Coronary chronic total occlusions and percutaneous coronary intervention

Coronary chronic total occlusions occur in a third of patients with coronary artery disease but percutaneous coronary intervention is attempted in a minority. The benefits and limitations of percutaneous coronary intervention for chronic total occlusion are discussed together with suggested management and future directions.

Coronary chronic total occlusions are characterized by heavy atherosclerotic plaque burden within the artery, resulting in (almost) complete vessel occlusion. They have been estimated to occur in approximately one-third of patients with suspected or known coronary artery disease undergoing coronary angiography in a community hospital setting. However, they constitute only 10–15% of all percutaneous coronary intervention activity because they are highly challenging and require considerable resource use, significant expertise and dedicated equipment to achieve adequate success rate. Furthermore, there is ongoing debate as to whether the ultimate benefits outweigh the associated risks. This article reviews available clinical data and discusses the current place of percutaneous coronary intervention for chronic total occlusion.

Definition, clinical presentation and therapeutic options

There are various definitions of chronic total occlusion, including lesions with distal thrombolysis in myocardial infarction (TIMI) 1 flow and with occlusions of 1–3 months' duration. The consensus among experienced European interventionists constituting the EuroCTO club is to define a chronic total occlusion as 'the presence of TIMI 0 flow within the occluded segment with an estimated occlusion duration of ≥3 months' (Di Mario et al, 2007). Clinical presentation varies from stable angina to unstable patients with recent onset angina or ST elevation myocardial infarction and undergoing primary percutaneous coronary intervention to an acute occlusion in a different culprit vessel. The former group gives the greatest management challenge and will be the focus of the discussion.

In stable patients with chronic total occlusion and associated significant left main and/or multivessel coronary artery disease, coronary artery bypass grafting is often the treatment of choice. It has an increased likelihood of achieving complete revascularization compared to percutaneous coronary intervention, as shown in the SYNTAX trial. In this trial percutaneous coronary intervention in patients with complex coronary artery disease including chronic total occlusions led to increased repeat revascularization rates during follow up without an associated increase in mortality and myocardial infarction (Serruys et al, 2009). Nonetheless some patients are refused coronary artery bypass grafting as they are deemed to be frail, high-risk subjects and are referred for percutaneous coronary intervention. With regard to isolated chronic total occlusions in symptomatic patients, revascularization decision is more debatable. Optimized medical treatment may be inadequate for symptomatic and/or prognostic benefit while coronary artery bypass grafting may be deemed too invasive for single vessel disease, thus resulting in patient referral for percutaneous coronary intervention (*Figure 1*).

Current guidelines regarding percutaneous coronary interventions for chronic total occlusion are quite reserved (Task Force on Myocardial Revascularization of the European Society of Cardiology et al, 2010; Levine et al, 2011), so an individualized approach is suggested with thorough analysis of the advantages and disadvantages of recanalization for each patient. Predictors of failure in percutaneous coronary interventions for chronic total occlusion should also be identified (*Table 1*). This requires long acquisition runs to outline clearly the size and extent of filling via collateral channels. In controversial cases, discussion within the heart team (see below) is recommended (Di Mario et al, 2007).

Benefits of percutaneous coronary interventions for chronic total occlusion

While chronic total occlusions with angiographically visible collaterals may provide sufficient blood supply to the occluded segment, coronary steal occurs in one-third of chronic total occlusion patients without prior myocardial infarction. Coronary steal is mainly the result of either a haemodynamically significant donor artery lesion or an impaired vasodilatory reserve of the microcirculation (Werner et al, 2006a), thus adversely influencing the preservation of myocardial function by collaterals. Also, collaterals exhibit only a limited increase in flow during exercise with consequent exercise-induced ischaemia (Werner et al, 2006b).

Dr Caroline J Magri *is Higher Specialist Trainee in the Department of Cardiac Services, Mater Dei Hospital, Tal-Qroqq, Msida MSD 2090, Malta,* **Dr Mauro Carlino** *is Consultant Cardiologist, San Raffaele Scientific Institute, Milan, Italy, and* **Dr Robert G Xuereb** *is Consultant Cardiologist in the Department of Cardiac Services, Mater Dei Hospital, Tal-Qroqq, Msida MSD 2090, Malta*

Correspondence to: Dr CJ Magri

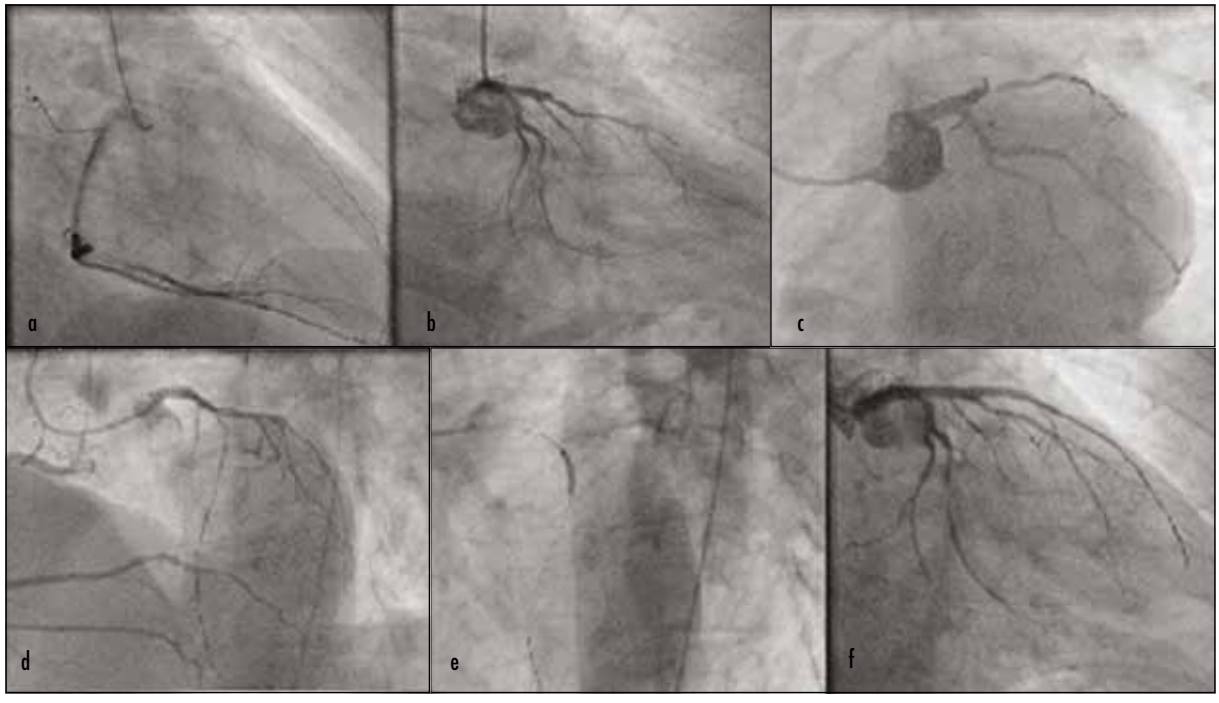

Figure 1. A 50-year-old ex-smoker presented with stable angina and a positive exercise stress test. a. Coronary angiogram revealed occluded left anterior descending coronary artery with (b) the distal left anterior descending artery filling retrogradely from a dominant right coronary artery. Following discussion with the patient, percutaneous coronary intervention of the left anterior descending chronic total occlusion was opted for. This was performed via right radial artery access while the right coronary artery was accessed via the right femoral artery. c and d. A Balance Middleweight wire was passed down a side-branch for support and the left anterior descending chronic total occlusion was crossed with a Cross-It 300 wire. e. Gradual pre-dilation was performed enabling deployment of an everolimus-eluting stent. f. The end-result was excellent with antegrade thrombolysis in myocardial infarction (TIMI) 3 flow. The patient has since remained completely asymptomatic.

Current data suggest various benefits associated with percutaneous coronary interventions for chronic total occlusion. First, recanalization of chronic total occlusions leads to symptomatic benefit up to 6 years following the procedure (Joyal et al, 2010). Symptomatic improvement together with improved left ventricular function and reduced referral for coronary artery bypass grafting lead to better quality of life (Puma et al, 1995) which is evident within 1 month of the procedure (Grantham et al, 2010).

Table 1. Lesion characteristics reducing recanalization success

Lesion localization: left anterior descending coronary artery best outcome, right coronary artery worst outcome
Ostial chronic total occlusion lesion
Vessel diameter <3.0 mm
Chronic total occlusion lesions in one or more vessels
Presence of bridge collaterals
Abrupt occlusion (as opposed to a tapered stump)
Long occlusions >20 mm
Severe calcification and/or tortuosity in occluded segment
Severe disease of the proximal and/or distal segment
Severe tortuosity proximal to the occlusion
Presence of a side branch at the level of the chronic total occlusion

Successful percutaneous coronary interventions for chronic total occlusion has also been correlated with improved left ventricular function (Sirnes et al, 1998) when performed in patients with viable myocardium (Chung et al, 2003). Cheng et al (2008) showed that increased hyperaemic myocardial blood flow and contractility occurred as early as 24 hours post-procedure while improvements in left ventricular remodelling and ejection fraction were observed up to 3 years after recanalization (Kirschbaum et al, 2008).

Chronic total occlusion recanalization might also improve autonomic nervous system function, as suggested by a trend towards increased baroreceptor sensitivity 3 months after successful percutaneous coronary interventions for chronic total occlusion of the left anterior descending artery (Szwoch et al, 2009). However, this study was probably underpowered so further studies are needed.

Observational studies have indicated an association between successful percutaneous coronary interventions for chronic total occlusion and survival benefit. In a meta-analysis of 13 observational studies, successful chronic total occlusion revascularization was associated with a decrease in mortality (odds ratio 0.56, 95% confidence interval 0.43–0.72, and subsequent coronary

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artery bypass grafting (odds ratio 0.22, 95% confidence interval 0.17–0.27) but not in myocardial infarction (odds ratio 0.74, 95% confidence interval 0.44–1.25) or major adverse cardiovascular events (odds ratio 0.81, 95% confidence interval 0.55–1.21) (Joyal et al, 2010). This could be secondary to reduction in distal ischaemia with consequent improvement in regional and global wall motion abnormality and decrease of ventricular arrhythmias. The recanalized artery can also act as the collateral source artery for the opposite arteries.

In a more recent large prospective multinational chronic total occlusion registry, successful percutaneous coronary interventions for chronic total occlusion was associated with reduced cardiac mortality (hazard ratio 0.40, 95% confidence interval 0.21–0.75, $P<0.001$) with a trend toward lower all-cause mortality (hazard ratio 0.63, 95% confidence interval 0.40–1.00, $P=0.05$) at 5-year follow up (Mehran et al, 2011).

It has been suggested that survival benefit depends on target lesion localization with percutaneous coronary intervention for chronic total occlusion of the left anterior descending artery only being associated with long-term survival (Safley et al, 2008). However, Jones et al (2012) have demonstrated survival benefit in patients with single-vessel disease with the right coronary artery being the major artery tackled. Furthermore, successful recanalization was independently predictive of all-cause mortality at 5-year follow up and persisted when incorporating a propensity score (hazard ratio 0.28, 95% confidence interval 0.15–0.52). Randomized studies are thus needed since it is possible that some adverse comorbidities in subjects with unsuccessful recanalization were not adjusted for.

Limitations of percutaneous coronary interventions for chronic total occlusion

Despite these potential benefits, percutaneous coronary interventions for chronic total occlusion is associated with increased risk of major adverse cardiovascular events following unsuccessful revascularization. The most feared acute complication is coronary perforation by a stiff guidewire followed by cardiac tamponade. Its incidence varies between 2 and 10%, depending on how aggressively the lesion is tackled. Coronary perforation with a guidewire on its own usually results in minimal extravasation. Complications arise mainly when the operator fails to realize that the wire is not intraluminal and proceeds with balloon dilation. Management includes reversal of heparin and balloon occlusion of target vessel. To limit bleeding if coronary perforation should occur, bivalirudin and GPIIb/IIIa inhibitors should be used sparingly and only after successful crossing of the chronic total occlusion. With cardiac tamponade, urgent pericardiocentesis is required together with aggressive fluid resuscitation and intravenous vasopressors in more severe cases.

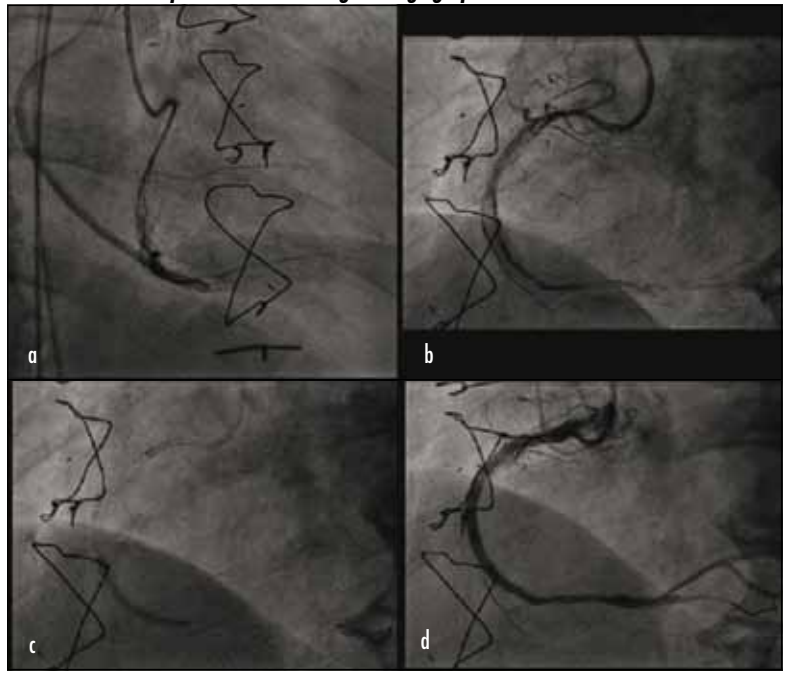
Coronary dissection can occur, either at the coronary ostium secondary to aggressive wire manipulation or in the body of the vessel as a result of subintimal wire tracking (*Figure 2*). This is usually treated by balloon inflations and/or stenting. Very rarely, aortic dissections ensue, mostly during percutaneous coronary intervention of the right coronary artery. Aortic dissection extending up the aorta >40 mm from the coronary os requires surgical intervention.

Periprocedural myocardial infarction (diagnosed by a significant rise in cardiac biomarkers) occurs in ~13% of cases, mainly as a result of side-branch obstruction (Paizis et al, 2009). Other potential mechanisms include coronary dissection, distal embolization and prolonged balloon inflation. A rise in cardiac biomarkers following percutaneous coronary intervention is associated with worse 2-year outcome (Prasad et al, 2007). However, in spite of heavy atherosclerotic plaque burden, it occurs at a similar rate to that after stenting of single-vessel disease (Paizis et al, 2009).

In a meta-analysis by Joyal et al (2010), high in-hospital myocardial infarction and mortality rates were noted in both subjects with successful *vs* unsuccessful percutaneous coronary intervention although lower rates were noted in the former group (1.7% *vs* 3.0% and 0.6 *vs* 2% respectively). However, the studies analysed were conducted over >2 decades, during which time both expertise and devices used improved considerably.

Major adverse cardiovascular events vary greatly with the operators' experience and facilities available. A high

Figure 2. a. A chronic total occlusion of the right coronary artery was crossed antegradely using a Finecross supporting catheter and a Conquest Pro guide-wire. b. Coronary dissection of the right coronary artery ensued secondary to subintimal wire tracking; this was effectively managed with implantation of four medical stents followed by (c) post-dilation with a compliant balloon. d. A good angiographic result was achieved.



in-hospital major adverse cardiovascular event rate was noted in Chinese hospitals without on-site surgical facilities (3% with successful recanalization *vs* 10% with unsuccessful recanalization, *P*=0.037) (Galla and Whitlow, 2010) while a low event rate was noted with the 3403 patients who underwent percutaneous coronary interventions for chronic total occlusion within the institutions of the EuroCTO club during 2006 (mortality 0.12%, Q-wave myocardial infarction 0.14%, any myocardial infarction 1.96%, emergency coronary artery bypass grafting 0.27% and cardiac tamponade 0.64%). A similarly low event rate was noted in 904 consecutive patients undergoing percutaneous coronary interventions for chronic total occlusion by experienced Japanese interventionists (mortality 0.6%, urgent coronary artery bypass grafting 0.2%, Q-wave myocardial infarction 0.6, cardiac tamponade 0.7%, significant perforation 0.6%).

This underlies the importance that recanalization of chronic total occlusions should be attempted in experienced centres with each operator performing a minimum number of 50 chronic total occlusion cases/year. If percutaneous coronary interventions for chronic total occlusions are attempted in a low volume centre, there should be the possibility of transferring patients to larger centres or establishing a programme of supervision. In addition, it is important that the centre can deal with all the complications associated with percutaneous coronary interventions for chronic total occlusion, while ensuring safe and rapid transfer to hospitals with coronary artery bypass grafting facilities (Di Mario et al, 2007).

Other important factors include radiation and contrast exposure. Subjects undergoing percutaneous coronary interventions for chronic total occlusion can develop radiation dermatitis (Saito, 2011). Methods of decreasing radiation exposure are outlined in *Table 2*. The patient should be given a report with the X-ray dose administered to enable monitoring of radiation given since repeat interventions are likely. With regard to contrast nephropathy, it is important to consider baseline renal function, to limit the amount of contrast administered (e.g. <300 ml), and have a low threshold for renal protection treatment including intravenous saline infusion and occasionally prophylactic haemodialysis (Saito, 2011).

Table 2. Recommendations to reduce radiation exposure during percutaneous coronary intervention for chronic total occlusion

Maintain low dose settings (110 kV) during fluoroscopy as much as possible
Use pulsed fluoroscopic mode for documentation
Use extra collimation
Use monoplane acquisition for balloon dilatation and stent implantation
Perform frequent movement of the image intensifier angle
Maximize distance from radiation source
Maximize imaging in the right anterior oblique views
Use accessory lead shielding between patient and operator

Improving outcome success

Success rates with percutaneous coronary interventions for chronic total occlusion have improved gradually (*Table 3*). First, the introduction of stents played a significant role. In a single-centre review from the Mayo Clinic, the procedural success rate increased from 51% between 1979 and 1989 to approximately 70% with the introduction of bare-metal stents (Prasad et al, 2007). However, no significant difference in outcome was noted with the introduction of drug-eluting stents. This contrasts with results from a meta-analysis of 14 non-randomized studies whereby drug-eluting stent significantly reduced major adverse cardiovascular events (relative risk 0.45, 95% confidence interval 0.34–0.60, *P*<0.001), target vessel revascularization (relative risk 0.40, 95% confidence interval 0.28–0.58, *P*<0.001), restenosis (relative risk 0.25, 95% confidence interval 0.16–0.41, *P*<0.001) and stent reocclusion (relative risk 0.30, 95% confidence interval 0.18–0.49, *P*<0.001) 3 years post-chronic total occlusion recanalization. A strong trend toward a higher rate of stent thrombosis was shown in drug-eluting stent-treated patients (relative risk 2.79, 95% confidence interval 0.98–7.97, *P*=0.06) (Colmenarez et al, 2010).

Mehran et al (2011) have shown similar results with target vessel revascularization at 5-year follow up although the definite or probable stent thrombosis rates were similar in the two groups. This difference in stent thrombosis rate might be accounted for by differential use of dual antiplatelet agents with longer use in drug-eluting stent patients coupled with decreased sensitivity in detecting late stent thrombosis in the bare-metal stent era.

Improved clinical outcomes up to 3 years after percutaneous coronary interventions for chronic total occlusion were also shown in the first randomized controlled trial comparing bare-metal stent *vs* sirolimus-eluting stent, the PRISON II trial, whereby a significant reduction in the need for target lesion or target vessel revascularization, and a decrease in major adverse cardiovascular events were noted in the sirolimus-eluting stent group without statistically significant differences in death, myocardial infarction, and stent thrombosis between the two groups (Rahel et al, 2009).

High success rates (>85%) have been quoted in centres with increasing experience and with the use of novel techniques and devices, such as the Toyohashi Heart Centre (Rathore et al, 2009) and the multicentre J-CTO registry (Garg et al, 2009). Advances in coronary guide-wire technology have played a role in improving success rates (Mitsudo et al, 2008). Development of interventional techniques, especially the retrograde approach, whereby the chronic total occlusion is crossed retrogradely via a wire passed from the feeding vessel into the collateral (*Figure 3*), has also resulted in increasingly successful recanalization (Thompson et al, 2009).

Other important advancements include preprocedural computed tomographic angiography to delineate the course and length of the chronic total occlusion. Intracoronary imaging with intravascular ultrasound plays an important role in identifying entry channels into chronic total occlusions and in redirecting wires from dissection planes into the true vessel lumen. It has been suggested that intravascular ultrasound is essential for selection of the correct stent size and of the landing zone since chronic total occlusion recanalization is followed by severe impairment of vasomotor tone with consequent increase in distal vessel diameter over time in the absence of positive remodelling (Galassi et al, 2012).

The heart team plays a crucial role in adequate individualized treatment. This is especially important in patients where the chronic total occlusion subtends a large territory and/or multivessel coronary artery disease is present. If it is decided to proceed with percutaneous coronary intervention, a staged procedure is preferred with multivessel disease to avoid excessively long procedures, excessive radiation and contrast exposure. Ultimately, to improve outcome success, the operator should also know when to stop the recanalization procedure and possibly repeat the attempt in 2–3 months. Variables that determine when to end a percutaneous coronary interventions for chronic total occlusion attempt are summarized in *Table 4* (Di Mario et al, 2007).

Considering the benefits and limitations of percutaneous coronary interventions for chronic total occlusions, it is reasonable to suggest a prudent individualized approach whereby initial treatment with β-blockers, calcium antagonists and nitrates, and evidence-based secondary prevention regimens, are started. If the patient remains symptomatic or significant ischaemia is noted on functional imaging, revascularization should be considered. If the patient has significant left main coronary artery disease, multivessel coronary artery disease or associated valve disease requiring surgery, coronary artery bypass grafting is recommended. However, if the patient has a single chronic total occlusion or else is refused coronary artery bypass grafting, percutaneous coronary intervention should be the next option. Nonetheless, adequate assessment of both the patient and the lesion is necessary before undertaking percutaneous coronary intervention. This should include myocardial viability assessment. Ad hoc percutaneous coronary intervention is not recommended for chronic total occlusions. Importantly,

Table 3. Devices and techniques that assist in crossing chronic total occlusions

Factors influencing crossing the chronic total occlusion		Explanation
Access route	Femoral	Dependent on individual patient selection and operator preference
	Radial	
Guiding catheter selection	Right coronary artery: Judkins Right, Amplatz Left 1/2	Dependent on operator's experience and preference
	Left anterior descending artery: Extra Backup, Voda	
	Left circumflex artery: Amplatz Left 2/3	
Contralateral injection		Enable assessment of retrograde or bridging collaterals
		Requires arterial access from two sites
Support catheter, e.g. Finecross, Progreat, Tracker, Transit, Tornus, Corsair		Provide reinforcement when attempting to penetrate demanding lesions
Guide-wires, e.g. Fielder, Miracle Bros, Confianza, Confianza Pro, Pilot, PT Graphix, Runthrough, Persuader, Whisper		Novel wires have tapered tip, strong torque transmission ability, different tip stiffness, good shaping memory and durable hydrophilic coating
Parallel wire technique		Used when the first wire has entered a false lumen. A second stiffer wire is advanced over a microcatheter to facilitate steering into the true lumen
Anchor balloon technique		Used to increase backup support. A floppy wire is positioned in a side branch and inflated gently to fix the guiding catheter position
STAR (sub-intimal tracking and re-entry) technique		Wire is advanced to a subintimal position, a loop is created and advanced with catheter support through occluded segment, followed by multiple balloon dilations until the true lumen is reached
CART (controlled antegrade and retrograde subintimal tracking) technique		Subintimal channel is enlarged by advancing and inflating the retrograde balloon, then a wire is advanced antegradely to penetrate the dissection and reach the retrograde wire positioned in the distal true lumen
Reverse CART technique		Antegrade wire is advanced from proximal true lumen and balloon inflated in subintimal plaque, creating a space for retrograde wire to enter and engage the proximal true lumen
Ablative technique, e.g. CROSSER catheter		Uses high frequency, low-amplitude vibrational energy to pulverise the chronic total occlusion

Parallel wire technique, anchor balloon technique and STAR are techniques used with the antegrade approach while the CART technique and reverse CART technique are used with the retrograde approach

informed consent must be obtained following discussion of the benefits and risks involved together with the individual's operator success rate.

Future directions

Novel developments include coronary chronic total occlusion modelling which will enable various preclinical evaluations of chronic total occlusion equipment, as well as transplantation of circulating progenitor cells following chronic total occlusion recanalization. Small studies have shown improvement in left ventricular perfusion and function (Thiele et al, 2009; Adler et al, 2011). More studies are now awaited.

A randomized controlled trial is needed but this is difficult to perform because of the large number of patients required, slow patient recruitment, difficulties in crossing the chronic total occlusion and restricted number of experienced operators. Currently, a randomized controlled trial is being performed by the EuroCTO club and a group from Korea (Decision CTO) whereby patients with chronic total occlusion and chronic stable angina are randomized to percutaneous coronary intervention *vs* optimized medical treatment. The combined primary end point of the study includes mortality, myocardial infarction, stroke and revascularization at 36 months. The results of this study will not be published before 2018, but they are expected to be highly informative (Brilakis et al, 2012).

Conclusions

Current observational data indicate that recanalization of chronic total occlusions in subjects with ongoing symptoms or reversible ischaemia despite optimized medical treatment is safe in experienced centres and will lead to both symptomatic and survival benefit. The success rate is dependent on the patient and lesion characteristics as well as the operator's experience, so an individualized approach is needed. In addition, interventional centres should embark on training in percutaneous coronary interventions for chronic total occlusion to ensure high-volume coronary artery chronic total occlusion operators who are familiar with novel interventional techniques and equipment. **BJHM**

Conflict of interest: none.

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Figure 3. a. The coronary angiogram of this 65-year-old man, known to suffer from hypertension, hypercholesterolaemia and coronary artery disease, revealed a chronic total occlusion of the right coronary artery (b) receiving collaterals from the circumflex artery. c. The chronic total occlusion was crossed retrogradely via collaterals using the guiding catheter Finecross and the wires Universal and Fielder Finecross. d. Contralateral externalization was achieved using the Radifocus guide-wire. Predilation of the lesion with a semi-compliant balloon, implantation of three medical stents (Resolute Integrity) from the distal end to the proximal part of the right coronary artery followed by (e) post-dilation with a non-compliant balloon resulted in (f) complete revascularization of the right coronary artery.

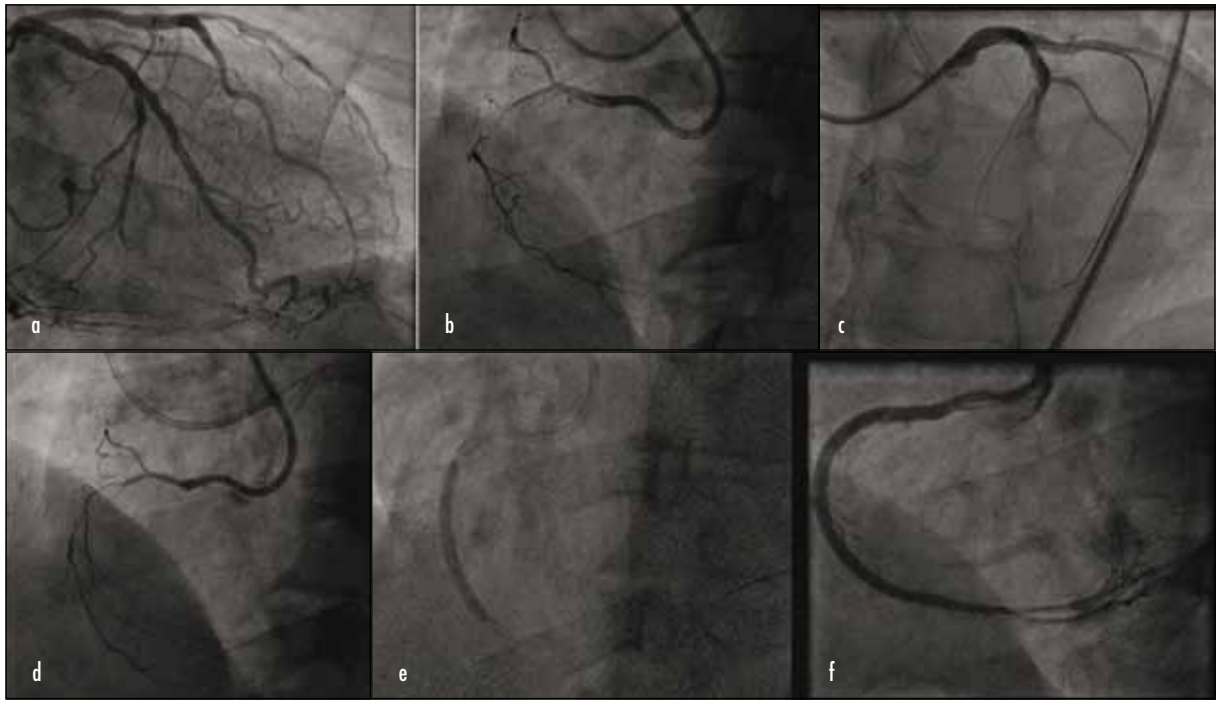

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Table 4. Factors determining end of an attempt at percutaneous coronary intervention for chronic total occlusion

Excessive dye use*
Excessive radiation exposure
Creation of a large false lumen
Intramural haematomas
Excessive patient or operator fatigue

*>600 ml in normoalbuminuric non-diabetic subjects; much less volume in patients at risk of contrast-induced nephropathy

KEY POINTS

- Coronary chronic total occlusions occur in about a third of patients with coronary artery disease, but percutaneous coronary intervention is attempted in only a minority of cases as they are highly challenging lesions.
- Successful percutaneous coronary intervention of chronic total occlusion is associated with symptomatic and prognostic benefit, and reduced cardiac mortality.
- Unsuccessful revascularization is associated with increased risk of major cardiovascular events, including coronary dissection, cardiac tamponade, peri-procedural myocardial infarction and emergency coronary artery bypass grafting.
- The success rate for percutaneous coronary intervention of chronic total occlusions has improved with increasing experience and with the use of novel devices and techniques.
- An individualized approach should be used whereby the pros and cons of the procedure are discussed within the heart team and with the patient, keeping in mind the patient and lesion characteristics as well as the operator's experience.