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# Intravascular Ultrasound Analysis of Intraplaque Versus Subintimal Tracking in Percutaneous Intervention for Coronary Chronic Total Occlusions and Association With Procedural Outcomes

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## ABSTRACT

**OBJECTIVES** Using intravascular ultrasound (IVUS), the authors compared outcomes by observed wire position (intraplaque vs. subintimal) achieved during successful chronic total occlusion (CTO) lesion treatment.

**BACKGROUND** Recent successes in CTO percutaneous coronary intervention (PCI) have used both intraluminal and subintimal wire tracking to improve procedural success. IVUS may be used to determine the course of wire tracking after crossing a CTO.

**METHODS** From March 2014 to March 2016, data were collected into a single-center database from 219 patients undergoing CTO PCI with concomitant IVUS imaging. IVUS-visualized wire tracking patterns were then retrospectively examined. Clinical outcomes with a composite in-hospital cardiovascular endpoint of all-cause death, periprocedural myocardial infarction, and in-hospital target lesion revascularization were analyzed along with IVUS-detected vascular injury.

**RESULTS** Of the 524 lesions assessed, 219 patients with successfully recanalized CTO lesions had adequate IVUS imaging and were included. Subintimal tracking was detected in 52.1% of overall cases (86.7% dissection re-entry, 27.9% wire escalation). Minimal stent area of the CTO segment and prevalence of significant edge dissection were similar in the 2 groups. In the subintimal tracking group, there was a higher rate of the composite endpoint, mostly driven by periprocedural myocardial infarction. Subintimal tracking was associated with significantly greater IVUS-detected vascular injury, angiographic dye staining/extravasation, and branch occlusion.

**CONCLUSIONS** IVUS-detected subintimal tracking is observed in approximately one-half of all successful CTO PCI cases and is associated with an expected higher, yet acceptable, event rate with no difference in minimal stent area or edge dissection among patients undergoing contemporary hybrid CTO PCI. (J Am Coll Cardiol Intv 2017;10:1011–21)


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**ABBREVIATIONS AND ACRONYMS**

**ADR** = antegrade dissection re-entry

**CABG** = coronary artery bypass grafting

**CI** = confidence interval

**CK** = creatine kinase

**CTO** = chronic total occlusion

**EEM** = external elastic membrane

**IVUS** = intravascular ultrasound

**OR** = odds ratio

**PCI** = percutaneous coronary intervention

**PMI** = periprocedural myocardial infarction

**RDR** = retrograde dissection re-entry

**VI** = vascular injury

The "hybrid" algorithm for the percutaneous treatment of chronic total occlusions (CTOs) has been associated with increased success rates in these complex lesions (1-4). The hybrid algorithm allows for serial, escalating approaches to crossing the CTO lesion on the basis of angiographic characteristics. Dissection reentry techniques (antegrade or retrograde) use the subintimal space to allow for crossing of the lesion with subsequent reentry into the true lumen (1). Wire escalation technique is thought to typically follow an intraplaque (intralumen) course (5). However, guidewire advancement into the subintimal space is no longer necessarily regarded as a mode of failure in CTO percutaneous coronary intervention (PCI) but instead could be viewed as a planned, "bail out" step in the dissection re-entry technique.

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Concerns remain regarding the prevalence of procedure-related complications due to subintimal guidewire tracking as the use of dissection re-entry has risen to 30% to 36% of antegrade and 62% to 72% of retrograde approaches (2-4,6,7). It is generally accepted that there are differences between expected and actual wire position after successful CTO crossing (8); however, the prevalence of each wiring pattern among contemporary techniques and their real-world outcomes has not been established. The aim of this study was to use intravascular ultrasound (IVUS) to identify guidewire location after successful CTO recanalization to compare the relative frequency of short-term outcomes between intraplaque and subintimal guidewire tracking wire positions.

## METHODS

**PATIENTS.** From March 2014 to March 2016, data were collected from 524 consecutively treated CTO lesions at New York-Presbyterian Hospital (New York, New York). Criteria previously described by Sianos et al. (9) were used to define CTO lesions (9). In patients without clinical evidence of occlusion duration, chronicity was based on angiographic anatomy suggestive of long-standing occlusion such as degree of calcification, collateral development, and a blunt proximal cap.

We retrospectively analyzed data from patients who underwent technically successful recanalization, defined as restoration of antegrade TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 with <30% residual diameter stenosis within the treated segment (9). Exclusion criteria included no available IVUS images after guidewire crossing, inability of the IVUS catheter to pass the lesion, poor image quality, and in-stent restenosis with occlusion (**Figure 1**). The baseline demographics, angiographic and IVUS characteristics, procedural data, and in-hospital outcomes were prospectively collected. The study complied with the Declaration of Helsinki. The ethics committee of New York-Presbyterian Hospital approved the research protocol.

**PROCEDURES.** Treatment strategy, techniques, and device selection were determined according to the operator's discretion based on the previously defined "hybrid" treatment algorithm and were recorded in the study database immediately post-procedure (1). Procedures were performed by 1 of 5 experienced operators (A.J.K., J.W.M., M.A.P., Z.A.A., and D.K.), each with >100 CTO cases experience. Two guiding catheters were placed to facilitate a seamless transition among 4 techniques using the hybrid algorithm approach (1): antegrade wire escalation, retrograde wire escalation, antegrade dissection re-entry (ADR), and retrograde dissection re-entry (RDR). The initial directional strategy, as well as subsequent and final strategies of antegrade or retrograde, was dependent on the anatomy confirmed by dual angiography and was recorded at the time of the procedure. IVUS was performed after successful wire crossing into the true lumen with post-balloon dilatation and was repeated at the conclusion of the procedure after successful stenting. All patients had normal cardiac enzymes (creatine kinase [CK]) before the beginning of the procedure and had routine follow-up CK drawn within 24 h per institutional protocol. CK-myocardial band (CK-MB) or troponin I/T were collected post-procedure in patients with clinical evidence suggestive of myocardial infarction.

Dr. Mintz is a consultant to Boston Scientific and ACIST; has received fellowship/grant support from Volcano, Boston Scientific, and InfraReDx; and has received honoraria from Boston Scientific and ACIST. Dr. Karmpaliotis is on the speakers bureaus of Abbott Vascular, Boston Scientific, and Medtronic; and is a consultant for Vascular Solutions. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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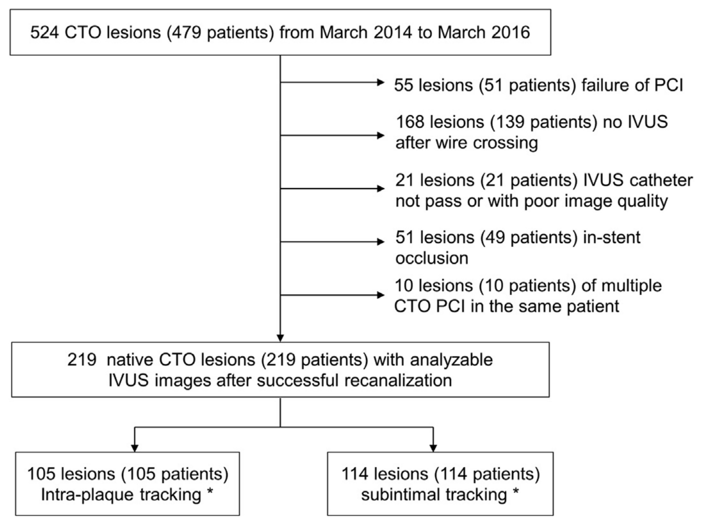
**ENDPOINTS AND DEFINITIONS.** The in-hospital primary endpoint included a composite of all-cause death, periprocedural myocardial infarction (PMI), or in-hospital target lesion revascularization (10). Causes of death were considered cardiac-related unless an unequivocal non-cardiac cause could be established. PMI was diagnosed on the basis of the Society for Cardiovascular Angiography and Interventions criteria plasma level of troponin I/T ≥70× or CK-MB ≥10× the upper limit of normal or troponin ≥35× or CK-MB ≥5× the upper limit of normal and the presence of new Q waves or left bundle branch block (11) or the third universal definition of MI as previously defined by Thygesen et al. (12). Target lesion revascularization was defined as any percutaneous or surgical revascularization of an index lesion (10). Secondary endpoints included the individual components of the composite endpoint, target vessel revascularization, in-hospital coronary artery bypass grafting (CABG), clinically significant perforation, tamponade, stroke, acute renal failure, and stent thrombosis according to the Academic Research Consortium definition (13). Individual events were confirmed by investigator consensus based on the predefined criteria detailed in the preceding text.

**ANGIOGRAPHIC EXAMINATION.** Lesion complexity was graded using the Japanese Multicenter CTO Registry (J-CTO) score based on angiographic findings and calculated according to techniques previously described by Morino et al. (14). Calcification was identified as none/mild, moderate, and severe (15), and branch occlusion as final TIMI flow grade ≤1 within a ≥1.5-mm branch. Coronary perforation was defined as dye staining or extravasation with or without hemodynamic effects and classified as clinically significant if the perforation required treatment with pericardiocentesis, prolonged balloon inflation, beads, coils, thrombin, a covered stent, or surgery (16). The dissection re-entry techniques (intentional or "bail-out") were defined as angiographic presence of wire tip, CrossBoss (Boston Scientific, Natick, Massachusetts), or knuckle in the subintimal space followed by CrossBoss/Stingray (Boston Scientific) device (antegrade) or reverse controlled antegrade and retrograde subintimal tracking (retrograde) assisted re-entry. Successful crossing of the CTO was reported intraprocedurally by the operator when true lumen wire position was obtained.

**IVUS EXAMINATION.** IVUS was performed after guidewire crossing and pre-dilation with a 1.5- to 2.5-mm compliant balloon using commercially available IVUS systems (Boston Scientific; Volcano Corporation, Rancho Cordova, California). The IVUS catheter was advanced at least 5 mm beyond the CTO segment, and an imaging run was performed using either automatic pullback (n = 219) at a speed of 0.5 to 1.0 mm/s or slow manual pullback (n = 12). Using planimetry software (echoPlaque, INDEC Medical Systems, Santa Clara, California), quantitative IVUS analysis was performed within the CTO and the proximal and distal 5-mm reference segments every 1 mm to delineate: external elastic membrane (EEM), lumen, plaque and media (EEM minus lumen), as well as stent cross-sectional area, and plaque burden cross-sectional area (plaque and media divided by EEM). Occlusion lengths were calculated from the pullback speed and duration. The proximal and distal ends of the CTO were identified by matching IVUS images with the coronary angiogram according to the landmarks within the vessel (generally, side branches), calcification, or other perivascular structures. Qualitative and quantitative IVUS analyses were performed by experienced cardiologists (L.S. and A.M.) blinded to patient baseline clinical characteristics according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement, and Reporting of Intravascular Ultrasound Studies (17).

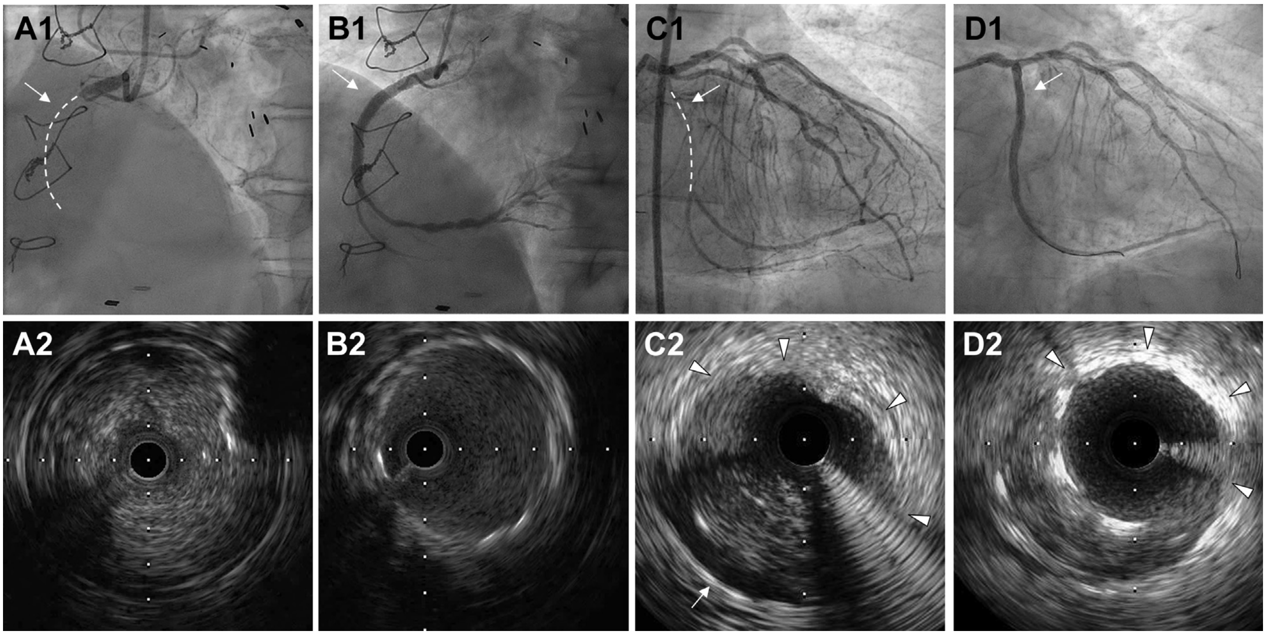
Translesional guidewire tracking was categorized as intraplaque or subintimal by IVUS (Online Figure 1). Intra-plaque tracking was defined as the IVUS catheter in the center of plaque (**Figures 2A and 2B**). Subintimal tracking was defined as the

**FIGURE 1** Flow Chart of Patient Inclusion in the Current Study




*IVUS visualized. CTO = chronic total occlusion; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

**FIGURE 2 Example of Intraplaque and Subintimal Guidewire Tracking**



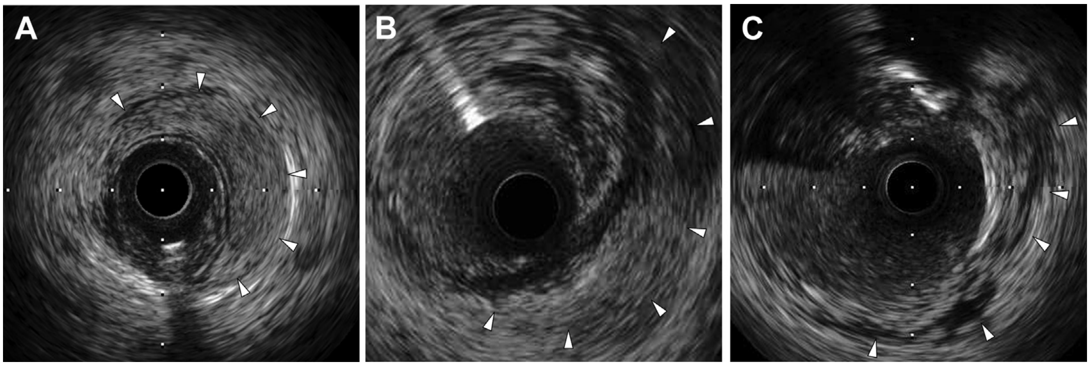

**(A1)** The expected angiographic route of the CTO is marked by **dashed lines**. **(A2)** Intraplaque tracking shown using IVUS after pre-dilation. The **arrow in A1** marks the location of the IVUS cross section **(A2)** where the IVUS catheter is located in the center of the plaque. Post-stent angiogram **(B1)** and IVUS **(B2)**. The **arrow in B1** shows the location of the IVUS catheter location for the cross-sectional imagine **(B2)** demonstrating full stent expansion. **(C1)** The expected angiographic route of the CTO is again marked by **dashed lines**. **(C2)** Subintimal tracking shown using IVUS after pre-dilation **(C2)**. The **arrow in C1** shows the location of the IVUS cross-section **(C2)** with the IVUS catheter in the subintimal space **(arrowheads)**. Subintimal catheter position is indicated by the absence of 3 layers of arterial wall and the presence of the collapsed true lumen (**arrow** seen at 6 to 8 o'clock). Post-stent angiogram **(D1)** and IVUS **(D2)**. The **arrow in D1** shows the location of the IVUS cross-section corresponding to the stent **(arrowheads in D2)** in subintimal space which is compressing the true lumen behind the stent at 5 to 11 o'clock. Abbreviations as in Figure 1.

IVUS catheter located in the subintimal space, which was identified by the absence of arterial wall 3-layer appearance (**Figures 2C and 2D**) (8). The patterns of subintimal tracking were divided into 4 subtypes depending on the location of CTO segment and entry/endpoint of the guidewire in the subintimal space (Online Figure 2A). IVUS-detected vascular injury (IVUS-VI) was categorized into 3 distinct patterns: 1) intramedial hematoma, defined as a crescent-shaped, homogeneous, hyperechoic structure within the medial space displacing the internal elastic membrane inward and the EEM outward (**Figure 3A**); 2) perivascular hematoma, defined as a crescent-shaped hyperechoic accumulation outside the vessel wall, visually continuous with the adventitia or peri-adventitial structures (**Figure 3B**); and 3) perivascular blood speckle, defined as free blood signal (typically a new echolucent structure) outside the vessel wall, with or without communication with the lumen (**Figure 3C**) (18). The maximum arc and total length of the hematoma were measured. (For additional IVUS definitions/methods, see the Online Appendix).

**STATISTICAL ANALYSIS.** Statistical analyses were performed with SPSS version 20.0 (IBM, Armonk, New York). Normally distributed continuous variables were reported as means with SD and compared with the Student *t* test; continuous variables that were non-normally distributed were reported as median with first and third quartiles and compared with the Mann-Whitney *U* test. Categorical variables were summarized as numbers (percentages) and compared using chi-square statistics or Fisher exact test, as appropriate. Interobserver and intraobserver variability of guidewire tracking pattern by IVUS were assessed using Kappa analysis in 20 cases (intraplaque 10 cases, subintimal 10 cases) by 2 independent observers and by the same observer at 2 separate time points.

Three multivariable regression models were constructed to investigate factors associated with the predictor and outcome variables in the dataset. Covariates were chosen based on their historical and pathophysiological relationship to each event type with 1 variable entered for ~10 events in each model

**FIGURE 3** Representative Images of IVUS-VI




**(A)** Intramedial hematoma, defined as an accumulation of blood **(arrowheads)** that appear as a crescent-shaped homogeneous hyperechoic structure within the medial space. **(B)** Perivascular hematoma, defined as an accumulation of blood **(arrowheads)** that appear as a crescent-shaped homogeneous hyperechoic structure outside the vessel wall, visually continuous with the adventitia or peri-adventitial structures. **(C)** Perivascular blood speckle, defined as free blood speckle **(arrowheads)** and new echolucent structures outside the vessel wall, with or without communication with the lumen. IVUS = intravascular ultrasound; VI = vascular injury.

to avoid overfitting. Covariates included in the modeling were sex, diabetes, age >65 years, prior CABG, prior PCI, retrograde approach, dissection re-entry, and the 5 individual components of the J-CTO score. The first model was constructed to estimate associations of subintimal wire position; the second and third models for the composite endpoint of dye staining/extravasation, branch occlusion, or PMI. Given significant collinearity, dissection re-entry and subintimal wire position could not be within the same model and were analyzed separately with dissection re-entry in model 2 and subintimal wire position in model 3. The regression results were reported as odds ratio (OR) with 95% confidence interval (CI). A p value <0.05 was considered statistically significant.

## RESULTS

A total of 219 patients undergoing post-recanalization IVUS evaluation were included in the current study with (n = 182) or without (n = 37) final (post-stent) IVUS imaging. Manual pullback was performed in only 12 of 219 cases (5.5%) and was evenly distributed between intraplaque and subintimal groups (p = 0.30). Mean patient age was 64.3 ± 9.9 years, and 84% of the patients were men. Other than a greater percentage of smoking history and individuals with a history of PCI in the subintimal tracking group, there were no other statistically significant differences in baseline demographics or clinical presentation between groups (Table 1). By IVUS, subintimal tracking was detected in 52.1% (n = 114) of overall cases (86.7% of successful dissection re-entry approaches vs. 27.9% of successful guidewire escalation approaches) (Figure 2), and intraplaque tracking was detected in 47.9% (n = 105) of cases. Observer estimation of guidewire tracking pattern by IVUS was assessed using kappa analysis, and good concordance of interobserver (κ = 1.0) and intraobserver (κ = 0.90) variability was observed.

**PRE-PROCEDURE ANGIOGRAPHIC FINDINGS.** Lesion complexity measured by J-CTO score was significantly higher in subintimal versus intraplaque tracking (2.5 ± 1.1 vs. 1.6 ± 1.1; p < 0.001). Blunt proximal stump, moderate calcification, tortuosity, and longer CTO length were more common in the subintimal group (Table 2).

**POST-PROCEDURE ANGIOGRAPHY AND IVUS FINDINGS.** The prevalence of the 4 subtypes of subintimal tracking depending on the entry/endpoint of the subintimal space is shown in Online Figures 2A and 2B. The classic pattern of dissection re-entry (with subintimal entry within the plaque body and re-entry distal to the index lesion) was seen in only 48% of antegrade and 27% of retrograde approaches with fewer classic tracking patterns observed in the majority of cases.

The prevalence of guidewire tracking patterns among different J-CTO scores is shown in Figure 4 and Online Table 1 and demonstrates an increased propensity for subintimal tracking with greater lesion complexity on the basis of the J-CTO score.

**TABLE 1 Clinical Characteristics in Successful Recanalized CTO Lesions**

| | Intraplaque Tracking (n = 105) | Subintimal Tracking (n = 114) | p Value |
|---|---|---|---|
| Age, yrs | 64.1 ± 10.5 | 64.5 ± 9.2 | 0.71 |
| Male | 83 (79.4) | 101 (88.6) | 0.054 |
| Diabetes mellitus | 41 (39.0) | 38 (33.3) | 0.38 |
| Hypertension | 96 (91.4) | 108 (94.7) | 0.33 |
| Hyperlipidemia | 100 (95.2) | 110 (96.5) | 0.74 |
| Smoking history | 44 (41.9) | 68 (59.6) | 0.01 |
| Glomerular filtration rate <60 ml/min | 30 (28.6) | 27 (23.7) | 0.41 |
| Current dialysis | 7 (6.7) | 5 (4.4) | 0.46 |
| Peripheral artery diseases | 11 (10.5) | 19 (16.7) | 0.18 |
| Prior myocardial infarction | 31 (29.5) | 44 (38.6) | 0.16 |
| Prior percutaneous coronary intervention | 66 (62.9) | 86 (75.4) | 0.04 |
| Prior coronary artery bypass grafting | 29 (27.6) | 44 (38.6) | 0.09 |
| Prior heart failure | 22 (21.0) | 32 (28.1) | 0.22 |
| Ejection fraction <40% | 12 (11.4) | 24 (21.1) | 0.06 |
| Clinical presentation | | | |
| Unstable angina | 49 (46.7) | 52 (45.6) | 0.88 |
| Stable angina | 43 (41.0) | 52 (45.6) | 0.49 |
| Silent ischemia | 13 (12.4) | 10 (8.8) | 0.38 |

Values are mean ± SD or n (%).
CTO = chronic total occlusion.

**TABLE 2 Angiographic/Procedural Characteristics of Successful Recanalized CTO Lesions**

| | Intraplaque Tracking (n = 105) | Subintimal Tracking (n = 114) | p Value |
|---|---|---|---|
| Multivessel disease* | 86 (81.9) | 97 (85.1) | 0.53 |
| Target vessel | | | |
| Right | 48 (45.7) | 60 (52.6) | 0.31 |
| Left anterior descending | 34 (32.4) | 30 (26.3) | 0.32 |
| Left circumflex | 23 (21.9) | 24 (21.1) | 0.88 |
| Target location | | | |
| Ostial | 8 (7.6) | 13 (11.4) | 0.34 |
| Proximal | 18 (17.1) | 19 (16.7) | 0.93 |
| Middle | 65 (61.9) | 66 (57.9) | 0.55 |
| Distal | 14 (13.3) | 16 (14.0) | 0.88 |
| Side branch at proximal stump | 46 (43.8) | 49 (43.0) | 0.90 |
| Blunt proximal stump | 28 (26.7) | 57 (50.0) | <0.001 |
| Moderate calcification | 29 (27.6) | 47 (41.2) | 0.04 |
| Severe calcification | 33 (31.4) | 44 (38.6) | 0.27 |
| Tortuosity | 31 (29.5) | 51 (44.7) | 0.02 |
| Occluded length, mm | 15.6 ± 9.0 | 24.5 ± 14.1 | <0.001 |
| Length ≥20 mm | 27 (25.7) | 65 (57.0) | <0.001 |
| Prior attempt failure | 21 (20.0) | 25 (21.9) | 0.73 |
| Japan CTO score | 1.6 ± 1.1 | 2.5 ± 1.1 | <0.001 |
| ≥2 | 53 (52.4) | 96 (84.2) | <0.001 |
| Rentrop class 3 | 50 (47.6) | 44 (38.6) | 0.18 |
| Retrograde approach | 12 (11.4) | 49 (43.0) | <0.001 |
| Dissection re-entry technique | 12 (11.4) | 78 (68.4) | <0.001 |
| Non-CTO vessel treated | 18 (17.1) | 21 (18.4) | 0.81 |
| Drug-eluting stent implantation | 105 (100) | 109 (95.6) | 0.06 |
| Number of stents in CTO vessel | 1.4 ± 0.7 | 2.0 ± 1.0 | <0.001 |
| Total stent length, mm | 61.0 ± 27.6 | 84.1 ± 30.2 | <0.001 |
| Branch occlusion (diameter >1.5 mm) | 17 (16.2) | 55 (48.2) | <0.001 |
| Fluoroscopy time, min | 41.0 ± 23.1 | 70.0 ± 33.0 | <0.001 |
| Contrast volume, ml | 270 ± 129 | 367 ± 163 | <0.001 |
| Radiation exposure dose, Gy | 1.4 ± 1.0 | 2.4 ± 1.7 | <0.001 |

Values are n (%) or mean ± SD. *≥50% luminal diameter stenosis in ≥2 major epicardial arteries.
CTO = chronic total occlusion.

Subintimal tracking was also observed more frequently with the retrograde approach (43.0% vs. 11.4%; $p < 0.001$) than the antegrade approach and was associated with more stents, longer stent length, more contrast and radiation exposure, and longer fluoroscopy time (**Table 2,** Online Table 2). Patients with subintimal tracking had more angiographically evident dye staining/extravasation (14.0% vs 3.8%; $p = 0.01$), angiographic branch occlusion (48.2% vs. 16.2%; $p < 0.001$), and IVUS-VI, defined as intramedial hematoma, perivascular hematoma, and blood speckle (89.5% vs. 52.4%; $p < 0.001$). There was no significant difference in CTO segment minimum stent area with subintimal tracking compared with intraplaque tracking (subintimal 6.2 $mm^2$ vs. intraplaque 6.1 $mm^2$; $p = 0.55$) or in the prevalence of significant edge dissection between the 2 groups (subintimal 7.1 $mm^2$ vs. intraplaque 4.1 $mm^2$; $p = 0.52$) (**Tables 2 to 4, Figure 5**).

In the multivariable analysis, CTO length >20 mm by quantitative coronary angiography (OR: 3.4, 95% CI: 1.5 to 7.8; $p = 0.003$), dissection re-entry technique (OR: 15.2, 95% CI: 6.5 to 35.7; $p < 0.001$), age > 65 years (OR: 2.5, 95% CI: 1.1 to 5.5; $p = 0.03$) were independent predictors for subintimal guidewire tracking.

**IN-HOSPITAL OUTCOMES.** Subintimal tracking cases showed significantly higher rates of the composite cardiovascular endpoint (7.9% vs. 1.9%; $p = 0.04$), mostly driven by PMI (7.0% vs. 1.9%; $p = 0.10$). There was no significant difference on subgroup analysis of the individual components of the composite endpoint (**Table 5**). Although the incidence of tamponade was similar in the 2 groups (subintimal 1.8% vs. intraplaque 1.0%; $p = 1.00$), clinically significant perforations were numerically higher in the subintimal group (6.1% vs. 1.0%; $p = 0.07$). A composite cardiovascular and imaging endpoint of dye staining/extravasation, branch occlusion, or PMI had a significantly greater number of adverse events in the subintimal compared with intraplaque tracking group (56.1% vs. 21.0%; $p < 0.01$).

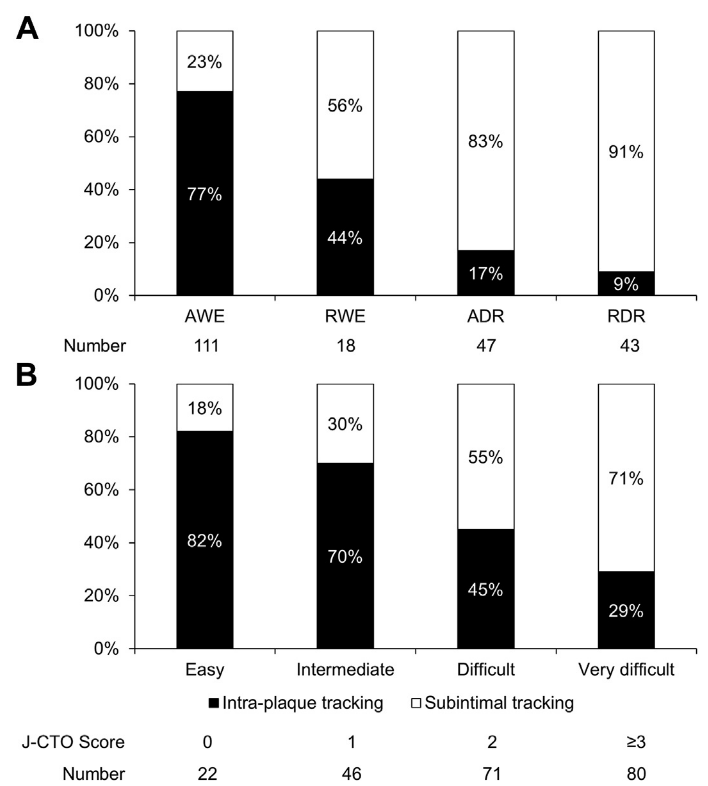
On adjusted analysis, subintimal tracking was noted to be associated with a greater odds of dye staining/extravasation, branch occlusion, or PMI (OR: 4.5, 95% CI: 2.3 to 8.9; $p < 0.001$). Prior failed attempt (OR: 2.5, 95% CI: 1.2 to 5.2; $p = 0.02$) and dissection re-entry technique (OR: 3.2, 95% CI: 1.6 to 6.2; $p = 0.001$) were also independent predictors of the composite of dye staining/extravasation, branch occlusion, or PMI after multivariable adjustment.

## DISCUSSION

The intended successful crossing technique is often believed to accurately reflect the pattern of guidewire tracking: wire escalation usually implies intraplaque tracking and dissection re-entry implies some component of subintimal wire tracking (19). However, there is limited knowledge regarding the likelihood of achieving expected wire position with the final approach to CTO crossing. Recently, the J-PROCTOR (Promus Stent Treatment of Chronic Total Occlusions Using Two Different Recanalisation Techniques in Japan) registry (including 27 centers in Japan) demonstrated subintimal tracking in 12% (7 of 57) of the antegrade approach-treated patients versus 24% (24 of 99) in the retrograde approach group (8). In the present study, we observed subintimal tracking in approximately 50% of successful PCI cases when carefully assessed by IVUS. These registry data demonstrate that it may be difficult to precisely control wire position intraprocedurally solely based on the successful CTO crossing approach. Furthermore, the clinical impact of subintimal wire position on short-term and longer-term angiographic (i.e., branch occlusion and perforation), IVUS (i.e., perivascular hematoma and stent edge dissection), and clinical outcomes (i.e., PMI and TLR) has been inadequately studied.

The overall safety of subintimal tracking remains largely unknown and is an important issue routinely faced by hybrid CTO operators. Given this uncertainty, we evaluated 219 CTO lesions using IVUS imaging and investigated IVUS visualized wire-crossing location (subintimal vs. intraplaque tracking). We then sought to measure the effect of subintimal position on in-hospital adverse cardiac events. This is, to the best of our knowledge, the largest IVUS CTO PCI study implementing the "hybrid" approach. Furthermore, it includes a very complex patient population (83.6% with multivessel disease, 33.3% with prior CABG, 34.2% with a prior myocardial infarction, and 68.0% with a J-CTO score of ≥2), which is reflective of the contemporary (2014 to 2016) CTO PCI practice at a tertiary referral institution.

**FIGURE 4** Guidewire Tracking Pattern Compared With Angiography-Defined Successful Approach and Difficulty Grades




**(A)** Guidewire tracking pattern and successful approach by angiography. **(B)** Guidewire tracking pattern and difficulty grades. ADR = antegrade dissection re-entry; AWE = antegrade wire escalation; J-CTO = Multicenter CTO Registry in Japan; RDR = retrograde dissection re-entry; RWE = retrograde wire escalation.

**IVUS-DETERMINED PATTERNS OF GUIDEWLIRE TRACKING.** As anticipated, subintimal tracking was observed significantly more frequently in dissection re-entry than wire escalation (86.7% vs. 27.9%) and with retrograde approach than antegrade approach (80.3% vs. 41.1%). However, despite the intended crossing strategy used in CTO PCI, in a notable percentage of cases, the ultimate wire position was discordant to the expected position (Figure 4A). Particularly with use of wire escalation to successfully cross the CTO, the rate of intraplaque tracking was only 77% of antegrade wire escalation and 44% in retrograde wire escalation.

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**TABLE 3 Pre-Stenting IVUS Findings in Successfully Recanalized CTO Lesions**

| | Intraplaque Tracking (n = 105) | Subintimal Tracking (n = 114) | p Value |
|---|---|---|---|
| Occluded segment length, mm | 12.2 (8.0-19.9) | 19.4 (11.6-29.7) | <0.001 |
| Maximum PB post-balloon, % | 82.1 (78.6-85.5) | 84.8 (81.2-89.6) | <0.001 |
| Subintimal length, mm | – | 21.5 (7.3-37.2) | – |
| >10 mm | – | 68 (59.6) | – |
| Calcification in CTO lesion | 92 (87.6) | 101 (88.6) | 0.82 |
| Intramedial hematoma | 22 (21.0) | 59 (51.8) | <0.001 |
| Perivascular hematoma | 12 (11.4) | 44 (38.6) | <0.001 |
| Total length of hematoma, mm | 9.3 (5.5-13.7) | 13.8 (7.1-23.6) | 0.06 |
| Perivascular blood speckle | 48 (45.7) | 90 (78.9) | <0.001 |
| Any IVUS-VI* | 55 (52.4) | 102 (89.5) | <0.001 |

Values are median (interquartile range) or n (%). *Includes intramedial hematoma, extramedial hematoma, or perivascular blood speckle.

CTO = chronic total occlusion; IVUS = intravascular ultrasound; PB = plaque burden; VI = vascular injury.

In analyzing what factors were likely to determine subintimal wire position with multivariable logistic regression, we found that after adjustment for important covariates, dissention re-entry technique had the greatest predictive effect (OR: 15.2, 95% CI: 6.5 to 35.7; $p < 0.001$) followed by longer lesion length (OR: 3.4 95% CI: 1.5 to 7.8; $p = 0.003$). The retrograde approach was associated with subintimal tracking on univariable analysis; however, the adjusted analysis revealed that the retrograde approach was not an independent predictor for subintimal tracking, contrasting with previous reports (8,20,21). Greater than 70% of lesions successfully treated with the retrograde approach used the RDR technique, making the adjusted result somewhat surprising. Smoking history, calcification, blunt stump, and tortuosity were associated with subintimal wire location on univariable analysis; however, they were no longer predictive after adjustment.

**TABLE 4 Post-Stent IVUS Findings of Successful Recanalized CTO Lesions**

| | Intraplaque Tracking (n = 98) | Subintimal Tracking (n = 84) | p Value |
|---|---|---|---|
| Total stent length, mm | 47.2 (35.8-60.5) | 69.9 (54.9-84.7) | <0.001 |
| Subintimal stent length, mm | – | 16.7 (7.3-32.2) | – |
| MSA in entire stent, mm$^2$ | 5.4 (4.2-7.3) | 4.8 (3.9-6.1) | 0.25 |
| MSA in CTO segment, mm$^2$ | 6.1 (5.1-8.3) | 6.2 (4.8-6.9) | 0.55 |
| Malapposition | 16 (16.3) | 12 (14.3) | 0.70 |
| Significant* | 10 (10.2) | 7 (8.3) | 0.67 |
| Tissue protrusion | 5 (5.1) | 17 (20.2) | 0.002 |
| Significant† | 3 (3.1) | 7 (8.3) | 0.19 |
| Stent edge dissection | 10 (10.2) | 13 (15.5) | 0.29 |
| Hematoma‡ | 4 (4.1) | 1 (1.2) | 0.38 |
| Significant§ | 4 (4.1) | 6 (7.1) | 0.52 |

Values are median (interquartile range) or n (%). *Malapposition area >10% lumen area. †protruded tissue area >10% stent area. ‡including intramedial hematoma or perivascular hematoma. §dissection >3 mm in length and >60° in angle.

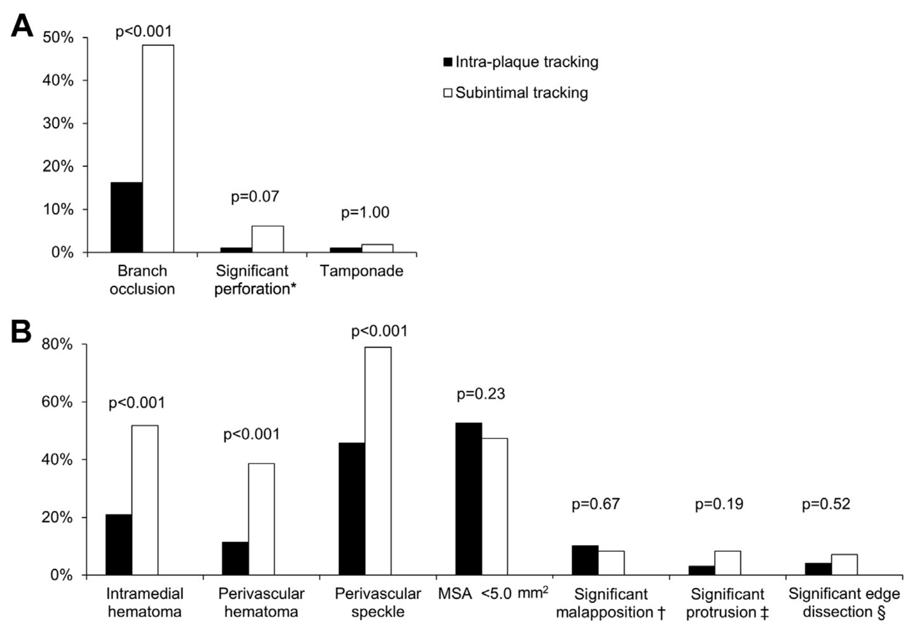
CSA = cross-sectional area; CTO = chronic total occlusion; EEM = external elastic membrane; MSA = minimum stent area.

**PROCEDURE-RELATED OUTCOMES.** The composite primary endpoint showed a significantly increased short-term event rates with subintimal tracking (7.9% vs. 1.9%; $p = 0.04$) driven by a trend toward higher rates of PMI (7.0% vs. 1.9%; $p = 0.10$). This higher rate of PMI may be explained by a greater percentage of branch occlusions with the subintimal approach (48.2% vs. 16.2%; $p < 0.001$). Whether branch occlusion-based enzyme elevation has an impact on long-term outcomes remains controversial (22,23) and was not assessed by our data due to the short follow-up of the study.

The observed higher event rates in the subintimal wire tracking group should be taken in the context of a low overall adverse event rate (5.0%, 11 of 219 patients met the primary endpoint) with an overall high success rates (89.5% of CTO interventions in the overall cohort were successful) comparable to recent hybrid studies from Europe and the United States (24,25). Although patient characteristics between subintimal and intraplaque groups were similar, the subintimal group had significantly higher J-CTO scores, which may partially explain the trend toward higher event rates in this group; however, after adjustment for important covariates (including components of the J-CTO score), both subintimal wire location and dissection re-entry were independently associated with a higher rate of the secondary composite endpoint of dye staining/extravasation, branch occlusion, or PMI.

IVUS-VI was frequent in the current study and was particularly common with subintimal tracking (89.5% in subintimal tracking and 52.4% in intraplaque tacking). Previous non-CTO studies reported that a hematoma without appropriate treatment was associated with an increased rate of PMI and the need for repeat revascularization (26). Additionally, perivascular hematoma or blood speckle may evolve to angiographic perforation after ballooning/stenting (18). Of the 20 cases in the study with any dye staining, 8 were clinically significant; and 6 of these had an IVUS-detected perivascular hematoma. Three of these 6 patients would later develop hemodynamic

**FIGURE 5 Procedure-Related Complications During CTO Intervention**




**(A)** Complications detected by angiography. **(B)** Complications detected by IVUS. *Perforation requiring treatment with pericardiocentesis, covered stent, or surgery; †malapposition area >10% lumen area; ‡protruded tissue area >10% stent area; §dissection >3 mm in length and >60° in angle. MSA = minimum stent area; other abbreviations as in Figure 1.

instability, and 5 experienced PMI. This further demonstrates that when perivascular injuries are detected by IVUS, operators should have a high index of suspicion for impending additional complications proceeding with lower balloon pressure inflations and careful clinical follow-up. Also of note, we found less IVUS-VI with ADR (mostly using CrossBoss/Stingray) than with RDR (83.0% vs. 97.7%; p = 0.03). This may be explained by the shorter subintimal wiring length observed with ADR approaches (21.3 mm vs. 30.0 mm; p = 0.046), possibly due to improved control of vessel re-entry with modern devices as well as less complex lesions selected for ADR than RDR.

**STUDY LIMITATIONS.** First, this was a single-center study done at a high-volume institution with experienced operators. There were higher rates of dissection re-entry and retrograde approaches than may be seen at other centers. Therefore, the results may not be readily applicable to other CTO programs. Second, although data were collected prospectively, the analysis and design were done retrospectively, which may introduce unmeasured

**TABLE 5 In-Hospital Outcomes**

| | Intraplaque Tracking (n = 105) | Subintimal Tracking (n = 114) | p Value |
|---|---|---|---|
| Composite cardiovascular endpoint* | 2 (1.9%) | 9 (7.9%) | 0.04 |
| All-cause death | 0 | 0 | – |
| SCAI PMI | 2 (1.9%) | 8 (7.0%) | 0.10 |
| Universal definition PMI | 3 (2.9%) | 10 (8.8%) | 0.06 |
| Target lesion revascularization | 0 | 1 (0.9%) | 1.00 |
| Secondary cardiovascular endpoint† | 22 (21.0%) | 64 (56.1%) | <0.01 |
| Any dye staining/extravasation | 4 (3.8%) | 16 (14.0%) | 0.01 |
| Clinically significant perforation‡ | 1 (1.0%) | 7 (6.1%) | 0.07 |
| Collateral injury | 1 (1.0%) | 0 | 0.48 |
| Wire perforation | 0 | 3 (2.6%) | 0.25 |
| Balloon/stent related | 0 | 4 (3.5%) | 0.12 |
| Tamponade | 1 (1.0%) | 2 (1.8%) | 1.00 |
| Stent thrombosis | 0 | 0 | – |
| In-hospital CABG | 0 | 0 | – |
| Stroke | 1 (1.0%) | 0 | 0.48 |
| Acute renal failure | 1 (1.0%) | 1 (0.9%) | 1.00 |

Values are n (%). *Composite of all-cause death, PMI (SCAI definition), and target lesion revascularization. †Secondary composite of imaging and cardiovascular endpoint: dye staining/extravasation, branch occlusion, or PMI. ‡Perforation requiring treatment with pericardiocentesis, prolonged balloon inflation, beads, coils, thrombin, a covered stent, or surgery.

PMI = peri-procedural myocardial infarction; SCAI = Society for Cardiac Angiography and Interventions; CABG = Coronary Artery Bypass Grafting.

confounding compared with prospective/randomized trials. Third, multiple IVUS systems were used, and patients with manual pullback were included. This may reduce the accuracy of observer wire location ascertainment. However, intraobserver and interobserver variability were tested with low variability in the study (x = 1.0 and x = 0.9, respectively). Manual pullback was performed in only 12 of 219 cases (5.5%) with no difference between the 2 groups (p = 0.58). Lastly, only in-hospital outcomes were evaluated in this study. The longer-term impact of subintimal wire position, subintimal stent location, and IVUS-VI are being evaluated in ongoing studies at our center.

## CONCLUSIONS

The presented analysis demonstrates that the final successful crossing strategy in CTO PCI does not precisely predict ultimate wire tracking pattern (subintimal vs. intraplaque), particularly in cases of wire escalation. Subintimal tracking, intentional or unintentional, is associated with higher, yet acceptable, rates of adverse events and IVUS-VI during hybrid CTO PCI in a large contemporary cohort. These data favor continued use of the hybrid approach to obtain high success rates with the knowledge that subintimal wire position will occur more frequently with more complex angiographic lesions. Furthermore, given that subintimal tracking position may result in higher complication rates, greater complexity CTO procedures should be performed at centers of excellence with experience in treating coronary complications.

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## PERSPECTIVES

**WHAT IS KNOWN?** IVUS-determined wire position (subintimal or intraluminal) with successful crossing of CTOs can be difficult to predict based on lesion crossing strategy within the hybrid algorithm. Whether patients have a greater rate of adverse outcomes with subintimal wire position after CTO crossing remains poorly studied.

**WHAT IS NEW?** Wire position (intraluminal vs. subintimal) was evaluated by IVUS imaging during 219 successful CTO procedures. Subintimal tracking was identified in 52% of successful CTOs (86.7% of dissection re-entry and 27.9% of wire escalation approaches). Higher, yet tolerable, rates of adverse events and IVUS-determine vascular injury during hybrid CTO percutaneous coronary intervention occurred with subintimal wire tracking in a large, modern cohort.

**WHAT IS NEXT?** Longer-term follow-up will be carried out to answer remaining important questions: for example, what is the long-term stent patency based on wire crossing location, and do the greater rates of vessel injury seen with subintimal tracking affect late event rates?

## REFERENCES

**1.** Brilakis ES, Grantham JA, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. J Am Coll Cardiol Intv 2012;5:367–79.

**2.** Wilson WM, Walsh SJ, Yan AT, et al. Hybrid approach improves success of chronic total occlusion angioplasty. Heart 2016;102:1486–93.

**3.** Christopoulos G, Karmpaliotis D, Alaswad K, et al. Application and outcomes of a hybrid approach to chronic total occlusion percutaneous coronary intervention in a contemporary multicenter US registry. Int J Cardiol 2015;198:222–8.

**4.** Karmpaliotis D, Karatasakis A, Alaswad K, et al. Outcomes with the use of the retrograde approach for coronary chronic total occlusion interventions in a contemporary multicenter US registry. Circ Cardiovasc Interv 2016;9:e003434.

**5.** Joyal D, Thompson CA, Grantham JA, Buller CE, Rinfret S. The retrograde technique for recanalization of chronic total occlusions: a step-by-step approach. J Am Coll Cardiol Intv 2012;5:1–11.

**6.** Patel VG, Brayton KM, Tamayo A, et al. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. J Am Coll Cardiol Intv 2013;6:128–36.

**7.** Tsuchikane E, Yamane M, Mutoh M, et al. Japanese multicenter registry evaluating the retrograde approach for chronic coronary total occlusion. Catheter Cardiovasc Interv 2013;82:E654–61.

**8.** Muramatsu T, Tsuchikane E, Oikawa Y, et al. Incidence and impact on midterm outcome of controlled subintimal tracking in patients with successful recanalisation of chronic total occlusions: J-PROCTOR registry. EuroIntervention 2014;10:681–8.

**9.** Sianos G, Werner GS, Galassi AR, et al. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. EuroIntervention 2012;8:139–45.

**10.** Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

**11.** Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol 2013;62:1563–70.

**12.** Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Glob Heart 2012;7:275–95.

**13.** Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7-8, 2006. Circulation 2007;115:2352–7.

**14.** Morino Y, Abe M, Morimoto T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. J Am Coll Cardiol Intv 2011;4:213–21.

**15.** Mintz GS, Popma JJ, Pichard AD, et al. Patterns of calcification in coronary artery disease. A statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. Circulation 1995;91:1959–65.

**16.** Di Mario C, Werner GS, Sianos G, et al. European perspective in the recanalisation of Chronic Total Occlusions (CTO): consensus document from the EuroCTO Club. EuroIntervention 2007;3:30–43.

**17.** Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). J Am Coll Cardiol 2001;37:1478–92.

**18.** Maehara A, Mintz GS, Bui AB, et al. Intravascular ultrasound evidence of perivascular trauma during routine percutaneous coronary intervention. Int J Cardiovasc Imaging 2014;30:849–56.

**19.** Whitlow PL, Burke MN, Lombardi WL, et al. Use of a novel crossing and re-entry system in coronary chronic total occlusions that have failed standard crossing techniques: results of the FAST-CTOs (Facilitated Antegrade Steering Technique in Chronic Total Occlusions) trial. J Am Coll Cardiol Intv 2012;5:393–401.

**20.** Tsujita K, Maehara A, Mintz GS, et al. Intravascular ultrasound comparison of the retrograde versus antegrade approach to percutaneous intervention for chronic total coronary occlusions. J Am Coll Cardiol Intv 2009;2:846–54.

**21.** Karmpaliotis D, Michael TT, Brilakis ES, et al. Retrograde coronary chronic total occlusion revascularization: procedural and in-hospital outcomes from a multicenter registry in the United States. J Am Coll Cardiol Intv 2012;5:1273–9.

**22.** Hahn JY, Chun WJ, Kim JH, et al. Predictors and outcomes of side branch occlusion after main vessel stenting in coronary bifurcation lesions: results from the COBIS II Registry (COronary BIfurcation Stenting). J Am Coll Cardiol 2013;62:1654–9.

**23.** Werner GS, Coenen A, Tischer KH. Periprocedural ischaemia during recanalisation of chronic total coronary occlusions: the influence of the transcollateral retrograde approach. EuroIntervention 2014;10:799–805.

**24.** Danek BA, Karatasakis A, Karmpaliotis D, et al. Development and validation of a scoring system for predicting periprocedural complications during percutaneous coronary interventions of chronic total occlusions: the Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS CTO) complications score. J Am Heart Assoc 2016;5:e004272.

**25.** Maeremans J, Walsh S, Knaapen P, et al. The hybrid algorithm for treating chronic total occlusions in Europe: The RECHARGE Registry. J Am Coll Cardiol 2016;68:1958–70.

**26.** Maehara A. Incidence, morphology, angiographic findings, and outcomes of intramural hematomas after percutaneous coronary interventions: an intravascular ultrasound study. Circulation 2002;105:2037–42.

**KEY WORDS** chronic total occlusion, intravascular ultrasound, percutaneous coronary intervention

**APPENDIX** For an expanded Methods section and supplemental figures and tables, please see the online version of this article.