For reprint orders, please contact:
reprints@future-drugs.com

New percutaneous approaches for chronic total occlusion of coronary arteries

Giora Weisz and Jeffrey W Moses†

Successful recanalization and percutaneous revascularization of coronary arteries with chronic total occlusion (CTO) is one of the 'last frontiers' in coronary interventions. Conquering this obstacle will enable complete percutaneous revascularization in an increasing number of patients. The introduction within the last few years of enhanced guidewires combined with increasing operator experience and creative procedural techniques, such as the retrograde approach and the re-entry subintimal tracking technique (STAR), have significantly reduced the number of CTOs that should now be considered unapproachable. In addition, novel devices have been developed over recent years that may increase the success rate, as well as the safety, of the procedure. The Safe-Cross radiofrequency combines optical coherence reflectometry that warns the operator when the wire tip moves to within 1 mm of the outer vessel wall, combined with radiofrequency energy pulses to facilitate the passage. The CROSSER catheter mechanically vibrates against the face of the CTO at 20 kHz at a stroke depth of approximately 20 µm, creating a channel through the CTO. The most novel approach is the biologic one, in which proteolytic enzymes that digest the CTO cap to facilitate mechanical passage. The success rates for otherwise refractory CTOs will continue to improve with the development and validation of new imaging modalities and active energy source catheters.

Expert Rev. Cardiovasc. Ther. 5(2), 231–241 (2007)

CONTENTS

Angiography & access of CTO
Intravascular ultrasound
Novel imaging approaches
Wires-based recanalization techniques
Other mechanical devices
Ablative technology
Vibration & ultrasound
Nonmechanical (biological) approach
Drug-eluting stents
Expert commentary
Five-year view
Key issues
References
Affiliations

†*Author for correspondence*
Columbia University Medical Center, Center for Interventional Vascular Therapy, 161 Fort Washington Avenue, IP-5 Floor, New York, NY 10032, USA
Tel.: +1 212 305 7060
Fax: +1 212 342 3660
jmoses@crf.org

KEYWORDS:
angioplasty, chronic total occlusion, coronary artery disease, percutaneous intervention, stent

Over the last decade there has been remarkable progress in the percutaneous management of coronary artery disease, as an established alternative to coronary artery bypass surgery. When compared with dilatation of coronary lesions using balloons, the scaffolding properties of stents have resulted in increased safety and predictable results, with reduced rates of acute closure and late restenosis. Recently, the addition of antiproliferative agents on the surface of the metal stents (drug-eluting stents) has been shown to markedly attenuate the vascular responses of neointimal hyperplasia, resulting in a marked reduction in the rate of restenosis [1,2].

Successful recanalization and percutaneous revascularization of coronary arteries with chronic total occlusion (CTO) is one of the 'last frontiers' in coronary interventions. Conquering this objective will enable complete percutaneous revascularization in an increasing number of patients. Revascularization of CTOs carries multiple advantages, such as improvement in abnormal wall motion and left ventricular function and, ultimately, increased long-term survival. In the long term, when coronary disease may progress, having an open artery may increase the tolerance to future coronary events. Reducing or abolishing myocardial ischemia improves electrical stability and reduces predisposition to arrhythmic events. The definitions, clinical relevance, indication for treatment and results were recently reviewed and summarized in a three-part consensus document [3–5]. Recently, the recanalization of CTO in patients with persistant occlusion after myocardial infarction (MI) has been questioned. In the Occluded Artery Trial (OAT), a randomized study of a selected group of patients, in which the infracted related artery has been persistently occluded 3–28 days

10.1586/14779072.5.2.231

ISSN 1477-9072

post-MI, routine percutaneous coronary intervention (PCI) of the CTO did not reduce the occurence of death, reinfarction or heart failure [6]. Unfortunately, not only did this study enroll only stable patients unrelated to their clinical symptoms or demonstration of myocardial ischemia, patients that had triple vessel disease or had a stress test that documented severe ischemia were excluded.

The prevalence of CTO in the general population is not clear. In the early 1990s it was reported that a chronically occluded coronary artery was found in approximately one third of patients undergoing angiography, approximately half of them suitable for angioplasty [7]. Despite this high prevalence, recanalization of CTO has been reported to be attempted in only 8–15% of the patients undergoing PCI [8–10]. The disparity between the frequency of CTO and percutaneous treatment underscores not only the technical and procedural complexities of this lesion subtype but also the clinical uncertainties with regard to which patients benefit from CTO revascularization [3].

The histopathology of the chronically occluded coronary artery has been described comprehensively [11,12]. Chronic coronary occlusion most often arises from thrombotic occlusion, followed by thrombus organization and fibrosis. Approximately half of all CTOs are less than 99% stenotic when observed by histopathology, despite the angiographic appearance of total occlusion. The typical atherosclerotic plaques of CTO consist of intracellular and extracellular lipids, smooth muscle cells, extracellular matrix and calcium. Collagens are the major structural components of the extracellular matrix. Another hallmark of CTOs is the extensive neovascularization, which occurs throughout the vessel wall.

Learning and mastering the skills to recanalize CTO is an advanced stage procedure that is left for the experienced operator. The variety of CTO cases is wide and special expertise is needed to differentiate between different anatomic situations, selecting the appropriate devices, being able to change strategies as the cases progresses and keep it safe – avoiding and treating potential complications. Needless to say, the success rate of CTO treatment is related to the accumulative general PCI experience of the operator in general and CTO cases in particular. The operator who takes on CTOs should approach cases of increasing difficulty; progressing gradually from tapered to flash occlusions, from short occlusions to longer ones, from straight segments to more tortuous vessels and, with time, to being able to tackle long-standing complete CTOs.

Angiography & access of CTO

In the modern approach to the treatment of CTO, angiography is the key point for success. Correct evaluation of the occluded segment, vessel course, CTO morphology, edges and bifurcations will enable the operator to select the appropriate strategy and devices, leading to high success rates. Features considered to be favorable (which increase the success rate of recanalization) include occlusion of less than 3 months, occlusion segment less than 1.5 cm, some antegrade blood flow and visible stump (dimple). Unfavorable features are long-standing occlusion, long segment, thrombolysis in MI (TIMI) 0 flow and bifurcating branches at either the proximal or distal edge of the occlusion segment [13–15].

The documentation of collaterals, which serves to evaluate the segments of the artery, distal to the occlusion, is essential to the success of CTO. In addition to valuable information, such as the size of the ischemic territory, the operator can evaluate the length of the occluded segment and the size and location of the run-off. One should never blindly cross an occlusion without clearly knowing where the wire should be directed and whether it is inside the lumen or in a dissection plane. Having a simultaneous contralateral injection can simplify the procedure and increase the chances of conducting successful and safer procedure if ipsilateral collaterals are insufficient. The contralateral injection is performed by using a 4–5 F diagnostic catheter, which is inserted through an additional arterial access, usually the contralateral groin.

As is true in regular interventions, the guiding catheter is of paramount importance in providing safe access of interventional tools to the treatment area, while providing adequate support. In CTO cases, extra support is usually needed in order to deliver devices. This is especially important after crossing with the wire. Often there is significant resistance to lesion crossing even with a very low profile balloon, and having an extra support guiding catheter can be of help. When the support of the guiding catheter is insufficient, the success rate is lower, especially in cases with unusual anatomic variations, calcified vessels and tortuousity.

In the left coronary artery, good guiding catheter support can be achieved with a broad transition guiding catheter that has a secondary curve that leans against the opposite wall of the aorta (passive back-up), usually extra back-up (EBU; Medtronic), XB (Cordis) or Voda (Boston Scientific) will be sufficient, with rare cases requiring an Amplatz curve catheter.

In the right coronary artery, excellent support can be achieved with the left Amplatz family of catheters, usually Amplatz left (AL)1, with AL 0.75 for small aortas and AL 1.5 or 2.0 for dilated roots.

Additional active back-up maneuvers can help to improve support for forward advancement of the hardware. The anchor wire or balloon techniques are used frequently:

- Anchor wire technique: if there is a reasonable size side branch proximal to the occlusion (such as a proximal diagonal for mid-left anterior descending [LAD] occlusion or the left circumflex [LCx] for ostial LAD occlusion), a second wire can be inserted into this branch, helping to fix the catheter position in place. A relatively stiff support wire is preferred;
- Anchor balloon technique: with this technique, a wire, followed by a balloon, is introduced into a side branch proximal to the occlusion. The balloon is inflated to a low pressure and size that are just sufficient to anchor the guiding catheter and enable deeper engagement, while pushing the guide over the

balloon catheter shaft. Again, the operator should keep in mind the risk of proximal dissection with this procedure, which may necessitate a longer segment of stenting.

Intravascular ultrasound

Sometimes, despite multiple view angiography, it is still difficult to assess the exact entry point of the proximal edge of the CTO. This is typical of any flush occlusion at a bifurcating branch. Thus, intravascular ultrasound guidance allows identification of the origin of the true lumen [16]. In such cases, the location of the entry point can be obtained by wiring the side branch and performing thorough intravascular ultrasound (IVUS) interrogation by pulling back from the side branch to the main branch origin and directing the crossing wire to the spot that was identified by the IVUS image. The IVUS will be less useful in cases of heavy calcification in the vessel wall at the CTO ostium or side branch. A similar technique can be used, placing the IVUS in a false lumen and identifying the true lumen paralleled and placing the crossing wire in the spot on the IVUS, but this carries the risk of increasing the size of the false lumen and perforation.

The current available IVUS technology is limited owing to its ‘looking aside’ characteristics. The development of ‘forward-looking’ IVUS may be helpful in the identification of the proximal cap and differentiating between true and false lumen.

Novel imaging approaches

Computerized tomographic angiography

Computerized tomographic (CT) angiography has made significant progress in coronary imaging with the introduction of the 64-slice CT. This improved technology allows rapid acquisition of superior studies, in terms of temporal resolution and image quality, compared with previous generations. In the evaluation of a CTO, the CT angiogram is able to provide complementary data to that of conventional angiography that may be relevant to the success of the CTO recanalization. Such information may include precise quantification of the length of the occlusion, defining the composition of the plaque, identification of the amount and depth of calcification and evaluation of the distal vessel beyond the occlusion. In addition to these lesion characteristics, the CT angiogram can also define bends and angles inside the occluded segment, important features that help the operator to navigate the wire safely and successfully through the occlusion to the distal vessel.

This imaging technology is most beneficial when the CT images can be used side by side with the angiographic and other imaging modalities (FIGURE 1).

Mollete and colleagues performed multislice CT coronary angiography in 45 patients who had CTOs and were scheduled for percutaneous recanalization [17]. Using this new imaging technique, they were able to identify the predictors of procedural

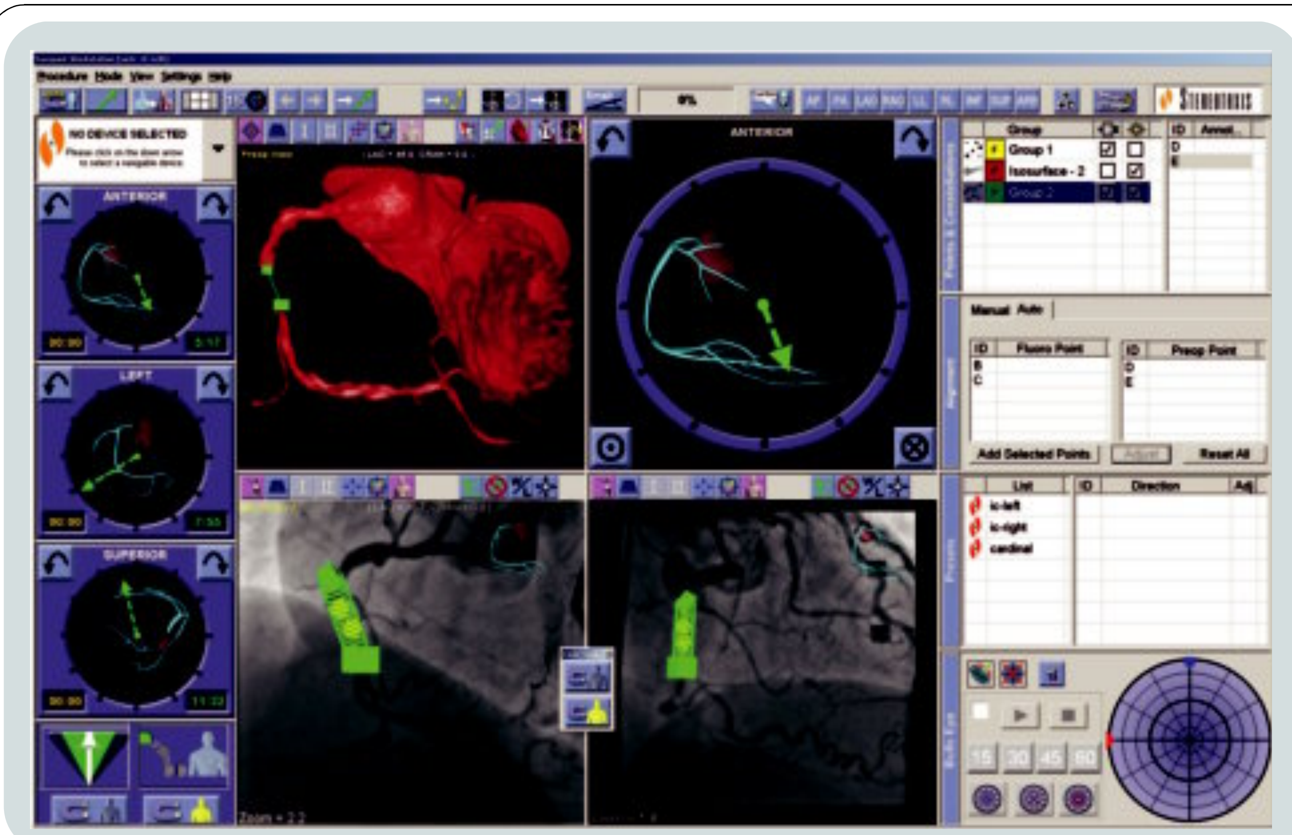

Figure 1. Coregistration of computerized tomographic angiography with angiogram of a chronic total occlusion in the mid right coronary artery. This new imaging modality can support the procedure with better evaluation of the anatomy and enable accurate and safe use of a combined device for recanalization.

failure: blunt stump (as by conventional angiography), occlusion length greater than 15 mm and severe calcification (by multislice CT coronary angiography).

Magnetic-assisted navigation

Another novel imaging system that may be helpful in the treatment of CTOs is the magnetic-assisted navigation system, NIOBE® (Stereriotaxis, MO, USA). The system utilizes two permanent magnets mounted on articulating or pivoting arms that are enclosed within a stationary housing, with one magnet on either side of the patient table. These magnets generate magnetic navigation fields that are less than 10% of the strength of fields typically generated by magnetic resonance imaging (MRI) equipment and therefore require significantly less shielding, and cause significantly less interference than MRI equipment. The NIOBE magnets precisely steer the working tip of the dedicated guidewires, using the 3D reconstruction of the coronary arteries. Coregistration of the 3D map with CT angiography data may assist the operator in navigating the wire through torteousity inside the occluded segment, keeping it coaxial along the vessel throughout its course. If it can be effectively coupled with a radiofrequency (RF) source at the wire tip, such a system could conceivably evolve into a remote controlled semi-automated method (FIGURE 1).

Wire-based recanalization techniques

Guidewire technology for CTO

Coronary guidewires have remained the most common technology for CTO revascularization, ranging in variable degrees of stiffness and the presence or absence of a hydrophilic coating. Two groups of wires are usually used for CTOs: polymer-coated and coil wires. The polymer coated wires have a hydrophilic coating that markedly lowers friction, helping it to move very easy through the vessel lumen [18]. This feature may also increase the risk of advancing the wire into subluminal planes and creating a false lumen, long dissections or perforations. The coil wires maintain good torquability, even inside the fibrosed CTO segment, while retaining excellent pushability. The stiffer the wire tip, the higher the torquability of the wire but the less resistance at the tip felt by the operator and the higher the risk of entering a false channel. With tapered tip wires (e.g., Confienza 0.014–0.009” or Crossit 0.014–0.010”) there is a greater chance to enter microchannels than normal 0.014 ‘tip coil wires’ [19]. With stiffer coil wires, such as the Crossit 300–400 (Abbott Vascular, Inc., CA, USA), Miracle 9, 12 g (Asahi, Inc./Abbott Vascular, Inc., CA, USA) (FIGURE 2) or Persuader (Medtronic), the stiffer tips can increase penetration ability but do run the risk of ending up in a false lumen, especially after bends. Using these specific wires requires close attention by the operator to the 3D wire orientation at all times to reduce the likelihood of perforations. These wires should be used only by experienced operators after the use of more conventional wires has been attempted. In a registry of 214 CTO revascularizations initially attempted with tapered guidewires, overall technical success was achieved in 82% of patients. In the presence of a visible microchannel, however,

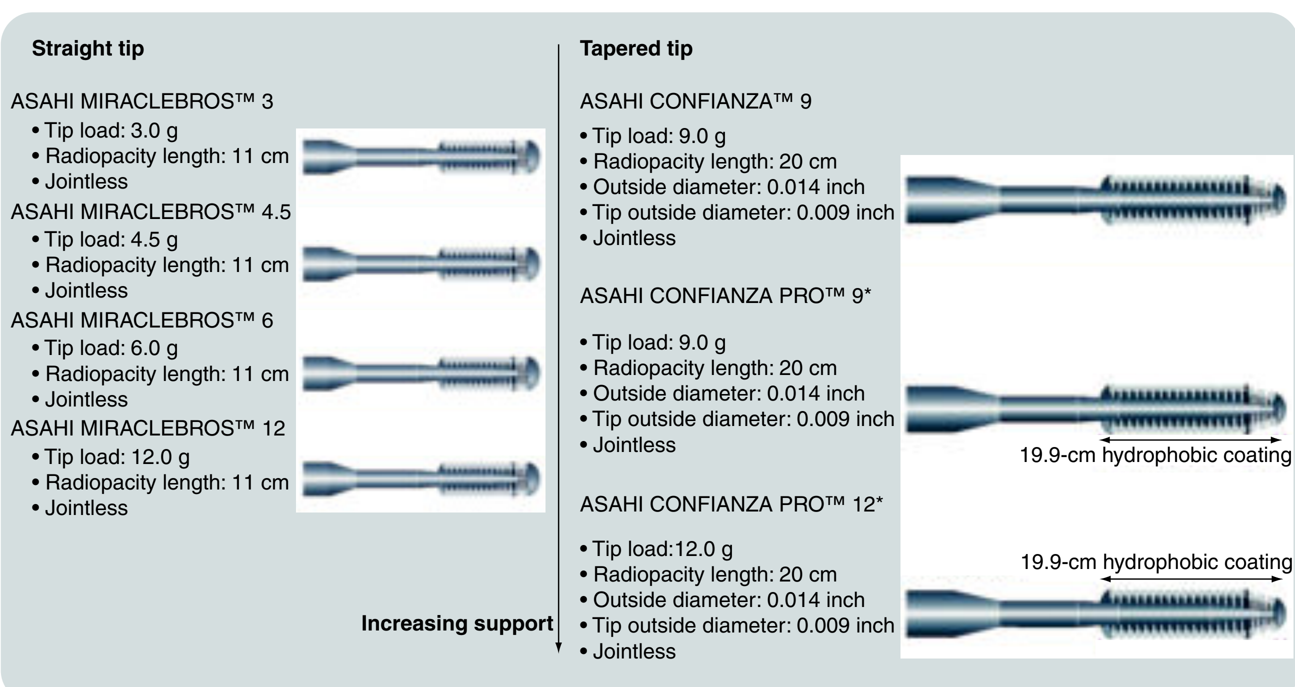

Figure 2. Example of a series of guide wires designed for recanalization of chronic total occlusion lesions. Asahi (Abbott Vascular), Japan.
*The working length has a hydrophilic coating to ease navigation while the distal 1-mm tip is hydrophobic for increased control and tactile feedback in chronic occlusions.

the success rates ranged from 81% (incomplete microchannel) to 100% (microchannel with distal filling) [20]. Another series comparing multiple techniques underscored the improved recanalization success with the use of tapered-tip wires (a positive predictor of success, p = 0.002) [21].

Which wire to choose is a difficult question with no straightforward answer. Our practice is to go from the light to the heavy, always starting with a soft tip, changing to harder and stiffer wire if the lighter and softer wires do not work. For occlusions that are less than 6 months old, an intermediate wire will usually work. The Miracle Bro 3g (Asahi) has excellent torquability and will often be a good choice. For harder lesions, older than 6 months, wires with harder tips will often be needed.

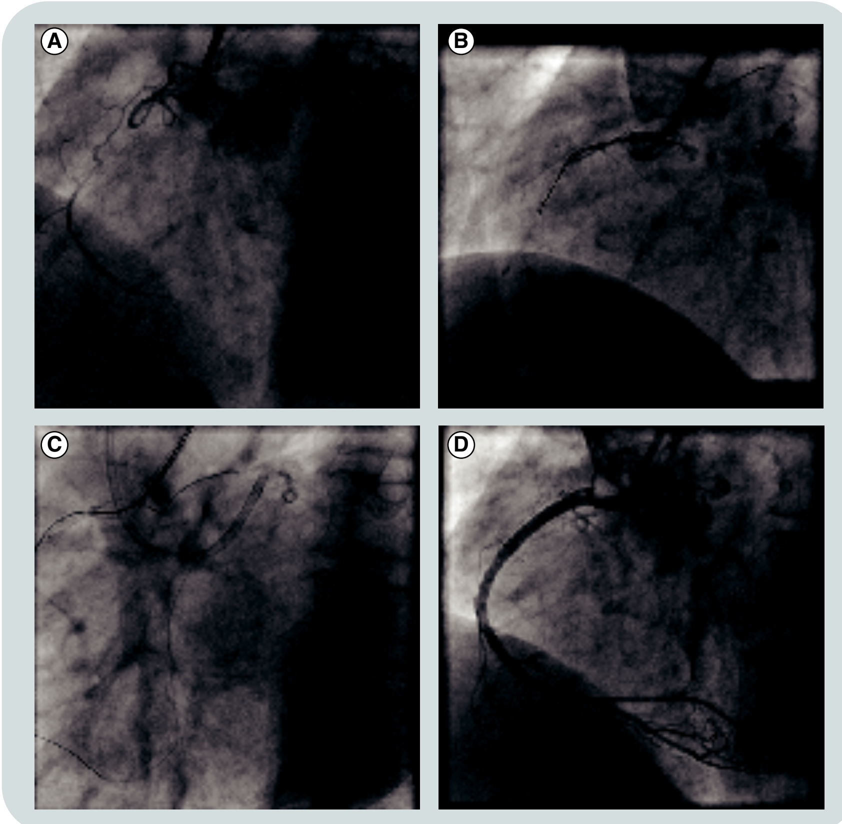

Figure 3. A 76-year-old man with exertional shortness of breath was found to have triple vessel disease, he refused to have coronary artery bypass graft surgery. The left anterior descending and chronic total occlusion (CTO) of the left circumflex were stented in the first procedure, and the right coronary artery occlusion staged. **(A)** Despite multiple orthogonal views, no dimple was found to reveal the entrance point of the occlusion. The conal branch takes off at this CTO. **(B)** An 8 F JR 4 with side holes was used to enable multiple devices and support. A floppy wire (Prowater, Abbott) was placed in the conal branch and a pull-back intravascular ultrasound interrogation was done to demonstrate the exact entry point. A miracle 3 (Asahi) wire was manipulated to the identified point of entry and exchanged with stiffer wires (Miracle 6 and 12, Asahi), using the parallel-wire methods, but without success. **(C)** A 7 F EBU guiding catheter (Medtronic) angiographically demonstrated multiple septal branches that connect directly to the posterior descending artery. The widest and most straight branch was selected for retrograde wiring. A Ryujin wire (Terumo) was directed to this branch, using a 1.5 X 15 mm Maverick® 2 balloon (Boston Scientific) that followed the wire as it was advanced. **(D)** The wire was advanced to the distal cup and the proximal stiff wire was advanced antegrade. Stenting the right coronary artery resulted in excellent angiographic result.

Parallel wire techniques

In cases that a wire is repeatedly advanced into the wrong plane, it can be left in place (subintimal) as a marker of the incorrect path, while a new wire is used and directed to the proper exit point (FIGURE 3). In a modification of this technique, the 'seesaw wiring method', the parallel wires are used using two support catheters (such as over the wire balloon or transit catheter [Cordis, Johnson & Johnson]). This enables alternate use of the wires, easily alternating their roles as 'marking wire' and 'advancing wire' through the occluded segment.

Re-entry: the STAR technique

A promising but potentially treacherous wire-based technique is using the 're-entry' subintimal tracking (STAR) approach. This approach is similar to the one utilized in treating peripheral artery occlusions, with the aim of creating a subintimal dissection with distal re-entry. A 0.014' hydrophilic wire with a J-configuration is utilized for this purpose. The hydrophilic wire is pushed through the subintimal dissection plane. When pushed distal to the occlusion, the J tip is directed towards the true lumen, attempting to re-enter. In a report of 31 patients with CTO, most of them with a previous failed attempt, recanalization with this technique was successful in 21 patients [22]. However, it carries a higher potential for perforation than most others. In patients that previously had the STAR technique applied and the artery reoccluded, it is very difficult to get into the true lumen.

Retrograde wire technique

An exciting new wire-based approach has recently been introduced in Japan and is gaining increasing popularity by top of the line operators [23,24]. This is the retrograde approach (FIGURE 3). When antegrade crossing of a CTO fails, the retrograde approach may be considered. In this technique, the operator generally utilizes transeptal from left to right or right to left collaterals, as demonstrated by bilateral injection angiography, and subselective injection. The selection of the guiding catheter should be thoughtful: a supportive (at least 7 F) short guide (85–90 cm) should be used to enable longer coronary segment to pass through. A hydrophilic soft wire, supported by 1.25–1.5 mm over the wire balloon, is advanced through the collateral for the retrograde approach to CTO. Frequently, a gentle dilatation of the septal branch with the balloon is

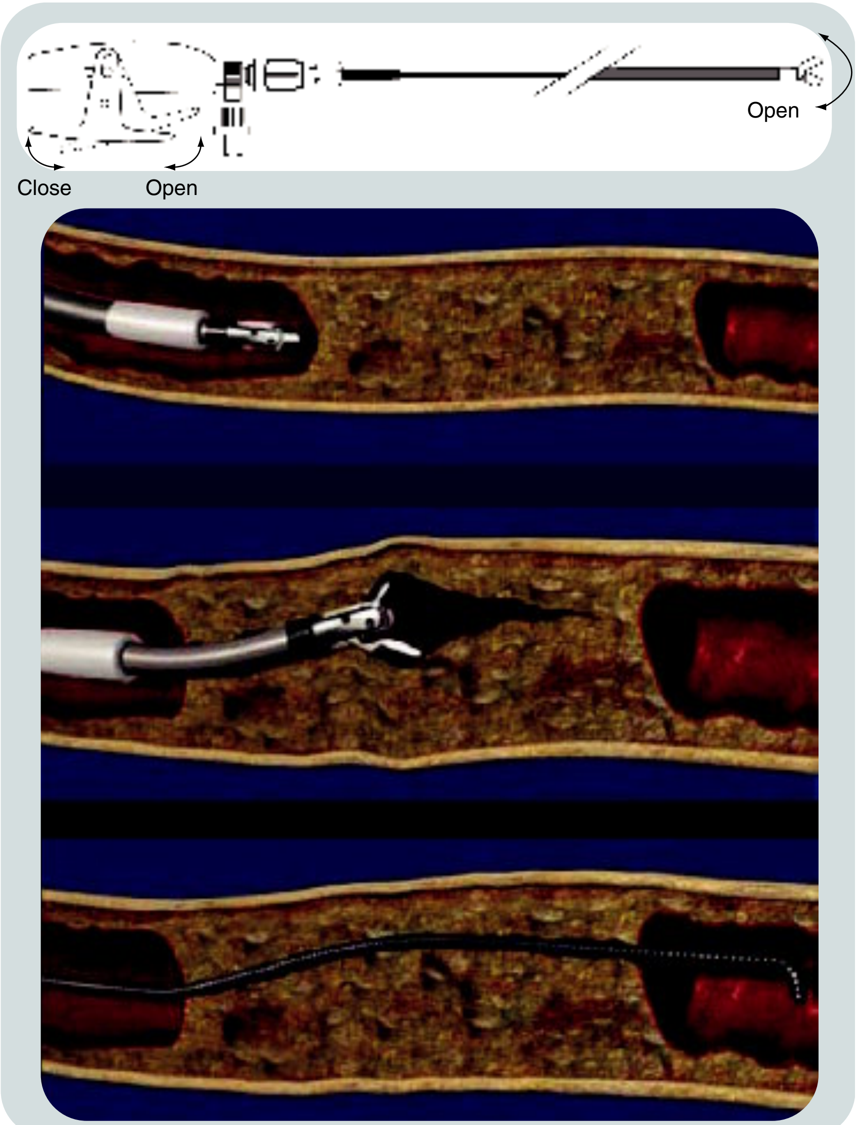

Figure 4. The Frontrunner® (LuMed, Cordis, Johnson & Johnson). Facilitates placement of a conventional guide wire across stenotic lesions or chronic total occlusions in the peripheral vasculature by creating a pathway through the occluded vessel via blunt microdissection.

needed to facilitate the further delivery of the support balloon. After advancing the supporting balloon close to the occlusion, the wire can be exchanged to one with a stiffer tip to cross the occlusion. In some cases, especially in those when the antegrade wire went into a false lumen, a retrograde wire can be used to give an idea about the location of the true lumen, thus helping the operator to correctly direct forward the antegrade wire, or further subintimal retrograde dilatation (CART) can be performed to widen the target for the antegrade wire.

Laser technology

In the previous decade, laser-based wire technology attracted interest. This 0.018¨ guidewire technology has made use of the unique debulking properties of excimer laser light. Despite an initial report that suggested its feasibility and safety [25–27], the Total Occlusion Trial with Angioplasty by using a Laser wire (TOTAL) study demonstrated no superiority of this technique over conventional (and, by today's standards, inferior) wire-based technology [28]. However, in cases where the stenosis has been crossed with a guidewire, which a balloon cannot cross, the laser-based catheter can be used for initial debulking. In contrast to rotational atherectomy, the use of an excimer laser does not require wire exchange and can be used with high power (80 J/80 Hz), crossing the lesion and creating a lumen that enables the delivery of balloons and stents. The point 9 X-80 catheter (Spectranetics Corporation, CO, USA) can cross even heavily calcified lesions. The point 7 is also available soon.

Other mechanical devices

Frontrunner

A second-line device to attempt recanalization of CTO is the Frontrunner (LuMed, Cordis, Johnson & Johnson) (FIGURE 4). It is usually used when the wire-based attempts have been exhausted and have failed [29]. This device is designed to create intra-luminal blunt microdissection to facilitate penetration of the fibrous cap. The Frontrunner catheter is steered and delivered through the coronary artery, just proximal to the occlusion, so the blunt tip engages the proximal cap of the CTO. The actuation of jaws on the distal end of a 0.039" diameter catheter creates a 2.3 mm excursion that separates tissue planes within the occluded segment. The tip is pushed forward gently to displace the plaque and remote opening of the small forceps separates atherosclerotic plaque in various tissue planes by inducing a blunt dissection. Repetitive opening and steering of the catheter creates a microchannel through the occlusion, facilitating the placement of a guide wire across the occlusion. The blunt dissection strategy takes advantage of the elastic properties of the adventitia, as compared with the inelastic characteristics of the fibroblastic plaque, to create the fracture planes. This device may have a special role in refractory in-stent CTO, wherein the stent serves to confine the device as it passes through the occlusion. Currently, this device is used rarely in *de novo* coronary occlusions and is almost exclusively used in peripheral interventions.

In single-center experiences of patients with CTOs, in which most of them have prior failure to recanalize the occlusion, the use of the Frontrunner device helped to achieve successful

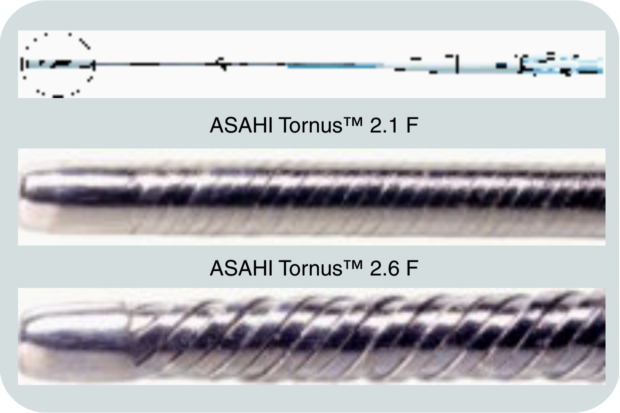

Figure 5. The Tornus device (Asahi, Japan) is a catheter made of eight stainless steel strands woven together to enhance flexibility and strength in exchanging wires, delivering balloons, and providing support for chronic total occlusion procedures.

recanalization in 42–77% of patients [30,31]. In a registry of 107 patients, the company reports 56% success in previously failed CTOs and the perforation rate was 1.9%.

Tornus

The Tornus device (Asahi, Japan) is a catheter made of eight stainless steel strands woven together to enhance flexibility and strength in exchanging wires, delivering balloons and providing support for CTO procedures (FIGURE 5). It is used after a wire has crossed a chronic occlusion, when a balloon will not cross. The Tornus is advanced into the CTO by up to 20 counter-clockwise rotations without strong back-up support once the tip is encroached. The device can make a smooth channel without dissection, allowing for passage of a low-profile balloon [32,33]. In addition, it can also be 'screwed in' to an occlusion to provide excellent backup for guidewire crossing.

Ablative technology

Safe-Cross

The Safe-Cross system (Kensey Nash) has further extended the platform of wire-based technology. This system uses forward-looking optical coherence reflectometry (OCR) coupled with a RF energy light transmission through an optical fiber within a 0.014" guide wire. The back-scattered light (reflection time and intensity) from tissue in front of the guide wire is measured and an algorithm analyzes the back-scattered light to identify the interface between normal arterial wall and diseased plaques. A visible and audible signal warns the operator when the tip approaches within 1 mm of the outer vessel wall, allowing the operator to redirect the wire before dissecting or perforating (FIGURE 6). The Safe-Cross RF system combines OCR technology with a controlled RF energy that the operator can discharge through the wire tip when he gets an OCR 'green' signal, that is, the tip of the wire is facing an intraluminal plaque and not the vessel wall. Delivery of a train of RF energy pulses can facilitate crossing hard fibrotic material within the occluded vessel, minimizing the risk of perforation. The early RF wire, as developed by Hara and Heuser, also formed the basis of Stereotaxis application of RF energy.

Recent evaluations in both coronary and peripheral interventions have demonstrated the potential of this technology, particularly following guidewire failures [34].

The Guided Radio Frequency Energy Ablation of Total Occlusions Registry was a prospective, nonrandomized, multicenter registry that enrolled 116 patients who had long-term

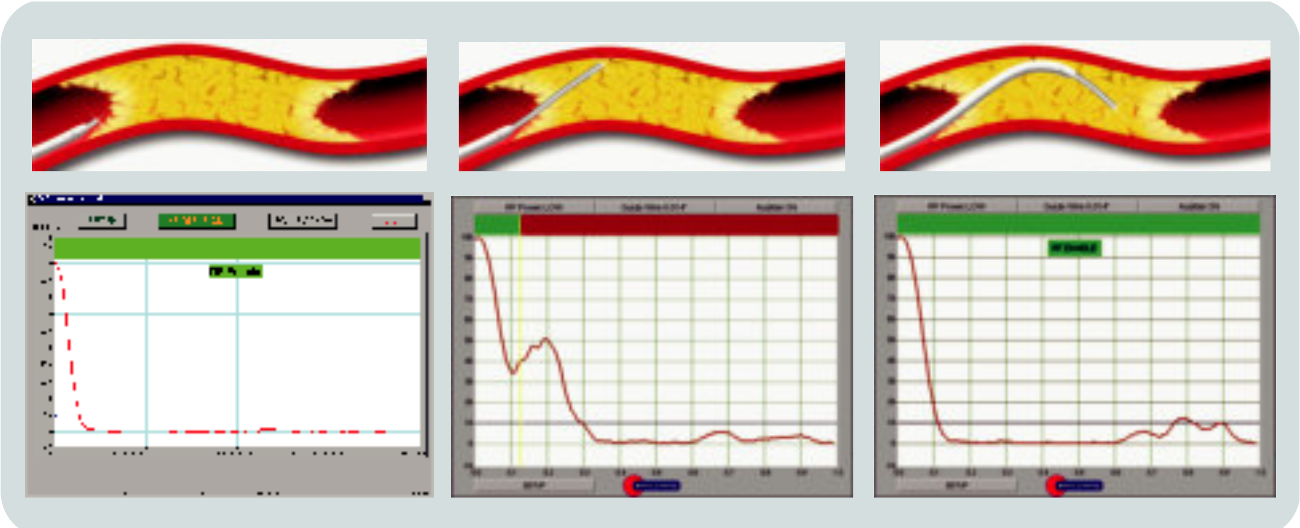

Figure 6. The Safe-Cross system (Kensey Nash) uses forward-looking optical coherence reflectometry and light transmission through an optical fiber within a 0.014" guide wire. The back-scattered light (reflection time and intensity) from tissue in front of the guide wire is measured and an algorithm analyzes the back-scattered light to identify the interface between normal arterial wall and diseased plaques. A visible and audible signal warns the operator when the tip approaches within 1 mm of the outer vessel wall, allowing the operator to redirect the wire before dissecting or perforating.

coronary total occlusions and in whom a greater than 10-min good-faith attempt to cross the occlusion using conventional guidewires had failed [35]. Device success was achieved in 63 out of 116 patients (54.3%). Clinical perforation occurred in 2.6% of patients; of these, perforation in only one patient (0.9%) was adjudicated to be related directly to the Safe-Cross RF wire rather than to the stiff and/or hydrophilic wires used after an inability to advance with the Safe-Cross. Based on these encouraging data, the device has been approved in Europe and was granted 510K clearance by the US FDA in January 2004.

Vibration & ultrasound

Another novel ablative strategy is the use of vibration energy. The tip of the CROSSER catheter (FlowCardia, CA, USA) mechanically vibrates against the face of the CTO at 20,000 cycles per second (20 kHz) at a stroke depth of approximately 20 µm. This high frequency, low amplitude longitudinal stroke pulverizes the CTO by mechanical impact, creating a channel through the CTO. In addition, high-frequency vibration can create vapor-filled microbubbles in the fluid (blood and saline) at the tip of the CROSSER catheter. As the CROSSER catheter is activated, these microbubbles expand and implode, producing liquid jets that can break the molecular bonds and erode the solid surface of the CTO. The vibrating energy is transmitted to the catheter from a generator that converts AC line power into a high frequency current. Initial reports from Europe have demonstrated the safety and feasibility of this system [32,36,37]. In the pivotal US study, Flowcardia's Approach to Chronic Total Occlusion Recanalization (FACTOR), the use of this device was successful in 76 out of 125 (61%) patients with 'wire refractory CTO'.

Nonmechanical (biological) approach

The nonmechanical (biological) approach to treat CTO is based on the concept of altering the composition of the occlusion to improve success rates. It was tried first with prolonged infusions of the plasminogen activator urokinase to reduce the clot component of the occlusion sufficiently to facilitate passage of the guidewire across the occlusion [38]. The activation of proteolytic enzymes by plasmin may also contribute to its activity [39]. In a series of 85 patients who underwent unsuccessful PCI, procedures of CTO (more than 3-months duration) had a repeat attempt of recanalization with the use of preprocedural intracoronary fibrin-specific lytic infusion. Patients received a weight-adjusted dose of either alteplase (tPA) or tenecteplase for a total of 8 h. The total dose of intracoronary lytics (ICL) therapy infused was split between the guiding catheter and an intracoronary infusion catheter. The procedure was successful in 46 out of 85 cases (54%) [40].

Collagenase, or tissue-type matrix metalloproteinase (MMP)-1 could be advantageous in the setting of CTOs by altering the composition of the occluding plaques to make them more amenable to crossing with conventional guidewires. Strauss has shown initial success in using collagenase in a rabbit model of CTO [41,42].

Drug-eluting stents

With the introduction of coronary stents, multiple randomized trials have demonstrated that stents are superior to plain balloon angioplasty in CTO intervention in terms of angiographic restenosis. Overall, the rate of angiographic restenosis with bare metal stents for CTOs has been reported to vary from 32 to 55% [43].

Since the introduction of drug-eluting stents into the USA, there has been a dramatic change in the interventional treatment paradigm, such that greater than 90% of current patients receive drug-eluting stents during PCI procedures. Studies examining angiographic, intravascular ultrasound and clinical end points have demonstrated safety and efficacy of these devices during the first year after therapy. Several registries have reported high success rates with drug-eluting stents, with significant lower rates of restenosis, need for repeat revascularization and long-term cardiac adverse events (major adverse coronary event [MACE]), when compared with parallel or historical registries of bare-metal stents [44–51]. These studies are summarized in TABLE 1.

Table 1. Registries of drug-eluting stents after successful recanalization of chronic total occlusion.

Trial	Patients (n)	DES	Length of follow-up (month)	TVR	MACE	Ref.
Research	56	Cypher	6	3.6	3.6	[44]
Werner	82	Taxus	12	10.0	13.3	[45,46]
Nakamura	60	Cypher	12	3.0	3.0	[47]
Ge	122	Cypher	6	9.0	16.4	[48]
SITCO	25	Cypher	6	12.0	4.0	[49]
Jang	26	Taxus			14.2	[50]
Jang	107	Cypher			4.2	[50]
Migliorini	104	Unknown	6	7.6	9.8	[51]

DES: Drug-eluting stent; MACE: Major adverse coronary event; TVR: Target vessel revascularization.

In a recent prospective, randomized, single-blind, two-center trial, in patients with total coronary occlusions, use of the sirolimus-eluting stents are superior to the bare metal stents [52]. A total of 200 patients with total coronary occlusions were randomly assigned to receive bare metal Bx Velocity® stents and or Cypher® stents. The Cypher stent group showed a significantly lower rate of in-stent binary restenosis (7 vs 36%; $p < 0.001$) and a lower rate of target lesion revascularization (4 vs 19%; $p < 0.001$).

A nonrandomized study from South Korea compared the clinical and angiographic effectiveness of Cypher and Taxus® stents ($n = 136$) and showed more favorable results regarding restenosis and clinical outcomes with the Cypher stent [50]. At 6-month angiographic follow-up, the restenosis rate was significantly higher in the Taxus group (28.6 vs 9.4%; $p = 0.020$). At 1-year follow-up, the MACE-free survival rate was also significantly higher in the cypher group (95.8% vs 85.8%; $p = 0.049$). Thus, in this nonrandomized report, the implantation of Cypher stent in the treatment of CTO lesions showed more favorable results regarding restenosis and clinical outcomes compared with taxus stent implantation.

Expert commentary

With advances in imaging, experience and emerging new devices, experienced operators are able to recanalize and treat the majority of occluded coronary arteries. Learning and mastering the skills to recanalize CTO is an advanced stage procedure that is left for the experienced operator. The variety of CTO cases is wide and special expertise is needed to differentiate between different anatomic situations, selecting the appropriate devices, being able to change strategies as cases progress, and maintaining safety – avoiding and taking care of potential complications.

The experienced operator selects the guiding catheter that will give him the best combination of optimal back-up support and delivering wires and devices. The first step in attempting recanalization of a CTO is to use wires. Our practice is to go from the light to the heavy, always starting with a soft tip, changing to harder and stiffer wire if the lighter and softer wires do not work. If this strategy fails, the experienced operator may use more complex wire-based techniques, such as the retrograde approach or STAR or new energy delivery devices, such as the Safe-Cross or the FlowCardia. When the occlusion is not crossed, the experienced operator has to make the timely decision of when to abort the procedure before risking the development of complications in the patient.

Five-year view

The introduction during recent years of enhanced guidewires, combined with increasing operator experience, has significantly reduced the number of CTOs that should now be considered unapproachable. Over the next 5 years, more studies will be conducted to evaluate which specific groups of patients benefit most from treatment of CTO and what are the predictive factors for success. With the continuous development of imaging techniques and their utilization in the process, operators will have better understanding and planning of the procedure. We expect the success rates for otherwise refractory CTOs to continue to improve with the development and validation of new guidewires, support devices and active energy-source catheters.

Key issues

- Percutaneous recanalization and treatment of chronic total occlusion (CTO) is a challenging target, requiring expertise, diversity of techniques and devices.
- Emerging imaging technologies, such as computerized tomographic angiography, may support better planning of the procedure and aid as a platform for supplementary technologies, such as radiofrequency ablation.
- Guidewires are still the most used technology to recanalize CTOs.
- Active energy source catheters that conquer the CTO by vibration or radiofrequency energy were approved recently by the US FDA for the treatment of CTO.
- Drug-eluting stents have significantly reduced the rate of in-stent restenosis and the need for recurrent procedures.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Moses JW, Leon MB, Popma JJ *et al.* Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N. Engl. J. Med.* 349, 1315–1323 (2003).

2 Stone GW, Ellis SG, Cox DA *et al.* A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N. Engl. J. Med.* 350, 221–231 (2004).

3 Stone GW, Kandzari DE, Mehran R *et al.* Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation* 112, 2364–2372 (2005).

• **Part 1 of a comprehensive review based on a consensus document of 47 top experts in the field of chronic total occlusion (CTO).**

4 Stone GW, Reifart NJ, Moussa I *et al.* Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. *Circulation* 112, 2530–2537 (2005).

• **Part 2 of a comprehensive review based on a consensus document of 47 top experts in the field of CTO.**

5 Stone GW, Colombo A, Teirstein PS *et al.* Percutaneous recanalization of chronically occluded coronary arteries: procedural techniques, devices, and results. *Catheter Cardiovasc. Interv.* 66, 217–236 (2005).

• **A comprehensive review on the technical aspects of the treatment of CTO.**

6 Hochman JS, Lamas GA, Buller CE *et al*. Coronary intervention for persistent occlusion after myocardial infarction. *N. Engl. J. Med.* 355, 2395–2407 (2006).

- **A randomized study evaluating the effectiveness of treatment of occlusions in stable patients 3–28 days after myocardial infarction.**

7 Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. *Am. Heart J.* 126, 561–564 (1993).

8 Anderson HV, Shaw RE, Brindis RG *et al*. A contemporary overview of percutaneous coronary interventions. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *J. Am. Coll. Cardiol.* 39, 1096–1103 (2002).

9 Williams DO, Holubkov R, Yeh W *et al*. Percutaneous coronary intervention in the current era compared with 1985–1986: the National Heart Lung, and Blood Institute Registries. *Circulation* 102, 2945–2951 (2000).

10 Srinivas VS, Brooks MM, Detre KM *et al*. Contemporary percutaneous coronary intervention versus balloon angioplasty for multivessel coronary artery disease: a comparison of the National Heart Lung and Blood Institute Dynamic Registry and the Bypass Angioplasty Revascularization Investigation (BARI) study. *Circulation* 106, 1627–1633 (2002).

11 Srivatsa SS, Edwards WD, Boos CM *et al*. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J. Am. Coll. Cardiol.* 29, 955–963 (1997).

12 Katsuragawa M, Fujiwara H, Miyamae M *et al*. Histologic studies in percutaneous transluminal coronary angioplasty for chronic total occlusion: comparison of tapering and abrupt types of occlusion and short and long occluded segments. *J. Am. Coll. Cardiol.* 21, 604–611 (1993).

13 Dong S, Smorgick Y, Nahir M *et al*. Predictors for successful angioplasty of chronic totally occluded coronary arteries. *J. Interv. Cardiol.* 18, 1–7 (2005).

14 Noguchi T, Miyazaki MS, Morii I *et al*. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Determinants of primary success and long-term clinical outcome. *Catheter Cardiovasc. Interv.* 49, 258–264 (2000).

15 Maiello L, Colombo A, Gianrossi R *et al*. Coronary angioplasty of chronic occlusions: factors predictive of procedural success. *Am. Heart J.* 124, 581–584 (1992).

16 Surmely JF and Suzuki T. Intravascular ultrasound-guided recanalization of a coronary chronic total occlusion located in a stent implanted subintimally: a case report. *J. Cardiol.* 48, 95–100 (2006).

17 Mollet NR, Hoye A, Lemos PA *et al*. Value of preprocedure multislice computed tomographic coronary angiography to predict the outcome of percutaneous recanalization of chronic total occlusions. *Am. J. Cardiol.* 95, 240–243 (2005).

18 Heuser RR. The use of a new wire in a 6-year-old coronary artery occlusion: the Jagwire recanalization guidewire. *Cathet. Cardiovasc. Diagn.* 29, 173–176 (1993).

19 Strauss BH, Segev A, Wright GA *et al*. Microvessels in chronic total occlusions: pathways for successful guidewire crossing? *J. Interv. Cardiol.* 18, 425–436 (2005).

20 Buettner HJ, Mueller C, Petersen J *et al*. High success rate in recanalization of chronic total coronary occlusions with a novel guidewire principle using the guidance of micro channels. *J. Am. Coll. Cardiol.* 30A (2002) (Abstract).

21 Saito S, Tanaka S, Hiroe Y *et al*. Angioplasty for chronic total occlusion by using tapered-tip guidewires. *Catheter Cardiovasc. Interv.* 59, 305–311 (2003).

22 Colombo A, Mikhail GW, Michev I *et al*. Treating chronic total occlusions using subintimal tracking and reentry: the STAR technique. *Catheter Cardiovasc. Interv.* 64, 407–411 (2005).

- **Description and initial results of coronary subintimal approach to resistant CTOs.**

23 Ozawa N. A new understanding of chronic total occlusion from a novel PCI technique that involves a retrograde approach to the right coronary artery via a septal branch and passing of the guidewire to a guiding catheter on the other side of the lesion. *Catheter Cardiovasc. Interv.* 68, 907–913 (2006).

- **Introduction of the novel strategy of a retrograde approach to the occlusion, through collaterals.**

24 Surmely JF, Tsuchikane E, Katoh O *et al*. New concept for CTO recanalization using controlled antegrade and retrograde subintimal tracking: the CART technique. *J. Invasive Cardiol.* 18, 334–338 (2006).

25 Hamburger JN, Gijsbers GH, Ozaki Y *et al*. Recanalization of chronic total coronary occlusions using a laser guide wire: a pilot study. *J. Am. Coll. Cardiol.* 30, 649–656 (1997).

26 Hamburger JN, Serruys PW, Scabra-Gomes R *et al*. Recanalization of total coronary occlusions using a laser guidewire (the European TOTAL Surveillance Study). *Am. J. Cardiol.* 80, 1419–1423 (1997).

27 Oesterle SN, Bittl JA, Leon MB *et al*. Laser wire for crossing chronic total occlusions: "learning phase" results from the U.S. TOTAL trial. Total Occlusion Trial With Angioplasty by Using a Laser Wire. *Cathet. Cardiovasc. Diagn.* 44, 235–243 (1998).

28 Serruys PW, Hamburger JN, Koolen JJ *et al*. Total occlusion trial with angioplasty by using laser guidewire. The TOTAL trial. *Eur. Heart J.* 21, 1797–1805 (2000).

29 Yang YM, Mehran R, Dangas G *et al*. Successful use of the frontrunner catheter in the treatment of in-stent coronary chronic total occlusions. *Catheter Cardiovasc. Interv.* 63, 462–468 (2004).

30 Orlic D, Stankovic G, Sangiorgi G *et al*. Preliminary experience with the Frontrunner coronary catheter: novel device dedicated to mechanical revascularization of chronic total occlusions. *Catheter Cardiovasc. Interv.* 64, 146–152 (2005).

31 Loli A, Liu R, Pershad A. Immediate- and short-term outcome following recanalization of long chronic total occlusions (> 50 mm) of native coronary arteries with the Frontrunner catheter. *J. Invasive Cardiol.* 18, 283–285 (2006).

32 Ali I, Butman S, Heuser RR. Crossing a Chronic Total Occlusion using Combination Therapy With Tornus and Flow Cardia. *J. Invasive Cardiol.* 18, E258–E260 (2006).

33 Niccoli G, Ochiai M, Mazzari MA. A complex case of right coronary artery chronic total occlusion treated by a successful multi-step Japanese approach. *J. Invasive Cardiol.* 18, E230–E233 (2006).

34 Morales PA, Heuser RR. Chronic total occlusions: experience with fiber-optic guidance technology – optical coherence reflectometry. *J. Interv. Cardiol.* 14, 611–616 (2001).

35 Baim DS, Braden G, Heuser R *et al*. Utility of the Safe-Cross-guided radiofrequency total occlusion crossing system in chronic coronary total occlusions (results from the Guided Radio Frequency Energy Ablation of Total Occlusions Registry Study). *Am. J. Cardiol.* 94, 853–858 (2004).

- **Pivotal registry demonstrating the success with the Safe-Cross radiofrequency guidewire. Based on these data, the device has been approved in Europe and was granted 510K clearance by the US FDA.**

36 Grube E, Sutsch G, Lim VY *et al.* High-frequency mechanical vibration to recanalize chronic total occlusions after failure to cross with conventional guidewires. *J. Invasive Cardiol.* 18, 85–91 (2006).

37 Melzi G, Cosgrave J, Biondi-Zoccai GL *et al.* A novel approach to chronic total occlusions: the crosser system. *Catheter Cardiovasc. Interv.* 68, 29–35 (2006).

38 Zidar FJ, Kaplan BM, O'Neill WW *et al.* Prospective, randomized trial of prolonged intracoronary urokinase infusion for chronic total occlusions in native coronary arteries. *J. Am. Coll. Cardiol.* 27, 1406–1412 (1996).

39 Davis GE, Pintar Allen KA, Salazar R *et al.* Matrix metalloproteinase-1 and -9 activation by plasmin regulates a novel endothelial cell-mediated mechanism of collagen gel contraction and capillary tube regression in three-dimensional collagen matrices. *J. Cell. Sci.* 114, 917–930 (2001).

40 Abbas AE, Brewington SD, Dixon SR *et al.* Intracoronary fibrin-specific thrombolytic infusion facilitates percutaneous recanalization of chronic total occlusion. *J. Am. Coll. Cardiol.* 46, 793–798 (2005).

- **Report of a novel strategy with intracoronary infusion of fibrin-specific thrombolytic therapy that may provide a valuable and safe option for facilitating percutaneous revascularization of CTO.**

41 Strauss BH, Goldman L, Qiang B *et al.* Collagenase plaque digestion for facilitating guide wire crossing in chronic total occlusions. *Circulation* 108, 1259–1262 (2003).

- **A promising novel nondevice strategy to facilitate recanalization of CTO.**

42 Segev A, Nili N, Qiang B *et al.* Human-grade purified collagenase for the treatment of experimental arterial chronic total occlusion. *Cardiovasc. Revasc. Med.* 6, 65–69 (2005).

43 Segev A and Strauss BH. Novel approaches for the treatment of chronic total coronary occlusions. *J. Interv. Cardiol.* 17, 411–416 (2004).

44 Hoye A, Tanabe K, Lemos PA *et al.* Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. *J. Am. Coll. Cardiol.* 43, 1954–1958 (2004).

- **The superiority of sirolimus-eluting stents over bare metal stent after recanalization of CTO.**

45 Werner GS, Krack A, Schwarz G *et al.* Prevention of lesion recurrence in chronic total coronary occlusions by paclitaxel-eluting stents. *J. Am. Coll. Cardiol.* 44, 2301–2306 (2004).

- **The superiority of paclitaxel-eluting stents over bare metal stent after recanalization of CTO.**

46 Werner GS, Schwarz G, Prochnau D *et al.* Paclitaxel-eluting stents for the treatment of chronic total coronary occlusions: a strategy of extensive lesion coverage with drug-eluting stents. *Catheter Cardiovasc. Interv.* 67, 1–9 (2006).

47 Nakamura S, Muthusamy TS, Bae JH *et al.* Impact of sirolimus-eluting stent on the outcome of patients with chronic total occlusions. *Am. J. Cardiol.* 95, 161–166 (2005).

48 Ge L, Iakovou I, Cosgrave J *et al.* Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. *Eur. Heart J.* 26, 1056–1062 (2005).

49 Lotan C, Almagor Y, Kuiper K *et al.* Sirolimus-eluting stent in chronic total occlusion: the SICTO study. *J. Interv. Cardiol.* 19, 307–312 (2006).

50 Jang JS, Hong MK, Lee CW *et al.* Comparison between sirolimus- and Paclitaxel-eluting stents for the treatment of chronic total occlusions. *J. Invasive Cardiol.* 18, 205–208 (2006).

51 Migliorini A, Moschi G, Vergara R *et al.* Drug-eluting stent-supported percutaneous coronary intervention for chronic total coronary occlusion. *Catheter Cardiovasc. Interv.* 67, 344–348 (2006).

52 Suttorp MJ, Laarman GJ, Rahel BM *et al.* Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. *Circulation* 114, 921–928 (2006).

- **The superiority of sirolimus-eluting stents over bare metal stent after recanalization of CTO.**

Affiliations

- *Giora Weisz, MD*
  Codirector of clinical services, Center for Interventional Vascular Therapy, Assistant Professor of Medicine, Columbia University Medical Center, Center for Interventional Vascular Therapy, 161 Fort Washington Avenue, IP-5 Floor, New York, NY 10032, USA
  Tel.: +1 212 305 7060
  Fax: +1 212 342 3660
  gweisz@crf.org
- *Jeffrey W Moses, MD*
  Director, Center for Interventional Vascular Therapy, Professor of Medicine, Columbia University Medical Center,
  Center for Interventional Vascular Therapy, 161 Fort Washington Avenue, IP-5 Floor, New York, NY 10032, USA
  Tel.: +1 212 305 7060
  Fax: +1 212 342 3660
  jmoses@crf.org