Cardiac and extracardiac complications during CTO interventions: prevention and management

Percutaneous coronary intervention of chronic total occlusion carries the risk of severe complications that are responsible for a significant morbidity and mortality rate associated with these procedures. Complications may be cardiac, such as acute myocardial infarction and coronary perforation, or extracardiac, such as aortic dissection, contrast-induced nephropathy and radiation skin injuries. The mechanisms, prevention and treatment of complications associated with percutaneous coronary intervention of chronic total occlusion are reviewed in this article.

KEYWORDS: chronic total occlusion, complication, percutaneous coronary intervention

Background
The knowledge of type, rate and natural history of complications that may occur during chronic total occlusion (CTO) intervention is an essential step of the decision-making process for evaluating the risk:benefit ratio of treating a CTO and the need to stop the procedure. Despite the traditional conviction that percutaneous coronary intervention (PCI) of CTO is a low-risk procedure, even in high volume and experienced centers, death may occur in up to 1% of patients, and in-hospital myocardial infarction (MI) may occur in up to 5% of cases [1]. In a series of 2007, PCIs for CTO performed over a 25-year period in a large volume center, the causes of death and MI were coronary perforation, acute ischemia owing to proximal damage of donor artery and aortic dissection [2]. However, as with other lesion subsets, in-hospital major adverse cardiac events associated with PCI of CTO have decreased over time. A great improvement in terms of reduction of urgent coronary artery bypass graft (CABG) and re-PCI has been observed after the introduction of stents in the 1990s. Similarly, there has been a progressive decrease in periprocedural MI and rate of death reflecting the evolution and amelioration of PCI techniques, the development of dedicated devices and the utilization of adjunctive pharmacological therapy [3]. For didactic purpose, we divided CTO-related complications into cardiac and extracardiac complications. The in-hospital complications reported in the main studies of CTO intervention are shown in Table 1 [2–5].

Cardiac complications

- Acute myocardial infarction
Acute myocardial infarction during attempt of CTO recanalization may occur as a result of several mechanisms [5,6]. Flow limit dissection of the proximal vessel owing to aggressive manipulation or deep engagement of the guiding catheter could compromise the ipsilateral collateral circulation. Extensive dissection of the nondiseased vessel distal to the occluded segment may occur with aggressive wire utilization, injection of contrast through the over-the-wire catheter in a false lumen or balloon dilatation of the false lumen, and this could abolish the protective effect of ipsilateral and contralateral collateral flow precipitating acute myocardial ischemia (Figures 1 & 2). Notably, dissection or thrombotic damage of the nondiseased contralateral donor vessel is a serious complication, which could lead to large acute ischemia with hemodynamic compromise and arrhythmias. Side branch occlusion, usually proximal to the occluded segment, could lead to myocardial ischemia [7]. Thrombus formation and air embolism, which can occur particularly in prolonged and complex procedures, could be responsible for acute ischemia and infarction. Numerous precautions could be taken to limit or avoid peri-procedural MI. When the probability of success of an antegrade approach is particularly high, it is advisable to utilize a 4- or 5-Fr diagnostic catheter for contralateral injection in order to avoid the possibility of mechanical damage of the contralateral donor vessel. Meticulous and frequent evaluation of the activated clotting time could avoid suboptimal anticoagulation and thrombus
Table 1. In-hospital complications reported in the main studies of chronic total occlusion intervention.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients (n)</th>
<th>Death (%)</th>
<th>AMI (%)</th>
<th>CT (%)</th>
<th>UR. CABG (%)</th>
<th>UR. re-PCI (%)</th>
<th>CVA (%)</th>
<th>VC (%)</th>
<th>MACE (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suero et al. (2001)</td>
<td>2007</td>
<td>1.3</td>
<td>2.4</td>
<td>0.5</td>
<td>0.7</td>
<td>1.5</td>
<td>0.01</td>
<td>1.7</td>
<td>3.8</td>
<td>[2]</td>
</tr>
<tr>
<td>Olivari et al. (2003)</td>
<td>376</td>
<td>0.26</td>
<td>4.6</td>
<td>2.1</td>
<td>0.53</td>
<td>0.53</td>
<td>0</td>
<td>2.1</td>
<td>5.1</td>
<td>[4]</td>
</tr>
<tr>
<td>Di Mario et al. (2007)</td>
<td>3403</td>
<td>0.12</td>
<td>1.96</td>
<td>0.6</td>
<td>0.27</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.99</td>
<td>[5]</td>
</tr>
<tr>
<td>Prasad et al. (2007)</td>
<td>482</td>
<td>0.4</td>
<td>8</td>
<td>0.8</td>
<td>1.7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
<td>[3]</td>
</tr>
<tr>
<td>Prasad et al. (2007)</td>
<td>152</td>
<td>0</td>
<td>5</td>
<td>1.3</td>
<td>0.7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.3</td>
<td>[3]</td>
</tr>
</tbody>
</table>

†All perforation without clinical sequela.
AMI: Acute myocardial infarction; CT: Cardiac tamponade; CTO: Chronic total occlusion; CVA: Cerebral vascular accident; MACE: Major adverse cardiovascular event; NA: Not applicable; UR. CABG: Urgent coronary artery by pass graft; UR. re-PCI: Urgent repeat percutaneous coronary intervention; VC: Vascular complication.

Coronary perforation

Coronary artery perforation is generally due to the passage of the wire into subintimal space or into a thin-walled vasa vasorum (which are prone to rupture). Perforation with extravasation could be caused directly by the wire or by subsequent balloon advancement and dilatation of subintimal space or vasa vasorum. It must be emphasized that in CTO intervention, wire exit is the rule rather than the exception but significant blood extravasation is unlikely when the wire goes extraluminally through an occluded segment. In case of subsequent successful crossing, the vessel perforation will be sealed by the dilatation and stent implantation of the true lumen. Major blood extravasation is usually the result of advancement of the balloon or, worse, dilatation of the balloon on a wire which is not intraluminal (Figure 3). This may cause pericardial effusion possibly leading to cardiac tamponade, intramural hematoma or iatrogenic fistula between the coronary and a cardiac cavity. A classification of coronary perforation is shown in Table 2 [8]. Even so, in most cases prolonged balloon occlusion of the perforated vessel segment and reversal of heparin action with protamine sulfate is normally sufficient to stop the leakage. Sometimes, gelfoam or microcoils embolization is required to seal distal perforation and, when the rupture occurs after predilatation or stent implantation, covered stent deployment can be necessary (Figure 3). Cardiac tamponade requires immediate pericardiocentesis, which is generally performed using fluoroscopy guidance and not echocardiography, since the dye leak into the pericardial space allows a relatively easy identification of the correct site of puncture under x-ray guidance (Figure 4). After effective pericardiocentesis, a drainage catheter is left in the pericardial space until bleeding stops. On rare occasions, the persistence of active pericardial bleeding requires cardiac surgery to repair the leakage. The following general rules could limit the occurrence of coronary perforation. First, special care should be taken when hydrophilic wires are used owing to their propensity for subintimal passage and wall perforation. The distal tip of the wire should always be visualized and, after crossing the occlusion, the CTO specific wire should be exchanged to a floppy wire. Adequate preparation of calcified occlusion with rotablator could avoid extremely high pressure balloon dilatation, which may lead to coronary rupture. Intravascular ultrasound guidance enables adequate selection of the size of the balloons and stents and also avoids oversizing. Finally, antithrombotics that cannot be immediately reverted should not be used. Agents such as bivalirudin, abciximab or other IIb/IIIa inhibitors should be avoided in CTO interventions or they should be used only after successful crossing of the occlusion and exclusion of vessel perforation [1,5,9,10].

Table 2. Proposed classification of coronary perforation.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A crater extending outside the lumen only in the absence of linear staining is angiographically suggestive of a dissection</td>
</tr>
<tr>
<td>2</td>
<td>Pericardial or myocardial blush without an exit hole of larger than 1 mm</td>
</tr>
<tr>
<td>3</td>
<td>Frank streaming of contrast through an exit hole of larger than 1 mm</td>
</tr>
<tr>
<td>3-cavity spilling Perforation into an anatomic cavity chamber, such as the coronary sinus and the right ventricle.</td>
<td></td>
</tr>
</tbody>
</table>

Data taken with permission from [8].
Cardiac & extracardiac complications during CTO interventions

Wire entrapment
Aggressive guidewire manipulation in totally calcified occluded arteries could result in wire entrapment. This complication may be relieved sometimes by selective intracoronary injection of nitroglicerine or verapamil [11]. Careful advancement of a small balloon or a microcatheter may also help to retrieve the entrapped wire.

Complications of the retrograde approach
The particular technique of retrograde approach entails an augmented risk of donor artery injury owing to spasm, dissection or thrombus formation. This complication could be observed during antegrade recanalization as well, when donor artery angiography is performed in order to visualize the vessel segment distally to the occlusion via collaterals, but the risk is particularly high with the retrograde approach, as it requires larger guiding catheters and the advancement of the guidewires and microcatheters into the donor artery. Complications exclusive to the retrograde approach are guidewire and balloon kinking or entrapment into collateral channels, collateral channel dissection or rupture (Figure 5) and hematoma formation at the level of the intraventricular septum (Figure 6). The latter are usually self-limiting complications, with spontaneous sealing observed in the follow-up, and septal branch embolization is required only in case of large false aneurysm formation [12–15].

Unresolved issues: potential late hazards
Stent thrombosis
Since drug-eluting stents (DES) are superior to bare-metal stents in reducing the rate of binary restenosis and target vessel revascularization, the currently recommended technique for PCI of CTO encompasses the implantation of DES [16–19]. Owing to the frequent presence of diffuse coronary disease, multiple DES are often implanted to treat a CTO. Thus, an increased risk of stent thrombosis (ST) after CTO intervention could be expected [20]. Furthermore, following reopening of a CTO, the vessel may appear smaller than it really is and this may lead to stent undersizing, which increases the risk of ST [21]. Therefore, intracoronary nitrate administration and routine utilization of intravascular ultrasound could help to accurately estimate the vessel diameter and avoid stent undersizing. Available randomized studies comparing DES with BMS in CTO intervention do not demonstrate an excess of ST in patients who received DES at early- and mid-term follow-up [16–19]. However, an increased risk for very late ST in the DES cohort has been recently suggested [22]. The issue of ST, leading to acute coronary occlusion, is particularly relevant since the presence of well-developed collateral circulation at the index CTO procedure does not appear to protect against late target vessel acute occlusion. It has been elegantly demonstrated that collateral circulation function decreases after CTO recanalization, and only a fifth of patients with patent artery at follow-up would be protected from ischemia in the case of acute occlusion by immediately recruitable collaterals [23,24].

Late-stent malapposition
An intravascular ultrasound study demonstrated that late-stent malapposition (LSM) is found in more than a quarter of CTO lesions treated with DES (Figure 7) [25]. Subintimal passage of the guidewire, creation of a false lumen or stenting of the false lumen have been suggested to be the mechanisms of injury to the adventitial layer during DES implantation of CTO lesions, contributing to LSM. In the same study, LSM was not associated with any major adverse cardiac event [25,26]. However, in a recent meta-analysis, the risk of LSM was increased after DES implantation and LSM appeared to be associated with very late ST [27].

Table 3. Proposed classification of iatrogenic aortic dissection.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Limited to the ipsilateral coronary sinus of Valsalva</td>
</tr>
<tr>
<td>2</td>
<td>Extending to the proximal ascending aorta (&lt;40 mm)</td>
</tr>
<tr>
<td>3</td>
<td>Extending over to the proximal ascending aorta (&gt;40 mm)</td>
</tr>
</tbody>
</table>

Data adapted from [29].

Extracardiac complications
Aortic dissection
In a retrospective study addressing iatrogenic aortic dissection during heart catheterization, treatment of CTO was a factor related to the onset of such a complication [28]. Dissection of the ascending aorta could be the result of guide catheter trauma, forceful contrast injection with a ‘wedged’ guiding catheter or retrograde propagation of dissection from the proximal or ostial segment of the coronary artery. Recanalization of CTO of the right coronary artery is the most frequent scenario for this complication (Figure 8). Dissection may be limited to the coronary sinus, may extend to the proximal ascending aorta or, in the worst scenario, could extend beyond the ascending aorta (Table 3) [29]. Predisposing factors...
are deep coronary engagement and the utilization of aggressive guiding catheters, such as 8 Fr Amplatz catheters (Figure 8). It has been suggested that the use of guiding catheters with side holes could limit the incidence of this severe complication. In the case of dissection limited to the coronary sinus or proximal ascending aorta, the suggested conservative management consists of anticoagulation reversion, heart rate and blood pressure control and close monitoring of the progression of the dissection with computed tomography or transesophageal echocardiography. When the etiologic mechanism relies on retrograde propagation of a dissection originating from the proximal coronary artery segment, implantation of a stent at the coronary ostium could limit further dissection expansion. In case of dissection extending over the ascending aorta or it being complicated by aortic regurgitation or pericardial effusion, management consists of emergent surgery (Figure 8).

- **Contrast-induced nephropathy**
  Angioplasty of CTO entails a significant risk of contrast-induced nephropathy mainly because the long procedure requires large contrast volume, and often a second (or third) attempt is needed for successful recanalization [38]. As for non-CTO PCI, in each patient undergoing a CTO procedure, the risk for contrast-induced nephropathy must be preliminarily estimated according to a validated score [31] and all the available prophylactic modalities must be adopted, keeping in mind that it is probable that the first line of prevention consists of a strict limitation of contrast amount and avoidance of repeated use of contrast within a short period of time (Box 1) [32].

- **Radiation injury**
  Radiation skin injury could be a deterministic, dose-dependent complication of CTO procedure [33,34]. Transient erythema, permanent epilation and delayed dermal necrosis can occur at 2, 7 and 12 Gy, respectively [35,36]. It has been demonstrated that total fluoroscopy time, total number of cine frames and entrance skin dose are greater in CTO than in non-CTO interventions. Furthermore, although the initial success of CTO intervention has become higher than in the past, on average, a quarter of procedures fail and repeat intervention may needed [5]. In addition, even with the utilization of DES, the restenosis rate is not negligible [37]. Therefore, reducing both the patient’s skin dose during each procedure, as well as the cumulative dose in the same area of skin during repeat procedure, should be pursued. Several methods allow for the reduction of the patient’s maximum skin dose during CTO procedures. Utilization of latest generation equipment with extra beam filtering and extrashielded x-ray tubes, together with the use of pulsed fluoroscopy and choice of low-dose settings, should be considered mandatory for CTO procedures. Furthermore, for angiographic documentation, rather than the digital cine mode storage, the pulsed fluoroscopy mode could be used (reducing radiation exposure by a factor of four) [5]. In addition, altering the beam angulation by rotating the x-ray tube more than 40° may reduce the patient’s skin radiation dose. Radiation monitoring is important; therefore, a detailed record of the exact radiation exposure in every patient should be kept. When the cumulative dose in the same area of the skin is so high as to be associated with risk of injury, dermatological follow-up should be scheduled [5,36].

- **Other complications**
  Despite the utilization of 7 or 8 Fr sheaths and bilateral approach, available data suggest that the incidence of vascular complication related to CTO intervention is similar to that for non-CTO intervention. A useful strategy to limit vascular complication could be the use of the radial approach or the utilization of a 4 Fr diagnostic catheter from the femoral access to perform the angiography of the donor artery. The rate of cerebrovascular complication during CTO procedures is the same as for other types of PCIs [2–4].

**Box 1. Modalities for prevention of contrast-induced nephropathy.**

- Iso-osmolar contrast media
- Limitation of contrast amount
- Avoidance of multiple contrast administration within a short period of time
- Adequate hydration
- Avoidance of hypotension
- N-acetylcysteine
- Sodium bicarbonate
- Hemofiltration
- Withdrawal of ACE-inhibitors, diuretics, NSAIDs, nephrotoxic antibiotics and cyclosporine

ACE: Angiotensin-converting enzyme.
Data adapted from [32].

**When to stop a CTO procedure**

In general, the occurrence of a clinically relevant complication during a CTO procedure requires prompt and proper treatment and is a sufficient reason to stop the procedure. Clinically silent procedural complications, such as intramural coronary hematoma with loss of distal vessel visualization or the formation of a long dissection,
may also drastically reduce the probability of success (Figure 7). In these circumstances, the CTO procedure should be stopped and at least 4 weeks should be allowed to pass before a second attempt, in order to allow the vessel wall to heal (Figure 9). As for non-CTO PCI, the excessive administration of dye should be considered a strong indication to stop the procedure owing to increased risk for contrast-induced nephropathy. Importantly, patient or operator fatigue may suggest another reason to stop the procedure and plan a second attempt. When further attempts are planned after a first failed CTO procedure, cumulative x-ray dose should be considered in order to avoid the onset of radiation-induced skin injury [1,5].

### Future perspective

The available data show that recanalization of a CTO may improve anginal symptoms and left ventricular function, and appears to have a positive long-term prognostic effect. However, further scientific evidence is required in order to better identify the subgroups of patients for whom the recanalization of a CTO has a favorable impact on the incidence of major clinical events, such as MI, heart failure or death.

The continuous development of dedicated devices, the spread of this knowledge (mainly from Japan) and, perhaps, the identification of special referral centers for recanalization of CTOs could help to both enhance the rate of successful intervention and to reduce the incidence of periprocedural complications.

### Bibliography

Papers of special note have been highlighted as:

- of interest


5. Large real-world registry of chronic total occlusion (CTO) intervention.

6. Large real-world registry of CTO intervention.

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**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.


* Discusses classification and management of coronary perforation of clinical utility.


* Multicenter registry of retrograde CTO intervention confirming the reproducibility of this approach outside of the highly experienced Japanese centers.


* Randomized study demonstrating the superiority of drug-eluting stents over bare-metal stents in CTO intervention in terms of reduction of restenosis and target lesion revascularization.


* Elegant study addressing the issue of radiation skin injury.


Figure 1. Coronary dissection during chronic total occlusion recanalization. (A) Baseline coronary angiography showing the chronic total occlusion of the proximal right coronary artery (RCA). (B) A good visualization of the distal RCA was obtained during left coronary artery angiography by means of contralateral collaterals. After predilatation (C), an occlusive dissection of the mid and distal RCA appeared (D), leading to acute myocardial ischemia. The mechanism of the distal dissection was probably related to the passage of the wire into a false path and subsequent dilatation of the false lumen.
Figure 2. Coronary dissection and perforation during chronic total occlusion recanalization. (A) A weak visualization of the distal right coronary artery (RCA) was obtained by means of ipsilateral collaterals. (B) With the support of an over-the-wire (OTW) 1.5 balloon, a guidewire was advanced in the distal RCA. (C) To check the position of the wire, injection of contrast through the OTW balloon (arrow) was performed, resulting in a large dissection of the distal RCA symptomatic of acute ischemia and mild pericardial effusion without hemodynamic significance. (D) The mechanism of the distal dissection and leakage was related to the passage of the wire and the OTW balloon in a false path and subsequent forced injection of contrast into the false lumen.
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**Figure 3. Coronary perforation during chronic total occlusion recanalization.** Baseline coronary angiography showing the chronic total occlusion of the proximal left anterior descending coronary artery in (A) cranial right anterior oblique and (B) caudal left anterior oblique views. After predilatation and stent implantation (C), a class 3 coronary perforation was manifest in the mid-left anterior descending artery (D). Reversal of anticoagulation by means of protamine sulfate administration and prolonged balloon inflation (E) did not stop the leakage (F). After covered stent implantation (G), cessation of dye extravasation was obtained (H). The mechanism of the coronary perforation was probably related to the passage of the wire in a false path and subsequent dilatation of the subintimal space.

**Figure 4. Cardiac tamponade secondary to coronary rupture requiring immediate pericardiocentesis.** (A) The presence of dye mixed with blood in the pericardial space (asterisks), which is delimited by the visceral pericardium (closed arrows) and the parietal pericardium (open arrows), allows an easy and quick identification of the correct site of puncture under x-ray guidance. (B) The pericardiocentesis is usually performed by means of a pigtail catheter inserted into the pericardial space and left in place until there is evidence of cessation of bleeding.
Figure 5. Septal branch injury during retrograde approach for recanalization of a chronic total occlusion of the right coronary artery. (A) Multiple attempts to advance a hydrophilic guidewire (arrows) on an over-the-wire microcatheter (B) resulted in a clinically silent dissection and rupture of the septal branch with persistent contrast staining in a small area of the intraventricular septum.

Figure 6. Septal branch injury during successful retrograde recanalization of a chronic total occlusion of the right coronary artery. (A) Advancement of a hydrophilic guidewire on an over-the-wire microcatheter into the septal branch. (B) Simultaneous angiography of the left coronary artery and the right coronary artery showing the good final result of the recanalization of the right coronary artery. A small hematoma was evident at the level of the intraventricular septum (arrow). (C) The hematoma was stable and was treated conservatively.
Figure 7. Late stent malapposition following chronic total occlusion recanalization. (A) Chronic total occlusion of the left anterior descending artery successfully recanalized with implantation of two 3.5 mm drug-eluting stent via antegrade approach (B & C). (D & E) Elective angiographic follow-up after 8 months showed no sign of restenosis except for a short segment of late stent malapposition (arrow) at the level of the drug-eluting stent in the mid-left anterior descending artery. (F) Intravascular ultrasound examination confirmed the presence of late stent malapposition (arrow). (G) Postdilatation of the stent with 5 × 8 mm noncompliant balloon at the level of the late stent malapposition zone led to focal overexpansion of the stent struts (dashed lines) and significant reduction of the area of malapposition (H, I, J & K). Clinical follow-up at 18 months was uneventful.
Figure 8. Type A aortic dissection complicating an attempt of chronic total occlusion recanalization. (A) Baseline coronary angiography showing the chronic total occlusion of the proximal right coronary artery. (B) The mid and distal right coronary artery was well visualized during left coronary artery angiography by means of contralateral collaterals. (A & B) An 8-Fr Amplatz-shaped guiding catheter was used for the antegrade attempt of recanalization (arrows). (C & D) During the procedure, the patient complained of chest pain, and supravalvular aortography showed aortic dissection extending from the right coronary sinus to the ascending aorta (type 3 of Dunning). Emergent surgery was performed. The mechanism of the aortic dissection was probably related to traumatic effect of the aggressive 8-Fr Amplatz catheter.
Figure 9. Successful chronic total occlusion recanalization after a first unsuccessful attempt led to complex dissection. 
(A) Chronic total occlusion (arrow) of the proximal left anterior descending artery with (B) well-developed contralateral collateral circulation from the right coronary artery. (C & D) A first attempt of antegrade recanalization was unsuccessful owing to the passage of the wire into a false path and the creation of a clinically silent complex dissection that could not be crossed despite repeat manipulations with different wires. (E) The procedure was terminated and a second attempt was scheduled. (F) After 4 weeks, following partial sealing of the dissection, it was relatively easy to gain access to the true lumen with the wire and (G) successfully recanalize the artery with multiple drug-eluting stent implantations.