprotected Left Main Bifurcation Disease: Insights From the FAILS-2 Study. *J Invasive Cardiol.* 2018;30(8):276-281.
28. Maximkin, DA , Shugushev Z , Goloshchapov-Aksenov R, et al. Five-year results of endovascular treatment of patients with left main coronary arteries bifurcation lesions. *Eur Heart J*. 2013; 34: P4823
29. Chen SL, Xu B, Han YL, et al. Clinical Outcome After DK Crush Versus Culotte Stenting of Distal Left Main Bifurcation Lesions: The 3-Year Follow-Up Results of the DKCRUSH-III Study. *JACC Cardiovasc Interv*. 2015; 8 (10):1335-42.
30. Rigatelli G, Zuin M, Vassilev D, et al. Culotte versus the novel nano-crush technique for unprotected complex bifurcation left main stenting: difference in procedural time, contrast volume and X-ray exposure and 3-years outcomes. *Int J Cardiovasc Imaging*. 2019; 3 (2) 5:207-214.
31. Takagi K, Chieffo A, Naganuma T, et al. The comparison between mini-crush and culotte stenting on mid-term clinical outcome in patients with unprotected left main. *EuroIntervention*. 2014. https://pcronline.com/eurointervention/AbstractsEuroPCR2014/128.
32. Rigatelli G, Zuin M, Dinh H, et al. Long-term outcomes of left main bifurcation double stenting in patients with STEMI and cardiogenic shock. *Cardiovasc Revasc Med.* 2019; 20 (8):663-668.
33. Chen E, Cai W, Chen LL. Crush versus Culotte stenting techniques for coronary bifurcation lesions: A systematic review and meta-analysis of clinical trials with long-term follow-up. *Medicine (Baltimore).* 2019;98 (14): e14865.