Use of Intravascular Ultrasound in the Assessment of Chronic Total Occlusions

Gerald S Werner
Department of Cardiology and Intensive Care, Darmstadt Clinic,
Academic teaching hospital of the University of Frankfurt, Germany
Professor Gerald Werner has been Director of the Department of Cardiology and Intensive Care at the Darmstadt Clinic, a teaching hospital of the University of Frankfurt, since 2005. This post followed a period of 7 years as Professor of Cardiology at the Friedrich Schiller University Jena, where he was Deputy Director of the Cardiology Department and Head of the catheter laboratory. Prior to this, Professor Werner held other positions at the University of Göttingen (Georgia Augusta) including Consultant in internal medicine-cardiology and Head of the echo cardiology laboratory.

Professor Werner’s research interests focus on the interventional therapy of coronary artery disease, including intravascular ultrasound, chronic total occlusions (CTOs) and collateral physiology, and the applications of lasers in interventional cardiology. He is a pioneer of coronary imaging by ultrasound; his earliest publications in this field date back to 1991, and he was among the first to describe the phenomenon of intramural coronary haematoma, and subintimal vessel pathways during recanalisation of a chronic coronary occlusion. He received the Franz–Maximilian Groedel Award of the German Cardiac Society (GCS) for his work on collateral physiology in CTOs. He has published over 150 original papers and is Fellow of the European Society of Cardiology (ESC), American College of Cardiology (ACC) and the Society of Cardiovascular Angiography and Interventions (SCAI). He is also co-Founder and past-President of the EuroCTO club.
Abstract

Percutaneous intervention (PCI) for chronic total occlusion (CTO) is a complex procedure requiring specific training, which has been an obstacle to its widespread use. Intravascular ultrasound (IVUS) is a valuable technique for assessing the anatomy of complex coronary lesions. In this white paper, evidence supporting the use of IVUS in the assessment of CTOs is presented. In addition, the author introduces a workflow algorithm that can help support research and clinical decision making for different scenarios of IVUS use in the CTO setting.

Introduction

A chronic total occlusion (CTO) is defined as a 100 % occlusion in a coronary artery with Thrombolysis In Myocardial Infarction flow 0 (no antegrade flow beyond point of occlusion) and occlusion duration of >3 months. CTOs are found about 20 % of patients with coronary artery disease and their presence often excludes patients from undergoing percutaneous coronary intervention (PCI). PCI of CTOs is the most challenging coronary intervention, and is associated with lower procedural success rates, increased restenosis and reocclusion compared with non-CTO procedures. The technical challenges include passage of a guidewire and balloon catheter across the CTO to enable successful PCI, and the maintenance of both short- and long-term patency. These require patience and skill, even for experienced operators. Effective wiring technique is the key to success in PCI of CTO; strategies include and combine the antegrade wire escalation, parallel wiring, dissection and reentry, and the retrograde transcatheter approach.

Patients with CTOs are often referred for coronary artery bypass surgery because of uncertainty regarding the procedural success and long-term benefit of PCI. However, successful PCI of CTO is associated with numerous benefits, including relief of angina, improved exercise tolerance, improvement in left ventricular function and improved mortality rates.
Intravascular Ultrasound in Chronic Total Occlusion

Angiography provides a two-dimensional image of contrast-filled lumen, which does not allow an accurate assessment of the plaque.\(^8\) By contrast, intravascular ultrasound (IVUS) provides cross-sectional images of the coronary artery, enabling measurement of luminal and vessel areas and thus providing valuable anatomic information about the coronary arterial lumen, wall, and plaques that cannot be assessed by coronary angiography alone.\(^9\) IVUS can be useful to clarify anatomical structures that cannot be satisfactorily identified by angiography alone, especially with an ambiguous position of the proximal occlusion cap. It is also particularly useful in complex CTO procedures when the course or position of the retrograde wire has to be identified. After opening the occluded artery, the final dimension of the distal vessel is often underestimated, and the sizing of the stents based on angiography alone may lead to underexpansion. Here, IVUS-guided stent implantation may result in improved long-term outcome.

During PCI procedures, IVUS assessment can assess expansion, apposition and edge dissection, which may necessitate further intervention.\(^10\) After PCI, IVUS can accurately measure the reference vessel diameter and lesion length to enable appropriate stent sizing when it is difficult for operators to accurately determine stent size with angiography alone, especially in CTO lesions. This is key to the success of IVUS-guided PCI in CTO lesions. IVUS can also determine the cause of stent failure, including in-stent restenosis and stent thrombosis (ST).\(^11,12\)

CTO recanalisation with a guidewire is the most important and difficult step in CTO intervention. The use of IVUS in the recanalisation of CTO enables precise location of the guidewires within an artery (i.e. true lumen versus subintima). It can also determine the optimal entry point and evaluate guidewire penetration of the proximal cap of a CTO. Even when the guidewire enters into the subintimal space and attempts to re-enter the true lumen under fluoroscopic guidance are unsuccessful, IVUS may facilitate the location of the true lumen. An IVUS catheter can be placed into the subintimal space after predilation with a balloon catheter, and then be advanced into the subintimal tract. A second guidewire can then be advanced alongside the IVUS catheter.\(^11,14\)

The use of IVUS also facilitates a wiring technique based on the fact that CTOs are often found distal to a branch artery. The IVUS catheter can be placed into a side branch just proximal to the CTO, allowing the proximal cap and central lumen of the CTO to be visualised. Such a technique is only possible if the angles of the side branch relative to the parent vessel and occlusion allow cross-sectional imaging.\(^15\)

IVUS is useful to guide complex retrograde approaches that involve approaching the lesion from both directions, advancing a balloon over the antegrade wire and inflating within the intimal or subintimal space, allowing the IVUS catheter to be advanced and positioned opposite to the retrograde wire. The retrograde wire can then be manipulated from the distal vessel position, which can be intimal or subintimal, into the true lumen and beyond the occluded segment.\(^14\)

Most experts agree that IVUS guidance improves the quality and outcomes of PCI. However, its use has been limited by a lack of appropriately powered randomised trials to provide robust evidence of the benefits of IVUS-guided PCI on clinical outcomes. Current European guidelines recommend the use of IVUS in PCI for all patients undergoing stent implantation optimisation (Class IIa, level B).\(^16\) IVUS is only used in a minority of CTO cases; in the 2011 European Registry of Chronic Total Occlusion (ERCTO) registry (N=1,914), IVUS was only employed in 2.9% of cases.\(^17\) This white paper presents evidence in support of the use of IVUS in the assessment of CTOs as well as introducing a workflow algorithm that can help support research and clinical decision making.
Clinical Evidence for the Use of Intravascular Ultrasound in Chronic Total Occlusion

IVUS offers the potential to overcome technical challenges in CTO: isolated case reports describe the advancement of the IVUS catheter into a side branch to identify the entry point of the major branch and also advancement into a false lumen to enable visualisation of the true lumen.15,18–20 A small case series (N=31) showed that an IVUS-guided wiring technique is useful and safe for the recanalisation of stumpless CTO lesions.21 Another small case series (N=31) showed a high success rate of IVUS-guided reverse-controlled antegrade and retrograde tracking (CART) in CTO renanalisation procedures.22 However, concerns persisted regarding device-related complications and prolonged procedure times when using IVUS.

Data on the relationship between successful CTO recanalisation using IVUS guidance and clinical outcomes after stent implantation are scarce. Larger trials have typically been underpowered to determine the impact of IVUS on outcomes, as event rates are generally low.

In the Angiography Versus IVUS Optimisation (AVIO) trial, which included patients with CTOs, IVUS guidance provided no statistically significant advantage in major adverse cardiac events (MACE) up to 24 months.23 However, 48 % of patients did not meet the pre-specified IVUS guidance criteria. A subgroup analysis showed a significant difference in terms of the final minimum luminal diameter (MLD) between both groups.

In a 2014 study of the Korean Chronic Total Occlusion Registry, IVUS-guided PCI was performed on 206 patients and propensity score-matched with 201 patients undergoing angiography guidance. A subgroup analysis showed a nonsignificant reduced incidence of MI (1.0 % versus 4.0 %; P=0.058). The rates of MACE were similar in both groups.

In a 2015 study, 230 patients with at least one CTO lesion that had been recanalised successfully were randomly assigned to IVUS- or angiography-guided PCI.25 Lower in-stent late lumen loss (0.28±0.48 mm; 95 % CI [0.003–0.355]) and a lower rate of diameter stenosis (21.1±19.9 %) was reported in the IVUS-guidance group, compared with 0.46±0.68 mm (95 % CI [0.001–0.356]) and 29.2±24.6 % in the angiography-guided group (P=0.002, respectively). However, there was no corresponding reduction in MACE, likely because the study was underpowered to demonstrate this. IVUS-guided stenting of CTO lesions had a lower rate of ST at 2 years, but the study was underpowered to demonstrate significance of this rare endpoint.

In another 2015 study, 402 patients with CTOs were randomised to the IVUS-guided PCI (n=201; randomisation occurred only when the wire successfully crossed the CTO) or angiography-guided PCI (n=201), and also underwent a second randomisation to Resolute zotarolimus-eluting stents or Nobori biolimus-eluting stents. At 12 months, rates of MACE were significantly lower in the IVUS-guided group than that in the angiography-guided group (2.6 % versus 7.1 %; hazard ratio 0.35; 95 % CI [0.13–0.97]; P=0.035; see Figure 1).26 Outcomes were similar between the two stents. In addition, patients in the IVUS-guided group were more likely to receive high-pressure dilatation after stenting with a higher maximum balloon pressure. Stenting resulted in a larger MLD in the IVUS group compared with the angiography group.

![Figure 1: Cumulative event rate analysis using the Kaplan-Meier method; IVUS-guide versus angiography-guided PCI of patients with CTO - a randomised study](image)

CTO = chronic total occlusion; IVUS = intravascular ultrasound; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention. Source: adapted from Kim et al., 201526
Practical use of Intravascular Ultrasound in Chronic Total Occlusion Interventions

The use of IVUS is beneficial in the following situations (see Figure 2):

1. **In antegrade approach:**
   - To identify the proximal cap
   - To puncture the true lumen from subintimal position

2. **In retrograde approach:**
   - To facilitate the reverse CART procedure
   - To prevent subintimal passage of retrograde wire into critical vessels (e.g. left main)

3. **After successful recanalisation:**
   - To optimise stent expansion
   - To clarify the stent extension required in diffusely diseased arteries

**Figure 2: Scenario of IVUS use in CTO**

**How to perform IVUS in antegrade approach**

1. **Identifying the proximal cap and IVUS-guided penetration of the cap**

   The applicability of this approach is dependent on the angle between a side branch located at the probable location of the cap, and the further course of the occluded segment. The shallower the angle, the better. At angles >90°, the visualisation might not be possible. However, the location can still be identified from the step-up of the vessel size when the IVUS probe is pulled back from the side branch.

   The major information to be procured by imaging will be the location of the cap, the structure of the cap regarding calcification or rather soft tissue, and the size of the target.

   There are two ways IVUS can be used to support the engagement of the wire into the occlusion stump. The first is direct on-line guidance with the probe left at the site with the best view of the stump so that the wire position can be monitored on-line and a successful entry of the wire, ideally centrally, into the stump can be documented. This method requires large guiding catheters to fit together the IVUS catheter and the CTO microcatheter ≥7 Fr. A disadvantage is that the bulky IVUS probe may impair the free movement of the wire and engagement of the stump. The preferred wire to perform the penetration will be a tapered tip medium to stiff wire. If a guide catheter larger than 6Fr cannot be used, serial examinations with IVUS are performed so that the puncture is done at the site where the angiographic roadmap shows the IVUS transducer when the probe was detected, but without the benefit of a continuous IVUS acquisition. Once the puncture is made where the stump was visualised with IVUS, subsequent IVUS passes are needed to confirm the intraluminal position of the wire. Especially if the side branch is relatively parallel to the CTO vessel, the wire progression can be successfully monitored for at least the first critical few millimetres. The use of IVUS for stumpless lesions is highly recommended and may prevent subintimal entry at proximal cap due to the wrong identification of the CTO stump. Specific expertise in the use of IVUS for this indication is highly recommended and proctoring by an experienced CTO operator liberally using of IVUS is mandatory to extract the full potential information from the IVUS imaging.
2. Identifying the subintimal position and directed luminal entry under IVUS guidance

There are two basic situations to use IVUS in the event of a suspected subintimal wire position. One is to confirm luminal and subintimal space and the wire location, the other is to use this information for a guided entry with a second wire. The first task is easy to do when there is a great volume of plaque, but if the wire is subintimal in a narrow vessel with no atherosclerosis it is difficult to identify the possible intimal space because it may be pressed against the wall and almost invisible. To identify the position, it is required to perform a slow and careful pullback with several manual fore and backward movements. To advance the IVUS probe into the space of the initial guide wire it may be necessary to predilate the space by a small balloon ≥ 2 mm. If the subintimal position is confirmed, it is important to identify the point of exit from the luminal route. This is most often a spot of calcium within the vessel where the antegrade wire is deflected into the subintimal space. To perform a successful re-entry into the true lumen, a second stiff wire, ideally a Confianza Pro 12g tapered tip wire with a sharp distal angle, is advanced parallel, supported by a microcatheter. Ideally, the puncture into the true lumen should occur at the site of deviation, because there is the biggest target for penetration. This is monitored by the IVUS probe in parallel position. Once the entry is achieved, the penetration wire should be replaced by a soft wire over the microcatheter to avoid a second exit into the false space. By this approach, the technique is not necessarily a re-entry, but an entry technique avoiding subintimal space. The entry should not be attempted too distal to where the intimal space might be compressed and renders a rather small target.

This technique is one of the most difficult to learn in CTO recanalisation and its use is more successful in the capable hands of operators who use complex algorithms to identify the direction where the new wire should puncture/be steered to remain in the true lumen.

How and when to perform IVUS in the retrograde approach

There are basically two different situations in which IVUS is of advantage or even mandatory to conclude the successful retrograde approach for a CTO. First, it is the direction of the retrograde wire towards a proximal cap that is ambiguous or it is an ostial occlusion of the left coronary artery branch. There is a high risk that the retrograde wire may enter the subintimal space and cause a dissection that may extend even towards the left main artery. In such a situation, a setup as described for the antegrade approach with an ambiguous cap is needed. The IVUS probe is positioned...
in a side branch close to the proximal cap to visualise the retrograde wire entry into the proximal lumen.

The specific problem of an ostial occlusion of the right coronary artery does not allow the positioning of the IVUS probe anterogradely. However, when in doubt whether the retrograde wire entered the aorta outside of the actual lumen or even ostium, an antegrade IVUS exploration after a low-profile balloon dilatation may help to avoid stent placement outside the arterial structure.

The more typical situation for the IVUS use in the retrograde approach would be the clarification of problems in advancement of the retrograde wire. When retrograde wire crossing is unsuccessful, a dissection and re-entry retrograde technique is mandatory to achieve success. It is important to recognise the relative position of the antegrade and retrograde wires within the CTO body as either intimal or subintimal. To advance the IVUS into the body of the CTO a predilatation with at least a 2.0 mm balloon is required. Short-tipped IVUS probes are advantageous as the lead into the occlusion may be limited. IVUS renders information to analyse the problem of lack of connection between antegrade and retrograde wire space. It may be due to heavy calcification or undersized balloon size for the reverse CART dilatation.

It is important to select the appropriate position within CTO vessel where to create connection between antegrade and retrograde guidewires (more proximally or more distally) when initial reverse CART strategy is unsuccessful due to severe calcifications.

### IVUS to optimise stent selection in CTOs

<table>
<thead>
<tr>
<th>Focal CTO with no proximal or distal disease</th>
<th>Diffuse disease</th>
<th>Proximal</th>
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<tr>
<td>Yes</td>
<td>IVUS to discriminate between plaque load and negative remodelling</td>
<td>Distal</td>
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<tr>
<td>Antegrade ballooning and stenting</td>
<td>Consider IVUS for stent sizing</td>
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After opening a CTO, IVUS represents a useful tool able to provide information about lesion length, morphology and identification of a landing zone for stent implantation. After stenting, expansion, apposition and extension can be optimised with IVUS assessment.

### Conclusion

There is a need for more studies that compare IVUS and angiography guidance for drug-eluting stent implantation in CTO lesions. There is also a need for longer follow-up to investigate the impact of IVUS-guided procedures on coronary endpoints. However, recent studies suggest that the use of IVUS is beneficial in the recanalisation of CTO lesions.
Case study #1
RCA CTO IVUS to guide proximal cap penetration

Patient history

- 56-year-old male
- Risk factors: hypercholesterolaemia, hypertension, smoker
- 1/2014 STEMI lateral wall
- Primary PCI for acute marginal branch occlusion, detection of chronic RCA occlusion
- Dobutamine stress echo: inferior and posterolateral ischaemia

Pre-procedural angiography

- CTO starts at a side branch with no identifiable proximal cap (A and B)
- Occlusion length is difficult to estimate due to retrograde filling until proximal of the crux cordis, and possible contrast filling in the distal segment with a RV branch
- J-CTO score 2

Procedural preparation: Identifying the proximal cap

- Solid structure
- No calcification
- Large target

Procedures

1. Puncture of the cap with Gaia 2
   - IVUS in place, next to IVUS Finecross microcatheter and Gaia 2 wire with distal extra bend (C)

2. Identifying the puncture point
   - IVUS pushed forward from proximal towards the side branch with the Gaia wire (circled) advanced into the proximal cap and entering the vessel in the centre (D and E)

3. Finecross microcatheterisation
   - Finecross microcatheter advanced into the proximal cap
   - Gaia wire then exchanged for a soft tapered Fielder XTR wire
   - Finecross is pushed further
   - The wire is exchanged for a Sion Black soft wire
   - Sion Black wire passed into distal RCA as confirmed by contralateral injection

4. Securing the PL branch at the distal bifurcation using a second wire (runthrough)
   - After balloon dilatation (2.5 mm) decision made on whether to cover the bifurcation with a stent, and the stent diameter (F)
   - IVUS is performed (G)

5. IVUS assessment – pullback from PDA to proximal RCA
   - IVUS demonstrated true lumen passage all the way with severe atherosclerosis extending until the crux
   - Therefore, the crux would be included into stent coverage with the distal stent towards the PL branch ostium

Case summary

- This case example of a complex RCA CTO demonstrates the use of IVUS for identifying the proximal cap, and identifying the correct wire position within the distal vessel
- Then in this diffuse case of atherosclerosis from proximal to distal vessel, the case demonstrates the relevance of IVUS for proper stent placement planning and execution as well as proper stent sizing and postdilatation (distal stent was 2.5 x 38 mm, proximal was 3 x 38, then distal postdilatation to 3.5 mm, proximal to 4.0 mm)
Case study #1

IVUS in Antegrade Approach

IVUS to Optimise Stent Selection in CTOs
Case study #2

RCA CTO IVUS to guide reverse CART wire manipulation

FIRST ATTEMPT

Patient history
- 59-year-old male
- Risk factors: current smoker (40 py)
- Since 10/2015 STEMI chest pain on exercise, three flights of stairs
- EKG: possible inferior infarct with ST depression in V5 and 6
- Echocardiography: hypokinesia of the inferior wall, slightly impaired LV function

Coronary angiography
- October 2015

PCI
- (Ad hoc) October 2015

Re-evaluation
- November 2015
- Angina during maximum exercise, during daily life still occasional symptoms
- Bicycle stress test: at 150 W with HR 136/min, ST depression in leads V5 and V6 and angina

Recanalisation attempt of RCA
- February 2016
- Diffuse small distal target
- J-CTO score 1

SECOND ATTEMPT

Patient history
- 59-year-old male
- Risk factors: smoking (40 py)
- Echo: slightly impaired ejection fraction with posterior hypokinesia
- Pathological bicycle stress test
- Creatinine 0.9 mg/dl, GFR 93 ml/min
- Height 176 cm; weight 76 kg

Procedures
1. Bilateral angiographic imaging
   - J-CTO score 2
2. Antegrade wire Fielder XT on Finecross microcatheter
   - Selection and passage of collateral
   - Retrograde wire Sion close to distal cap
   - Retrograde wire and antegrade balloon 2 x 20 mm: no connection made (A)
   - IVUS pullback performed (B)
3. IVUS pullback
   - IVUS guided entry into true lumen with retrograde wire (C)
   - PL branch secured with dual lumen catheter
   - After stent proximal placement, bifurcation treatment of crux cordis was performed (D)

Case summary
- This case example of a complex RCA CTO with problems in performing the reverse CART manoeuvre demonstrates the use of IVUS for identifying the position of the retrograde wire relative to the antegrade wire
- The retrograde wire could be steered into the proximal true lumen under live IVUS imaging and fluoroscopy
- IVUS helped identify the need for bifurcation treatment at the crux by showing massive plaque load of the PL branch ostium
Case study #2

IVUS in Antegrade Approach

- Proximal cap ambiguous
  - Yes to Side branch at cap
  - No to Antegrade wire escalation
- Antegrade wire escalation
  - No to Retrograde approach
  - Yes to IVUS-guided penetration
- IVUS-guided penetration
  - Yes to Subintimal dissection approach
  - No to Interventional collaterals
- Interventional collaterals
  - Yes to Retrograde approach
- Subintimal dissection approach
  - No alternative
- Antegrade wire subintimal
  - Yes to Interventional collaterals
  - No to Antegrade passage
- Antegrade passage
  - No alternative

IVUS in Retrograde Approach: Reverse CART

- Retrograde and antegrade wire ‘connect’
  - No to Wires overlap
  - Yes to Retrograde wire into antegrade guide
- Wires overlap
  - No to IVUS to assess antegrade luminal position
  - Yes to Correct antegrade wire knuckle, etc.
- Retrograde wire into antegrade guide
  - No to IVUS to assess connection zone:
    - Calcium: move entry zone
    - Outside the lesion: move the connection zone
    - Vessel too big: Increase antegrade balloon size
  - Yes to Main branch position
- IVUS to assess connection zone:
  - No to Correct antegrade wire knuckle, etc.
  - Yes to Advanced retrograde wire towards IVUS
- Main branch position
  - No to Correct antegrade wire knuckle, etc.
  - Yes to Antegrade balloononing and stenting
- Correct antegrade wire knuckle, etc.
  - No to Advanced retrograde wire towards IVUS
  - Yes to Assess retrograde wire tip
- Advanced retrograde wire towards IVUS
  - No to Assess retrograde wire tip
  - Yes to Antegrade balloononing and stenting
- Antegrade balloononing and stenting
  - No to Assess retrograde wire tip
  - Yes to Extrenalise RG3
- Extrenalise RG3
  - No to Antegrade balloononing and stenting
  - Yes to Retrograde wire into antegrade guide
Case study #2

IVUS to Optimise Stent Selection in CTOs

- **Focal CTO with no proximal or distal disease**
  - **Antegrade ballooning and stenting**
  - Yes

- **Diffuse disease**
  - **IVUS to discriminate between plaque load and negative remodeling**

- **Consider IVUS for stent sizing**
  - Proximal

**Side branch at cap**

**Externalise RG3**

**Antegrade passage**

**Interventional collaterals**

**Subintimal dissection approach**

**Interventional collaterals**

**IVUS-guided penetration**

**Subintimal dissection approach**

**Antegrade passage**

**IVUS-guided re-entry**

**Side branch at cap**

**Externalise RG3**

**Antegrade passage**

**Interventional collaterals**

**Subintimal dissection approach**

**Interventional collaterals**

**IVUS-guided penetration**