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Effectiveness, safety, and patient reported outcomes of a planned investment procedure in higher-risk chronic total occlusion percutaneous coronary intervention: Rationale and design of the invest-CTO study

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Abstract

Background: The anatomical complexity of a chronic total occlusion (CTO) correlates with procedural failure and complication rates. CTO modification after unsuccessful crossing has been associated with subsequent higher technical success rates, but complication rates remain high with this approach. While successful CTO percutaneous coronary intervention (PCI) has been associated with improved angina and quality of life (QOL) this has not been demonstrated in anatomically high-risk CTOs. Whether a planned CTO modification procedure, hereafter named Investment procedure, could improve patient outcomes has never been investigated.

Study Design: Invest-CTO is a prospective, single-arm, international, multicenter study, evaluating the effectiveness and safety of a planned investment procedure, with a subsequent completion CTO PCI (at 8–12 weeks), in anatomically high-risk CTOs. We will enroll 200 patients with CTOs defined as high-risk according to our Invest CTO criteria at centers in Norway and United Kingdom. Patients with aorto-ostial lesions, occlusion within a previous stent, or a prior attempt at target vessel CTO PCI within 6 months will be excluded. The co-primary endpoints are cumulative procedural success (%) after both procedures, and a composite safety endpoint at 30 days after completion CTO PCI. Patient reported outcomes (PROs), treatment satisfaction, and clinical endpoints will be reported.

Conclusion: This study will prospectively evaluate the effectiveness and safety of a planned two staged PCI procedure in the treatment of high-risk CTOs and may have the potential to change current clinical practice.

KEYWORDS
chronic total occlusion, complex high-risk and indicated percutaneous coronary interventions (CHIP-PCI), coronary artery disease, CTO PCI, percutaneous coronary intervention

1 | BACKGROUND

The prevalence of chronic total occlusions (CTOs) in patients referred for coronary angiography is as high as 18%–40%.[1,2] CTO percutaneous coronary intervention (PCI) is known to be associated with improved patient reported outcome measures (PROMs).[3–7] Despite guideline recommendations for appropriate revascularization in patients with angina resistant to medical therapy or with significant ischemia in the territory of the occluded vessel,[8,9] only approximately 10% of CTOs are treated by PCI.[10] Perceived procedural difficulty, lower success and higher complication rates are likely to explain the limited provision of treatment in comparison to non-CTO PCI.

Multiple large registries now report CTO PCI procedural success rates >80% by dedicated operators.[11–15] In less experienced centers success rates remain substantially lower at approximately 45%–69%,[16–18] with a higher incidence of subsequent major adverse cardiac events (MACE).[5,19]

Adverse event rates have remained high at 3%–10%, and even more so with complex anatomy.[13,20]

The complexity of a CTO includes an assessment of proximal cap ambiguity, occlusion length and tortuosity, calcium, disease or a bifurcation at the distal landing zone, and collaterals for retrograde access. These characteristics are known to correlate with both procedural failure[5–8] and complication rates.[4,14,21]

CTO crossing can be performed antegrade or retrograde, wiring the occlusive lesion intraplaque or tracking extra-plaque, re-entering the lumen using a dissection and re-entry technique (DART).[22]

While antegrade wiring (AW) is the most frequently used CTO PCI technique, antegrade or retrograde dissection and re-entry techniques (ADR or RDR) are required in 42%–63% of cases, with an increased risk of coronary perforation, tamponade, procedural myocardial infarction (PMI) due to side-branch loss, and ischemia induced while crossing the collateral circulation.[23] In addition, these more prolonged procedures are associated with higher radiation doses[24] and incidence of acute kidney injury (AKI).[25]

Following unsuccessful CTO crossing, plaque modification of the occlusive segment is sometimes performed, with the intention to improve subsequent procedural success.[13,16,19,26,27] CTO ARC defined a "modification procedure" as modifying the proximal cap and CTO body when complete CTO recanalization could not be achieved at the index procedure, with a scheduled second procedure considered part of the initial therapeutic strategy.[28]

Looking retrospectively at registries where an unplanned "CTO modification procedure" was performed, it appears to be safe and associated with higher subsequent procedural success (87%–96% vs. 69%–71%), shorter wire crossing, procedure and fluoroscopy time, and lower radiation and contrast dose during a second procedure.[13,20,27,29,30]

2 | STUDY RATIONALE

In real-world registries CTO PCI success rates remain low. In large registries from experienced centers, the final successful CTO crossing strategy is AW in 65%–81% of cases, with mean J-CTO scores ~2 reflecting a low-intermediate level of anatomical complexity.[12] As the complexity of a CTO increases a second staged procedure is more frequently required to complete recanalization of the occlusion. In the UK registry first attempt technical success rates by J-CTO score were 0 = 95%; 1 = 90%; 2 = 83%; 3 = 79%; 4 = 62%; 5 = 65%.[20]

A "modification procedure" is usually performed after a prolonged initial unsuccessful attempt at CTO crossing. While this is known to improve subsequent success it does not mitigate the risk of complications associated with the failed index procedure.

It has never been prospectively investigated whether a planned "modification procedure" or "investment procedure" could improve treatment effectiveness and safety through higher ultimate procedural success and lower complication rates, and also potentially improve PROMs.

The most common "failure modes" are inability to resolve the proximal cap, unsuccessful antegrade dissection re-entry (ADR) due to significant hematoma, uncrossable collaterals and failure to connect antegrade and retrograde spaces during retrograde dissection re-entry (RDR).[31]

The most frequent and significant complications of CTO PCI are procedural myocardial infarction (PMI) and perforations. PMI can result from side-branch loss, hematoma compression, or as a result of reduced perfusion with equipment across the collateral circulation.[23,32] Myocardial injury (defined as hsTnT >5x upper reference limit [URL]) is common during CTO PCI (34%–58%), more frequent with higher complexity anatomy (J-CTO ≥ 3) (Figure 1) or following the retrograde approach.[33–36] Perforations are often associated with cap and vessel course ambiguity and tortuosity, significant calcification requiring extensive modification,[37] or during collateral crossing. Thus in high complexity CTOs, where there is frequently the need for a second procedure, a strategy of an initial "investment procedure" to resolve the proximal cap and vessel course, then allow healing of hematoma and vessel modification, should increase the proportion of cases that can be completed antegrade, potentially reduce side-branch loss,[38] and result in increased cumulative procedural success and lower complication rates.

On review of the published literature, we identified the crossing strategies and anatomical characteristics associated with procedural failure, complications, AKI, high radiation exposure and MACE on

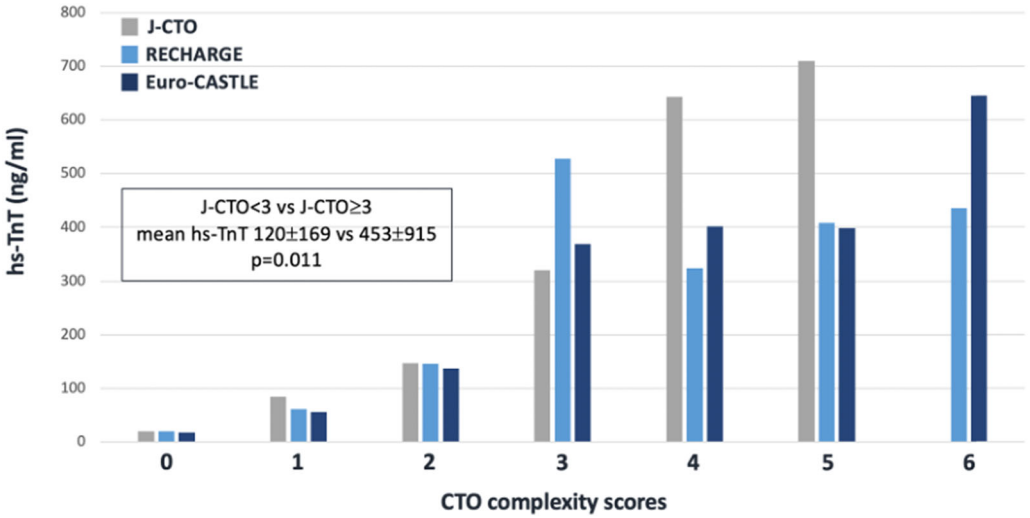

FIGURE 1 Procedural myocardial injury and chronic total occlusion complexity scores ($n = 122$). CTO, chronic total occlusion; hs-TnT; high-sensitivity troponin T; J-CTO, Japanese chronic total occlusion score.[36] [Color figure can be viewed at wileyonlinelibrary.com]

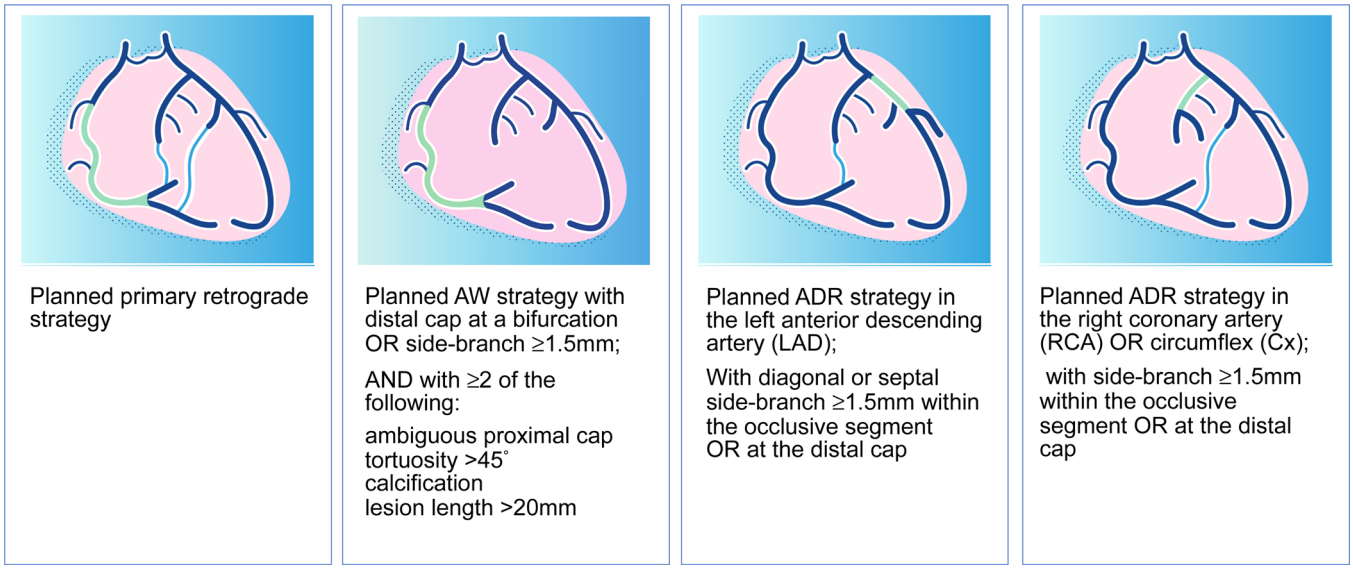

FIGURE 2 Invest chronic total occlusion criteria. [Color figure can be viewed at wileyonlinelibrary.com]

follow-up. Based on these data we have developed the Invest CTO criteria (Figure 2) which will be used as our key inclusion criteria to identify and recruit patients with the highest risk of complications or procedural failure.

3 | AIMS AND HYPOTHESES

The aim of the Invest-CTO study is to investigate whether in the treatment of complex CTOs a planned two stage PCI is associated with improved patient outcomes.

We hypothesize that in complex CTOs a planned investment procedure:

1. Will be associated with improved cumulative procedural success
2. Will be associated with improved patient safety
3. Will facilitate an increased proportion of cases being completed antegrade
4. Will be associated with improved PROMs

4 | MECHANISTIC HYPOTHESES OF INVESTMENT PROCEDURE

We hypothesize that the investment procedure will impact the CTO morphology in five ways (Figure 3):

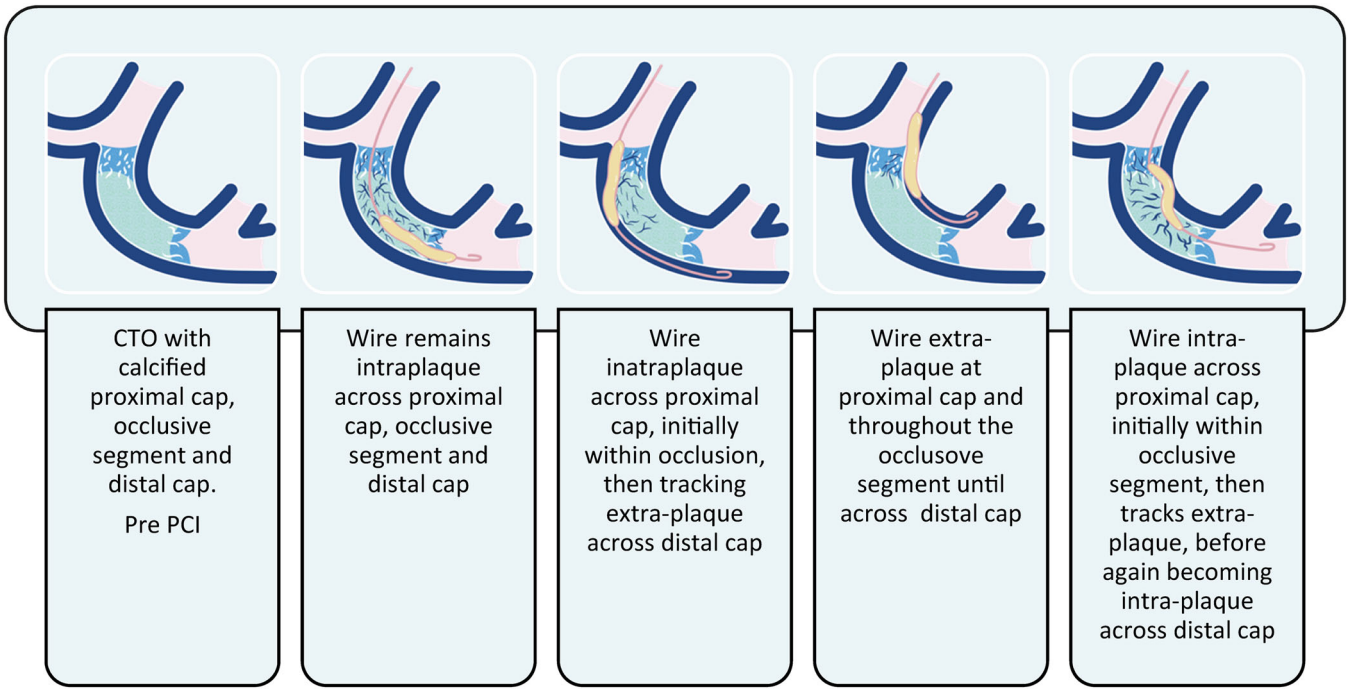

FIGURE 3 Mechanistic hypothesis of investment procedure. [Color figure can be viewed at wileyonlinelibrary.com]

1. It may create an intraplaque communication from the proximal to distal cap.
2. Puncturing and modifying or tracking around and crushing the proximal cap may facilitate more rapid crossing of the cap at the completion procedure.
3. Intra or extra-plaque modification of the occlusive segment will facilitate rapid antegrade tracking at the completion procedure and may create fenestrations between intra and extra-plaque tracks.
4. Puncturing and modifying or tracking around and crushing the distal cap will facilitate crossing at the completion procedure and may create fenestrations between the occlusive segment and distal lumen.
5. The investment procedure will delineate the vessel course when ambiguous.

We predict that this will impact on the success and safety of the completion procedure in several potential ways:

1. It may result in re-establishing antegrade flow.
2. Proximal cap and ambiguity of the vessel course will have been resolved.
3. Fenestrations may facilitate AW.
4. Rapid tracking to the distal landing zone and hematoma resolution will facilitate successful antegrade or retrograde re-entry.
5. More efficient CTO crossing at the completion procedure will result in shorter time working across the collaterals and thus reducing ischemic time.
6. Hematoma and vessel healing may reduce the risk of perforation.
7. Fenestrations may facilitate longer segments of intraplaque wiring resulting in shorter extra-plaque tracking and less side branch loss.

5 | STUDY DESIGN AND METHODS

This is a prospective, single-arm, international, multicenter study recruiting 200 patients at dedicated CTO PCI centers in Norway and the United Kingdom. Eligible patients who do not wish to participate will be asked to consent to a parallel registry. This will allow comparison of the study population outcomes with usual care and allow analysis for selection bias.

5.1 | Ethics

The study will be conducted in accordance with the protocol, applicable regulatory requirements in Norway and the UK, and in full conformity with the Declaration of Helsinki.[39] Approval has been obtained by the Regional Ethics Committees for Medical Research Norway (REC/195282) and UK (22/WS/0006). The study is registered on the clinicaltrials.gov [NCT04774913]. All patients will be provided with a patient information sheet and give written informed consent before inclusion.

The study conception, design, conduct and reporting are the responsibility of the chief investigators. Study data and imaging will be collected, stored, and transferred pseudo-anonymized on a

dedicated electronic case report form (eCRF) (VIEDOC). A joint clinical endpoint committee and data safety monitoring board (DSM-CEC) will evaluate the safety and conduct of the study after 25% and 50% study recruitment. The DSM-CEC charter will outline the study stopping criteria. The study is funded by an unrestricted grant from Boston Scientific Corporation.

5.2 | Study population

Consecutive patients referred for CTO PCI will be screened at each site for clinical appropriateness and study eligibility according to the inclusion and exclusion criteria.

6 | ELIGIBILITY CRITERIA

6.1 | Inclusion criteria

Subjects >18 years, ability to provide written informed consent and comply with the procedural and study follow-up schedule, planned CTO PCI in accordance with appropriateness criteria, and the presence of ≥1 of the Invest CTO criteria (Figure 2).

6.2 | Exclusion criteria

Invest CTO criteria not present, limited arterial access that may prohibit second procedure, CTO within previous stent, baseline transthoracic echo (TTE) or cardiac magnetic resonance (CMR) demonstrating nonviable target vessel territory, contra-indication to dual antiplatelet therapy, pregnancy, prior radiation skin injury, lack of informed consent, aorto-ostial occlusion, prior CTO PCI attempt to target vessel within 6 months.

6.3 | Study intervention

All study patients will have a planned two staged CTO PCI with an initial investment procedure, followed by a completion procedure at 8–12 weeks (Figure 4).

7 | INVESTMENT PROCEDURE

"Invest CTO PCI" is defined as a planned antegrade modification of the proximal cap, occlusive segment, and distal cap of the CTO with a 1:1 sized noncompliant balloon. The protocol does not allow attempted retrograde access or any wire or device-based re-entry during the investment procedure. A final contrast injection is strongly discouraged to avoid propagating dissection and hematoma. If there is successful AW during the index procedure the operator will proceed to CTO PCI completion. These patients will be identified as crossovers and remain in the study for intention-to-treat analysis.

8 | COMPLETION PROCEDURE

Patients will return for a planned completion procedure at 8–12 weeks following the investment procedure. The completion procedure will be performed using techniques and strategies at the operators discretion. On successful wire crossing intravascular ultrasound (IVUS) will be performed pre and post stenting.

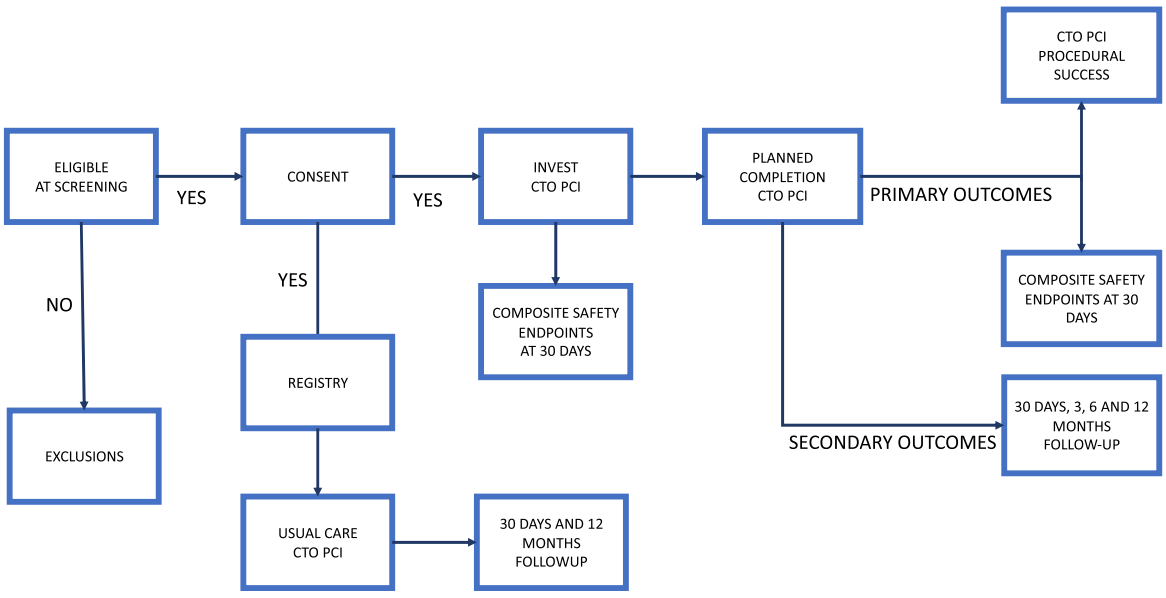

FIGURE 4 Study flow diagram. [Color figure can be viewed at wileyonlinelibrary.com]

9 | OUTCOMES

9.1 | Primary outcomes

The co-primary outcomes are cumulative CTO PCI procedural success after both procedures and a composite safety endpoint at 30 days post completion procedure (Figure 5).

9.2 | Secondary outcomes

In the secondary outcomes we will assess the technical success of the investment procedure, PROMS (Table 1), and composite clinical endpoints at 30 days, 3 and 12 months. (Investment procedure technical success; modification of the proximal cap, occlusive segment, and distal cap. Investment procedure partial technical success; modification of proximal cap ±occlusive segment). There are several prespecified substudies (Figure 5).

The aspects of the procedure most important to the patient will be explored using qualitative analysis of semistructural qualitative interviews using systematic text condensation (STC).[47,48]

10 | CORE LABS

Coronary angiography and IVUS will be analyzed by independent trained observers at the Cardiovascular Research Foundation (CRF) Core Lab in New York USA under the supervision of Professor Akiko Maehara.

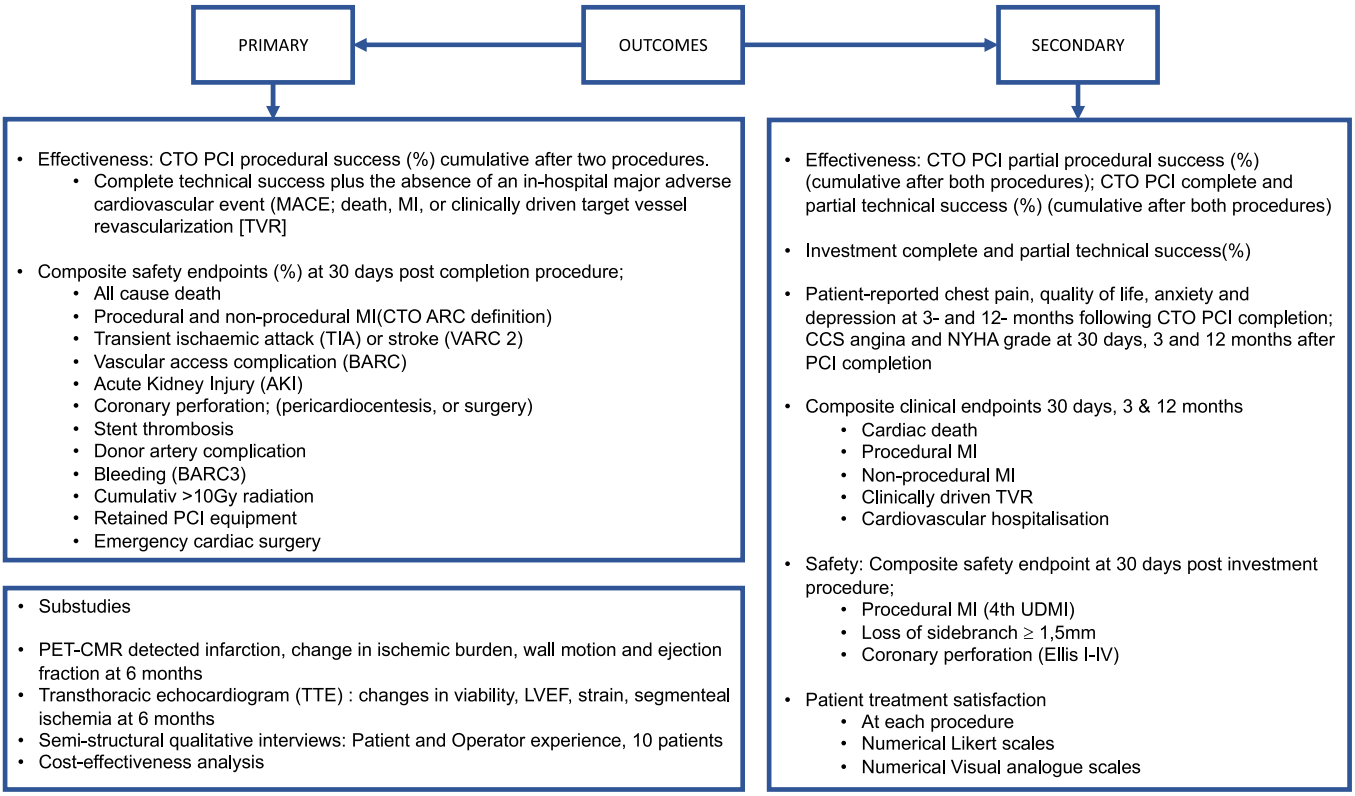

FIGURE 5 Study outcomes. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Patient-reported outcome measures (PROMs).

Questionnaire	Measurement
EQ-5D-5L[40]	Comprises five items and is widely used for measuring economic preferences for health states
Seattle Angina Questionnaire (SAQ-7)[6]	Comprises seven dimensions of coronary artery disease: Physical limitation, angina frequency and quality of life
Hospital Anxiety and Depression Scale (HADS)[41]	Comprises 14 items and determines the levels of anxiety and depression that a patient is experiencing, and generates two subscales: HADS-D and HADS-A
Rose Dyspnea Scale[42]	Comprises a four-item questionnaire that assesses a patients' dyspnoea level during common activities
Likert and Visual analogue scale (VAS) questionnaires[43–46]	Patient reported experience measures (PREM)

PET-CMR and TTE substudy analyses will be performed by dedicated staff at Haukeland University Hospital. Quality assurance will be determined by blinded repeat analysis for intra- and interobserver variability.

11 | STATISTICS

11.1 | Power calculation

Multiple dedicated CTO PCI registries have shown a strong association between procedural failure and occlusion complexity, with a success rate of ~75% when the J-CTO score >2.[4,13,14,21,37,49] Looking retrospectively at registries where an unplanned "CTO modification procedure" was performed in some patients after initial unsuccessful CTO crossing, this was associated with higher procedural success on a subsequent attempt (87%–96% vs. 69–71%).[13,20,27,29,30]

The sample size calculation for the primary endpoint was based on an expected cumulative procedural success rate of 85% compared to a reference value of 78%. Using a one-sample proportion test with a one-sided significance level of 0.05 and power (1–β) of 80%, a total of 190 subjects were required to test the hypothesis that the use of an investment procedure would achieve the performance goal. Allowing for a 5% attrition rate a sample size of $N = 200$ will be recruited.

11.2 | Feasibility

We estimate that 30% of CTO cases referred for PCI will be eligible and will consent to participation. We anticipate 5 centers will recruit 200 patients over 3 years. At the time of submission 20% of the study population has been recruited. The investigators involved have previously successfully completed the UK CTO Registry, Recharge Registry, and CONSISTENT CTO study.[14,20,50]

11.3 | Statistical analysis plan

Categorical variables will be expressed as proportions (±standard deviation, SD) and compared using χ^2 or Fisher exact test where appropriate. Continuous variables will be expressed as mean (±SD) or median (inter-quartile range, IQR), and compared using Student *t* test or nonparametric alternative. Treatment effect differences will be determined with 95% confidence intervals (CI) and *p* values with a significance level of 5%. In multivariate analysis, predictors for procedural success will be identified using logistic regression analysis and will include variables selected from previous research and clinical experience.

12 | DISCUSSION

Although CTO PCI success rates have improved significantly over the last decade, they remain substantially lower than with non-CTO PCI. More importantly, complication rates remain high, especially when dealing with more complex anatomy. The perceived technical difficulty and risks associated with these procedures are a barrier to patients receiving appropriate treatment. We have therefore designed a study to investigate a different approach to the treatment of this anatomically high-risk subpopulation of CTOs, with the aim of further improving success rates while mitigating some of the procedural risk.

A potential limitation is that this is not a randomized trial, but a prospective, single-arm study. This will in part be mitigated by our parallel registry of patients treated with usual care CTO PCI, and our intention to do a propensity score matched comparison of procedural outcomes and safety with case controls from larger registries. In addition, while our data could inform a power calculation for a randomized trial it is important to consider the limitations of randomized comparisons between complex therapeutic interventions such as CTO PCI.

This is a proof-of-concept study that will hopefully provide valuable insight into the selection of patients most likely to benefit from a preplanned two step approach. Furthermore, our "Invest CTO criteria" could potentially be used to select patients where a planned investment strategy would be appropriate.

We propose that "Invest CTO PCI" could be taught to operators early in their CTO PCI experience and become an incremental step during training while they acquire the skills to perform ADR and retrograde procedures. This could then facilitate a completion procedure with the support of a more experienced colleague or proctor. By removing the anxiety of tracking extra-plaque and the fear of failure while acquiring AW skills, it will encourage more operators to explore the advanced techniques required for CTO PCI. The ability to teach this approach to a wider range of PCI operators could in turn encourage collaboration and increase the provision of treatment for appropriate patients.

In contrast to CTO ARC, we chose to use the 4th UDMI of PMI. While acknowledging the fact that only large PMIs (SCAI definition) have been shown to predict subsequent mortality, and their use as endpoints in clinical trials comparing PCI to CABG minimize ascertainment bias, in a study like ours where the co-primary endpoint is safety the more sensitive definition is more appropriate. In addition, we feel it is important to do a prospective analysis of procedural myocardial injury, (post-PCI hsTnT elevation ≥5 × 99th percentile URL, as impact of isolated myocardial injury post PCI remains unclear.[34,51,52]

While successful CTO PCI has been shown to be associated with improved angina, physical endurance and quality of life,[53] this has not been demonstrated in high-risk CTOs, with study populations having anatomically low or intermediate complexity occlusions.[53,54] Confirming improvement in PROMs in this subset of patients is particularly important as they are also at the highest risk of procedural complications.[55]

The patient experience of CTO PCI has never been described. While a potential drawback of the Invest CTO PCI approach might be the need for two procedures, this is already required for a significant proportion of patients with more complex anatomy.[3,20] It is possible that a planned two stage intervention would be associated with an improved patient experience of what can be an arduous treatment. Within the study we will aim to elaborate the basis for shared

decision-making by providing more evidence regarding the risk-benefit discussion with the patient. Furthermore, in the future, in adjudicating CTO PCI success, we may consider shifting the metric from the technical success of an index procedure to encompass the full patient therapeutic journey.

13 | CONCLUSION

The Invest CTO study will evaluate the effectiveness and safety of a preplanned "investment procedure" in anatomically high-risk CTO PCI. We will report cumulative procedural success, safety, patient reported and clinical outcomes in this particularly challenging subset of patients.

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CONFLICTS OF INTEREST STATEMENT

Anja Øksnes; Proctor honoraria from Boston Scientific. Margaret B McEntegart; Honoraria from Boston scientific, Biosensors, Shockwave and Teleflex. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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