International Journal of Cardiology 253 (2018) 29–34

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Mid-term outcomes of chronic total occlusion percutaneous coronary intervention with subadventitial vs. intraplaque crossing: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 23 June 2017
Received in revised form 1 August 2017
Accepted 14 August 2017

Keywords:
Chronic total occlusion
Percutaneous coronary intervention
Subintimal
Subadventitial
Dissection and re-entry
Outcomes

ABSTRACT

Background: Some reports have demonstrated increased risk with subadventitial chronic total occlusion (CTO) crossing, whereas others suggest equipoise between subadventitial and intraplaque crossing techniques. We sought to clarify the effect of subadventitial lesion crossing on mid-term outcomes of CTO percutaneous coronary intervention (PCI).

Methods: We conducted a systematic review and meta-analysis of studies reporting post-discharge outcomes after CTO PCI performed via subadventitial vs. intraplaque approaches.

Results: Five studies comprising a total of 2,539 patients were included. Compared with intraplaque crossing (n = 1,654, 65.1%), subadventitial cases (n = 885, 34.9%) had a higher J-CTO score (2.9 ± 1.2 vs. 1.6 ± 1.2, $p < 0.001$), and required significantly longer stent lengths (difference in means: 19.66 mm [95% confidence interval (CI), 11.23 to 28.08]; $p < 0.001$). At a median follow-up of 12.0 months, subadventitial CTO crossing was associated with a higher overall rate of target vessel revascularization (TVR, crude rate, 11.5% vs. 7.6%, odds ratio [OR]: 2.19 [95% CI, 1.62 to 2.95]; $p < 0.001$); the risk was higher in studies of extensive compared with limited dissection and re-entry techniques (OR: 3.46 [95% CI: 2.24 to 5.36] vs. 1.52 [95% CI, 0.94 to 2.46], $p_{interaction} = 0.013$). The rates of stent thrombosis, myocardial infarction, and cardiovascular mortality did not vary significantly between subadventitial and intraplaque crossing.

Conclusions: CTOs treated with subadventitial crossing were significantly more complex as compared with CTOs treated with intraplaque crossing. Extensive subadventitial crossing techniques were associated with higher TVR rates as compared with limited techniques, supporting the important role of limited techniques in the treatment of complex CTOs.

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1. Introduction

The advent of advanced lesion crossing techniques, including antegrade and retrograde dissection and re-entry (DR) strategies, has enabled high success rates in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) [1–4]. Despite encouraging procedural and in-hospital outcomes, however, questions remain regarding the intermediate- and long-term outcome of patients in whom successful CTO PCI was achieved via subadventitial (also referred to as “subintimal”) lesion crossing: some studies reported outcomes comparable with intraplaque-only (“true-to-true” lumen) crossing [5,6], whereas others demonstrated higher incidence of major adverse cardiovascular events (MACE) with subadventitial crossing [7]. The risk appears to be higher with older extensive DR techniques (such as subintimal tracking and re-entry [STAR] (8)) that result in a less controlled dissection planes, higher vessel trauma, and re-entry points localized more distally in the

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http://dx.doi.org/10.1016/j.ijcard.2017.08.044
0167-5273/Published by Elsevier Ireland Ltd.

vessel [9], and which are currently not recommended except as bailout [10]. Given lack of randomized controlled trials on technique selection, we conducted a systematic review and meta-analysis of observational studies to examine whether subadventitial crossing of CTOs is associated with increased risk of MACE during follow-up as compared with traditional intraplaque crossing methods.

2. Methods

We conducted a systematic review of the literature and meta-analysis of observational studies according to established methods and standards recommended by the Cochrane collaboration [11]. Methodology and results are reported in accordance with the MOOSE (Meta-analysis Of Observational Studies In Epidemiology) checklist [12].

2.1. Data sources and searches

Two investigators (A.K. and B.A.D.) searched PubMed/Medline, Embase, and CENTRAL (Cochrane Central Register of Controlled Trials) up until April 4th, 2017. No restriction on study publication year was placed. The following keywords were used, with the use of wildcard characters to account for variations in spelling and plurals: “coronary chronic total occlusion”, “subintimal”, ‘subadventitial’, “dissection”, “tracking”, “re-entry”, “CART” (controlled antegrade and retrograde tracking), “STAR”, “LAST” (limited antegrade subintimal tracking), “CrossBoss” and “Stingray” (Boston Scientific). Citations were imported into a reference management software (EndNote version X8, Clarivate Analytics), and duplicates were removed. Citations were then screened at the title and abstract level and retrieved for full-text evaluation if they were considered potentially relevant. The reference lists of relevant citations were hand-searched to identify additional potentially relevant studies.

2.2. Study selection

We included all studies comparing successful CTO PCI after subadventitial vs. intraplaque CTO crossing and reporting clinical outcomes following discharge from the index hospitalization. No restriction on language or study size was applied. Subadventitial CTO crossing included successful subadventitial crossing of the occlusion after deliberate or inadvertent guidewire or device (e.g. CrossBoss) entry into the subadventitial space, established by intravascular ultrasound or angiography at the operator's discretion, as defined by each study. Both antegrade and retrograde subadventitial cases were included. Abstracts available in conference proceedings were considered for inclusion; unpublished studies were not considered.

2.3. Data extraction and quality assessment

Two investigators (A.K. and B.A.D.) independently abstracted data by using prespecified data collection forms, and evaluated study quality using the Newcastle-Ottawa scale based on study group selection, study group comparability, and outcome ascertainment [13]. In case of discrepancies, consensus was achieved with the help of a third investigator (E.S.B.). End-points abstracted include stent length, stent thrombosis (ST), myocardial infarction (MI), cardiovascular mortality, and target vessel revascularization (TVR). There was very good inter-rater agreement between the reviewers with respect to inclusion of studies, study quality, and data abstraction ($\kappa > 0.85$).

2.4. Data synthesis and statistical analysis

For dichotomous data (clinical events), odds ratios (ORs) calculated according to the Mantel-Haenszel method were used as a summary statistic; for continuous data (stent length), difference in means (MD) calculated according to the inverse-variance method was used. If not reported, mean values were estimated from median and interquartile range [14], and standard deviations were calculated from the standard error or confidence interval [11]. Heterogeneity and inconsistency were assessed by using the Cochran Q test and I^2 statistic. In cases of low to moderate heterogeneity ($I^2 < 50\%$), fixed-effects models were used for the primary analysis; alternatively, random-effects models were used. Both random- and fixed- effects models were computed and shown as part of the sensitivity analysis. Publication bias was examined by means of funnel plots and Egger's test. If there was evidence of publication bias ($p < 0.05$), the “trim and fill” method was used to adjust the summary effect as described by Duval and Tweedie [15]. “Remove one” analyses were performed to examine the effect of single studies. Subgroup analysis was performed after stratification by “extensive” vs. “limited” DR techniques. Extensive DR techniques were defined as LAST, STAR (for antegrade crossing), or CART (for retrograde crossing). Limited DR techniques were defined as CrossBoss/Stingray facilitated crossing (for antegrade crossing), and reverse CART (for retrograde crossing). For the purpose of this analysis, two studies from a large Japanese registry were not included, as both limited and extensive DR techniques were utilized and reported as pooled results [16,17]. For heterogeneity assessment analysis, a p-value of <0.10 was considered statistically significant; for all other analyses a two-tailed p-value of <0.05 was considered statistically significant. All analyses were performed using Review Manager version 5.3 (RevMan, Cochrane Collaboration) and Comprehensive Meta-Analysis Software version 3.3 (Biostat, Inc.).

3. Results

3.1. Study selection and patient population

The study identification flowchart for the present analysis is shown in Fig. 1. Five studies comprising a total of 2570 patients were included in the quantitative synthesis [7,9,16–18]. Two studies satisfying the inclusion criteria were not incorporated in the analysis due to sample overlap with a larger study [5,6]. Quality assessment of included studies is shown in online Table 1.

Follow-up data was available and abstracted for 2539 (99%) patients. Median follow-up duration was 12.0 months (interquartile range, 11.5 to 16.1). Baseline patient characteristics are shown in Table 1. Mean patient age was 64.9 years and 85.2% were men; 34.3% had diabetes mellitus, and 21.2% had undergone coronary artery bypass graft surgery. Compared with intraplaque crossing ($n = 1654$, 65.1%), subadventitial crossing cases ($n = 885$, 34.9%) had a higher J-CTO score (2.9 ± 1.2 vs. 1.6 ± 1.2, $p < 0.001$ [reported in 2 studies, 68.1% of patients]), and a higher frequency of failed prior attempts (24.5% vs. 15.7%, $p < 0.001$ [reported in 3 studies, 66.1% of patients]).

3.2. Stent length

Five studies (2563 patients) were included in the analysis of stent length (Fig. 2, Panel A). Compared with intraplaque crossing, CTO PCI after subadventitial crossing was associated with significantly longer stent length (MD: 19.66 mm [95% CI, 11.23 to 28.08]; $p < 0.001$, $I^2 = 88\%$, heterogeneity $p < 0.001$).

3.3. Stent thrombosis

Four studies (1615 patients) were included in the analysis of ST (Fig. 2, Panel B). The rate of ST did not vary significantly between subadvential and intraplaque crossing (crude rate, 1.7% vs. 0.8%, OR: 1.93 [95% CI, 0.74 to 5.01]; $p = 0.18$, $I^2 = 0\%$, heterogeneity $p = 0.99$).

3.4. Myocardial infarction

Five studies (2539 patients) were included in the analysis of MI (Fig. 2, Panel C). The rate of MI did not vary significantly between subadvential and intraplaque crossing (crude rate, 2.9% vs. 1.7%, OR: 1.59 [95% CI, 0.91 to 2.77]; $p = 0.10$, $I^2 = 0\%$, heterogeneity $p = 0.83$).

3.5. Cardiovascular mortality

Five studies (2539 patients) were included in the analysis of cardiovascular mortality (Fig. 2, Panel D). Compared with intraplaque crossing, CTO PCI after subadventitial crossing had similar cardiovascular mortality (crude rate, 1.5% vs. 1.5%, OR: 0.98 [95% CI, 0.50 to 1.91]; $p = 0.95$, $I^2 = 12\%$, heterogeneity $p = 0.33$). There was some funnel plot asymmetry, and Egger's test demonstrated the presence of publication bias ($p = 0.036$); adjustment of the effect summary by the trim and fill method did not significantly impact the results (adjusted OR: 0.76 [95% CI, 0.41 to 1.40]).

3.6. Target vessel revascularization

Five studies (2539 patients) were included in the analysis of TVR (Fig. 3, Panel A). Compared with intraplaque crossing, CTO PCI after subadventitial crossing was associated with higher rate of TVR (crude rate, 11.5% vs. 7.6%, OR: 2.19 [95% CI, 1.62 to 2.95]; $p < 0.001$, $I^2 = 14\%$, heterogeneity $p = 0.33$). In subgroup analysis stratifying by studies using extensive or limited DR techniques (specified in 3 studies, 81.1% of patients), extensive DR techniques were associated with higher TVR rates vs. intraplaque crossing (crude rate, 31.0% vs 13.1%, OR: 3.46