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The impact of dissection and re-entry versus wire escalation techniques on long-term clinical outcomes in patients with chronic total occlusion lesions following percutaneous coronary intervention: An updated meta-analysis

Running head: DR vs. WE in CTO PCI

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Abstract

Background: The meta-analysis was performed to evaluate the effect of dissection and re-entry (DR) vs. wire escalation (WE) techniques on long-term clinical outcomes in patients with chronic total occlusion (CTO) lesions undergoing percutaneous coronary intervention (PCI).

Methods: Studies were searched in electronic databases from inception to September, 2019. Results were pooled using random effects model and fixed effects model and are presented as risk ratios (RR) with 95% confidence intervals (CI).

Results: Pooled analyses revealed that patients with DR techniques had overall higher complexity CTO lesions than patients with WE techniques and required a greater number of stents and a greater mean stent length. The “extensive” DR techniques may have a higher incidence of target vessel revascularization (TVR) (RR = 2.30, 95% CI: 1.77–2.98), in-stent restenosis (RR = 1.71, 95% CI: 1.30–2.23), in-stent reocclusion (RR = 1.86, 95% CI: 1.03–3.3) and death/MI/TVR (RR = 2.10, 95% CI: 1.71–2.58), when compared with WE techniques, during the long-term follow-up. However, “limited” DR techniques result in more promising outcomes, and are comparable to conventional WE techniques.

Conclusions: Dissection and re-entry techniques were associated with increased risk of long-term negative clinical events, especially “extensive” DR techniques. However, “limited” DR techniques resulted in good long-term outcomes, comparable to WE techniques.

Key words: chronic total occlusion, percutaneous coronary intervention, dissection and re-entry, wire escalation, meta-analysis

Introduction

In the hybrid algorithm to chronic total occlusion (CTO) percutaneous coronary intervention (PCI), dissection and re-entry (DR) by either the antegrade or the retrograde approach has since evolved to an indispensable strategy for crossing the occlusion, and this has contributed in improving the technical success rate of CTO PCI, when compared to conventional wire escalation (WE) techniques, especially for complex lesions [1]. However, the long-term prognosis of patients with DR techniques remains controversial. Some concerns have been raised on the possible increased risk of a higher incidence of restenosis, while other concerns support the potential role of DR in the contemporary CTO PCI, when compared to a conventional true-to-true (TTT) lumen strategy [2, 3]. Furthermore, positive improvements have already been made with the development of new and better materials and equipment, such as device-based “controlled” antegrade DR (ADR) and retrograde DR (RDR) [4]. However, it remains unknown whether this can further improve the prognosis of patients. Although there has been a meta-analysis on the subject so far [5]. Moreover, many additional cohort studies have been published since. Therefore, a comprehensive updated meta-analysis is warranted. Therefore, the present meta-analysis was conducted to evaluate the impact of DR vs. WE techniques on long-term clinical outcomes in patients undergoing CTO PCI.

Methods

Search strategy

Eligible trials were identified by performing electronic searches on PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) using the following search items: “chronic total occlusion” or “CTO” AND “subintimal” OR “subadventitial” OR “dissection” OR “tracking” OR “re-

entry" OR "CART" OR "controlled antegrade and retrograde tracking" OR "STAR" OR "subintimal tracking and re-entry" OR "LAST" OR "limited antegrade subintimal tracking" OR "CrossBoss and Stingray" OR "Boston Scientific" OR "wire escalation" OR "intraplaque" OR "intimal" OR "true-to-true" OR "crossing". was provided in the supplementary data. The inclusion period was from the establishment of the databases to September 2019. YJZ and HYP independently performed the literature search, and any differences were resolved by discussion.

Study selection

Studies were included when the following were satisfied: (1) studies that directly compared the clinical outcomes of all-cause death, cardiac death, myocardial infarction (MI), target vessel revascularization (TVR), in-stent restenosis (ISR), in-stent occlusion (ISO) or stent thrombosis (ST), during the follow-up period, after the successful recanalization of CTO lesions. using the DR technique vs. WE technique is directly made; (2) observational studies and randomized controlled trials (RCTs) published as original articles.

Data extraction and quality assessment

Data were extracted by one reviewer (YJZ) and independently checked by another two reviewers (HYP and XNL). Any disagreements between the reviewers were resolved by discussion with a fourth investigator (JHL), and by referencing the original report. The quality of the cohort study was assessed using the Newcastle-Ottawa scale. A study was regarded as high-quality when it was awarded a total score of ≥ 6 in the Newcastle-Ottawa scale [6, 7].

Statistical analysis

For dichotomous data, the available risk estimates extracted were mostly rate ratios (RRs), while those in partial studies were hazard ratios (HRs), incidence rate ratios (IRRs), or odds ratios (ORs). When risk estimates and confidence intervals (CIs) were not provided, the RRs and CIs were calculated from the available data using the Woolf method in the Stata version 15.0 software. For continuous data, standard mean differences (SMD) and the corresponding 95% CIs were pooled to compare the continuous outcomes between the two groups [8, 9]. Heterogeneity across studies was determined using the I^2 statistic, which is a quantitative measure of

inconsistency across studies. The following criteria was used: I^2 < 50%: low heterogeneity; I^2 = 50–75%: moderate heterogeneity and I^2 > 75%: high heterogeneity. The heterogeneity was considered significant when the χ^2 test was significant ($p < 0.10$) or the I^2 was > 50% [9, 10]. The analysis was performed with random effects models at first, then further changed to the fixed effects models to calculate the RR and 95% CIs again to avoid interferences from small sample studies. The sensitivity was determined to evaluate the stability of the present results by removing each study one at a time (metaninf command). What is more, subgroup analyses stratified according to different approaches (anterograde or retrograde), different DR techniques ("limited DR" or "extensive DR") and different areas (Asia, Europe or America) were performed to explore potential sources of heterogeneity in outcomes (metan command). The "extensive DR" techniques were as follows: (1) subintimal tracking and re-entry (STAR, including mini-STAR and contrast-guided STAR); (2) limited antegrade subintimal tracking (LAST) for the antegrade approach; (3) controlled antegrade and retrograde tracking (CART) for the retrograde approach. The "limited DR" techniques were as follows: (1) reverse CART for the retrograde approach; (2) device-facilitated techniques (using the CrossBoss/Stingray system; Boston Scientific, Marlborough, MA) [11]. For dichotomous data, publication bias was assessed by Harbord's regression asymmetry test [12]. For continuous data, publication bias was assessed by the Egger regression asymmetry test [13]. The statistical tests were two-sided, and a significance level of $p < 0.05$ was used.

Results

Literature search and quality assessment

A total of 2,588 studies were identified through the electronic searches, and 561 were excluded due to duplication. Then, 2,027 studies were also excluded after reading the titles and abstracts. The remaining 65 studies were assessed by reading the full texts. Eventually, 12 cohort studies were included in qualitative synthesis and meta-analysis [11, 14–24]. The flow diagram of the study selection process is presented in Figure 1. The characteristics of the included studies are summarized in **Supplementary Table S1**. The quality of cohort studies assessed with the Newcastle-Ottawa scale were summarized in **Supplementary Table S2**. All included studies were of high quality, as determined by a Newcastle-Ottawa scale score of ≥ 6 for

cohort studies.

Long-term outcomes

Mortality

All-cause mortality. The outcome occurred in at least 76 events among the 3,166 participants from nine cohort studies [14–19, 21, 22, 24]. The pooled RR value of all-cause mortality in the DR technique group, when compared with that in the conventional WE technique group, was 1.52 (95% CI: 0.95–2.45; Fig. 2A), and there was no heterogeneity (I^2 = 0.0%, p = 0.858).

Cardiovascular mortality. Nine cohort studies (3,164 patients) reported this outcome [11, 14, 16-20, 22, 24], and no heterogeneity was found among these trials (I^2 = 0.00%, p = 0.637; Fig. 2B). The results were RR = 0.97 and 95% CI: 0.52–1.81, indicating no statistical differences.

Myocardial infarction

Ten cohort studies were included for the outcome, which involved 4,090 participants and 97 events, and no heterogeneity was found for MI incidence (I^2 = 0.00%, p = 0.890; Fig. 2C) [11, 14–19, 21, 22, 24]. The pooled results indicated that DR technique in CTO PCI may have a higher incidence of MI, when compared with the conventional WE technique, during long-term follow-up (RR = 1.59, 95% CI: 1.06–2.40; Fig. 2C).

Target vessel revascularization

Eleven studies with 4,260 patients were included, and low heterogeneity was found (I^2 = 26.50%, p = 0.192; Fig. 2D) [11, 14–22, 24]. The data revealed significant differences between the two groups with regard to TVR (RR = 1.61, 95% CI: 1.29–2.01; Fig. 2D). Compared with the conventional WE strategy, successful CTO PCI after DR crossing was associated with a higher rate of TVR in long-term follow-up.

Composite outcomes: Death/MI/TVR

The incidence of composite outcomes was 15.35% (n = 234) in the DR technique group and 13.58% (n = 480) in the WE technique group [11, 14–24]. There was a significantly higher incidence of death/MI/TVR in the DR technique group, when compared with that in the WE technique group (RR = 1.54, 95% CI: 1.27–1.87; Fig.

2E). There was a low heterogeneity among these trials (I^2 = 30.9%, p = 0.144; Fig. 2E).

In-stent restenosis, reocclusion and thrombosis

The pooled outcomes revealed that the DR technique in CTO PCI was associated with higher rates of ISR (RR = 1.62, 95% CI: 1.26–2.10; I^2 = 0.0%, p = 0.459; Fig.3A) and in-stent reocclusion (RR = 1.90, 95% CI: 1.09–3.31; I^2 = 0.00%, p = 0.891; Fig. 3B) [16, 19, 22, 24]. As shown in Figure 3C, no significant difference in stent thrombosis was observed during follow-up after successful CTO PCI between the DR technique and WE technique (RR = 1.59, 95% CI: 0.64–3.93; I^2 = 0.00%, p = 0.733) [14, 16–19, 22, 24].

Procedural characteristics in the real world

CTO occlusion length and J-CTO score

The CTO length was significantly longer in patients with subintimal DR techniques, when compared with conventional WE crossing (SMD: 0.64, 95% CI: 0.31–0.97, p < 0.001; I^2 = 83.4%, p < 0.001; Fig. 3D) [14, 16, 17, 19, 21]. Furthermore, patients with DR techniques had an overall higher complexity of CTO lesions than patients with WE techniques, which was evidenced by the J-CTO score (SMD: 0.90, 95% CI: 0.68–1.12, p < 0.001; I^2 = 79.4%, p < 0.001; Fig. 3E) [11, 14, 17, 20, 21].

Stent length and number of stents

Stent length were recorded by 9 cohort studies [11, 14, 16–22], while the number of stents were recorded by 7 cohort studies [14, 16, 18–20, 22, 24]. CTO PCI with DR tracking required a greater number of stents (SMD: 0.57, 95% CI: 0.49–0.66, p < 0.001; I^2 = 66.0%, p < 0.001; Fig. 3G) and a greater mean stent length (SMD: 0.80, 95% CI: 0.73-0.86, p < 0.001; I^2 = 59.1%, p = 0.007; Fig. 3F), when compared to WE tracking.

Subgroup analysis for long-term outcomes

Predefined subgroup analyses were conducted across key study characteristics summarized in Table 1. Specifically, the intension was to conduct subgroup analyses by different approaches and different DR techniques to clarify whether patients with

retrograde approach and “extensive/old” DR techniques were at particularly high cardiovascular risk. In the subgroup analyses by different approaches, no differences were found between the anterograde approach and retrograde approach in CTO PCI. However, there were significant statistical differences in the long-term clinical outcomes between “limited/new” DR techniques and “extensive/old” DR techniques. Subgroup analysis indicated that the use of “extensive” DR techniques was associated with higher risk of TVR (RR = 2.30, 95% CI: 1.77–2.98; Table 1), ISR (RR = 1.71, 95% CI: 1.30–2.23; Table 1), in-stent occlusion (RR = 1.86, 95% CI: 1.03–3.38; Table 1) and composite endpoints (RR = 2.10, 95% CI: 1.71–2.58; Table 1), while “limited” DR techniques did not higher the cardiovascular risk, when compared with WE techniques. Besides, considering different technologies in CTO PCI applied in different areas, subgroup analyses was conducted by different areas. The results showed that the incidence of MACCE with DR techniques in studies from Europe was reported higher than that of others (Table 1).

Sensitivity analysis

In sensitivity analysis, risk estimates all slightly changed after analysis while removing a study for all outcomes, indicating the robustness of the present findings, and that no single study drove the summary effects (Fig. 4).

Publication bias

The Harbord regression test suggested no obvious publication bias for all binary outcomes, as shown in Figure 5. The Egger regression test suggested no obvious publication bias for J-CTO score, stent length, and number of stents. However, a significant publication bias for the outcome of CTO occlusion length was detected using the Egger regression test ($p = 0.048$, Fig. 5I). The conclusion did not change after adjustment for publication bias using the trim and fill method.

Discussion

According to available research, this is the latest and largest meta-analysis reported to date on the effect of DR techniques *vs*. conventional WE techniques on long-term clinical outcomes in CTO PCI, which included 5,265 participants from 12 cohort studies. With accumulating evidence, the statistical power was enhanced to provide more precise and reliable risk estimates. The most-relevant heterogeneity

moderators have been identified by subgroup analyses. The sensitivity analysis and publication bias were performed to ensure the stability of the present results. The following are the main findings of the present meta-analysis:

— The application of DR techniques in CTO PCI is associated with similar risk of mortality, but with higher risk of MI, TVR, ISR and in-stent re-occlusion, when compared with WE techniques, during clinical follow-up of 12–24 months.

— DR techniques were more applied in patients with higher complexity CTO lesions, which was evidenced by higher J-CTO score and longer CTO occlusion length. Therefore, CTO PCI with DR tracking required a greater number of stents and longer stent length, that may explain the higher incidence of long-term adverse cardiovascular events in the DR techniques group as compared with WE techniques.

— Furthermore, extensive DR techniques raises the risk of long-term clinical adverse events. However, limited DR techniques for crossing CTO was associated with similar long-term MACE, as compared to WE crossing, highlighting the growing role of more controlled subintimal crossing technique utilization in achieving high procedural success.

The recanalization of coronary occlusion lesions remains one of the major challenges in interventional cardiology. Conventional WE techniques typically use an intraplaque course for CTO crossing. DR techniques exploit the subintimal space for coronary wire passage with subsequent re-entry into the true lumen, which is needed more often to obtain success, when compared to antegrade and/or retrograde wiring strategies, especially for treating higher complexity CTO lesions. With the positive improvement and development of dedicated equipment, DR techniques have since evolved to an indispensable strategy of contemporary CTO PCI [25]. According to previous reports, the frequency of subintimal tracking ranges from 8.7% to 45.5% in the antegrade approach, and from 24.2% to 50.0% in the retrograde approach [18]. Although DR strategies have been increasingly adopted, controversial data regarding long-term clinical prognosis of DR techniques have been published in this area, prompting the investigators to conducted the present meta-analysis to evaluate the long-term clinical outcomes of DR techniques, when compared to conventional WE techniques.

The findings of the present analysis indicated that DR techniques may increase the incidence of MI, TVR and ISR in patients with successful CTO PCI, when compared to a conventional WE strategy. Both ADR and RDR involves dissection and

subsequent stenting within the subintimal space. A previous intravascular ultrasound (IVUS) reported that subintimal stenting could disturb the vessel geometry, which may lead to late acquired malposition and microaneurysms, stent thrombosis, and re-occlusion [26–28]. Furthermore, the present meta-analysis showed that the overall higher risks of TVR and ISR with DR techniques could also be partially explained by the greater number of stents and longer stent length after subintimal tracking in CTO PCI. The impact of total stent length on long-term clinical outcomes has been reported [29]. In brief, the main reason for the negative clinical impact was not only the subintimal wire tracking itself but also the greater number and longer stent requirement.

It was found in the present meta-analysis that early subintimal DR strategies were associated with a greater risk of adverse events, which were mainly almost two-fold higher rates of TVR and ISR, when compared with WE techniques, during clinical follow-up of 12–24 months. Since the first application of STAR in 2005, continuous improvements have been made including mini-STAR, LAST for antegrade, and the CART technique for retrograde subintimal revascularization [30–33]. These early subintimal techniques pose a higher risk of subintimal hematoma formation and extensive dissection, causing a side-branch vessel occlusion to occur, potentially limiting distal outflow, and predisposing high TVR risk. Thus, this would further result in negative clinical events. Meanwhile, the disappointing clinical outcomes were also due to the unnecessary longer stent lengths, greater numbers of stents, as well as compression of the distal lumen with consequent under sizing of stents. Nevertheless, data regarding the outcomes with modern DR techniques were much more promising, indicating that neither TVR, nor the ISR rates, were increased by modern subintimal strategies, when compared to conventional WE crossing, from the present meta-analysis. Both the “new” ADR and “new” RDR involved proper wiring techniques and available equipment to minimize the subintimal space, potentially lowering the risks for TVR or ISR. In contemporary ADR, the dedicated CrossBoss and Stingray system (Boston Scientific, Natick, MA, USA) has the advantage of creating a safe and controlled antegrade dissection in the subintimal space, and a geographically precise and predictable successful re-entry [34]. In contemporary RDR, the subintimal space within the CTO segment is created by ballooning from antegrade direction (rCART), thereby limiting the length of dissection [35]. As a result, the present data provides evidence that support the

application of limited DR techniques in contemporary CTO PCI practice, even as a first-line strategy for DR.

Limitations of the study

There were some limitations in the present study. First, almost all the studies included in the present meta-analysis were observational studies, thereby making these susceptible to the effects of unidentified confounders. Thereby, RCTs should be performed in the future, in order to provide further support for the present results. Second, the intended crossing technique frequently does not frequently reflect the actual guidewire positioning, and this can be detected by IVUS [36, 37]. It has been previously reported that subintimal tracking occurs in approximately 50% of successful PCI cases, when carefully assessed by IVUS [38]. However, IVUS was utilized in only a minority of studies to differentiate the guidewire positioned in either the subintimal, or intimal. Hence, subintimal guidewire tracking is likely more common than expected in CTO-PCI practice, which may have affected the present results.

Conclusions

Dissection and re-entry techniques were applied more in patients with higher complexity CTO lesions and “extensive” DR techniques could increase the incidence of long-term negative clinical events. However, “limited” DR techniques resulted in good long-term outcomes, comparable to WE techniques, supporting the expanding use of more controlled DR techniques in contemporary CTO PCI practice. Further evidence from large RCTs is needed to define the optimal role of DR in hybrid CTO PCI.

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Conflict of interest: None declared

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Table 1. Subgroup and heterogeneity analyses of pooled risk ratios for long-term outcomes.

Factors	**N (studies)**	**Events/participants**		**RR (95% CI)**	I^2	**P[a]**
		DR	**WE**			
MYOCARDIAL INFARCTION						
Different approaches						
Anterograde	4	15/252	14/894	1.93 (0.94–3.99)	0.0%	0.475
Retrograde	5	2/261	3/322	0.45 (0.09–2.31)	0.0%	0.728
Different DR techniques						
Extensive/Old DR techniques	3	7/195	19/957	1.79 (0.60–5.30)	32.4%	0.224
Limited/New DR techniques	6	31/1120	29/2072	1.58 (0.93–2.71)	0.0%	0.657
Location						
Asia	4	0/126	1/652	1.67 (0.07–40.52)	-	-
Europe	4	30/1120	34/1862	1.47 (0.88–2.45)	0.0%	0.758
America	2	21/167	11/163	1.86 (0.92–3.76)	0.0%	0.357
TARGET VESSEL REVASCULARIZATION						
Different approaches						
Anterograde	4	34/252	65/894	1.19 (0.83–1.70)	0.0%	0.701

Retrograde	5	34/263	49/324	1.23 (0.75–2.02)	24.6%	0.257
Different DR techniques						
Extensive/Old DR techniques	3	62/197	115/959	2.30 (1.77–2.98)	3.1%	0.356
Limited/New DR techniques	6	72/1120	106/2072	1.37 (0.97–1.94)	17.0%	0.304
Location						
Asia	4	21/132	63/647	1.62 (1.04–2.52)	0.0%	0.688
Europe	5	119/1193	142/1958	1.69 (1.19–2.40)	52.6%	0.077
America	2	41/167	33/163	1.41 (0.68–2.93)	28.5%	0.237
DEATH/MYOCARDIAL INFARCTION/TARGET VESSEL REVASCULARIZATION						
Different approaches						
Anterograde	3	18/219	61/871	1.22 (0.74–2.02)	0.0%	0.479
Retrograde	4	31/264	59/525	1.17 (0.67–2.07)	43.8%	0.149
Different DR techniques						
Extensive/Old DR techniques	4	83/229	316/1725	2.10 (1.71–2.58)	0.0%	0.658
Limited/New DR techniques	6	114/1120	168/2072	1.24 (0.97–158)	5.1%	0.384
Location						
Asia	4	20/130	74/645	1.40 (0.89–2.20)	0.0%	0.622
Europe	6	175/1227	377/2726	1.61 (1.24–2.10)	54.7%	0.051
America	2	39/167	29/163	1.40 (0.74–2.64)	45.8%	0.174

IN-STENT RESTENOSIS						
Different DR techniques						
Extensive/Old DR techniques	2	45/92	94/331	1.71 (1.30–2.23)	0.0%	0.588
Limited/New DR techniques	1	4/22	13/100	1.40 (0.50–3.88)	–	–
Location						
Asia	2	15/51	46/230	1.47 (0.91–2.39)	0.0%	0.910
Europe	2	50/382	96/804	1.29 (0.61–2.71)	80.9%	0.022
America	0	–	–	–	–	–
IN-STENT OCCLUSION						
Different DR techniques						
Extensive/Old DR techniques	1	14/63	24/201	1.86 (1.03–3.38)	–	–
Limited/New DR techniques	1	1/22	3/100	1.52 (0.17–13.89)	–	–
Location						
Asia	2	2/35	6/220	2.17 (0.46–10.29)	0.0%	0.653
Europe	1	14/63	24/201	1.86 (1.03–3.38)	–	–
America	0	–	–	–	–	–

[a]P value for heterogeneity; DR — dissection and re-entry; WE — wire escalation; IVUS — intravascular ultrasound; CTO — chronic total occlusion; PCI — percutaneous coronary intervention; RCT — randomized controlled trial; RR — risk ratio; CI — confidence interval

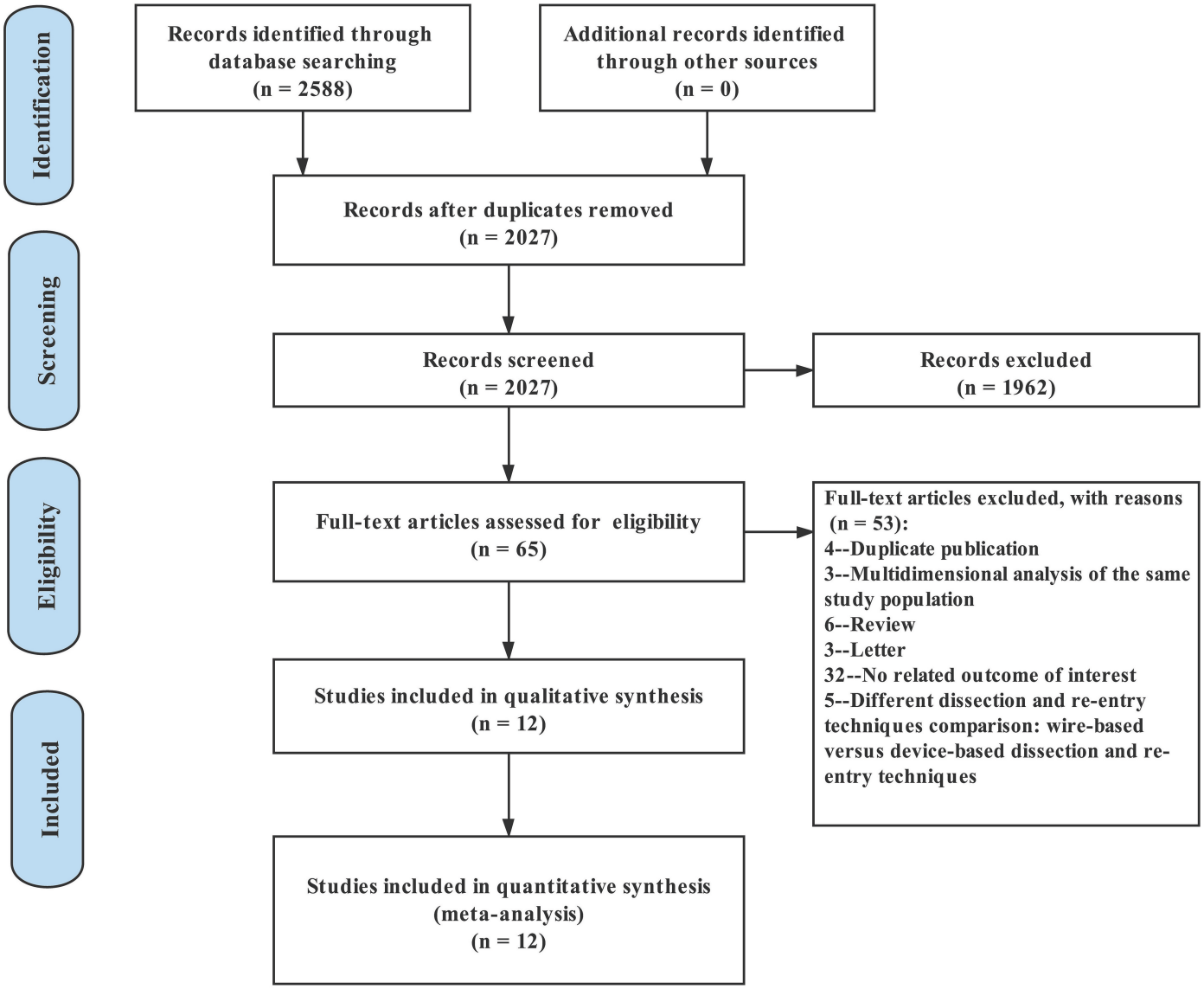
Figure 1. Flow diagram of the study selection process.

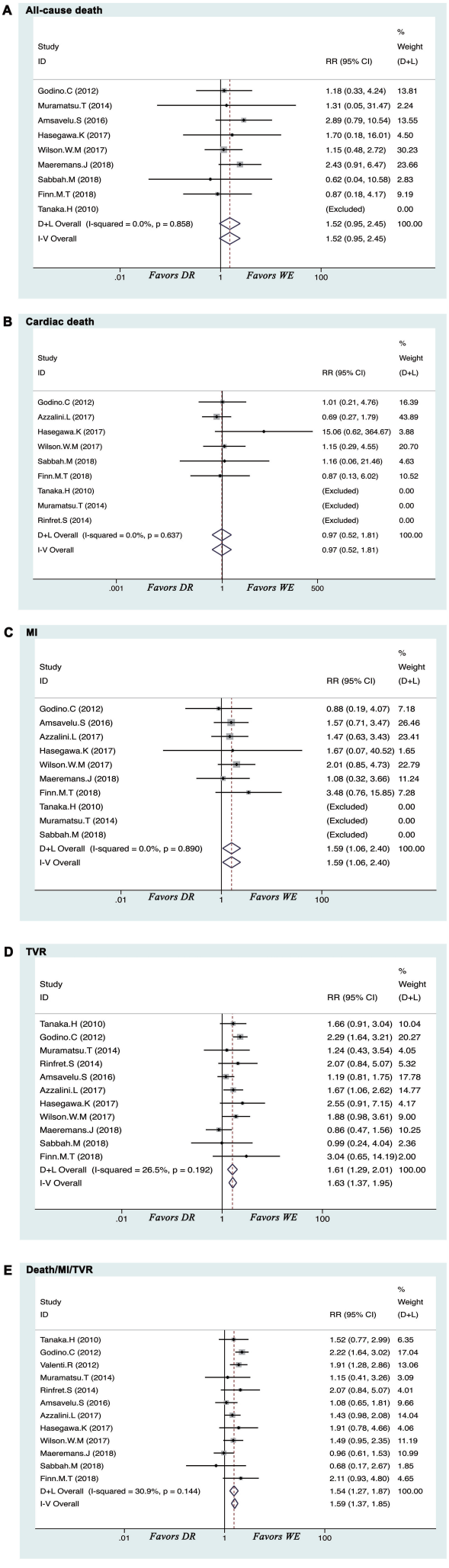
Figure 2. Forest plot for mortality, myocardial infarction (MI), target vessel revascularization (TVR) and composite outcomes (death/MI/TVR) in long-term follow-up. Forest plot demonstrates a pooled estimate of mortality during the follow-up period: **A.** All-cause mortality; **B.** Cardiovascular mortality; **C.** Myocardial infarction; **D.** Target vessel revascularization; **E.** Death/MI/TVR. The risk ratio of each study along with a pooled risk ratio with 95% confidence intervals is depicted.

Figure 3. Forest plot for in-stent restenosis, reocclusion, thrombosis in the long-term follow-up and the procedural characteristics of patients with chronic total occlusion (CTO). Forest plot demonstrating a pooled estimate of the following outcomes during the follow-up period: **A.** In-stent restenosis; **B.** In-stent reocclusion; **C.** Stent thrombosis. The risk ratio of each study along with a pooled risk ratio with 95% confidence intervals is depicted.

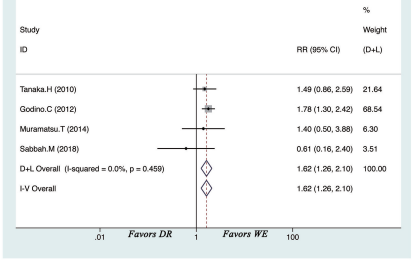
Figure 4. Sensitivity analyses of pooled rate ratios for outcomes. Sensitivity analyses for the following outcomes: **A.** All-cause mortality; **B.** Cardiac mortality; **C.** Myocardial infarction (MI); **D.** Target vessel revascularization (TVR); **E.** Death/MI/TVR; **F.** In-stent restenosis; **G.** In-stent reocclusion; **H.** Stent thrombosis; **I.** Chronic total occlusion (CTO) occlusion length; **J.** J-CTO score; **K.** Stent length; **L.** Stent numbers. The risk ratio of each study along with a pooled risk ratio with 95% confidence intervals (CI) is depicted. The vertical lines in the middle represent the total combined effect of all the studies, and the left and right vertical lines represent the upper and lower limits of 95% CI of the total combined effect. The corresponding horizontal line for each study represents the combined effect of the remaining studies after deletion of the corresponding study.

Figure 5. Publication bias plots of included studies. Publication bias of included studies for the following outcomes. **A.** All-cause mortality; **B.** Cardiac mortality; **C.** Myocardial infarction (MI); **D.** Target vessel revascularization (TVR); **E.** Death/MI/TVR; **F.** In-stent restenosis; **G.** In-stent reocclusion; **H.** Stent thrombosis; **I.** Chronic total occlusion (CTO) occlusion length; **J.** J-CTO score; **K.** Stent length; **L.** Stent numbers.

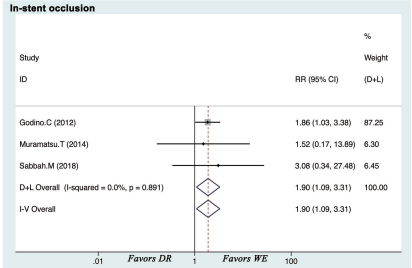

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2588)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 2027)
Records screened (n = 2027)
Records excluded (n = 1962)
Full-text articles assessed for eligibility (n = 65)
Full-text articles excluded, with reasons (n = 53):
4--Duplicate publication
3--Multidimensional analysis of the same study population
6--Review
3--Letter
32--No related outcome of interest
5--Different dissection and re-entry techniques comparison: wire-based versus device-based dissection and re-entry techniques
Studies included in qualitative synthesis (n = 12)
Studies included in quantitative synthesis (meta-analysis) (n = 12)


A
All-cause death
Study
ID
RR (95% CI)
% Weight (D+L)
Godino.C (2012) 1.18 (0.33, 4.24) 13.81
Muramatsu.T (2014) 1.31 (0.05, 31.47) 2.24
Amsavelu.S (2016) 2.89 (0.79, 10.54) 13.55
Hasegawa.K (2017) 1.70 (0.18, 16.01) 4.50
Wilson.W.M (2017) 1.15 (0.48, 2.72) 30.23
Maeremans.J (2018) 2.43 (0.91, 6.47) 23.66
Sabbah.M (2018) 0.62 (0.04, 10.58) 2.83
Finn.M.T (2018) 0.87 (0.18, 4.17) 9.19
Tanaka.H (2010) (Excluded) 0.00
D+L Overall (I-squared = 0.0%, p = 0.858) 1.52 (0.95, 2.45) 100.00
I-V Overall 1.52 (0.95, 2.45)
.01 Favors DR 1 Favors WE 100
B
Cardiac death
Study
ID
RR (95% CI)
% Weight (D+L)
Godino.C (2012) 1.01 (0.21, 4.76) 16.39
Azzalini.L (2017) 0.69 (0.27, 1.79) 43.89
Hasegawa.K (2017) 15.06 (0.62, 364.67) 3.88
Wilson.W.M (2017) 1.15 (0.29, 4.55) 20.70
Sabbah.M (2018) 1.16 (0.06, 21.46) 4.63
Finn.M.T (2018) 0.87 (0.13, 6.02) 10.52
Tanaka.H (2010) (Excluded) 0.00
Muramatsu.T (2014) (Excluded) 0.00
Rinfret.S (2014) (Excluded) 0.00
D+L Overall (I-squared = 0.0%, p = 0.637) 0.97 (0.52, 1.81) 100.00
I-V Overall 0.97 (0.52, 1.81)
.001 Favors DR 1 Favors WE 500
C
MI
Study
ID
RR (95% CI)
% Weight (D+L)
Godino.C (2012) 0.88 (0.19, 4.07) 7.18
Amsavelu.S (2016) 1.57 (0.71, 3.47) 26.46
Azzalini.L (2017) 1.47 (0.63, 3.43) 23.41
Hasegawa.K (2017) 1.67 (0.07, 40.52) 1.65
Wilson.W.M (2017) 2.01 (0.85, 4.73) 22.79
Maeremans.J (2018) 1.08 (0.32, 3.66) 11.24
Finn.M.T (2018) 3.48 (0.76, 15.85) 7.28
Tanaka.H (2010) (Excluded) 0.00
Muramatsu.T (2014) (Excluded) 0.00
Sabbah.M (2018) (Excluded) 0.00
D+L Overall (I-squared = 0.0%, p = 0.890) 1.59 (1.06, 2.40) 100.00
I-V Overall 1.59 (1.06, 2.40)
.01 Favors DR 1 Favors WE 100
D
TVR
Study
ID
RR (95% CI)
% Weight (D+L)
Tanaka.H (2010) 1.66 (0.91, 3.04) 10.04
Godino.C (2012) 2.29 (1.64, 3.21) 20.27
Muramatsu.T (2014) 1.24 (0.43, 3.54) 4.05
Rinfret.S (2014) 2.07 (0.84, 5.07) 5.32
Amsavelu.S (2016) 1.19 (0.81, 1.75) 17.78
Azzalini.L (2017) 1.67 (1.06, 2.62) 14.77
Hasegawa.K (2017) 2.55 (0.91, 7.15) 4.17
Wilson.W.M (2017) 1.88 (0.98, 3.61) 9.00
Maeremans.J (2018) 0.86 (0.47, 1.56) 10.25
Sabbah.M (2018) 0.99 (0.24, 4.04) 2.36
Finn.M.T (2018) 3.04 (0.65, 14.19) 2.00
D+L Overall (I-squared = 26.5%, p = 0.192) 1.61 (1.29, 2.01) 100.00
I-V Overall 1.63 (1.37, 1.95)
.01 Favors DR 1 Favors WE 100
E
Death/MI/TVR
Study
ID
RR (95% CI)
% Weight (D+L)
Tanaka.H (2010) 1.52 (0.77, 2.99) 6.35
Godino.C (2012) 2.22 (1.64, 3.02) 17.04
Valenti.R (2012) 1.91 (1.28, 2.86) 13.06
Muramatsu.T (2014) 1.15 (0.41, 3.26) 3.09
Rinfret.S (2014) 2.07 (0.84, 5.07) 4.01
Amsavelu.S (2016) 1.08 (0.65, 1.81) 9.66
Azzalini.L (2017) 1.43 (0.98, 2.08) 14.04
Hasegawa.K (2017) 1.91 (0.78, 4.66) 4.06
Wilson.W.M (2017) 1.49 (0.95, 2.35) 11.19
Maeremans.J (2018) 0.96 (0.61, 1.53) 10.99
Sabbah.M (2018) 0.68 (0.17, 2.67) 1.85
Finn.M.T (2018) 2.11 (0.93, 4.80) 4.65
D+L Overall (I-squared = 30.9%, p = 0.144) 1.54 (1.27, 1.87) 100.00
I-V Overall 1.59 (1.37, 1.85)
.01 Favors DR 1 Favors WE 100

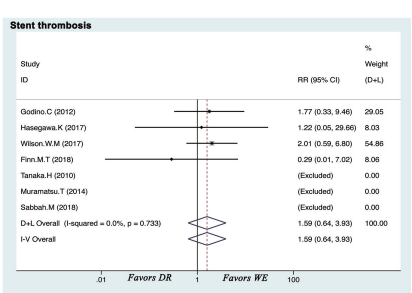
A **In-stent restenosis**



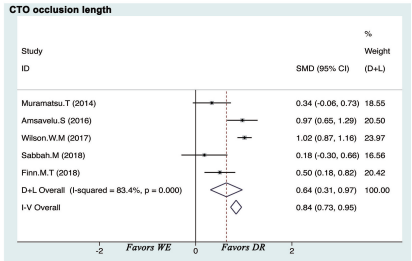
B **In-stent occlusion**



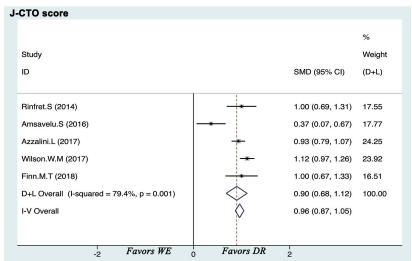
C **Stent thrombosis**



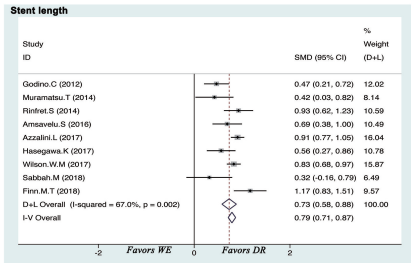
D **CTO occlusion length**



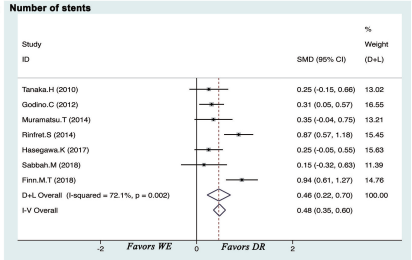
E **J-CTO score**



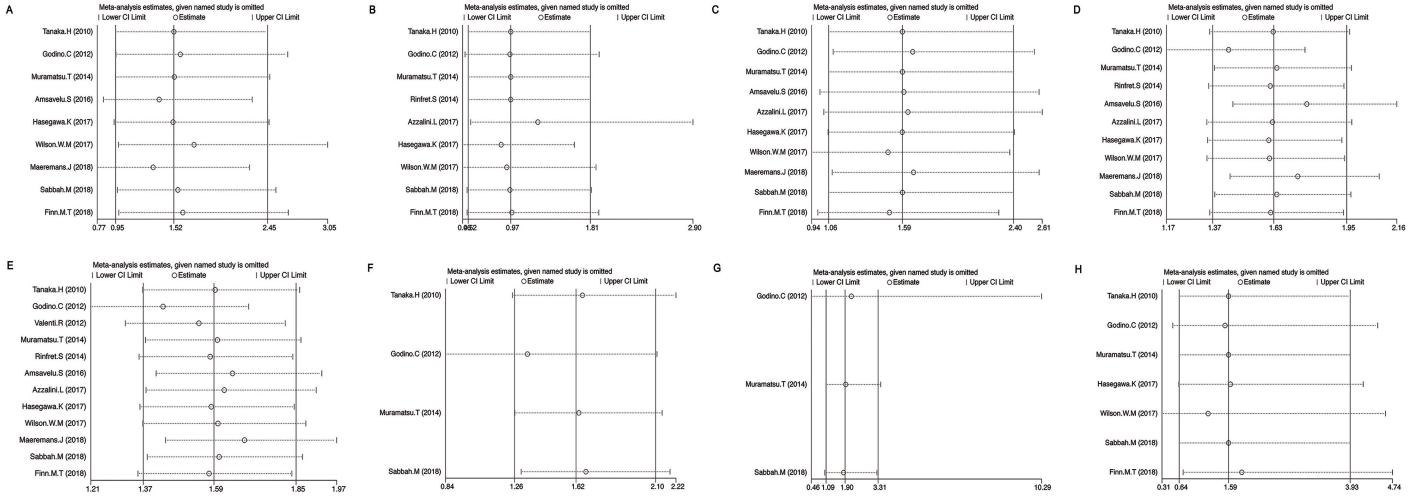
F **Stent length**



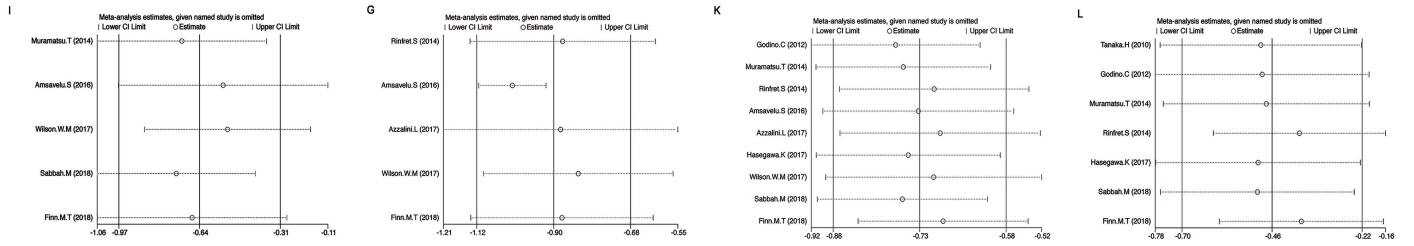
G **Number of stents**



Sensitivity analyses-Long-term outcomes

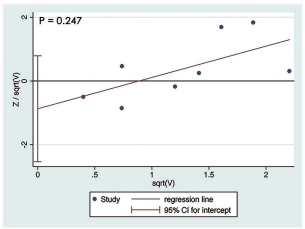


Sensitivity analyses-Procedural characteristics



Publication Bias - Long-term outcomes

A



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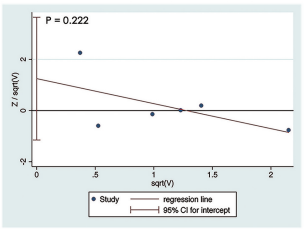

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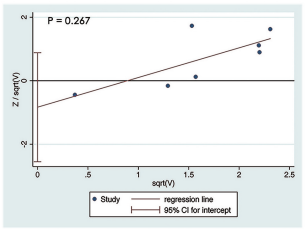

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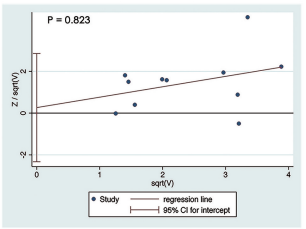

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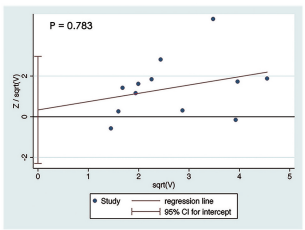

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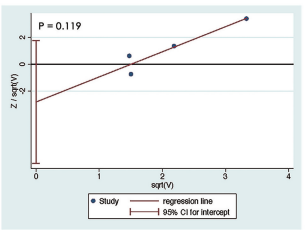

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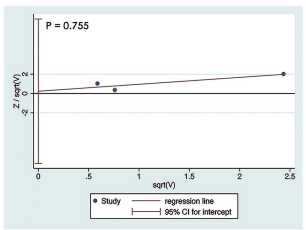
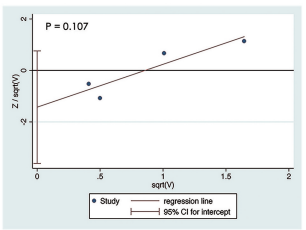
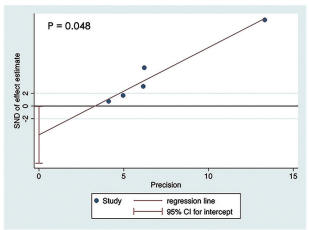


H



Publication Bias - Procedural characteristics

I



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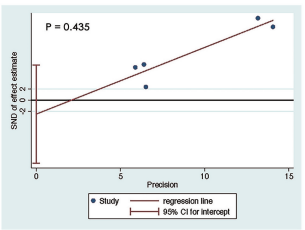

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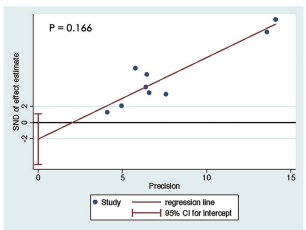

L